

Smart Medical Systems Ltd.

Study Protocol

**Study protocol number: G-EYE™ 15505,
Rev. 01**

Protocol Date: July 9, 2013

Project:

**Prospective randomized trial to compare the
clinical efficiency (Adenoma Detection Rate) of
G-EYE™ HD colonoscopy with Standard
Colonoscopy**

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Signature: _____ Date: _____

INVESTIGATOR AGREEMENT

Prior to participation in this study, a written approval must be obtained from the Ethics Committee, and copy should be provided to the Sponsor, Smart Medical Systems Ltd., or their authorized representatives, along with the Ethics Committee approved Informed Consent Form.

The Principal Investigator must also:

- Conduct the study in accordance with the study protocol, the Investigator Agreement, the Declaration of Helsinki, Good Clinical Practices, international harmonized standards for clinical investigation of medical devices (ISO 14155, Clinical investigation of medical devices for human subjects), the laws and regulations of the countries where the study will take place, applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA, indemnity/insurance requirements and any other applicable regulations.
- Supervise all testing of the device involving human subjects
- Agree to participate in an appropriate training program as part of the study initiation.
- Assure that informed consent is obtained from each subject prior to enrollment, using the Ethics Committee approved form.
- Assure that the study is not commenced until Ethics Committee approval has been obtained.
- Provide all required data and agree to source document verification of study data with subject's medical records.
- Allow staff of the Sponsor and its authorized representatives, as well as representatives from regulatory agencies, to review, inspect and copy any documents pertaining to this clinical investigation.
- Provide accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement as required by the FDA. This information shall be updated if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

The Principal Investigator (PI) may delegate one or more of the above functions to an associate or sub-investigator. However, the PI retains overall responsibility for proper conduct of the study, including obtaining and documenting subject informed consent, compliance with the study protocol, and the collection of all required data.

Investigator Signature

I have read and understand the contents of the clinical protocol. I agree to follow and abide by the guidelines set forth in this document.

Principal Investigator Signature: _____ Date: _____

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1. STUDY PROTOCOL SYNOPSIS

Smart Medical Systems Ltd. Clinical Study Protocol No. G-EYE 15600, Rev 01	
Sponsor:	Smart Medical Systems Ltd. 10 Hayetsira St., Ra'anana 43663, Israel. Tel: +972 9 7444321 Fax: +972 9 7444543
Title:	Comparative evaluation of G-EYE™ Colonoscopy vs. Standard Colonoscopy
The Device:	The NaviAid™ G-EYE System is intended for the optical visualization, diagnosis and endoscopic treatment in the gastrointestinal tract. It is also intended for positioning of the endoscope in the gastrointestinal tract.
Study design:	Multicenter, two-arm, randomized , open-label study
Number of subjects:	Total of 1000 patients, 500 patients in each group
Timing:	Patients will be followed in a short term scheduled visit, or via phone call within 48 - 72 hours post-procedure
Study objective:	The purpose of this study is to compare the adenoma detection rate of G-EYE™ high definition colonoscopy with that of standard high definition colonoscopy
Study endpoint:	Primary endpoint - G-EYE™ colonoscopy detection rate of adenomas and serrated lesions compared to the standard colonoscopy detection rate of the same. Secondary endpoints – polyp and adenoma detection, procedure times and safety.
Inclusion Criteria	<ol style="list-style-type: none"> 1. Patients over 50 years old 2. Referred to colonoscopy for screening, following positive FOBT testing, change of bowel habits or for surveillance colonoscopy (history of adenoma resection). 3. The patient must understand and provide written consent for the procedure.
Exclusion Criteria	<ol style="list-style-type: none"> 1. Subjects with inflammatory bowel disease; 2. Subjects with a personal history of polyposis syndrome; 3. Subjects with suspected chronic stricture potentially precluding complete colonoscopy; 4. Subjects with diverticulitis or toxic megacolon; 5. Subjects with a history of radiation therapy to abdomen or pelvis; 6. Pregnant or lactating female subjects; 7. Subjects who are currently enrolled in another clinical investigation. 8. Subjects with current oral or parenteral use of anticoagulants 9. Subjects with recent (within the last 3 months) coronary ischemia or CVA (stroke) 10. Any patient condition deemed too risky for the study by the

Smart Medical Systems Ltd. Clinical Study Protocol No. G-EYE 15600, Rev 01	
	investigator
	11. Previous colonic surgery (except for appendectomy)

2. LIST OF ABBREVIATIONS

ADR = Adenoma Detection Rate

AE = Adverse Event

BBPS = Boston Bowel Preparation Scale

CIP = Clinical Investigation Plan (protocol)

eCRF = Electronic Case Report Form

EC = Ethics Committee

PDR = Polyp Detection Rate

SAE = Severe Adverse Event

3. INTRODUCTION

This document is a clinical research protocol and the described study will be conducted in compliance with the protocol, Good Clinical Practices standards and associated regulations, and all applicable research requirements.

4. BACKGROUND

Colorectal cancer (CRC) is the second leading cause of cancer in the US and Europe, with more than 140,000 new cases and over 50,000 deaths annually in the USA alone.^{1,2,3} While being extremely lethal in its advanced stages, exhibiting a five-year survival rate of less than 10%,² it is by far a most preventable cancer by early detection. Over 90% of the CRC incidents develop over years from polyps that grow in the colon.² Timely detection and removal of these polyps prevent the disease.

Colonoscopy is the major GI endoscopy procedure, and is in particular the gold-standard method for CRC screening, as it enables detection and real-time removal of pre-cancerous polyps during the examination.

It is well known that lesions are missed during routine colonoscopy. A meta-analysis of 6 studies by Van Rijn et al.⁴, in which subjects went through two colonoscopies in the same day, reported an overall 22% polyp miss rate. A clinical study by Rex et al.,⁵ which performed same-day, back-to-back colonoscopy on 183 subjects, reported an overall adenoma (pre-cancerous polyp) miss rate of 24%. A back-to-back same-day colonoscopy study in 286 subjects by Heresbach et al.⁶ reported miss rate during the first colonoscopy of 28% polyps and 20% adenomas. The polyp missing effect and its consequences are well demonstrated when comparing actual colorectal cancer incidents to past colonoscopies performed in these CRC subjects. Postic et al.⁷ compared resected colon specimens with the results of colonoscopies performed

within 5 months prior to surgery and reported that 23.3% of the lesions in the resected specimens were missed during these colonoscopies. Pabby et. al.⁸ reported that 23% of subjects in whom colon cancer developed, went within 30 month prior to the CRC incident through colonoscopy in which no polyp was found in the cancer area of the colon.

An apparently leading cause of missed polyps during colonoscopy is attributed to polyps that are located behind austral folds in the colon, and are therefore hidden from the conventional, forward-viewing endoscope optics. It was demonstrated that occasional straightening of austral folds during colonoscopy, by a plastic cap mounted on the endoscope tip, increases polyp detection yield. While such mechanical stretching of colon folds is not systematic and not circumferential, it does have a positive effect on polyp detection rate. A 6,185 patient study by Westwood et. al.⁹ reported a miss-rate of 12.2% in the cap-assisted colonoscopy group vs. 28.6% miss rate in the standard colonoscopy group, implying a positive effect of cap employment on polyp detection rate. In contrast, another study performed by Tee et. al.¹⁰ in 400 subjects, reported that there was no significant polyp detection rate difference detection standard colonoscopy and cap-assisted colonoscopy (31.3% vs. 32.8%, respectively). Recently, a rearward viewing device was introduced for use during colonoscopy with standard endoscopes. The device – the Third Eye Retroscope (TER) (Avantis Medical, Sunnyvale, CA), is a disposable optical instrument which is passed through the instrument channel of a standard endoscope, and folds forwardly of the endoscope optics to provide retrograde viewing which is inspected in parallel to the endoscope's forward viewing image. This technique is aimed to allow inspection of the proximal surface of austral folds, which is not in the line-of-sight of the endoscope's forward-viewing optics, thereby allowing detection of polyps that are located behind such folds. Few clinical studies were performed to evaluate the ability of TER to detect additional polyps, beyond standard colonoscopy. Triadafilopoulos et. al.¹¹ performed a 24 patient study and reported additional 11.8% increase in polyp diagnostic yield using the TER. In this study, the endoscope was advanced in the colon to the cecum, and TER was employed during endoscope withdrawal. DeMarco et. al.¹² performed a 298 patient study with similar comparison, which demonstrated 13.2% and 11% increase in detection of polyps and adenomas, respectively, by using TER. A similar study by Waye et. al.¹³ in 249 subjects reported 14.8% and 16% TER-related increase in detection of polyps and adenomas, respectively. Leufkens et. al.¹⁴ performed a tandem (back-to-back) study in 349 subjects, investigating the TER-related second pass net increase in polyp detection, and reported respective TER-related increase in polyp and adenoma detection of 23.2% and 29.8%.

Overall, 5 major reasons can be detailed for missing polyps during colonoscopy:

1. Polyps that are hidden behind folds in the colon, and are thus not in the line-of-sight of the endoscope's optics.
 2. Polyps that are in the endoscope optics line-of-sight, but are masked by the colon's topography and natural folds, and are thus un-noticed.
 3. Shallow polyps which do not extend much beyond the mucosa surface.
-

4. Polyps located in an unscreened portion of the colon, due to incomplete colonoscopy.
5. Endoscope slippage during withdrawal, causing a portion of the colon that was pleated over the endoscope during advancement to be released in an uncontrolled manner and thus to remain unscreened, unless endoscope is re-advanced to inspect this portion.

The NaviAid™ G-EYE™ system presents a new and unique concept that overcomes all 5 items listed above, providing an overall solution to the two endoscopy key challenges of limited detection/treatment yield and limited operation range.

The NaviAid™ G-EYE™ system is aimed to create a comprehensive change of practice in the methodology, yield and range of concurrent GI endoscopy, while maintaining the existing practice, visualization technique and endoscopy room process flow.

The NaviAid™ G-EYE™ endoscope comprises a standard endoscope onto which a unique balloon is permanently integrated, at its bending section. The NaviAid™ G-EYE™ balloon is controlled by the NaviAid™ SPARK²C inflation system. The NaviAid™ G-EYE™ system components are presented in figure 1.

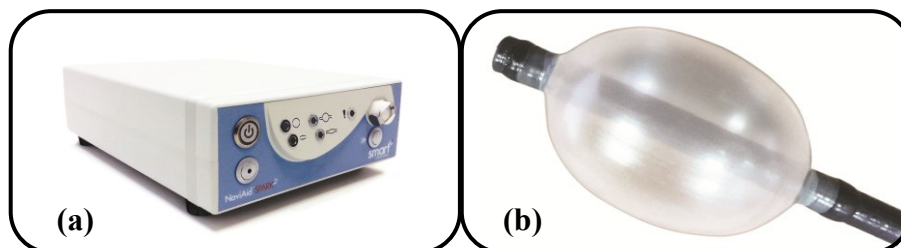


Figure 1: *The NaviAid™ G-EYE™ system, (a) SPARK²C inflation system, and (b) permanently integrated reusable balloon on standard endoscope's bending section*

A major attribute of the NaviAid™ G-EYE™ system is its Controlled Withdrawal™ technique of the endoscope, with the balloon moderately inflated is to expand and stretch the intestinal lumen during endoscope withdrawal. The balloon-endoscope system encompassing this controlled withdrawal method, will broadly improve endoscopy performance technique, clinical practice and diagnostic/therapeutic yield, by providing the following effects:

1. It straightens intestinal folds, thereby allowing detection and treatment of hidden lesions and polyps that were previously located behind these folds. In contrast to rearward-viewing optics, this solution does not detect the lesion in its rearward location, but rather brings the lesion towards the forward-viewing optics of the endoscope. A major advantage of this approach is that once the lesion is brought forwardly of the endoscope optics, it can be readily treated,

eliminating the need to manipulate the endoscope to be positioned facing the lesion.

1. The local stretching of the colon (or other portion of the GI tract) creates a smoother and more visually uniform background against which polyps and other lesions can more readily be seen by the physician and thus creates enhanced visual contrast between polyps and the interior of the colon.
2. This stretching causes polyps and other pathologies to protrude inwardly from the colon walls to an extent which is enhanced. Specifically, it provides enhanced visibility and access to shallow polyps.
3. The smooth engagement of the moderately inflated balloon with the colon (or other portion of the GI tract) provides the operator with full control over the withdrawal process, allowing thorough and continuous investigation of the colon, and very importantly – preventing endoscope slippage in the colon. As mentioned in reason 5 above, endoscope slippage may occur during withdrawal, when a portion of the colon, which was pleated over the endoscope during advancement, is released in an uncontrolled manner. Unless the endoscope is reinserted to inspect it, such a portion remains unscreened, adversely affecting detection yield.
4. Once a polyp or other lesion is detected, the endoscope's balloon can be readily inflated to anchoring pressure providing endoscope stabilization in the bowel during treatment. This attribute can be highly valuable when performing complex or time/effort consuming intervention, such as removing a shallow polyp, multiple polyp removal, suturing, clip application, ERCP sessions, and a variety of other interventions. In terms of impact on endoscopic intervention practice, the stabilization effect can be dramatic, substantially reducing operation time, failure rate, patient risk and sedation exposure level, and physician's required interventional experience and skills.

5. DEVICE DESCRIPTION

Smart Medical Systems Ltd. is an ISO 13485:2003+AC:2007, company that designs, develops and manufactures the G-EYE™ system. The NaviAid™ G-EYE™ system is CE and AMAR approved. ISO 13485:2003+AC:2007, CE and AMAR certificates are provided in appendix B.

The NaviAid™ G-EYE™ system is intended for the optical visualization, diagnosis and endoscopic treatment in the gastrointestinal tract. It is also intended for complete positioning of the endoscope in the gastrointestinal tract.

The NaviAid™ G-EYE™ system is comprised of a standard endoscope which is mounted with an integral re-used balloon and a second balloon that may be inserted through the instrument channel of the endoscope (either the NaviAid™ AB or NaviAid™ ABC) during procedure to enable deep or challenging intestinal advancement. The NaviAid™ G-EYE™ may also be used without a balloon catheter for performing controlled withdrawal and endoscope stabilization. The air supply and

control system – the NaviAid™ SPARK²C controls the inflation and deflation of the relevant balloon.

5.1 Device Intended Use

The G-EYE System is intended for the optical visualization, diagnosis and endoscopic treatment in the gastrointestinal tract. It is also intended for complete positioning of the endoscope in the gastrointestinal tract.

6. RISKS AND BENEFITS

The NaviAid™ G-EYE™ system is designed according to international standards for medical devices. Compliance with these standards ensures that the device can be used safely in human beings. All patient-contact materials are biocompatible and comply with ISO 10993. This study is intended to evaluate the performance of the NaviAid™ G-EYE™ system.

Smart Medical Systems Ltd. is an ISO 13485:2003+AC:2007 that designs, develops, manufactures the NaviAid™ G-EYE™ system.

Smart Medical Systems Ltd. is a company that follows application and compliance with the risk management standard ISO 14971:2007(E), the company performed biocompatibility and biological testing according to ISO 10993. The device was found to be biocompatible. An extensive design verification & validation bench tests in accordance with essential requirements listed in the Medical Device Directive (MDD 93/42/EEC).

Special considerations have been taken during the design of the device to ensure that it is safe and reliable.

Refer to the Investigator's Brochure for complete details regarding testing, specifications, design etc.

6.1 Anticipated Clinical Benefits

Previous studies indicate that the NaviAid™ G-EYE™ system enables the performance of Controlled Withdrawal™ during colonoscopy while straightening intestinal folds and enhancing diagnostic yield. Patients participating in this trial may benefit from potentially increased detection rate obtained by performing the NaviAid™ G-EYE™ procedure not available when performing standard colonoscopy.

6.2 Anticipated Adverse Events and Contraindications

Possible complications that may result from the procedure are similar to those relevant to standard endoscopy and include, but may not be limited to: perforation, hemorrhage and septicemia/infection.

Contraindications include those specific to the endoscopy procedure. Relative contraindications include the following:

- Bowel obstruction
- Concomitant Coumadin use
- Diverticulitis
- Recent (within the last 3 months) coronary ischemia or CVA (stroke).

In each of the above cases, it is not recommended to use the NaviAid™ G-EYE™ system. Final decision will be based on the actual case and the physician's decision.

All these risks can be reduced significantly when the device is operated by a qualified person that is experienced with similar procedures, and according to the product IFU.

7. STUDY CONDUCT

This study will be performed in accordance with the Declaration of Helsinki, the Israeli MOH guidelines, European Union's Medical Device Directive (93/42/EEC art.15) and local Member States transpositions. The study will be conducted in agreement with the guidelines for conducting a Clinical Investigation as outlined in the European Harmonized Standard, EN ISO 14155:2011(E), and in accordance with the principles of ICH GCP.

7.1 Study Objective

The purpose of this study is to compare the ADR obtained by performing G-EYE™ colonoscopy vs. the ADR obtained by performing standard colonoscopy. The study will enroll 1000 subjects.

7.2 Study Endpoints

Primary endpoint - G-EYE™ colonoscopy detection rate of adenomas and serrated lesions (combined), compared to the standard colonoscopy detection rate of the same. Secondary endpoints - comparison of polyp and adenoma detection, length of procedure and safety.

7.3 Subject Selection

In order to be included in this study, subjects will have to fulfill all the inclusion criteria and none of the exclusion criteria.

7.3.1 Inclusion Criteria

Any subject who meets all of the following criteria may be included in this study:

1. Patients over 50 years old
2. Referred to colonoscopy for screening, following positive FOBT testing, change of bowel habits or for surveillance colonoscopy (history of adenoma resection).
3. The patient must understand and provide written consent for the procedure

7.3.2 Exclusion Criteria

Any subject who meets any of the following criteria will not be included in this study:

1. Subjects with inflammatory bowel disease;
2. Subjects with a personal history of polyposis syndrome;
3. Subjects with suspected chronic stricture potentially precluding complete colonoscopy;
4. Subjects with diverticulitis or toxic megacolon;
5. Subjects with a history of radiation therapy to abdomen or pelvis;
6. Pregnant or lactating female subjects;
7. Subjects who are currently enrolled in another clinical investigation.
8. Subjects with routine oral or parenteral use of anticoagulants
9. Subjects with recent (within the last 3 months) coronary ischemia or CVA (stroke)
10. Any patient condition deemed too risky for the study by the investigator
11. Previous colonic surgery (except for appendectomy)

7.4 Study Design

This is a multicenter, two-arm, randomized, open-label study intended to compare the detection rate obtained by performing G-EYE™ high definition colonoscopy vs. the detection rate obtained by performing high definition standard colonoscopy.

The study will enroll 1000 subjects.

Consecutive adult subjects who were referred for elective colonoscopy will be asked to enroll into this randomized clinical study if the candidate meets the study inclusion and exclusion criteria.

Subjects will sign informed consent form and undergo randomization.

7.5 Randomization Process

Subjects will be randomized to one of two groups. Group A, the “Study Group,” and Group B, the “Control Group.”

Group A: Subjects will undergo a G-EYE™ colonoscopy.

Group B: Subjects will undergo a standard colonoscopy.

All subjects will be randomized at the time of informed consent. Randomization will take place at the study site under the direction of the investigating physician or the clinical study coordinator. Details on the randomization method are described in the statistical section (section 8).

The investigator will inform the patient of the Group designation prior to the start of the procedure.

7.6 Study Procedures

- All subjects will undergo routine bowel preparation according standard protocol for each institution.
 - The subject will undergo colonoscopy in accordance with the randomization process.
 - Standard colonoscopy will be performed using Pentax endoscope of EC-3890i series.
 - G-EYE™ colonoscopy will be performed using G-EYE™ colonoscope which is based on Pentax EC-3890i series.
 - When performing standard colonoscopy, the endoscopist and facility staff will follow their usual practice.
 - When performing the G-EYE™ colonoscopy, the endoscopist and facility staff will conduct the exam according to the NaviAid™ G-EYE™ system Instructions For Use (IFU).
 - During intubation and withdrawal, investigator will use standard clinical practice and will observe the video display.
 - No Buscopan will be used during the procedure.
 - All polyps detected during intubation will be removed; irrespective of size, color or subjective interpretation, with the possible exception of very small (<2 mm) polyps or clusters of rectal polyps and that – in the judgment of the endoscopists – are not clinically significant. Such lesions will be treated according to the endoscopists' standard practice with methods that the endoscopists consider to be in the best interest of their subjects. Possible approaches include a) removing all such lesions, b) removing one or more lesions for histological evaluation and leaving the rest behind or c) leaving all of the lesions in place. These lesions will be excluded whether removed or not.
 - Intubation time is defined as the duration of the time from the entry of the colonoscope into the anal verge to the time when the colonoscope arrives in the cecum, as determined by the investigator.
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- Investigator will record bowel preparation using the Boston Bowel Preparation Scale Score method¹⁵. Total score (0-9) will be obtained by adding the scores for individual evaluation of right, mid and left colon. Score in each segment should be ≥ 2 (2 or 3) to be acceptable. If score of either segment is < 2 (0 or 1), then the patient should be either excluded from the study or re-scheduled to a different session. If patient is rescheduled then he/she will not be re-randomized.
 - Intubation time, withdrawal time and total procedure time will be measured using time displayed on the monitor, on a wall clock or on a watch. Pause times will be measured by recording the time at the beginning of each therapeutic intervention and the time when intubation resumes. An acceptable alternative is to use a stopwatch to determine the time intervals, in which case the stopwatch will be stopped at the beginning of a pause and re-started as the procedure resumes.
 - Withdrawal time is defined as the duration of the time from initiation of cecal inspection to the time when the colonoscope is withdrawn from the anus.
 - During withdrawal, pause times will be measured by recording the time at the beginning of each therapeutic intervention and the time when intubation resumes. An acceptable alternative is to use a stopwatch to determine the time intervals, in which case the stopwatch will be stopped at the beginning of a pause and re-started as the procedure resumes.
 - Polyps observed during insertion will not be removed or marked with biopsies or color.
 - Polyp size will be measured by comparison to an open biopsy forceps
 - All polyps detected during withdrawal will be removed (except for complicated polypectomies – see below), irrespective of size, color or subjective interpretation, with the possible exception of very small ($< 2\text{mm}$) polyps or clusters of rectal polyps as described above.
 - After detection of a polyp, chromoendoscopy (e.g. NBI) can be used for polyp characterization.
 - Images of detected polyps will be taken in 3 states: iScan1, iScan2, after removal. Complicated polypectomies can be performed in a different session. The detection of the lesion will be noted in the files, and the histology results will be taken from the polypectomy phase. Such cases should be noted in the study files.
 - Withdrawal times should be targeted to a minimum of 6 minutes. Withdrawal times of less than 5 minutes will be regarded as a violation of the protocol.
 - All removed polyps have to be clearly marked and sent to histology.
 - Patients will be followed up in either short term scheduled visit (for instance following histology results) or via telephone call within 48 - 72 hours post-procedure, to assess safety. Follow up during either phone call or visit will be noted in patient study files.
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7.7 Data Collection

- Data will be collected using a computer based application. Non-identifiable patient information will be uploaded to web base database (i.e eCRF).
- If the procedure cannot be completed, the endoscopist will record the reason on the eCRF.
- Patient's demographics and medical history will be collected.
- The standard treatment and care provided to all subjects, alongside the application of the investigational device will be performed and recorded on the appropriate study eCRF.
- Data collection will also include investigator identification, device identification data and usage of the device, relevant concomitant medication.
- Data collection will also include time to cecum, withdrawal time, total procedure time, polyp size, polyp location, polyp histology, any other finding (including mass, bleeding, stricture, inflammation etc.), images of polyps, , etc.
- All data will be documented on the eCRF's, together with the occurrence of any adverse events during the device usage.
- Any complication attributed to the device will be recorded.
- All serious adverse events/complications will be reported immediately (within 48 hours) to the study sponsor/monitor, sponsor, EU representative and to the Ethics Committee (in accordance to European and national law).

7.8 Deviations from study protocol

Any deviations from the study protocol should be notified to the sponsor and documented on study deviation forms.

7.9 Informed Consent

Written informed consent must be obtained from each study subject. The subject will be asked to read the informed consent form and to sign the form to indicate consent to participate in the study.

The investigator will explain carefully to the subject the research nature of the study. The scope and aims of the research will be described together with known or foreseeable benefits, risks and discomforts that subjects may experience. Appropriate alternative treatments will be discussed so that the subject may determine whether or not he or she wishes to participate in the study. The subject must understand that throughout the study his or her participation remains voluntary and protected by the Declaration of Helsinki. The investigator is responsible for obtaining written (or

witnessed) informed consent from potential subjects prior to study entry. Subjects will be given time to read the informed consent and ask any questions before being asked to sign the form. The informed consent (approved by the sponsor and the Ethics Committee) must be signed and dated by the subject and the investigator. One copy of the signed consent will be given to the subject, a second copy will be sent to the referral investigator and the original will be retained by the investigator.

Subjects may withdraw their consent to participate in the study at any time without prejudice. The investigator may withdraw a subject if, in his clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol. Attempts should be made to complete any examinations and the sponsor must be notified of all withdrawals.

Should a protocol amendment be made, the subject's consent form may be revised to reflect the changes of the protocol. It is the responsibility of the investigator to ensure that an amended informed consent is approved or reviewed by the EC, and that it is signed by all subjects subsequently entered in the study and those currently in the study, if affected by the amendment.

7.10 Investigative Center Selection Criteria

The investigative site will meet the following selection criteria prior to inclusion in this study:

- Experience with colonoscopy
- Clinical research study experience and resources that demonstrate good compliance with study requirements and timely, complete documentation of subject follow-up.
- All investigative center personnel involved in this study must agree to allow sufficient time for comprehensive training in the use of the investigational device.
- Sufficient subject volume to meet enrollment timeframe.

7.11 Ethics Committee

The clinical protocol for this study must be reviewed and approved by the Ethics Committee (EC) at the institution(s) where the study will be conducted. The sponsor shall provide any additional information or assistance that may be requested. Should the EC suggest changes to the clinical protocol to conform to institutional rules or local regulations, these changes may be incorporated in a modification of this protocol with approval from the sponsor. A copy of the written EC approval must be provided to the sponsor prior to the beginning of the study.

Other investigator responsibilities relative to the EC include the following:

1. During the conduct of the study, the investigator will submit progress reports to the EC as required, and request re-review and approval of the study at least once a year;
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2. The investigator will report immediately to the EC of any unexpected serious adverse events that occur during the study, and provide the sponsor with a copy of the correspondence;
3. If the sponsor notifies about serious adverse events reported in other studies using this device, the investigator must report that information to the EC;
4. As required, the investigator must obtain approval from the EC for protocol amendments and for revisions to the consent form or subject recruitment advertisements;
5. The investigator should provide the EC with any other information it requests before or during conduct the study;
6. The investigator must maintain a file of study-related information that includes all correspondence with the EC;
7. The investigator must notify EC when study is completed (i.e. after the last study visit of the final study subject);
8. After study completion (within 12 months is recommended) the investigator should provide the EC with a final report on the study. The recommended components of a final report are as follows; dates of study start and completion, number of subjects enrolled/treated, number of subjects who discontinued participation early and reason why, itemization and discussion of any serious adverse event.

8. STATISTICAL CONSIDERATIONS

8.1 Study Design and Objectives:

This is a multicenter, two-arm, randomized, open-label study intended to compare the detection rate obtained by performing G-EYE™ colonoscopy vs. the detection rate obtained by performing standard colonoscopy.

8.2 Study Endpoints:

8.2.1 Primary Performance Endpoint:

The primary performance measure will be the detection rate of adenomas and serrated lesions combined (DR) which is defined as the percentage of subjects with at least one relevant lesion found, in each of the study groups.

8.2.2 Secondary Endpoints

Secondary endpoints include:

- Time to reach cecum,
- Withdrawal (of device) time,
- Total procedure time,
- Number of polyps,
- Number of adenomas
- Other findings (including mass, bleeding, stricture, inflammation etc.)

8.2.3 Safety Endpoints

- Incidences of known complications that may result from the procedure are similar to those relevant to standard endoscopy and include, but may not be limited to: perforation, hemorrhage and septicemia/infection.
- All adverse events and complications

8.3 Study hypothesis:

Null Hypothesis: $P_{sc} = P_{G-EYE}$

Alternative Hypothesis: $P_{sc} \neq P_{G-EYE}$

Where P_{sc} is the ADR in subjects who undergo standard colonoscopy, and P_{G-EYE} is the DR in subjects who undergo G-EYE™ colonoscopy.

8.4 Sample size estimation

A sample size is calculated to test the above described null hypothesis with 80% power at a 5% level of significance. From the literature it is known that the adenoma detection rate is 24%. If we power this study to detect a 35% increase in the DR with the G-EYE™ colonoscopy then 450 subjects will be required per study group, for a total sample size of 900 subjects. To allow for a potential 10% drop out rate we will enroll 500 patients in each group, for a total of 1000 subjects.

8.5 Randomization:

After a subject meets the eligibility criteria, he/she will be equally allocated (with a 1:1 ratio) to one of the following 2 treatment groups based on a randomization scheme with blocks stratified by center:

- Group A: Subjects will undergo a G-EYE™ colonoscopy.
-

- Group B: Subjects will undergo a standard colonoscopy.

The randomization scheme will be prepared by the study statistician using the SAS® (version 9.3.) random number procedure.

8.6 Blinding:

NR to open label study.

8.7 Data Analysis Sets:

8.7.1 Intent to Treat (ITT) analysis set:

The ITT analysis set will consist of all subjects randomized. In accordance with the ITT principle, all subjects randomized who were found eligible for the study will be kept in their originally assigned treatment group.

8.7.2 Per protocol (PP) analysis set:

The per-protocol analysis set will consist of all subjects who complete the study without major protocol violations; a list of protocol violations that are considered major will be prepared before statistical analysis is performed.

8.7.3 Statistical Analysis of analysis sets:

The ITT analysis set will serve as the main set for performance and safety assessments.

The primary performance assessment will also be performed on the PP analysis set

8.8 Statistical Analysis:

8.8.1 General Considerations

Statistical analyses will be performed using SAS® v9.3 or higher (SAS Institute, Cary NC, USA).

Baseline demographic and other baseline characteristics, together with safety analyses will be performed on all enrolled subjects. Baseline values are defined as the last valid value prior to treatment.

Study results will be presented in tables and graphs when relevant. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum, and categorical variables by a count and percentage

The required significance level of findings will be 5%. All statistical tests will be two-sided. If statistical tests are performed nominal p-values will be presented. Where

confidence limits are appropriate, a two-sided 95% confidence interval will be constructed, unless stated otherwise.

For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test will be used as appropriate. For comparison of proportions (categorical variables), the Chi-squared test or Fisher's exact test will be used as appropriate.

8.8.2 Demographic and Other Baseline Variables

Demographic and baseline condition related characteristics will be tabulated. Continuous variables such as age will be summarized by a mean, standard deviation, minimum, median and maximum, and categorical variables by a count and percentage.

8.8.3 Disposition of Subjects

Device tolerability will compare between the treatment groups, the number and percent of subjects who fail to complete the study and the number and percent of subjects who fail to complete the study because of Adverse Events will be presented.

8.8.4 Performance Analyses

A count and percentage of subjects with adenomas with each of the study devices will be presented, together with 95% exact confidence intervals. The null hypothesis will be tested using a chi-squared test,

Secondary endpoints will be summarized by descriptive statistics per study group; the groups will be compared according to data type as described in the general methods section.

Kaplan-Meier curves of the time to cecum, withdrawal time, total procedure time in each of the study groups will be presented and compared using the Log-Rank test.

8.8.5 Safety Analysis

Tables displaying the frequency and incidence of AEs will be presented by treatment group, an odds ratio and 95% confidence interval will be presented as well.

Adverse events (AEs) will also be presented by seriousness, severity and relation to device by study group.

8.8.6 Pooling

Subgroup analysis of the primary efficacy endpoints by center will be used to evaluate the poolability of the results. The ADR by center interaction will be tested with Fisher's exact test using a significance level of 10%. If the interaction is found significant, the reasons for these interactions will be further explored and rationalized. This evaluation may include demographic features, symptoms at presentation, clinical and treatment history, and center comparability in the features found to be associated with the primary efficacy variable. Sites with a small amount of subjects (<10) will be pooled together for this analysis by geographical location.

8.8.7 Handling of Missing Data

The study outcome will not be evaluated for patients who drop out or do not have data available for the analysis. Nevertheless a sensitivity analysis will be performed using a worst case scenario model where subjects who have dropped out or do not have the study evaluation available are considered as not detected.

8.8.8 Interim Analysis

No interim analyses are planned for this study.

9. ADVERSE EVENTS

9.1 Reporting requirements

Timely and complete reporting of Adverse Events (AE) and safety assessment allows:

- Protection of safety of study subjects.
- Greater understanding of the overall safety profile of the study treatment.
- Appropriate modification of study protocols and improvement in study design and procedures.
- Adherence to regulatory requirements

The definitions and reporting requirements adopted in this study are derived from the current International standard on clinical investigations: ISO 14155:2011 and MEDDEV 2.7.3.

9.2 Definitions:

Adverse Events (AE)

AE is defined as any untoward medical occurrence in a subject. This definition does not imply that there is a relationship between the adverse event and the device under investigation. An AE can therefore be any unfavorable and unintended sign, symptom, laboratory observations or disease temporally associated with the use of the investigational product, whether or not related to the investigational product. The following should be reported as AE:

- Untoward medical conditions or signs or symptoms that were absent before starting study treatment.
- Untoward medical conditions or signs or symptoms present before starting study treatment and worsen (increase severity or frequency) after starting study treatment.
- Abnormal laboratory value or test.
- Clinical signs or symptoms that require therapy.

Device Related Adverse Events

Device Related Adverse Events are defined as any untoward medical occurrence not present at baseline which is suspected of being related to the investigational device. Device-Related AE's MUST also be reported by the investigator to the sponsor within 24 hours of investigator's awareness of the event. The reporting should then be followed up by written notification within 5 days, using the appropriate form in the study file.

Device Deficiency

Device Deficiency is defined as Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling and when occurred it is regarded as a reportable event.

Adverse Device Effect (ADE)

ADE is defined as any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device, and any event that is a result of a user error. Therefore, some adverse device effects may be related to device failure, malfunction or misuse.

Device failures, Malfunctions and Misuse

Investigators are instructed to report all possible device failures, malfunctions or misuse observed during the course of the trial. These incidents will be documented in the case report form provided as follows:

Device Failure - A device failure has occurred when the device is used in compliance with the Instructions for Use, but does not perform as described in the Instructions for Use and also negatively impacts treatment of the study subject.

Device Malfunction - A device malfunction occurs when an unexpected change to the device that is contradictory to the Instructions for Use is observed, which may or may not affect device performance.

Device Misuse - Any use of the investigational device by the investigator that is contradictory to the application described in the Instructions for Use will be categorized as device misuse.

Unanticipated Adverse Device Effect (UADE)

An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on health or safety or any the life-threatening problem or death caused by or associated with the use of the investigational device that was not previously identified in the Investigational Plan or Instructions for Use in its nature, frequency or severity. UADEs may also include other serious problems associated with the device that affect the rights or welfare of study subjects.

Serious Adverse Events (SAE)

A SAE is an adverse event that:

1. Led to a death,
2. Led to a serious deterioration in the health of the subject that:
 - a. Resulted in a life-threatening illness or injury
 - b. Resulted in a permanent impairment of a body structure or a body function
 - c. Required in-patient hospitalization or prolongation of existing hospitalization
 - d. Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Serious Adverse Device Effect (SADE)

A Serious Adverse Device Effect is an adverse event caused by or associated with the use of the investigational device that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Unexpected Serious Adverse Device Effect (USADE)

An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or

application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9.3 Documentation

Adverse events must be listed on the appropriate eCRF page. All AEs will be characterized by the following criteria:

- Intensity or Severity
- Relatedness
- Outcome
- Treatment or Action Taken

Intensity or Severity

The following categories of the intensity of an adverse event are to be used:

Mild - Awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae.

Moderate - Interferes with the patient's usual activity and/or requires symptomatic treatment.

Severe - Symptom(s) causing severe discomfort and significant impact of the patient's usual activity and requires treatment.

Relatedness

The investigator will use the following definitions to assess the relationship to the device:

Not related - The cause of the AE is known and the event is not related to any aspect of study participation.

Possibly related - There is a reasonable possibility that the event may have been caused by study participation.

The AE has a timely relationship to the study procedure(s); however, follows no known pattern of response, and an alternative cause seems more likely or there is significant uncertainty about the cause of the event.

Probably related - It is likely that the event was caused by study participation.

The AE has a timely relationship to the study procedure(s) and follows a known pattern of response; a potential alternative cause, however, may explain the event.

Related - A related event has a strong temporal relationship and an alternative cause is unlikely.

Outcome

The clinical outcome of the AE or SAE will be characterized as follows:

Death - The SAE eCRF must be completed for this outcome

Recovered without sequelae - The patient returned to baseline status

Ongoing - Patient did not recover and symptoms continue;

Recovered with sequelae - The patient has recovered but with clinical sequelae from the event

Unknown - The patient outcome is unknown

Treatment or Action taken

The treatment or action taken after the occurrence of an AE or SAE will be reported as:

Interventional Treatment - Surgical, percutaneous or other procedure

Medical Treatment - Medication dose reduction/interruption or discontinuation, or medication initiated for event

None - No action is taken

9.4 Expedited Reporting of Serious Adverse Events

All adverse events occurring since the start of the study procedure must be recorded in the Case Report Form. Any Serious Adverse Event, must be reported to Smart Medical Systems Ltd. within 24 hours of knowledge, to the following contact person:

Name: Adva Yoselzon Tel: +972-9-7444321 Fax: +972-9-7444543 E-mail: ayoselzon@smartmedsys.com
--

The reporting should then be followed up by written notification within 5 days, using the Serious Adverse Event form in the study file.

In accordance with European regulations, all investigators will be notified of the occurrence of serious unexpected AEs, if such AEs are associated with the use of the study device (i.e., if there is a reasonable possibility that the AE may have been caused by the device and are thus deemed significant new adverse effects or risks with respect to the investigational device). The investigator must inform the relevant Medical Ethics Committee according the applicable national procedures.

It is also the responsibility of the investigator to inform the representative of the appropriate local Ethics Committee, within 24 hours of investigator's awareness of the event. A copy of the report cover letter will be filed with the subject's medical file.

9.5 Follow-Up of Unresolved Events

All serious adverse events should be followed until they are resolved or the subject's participation in the study ends.

9.6 Anticipated Adverse Events

Possible complications that may result from the procedure are similar to those relevant to standard endoscopy and include, but may not be limited to: perforation, hemorrhage and septicemia/infection.

10. STUDY MONITORING

Study monitoring activities will include study initiation visits, interim site monitoring visits and close-out visit. The study initiation visit enables the study monitor and/or sponsor to review thoroughly the study protocol and case report forms with the investigator's staff, in order to assure that the investigator understands the Clinical Study Protocol, including records and reports, has sufficient background, facilities, subject load, time, and willingness to comply with the study requirements; submits the Clinical Study Protocol to the Ethics Committee for review and approval, maintains all correspondence, the Clinical Study Protocol, and all required records on file; and submits required reports, assumes responsibility for the investigation at her/his institution, which may include supervision of some tasks; and has sufficient experience with the study population.

Interim site monitoring visits will be scheduled depending on the rate of subject enrollment. During the interim site monitoring visits the following treatments will be followed; the monitor will review the case report forms of each subject in the study to make certain that the data provided are accurate and obtained in the manner specified in the protocol. The subjects' clinical records will be reviewed to confirm that the case report form data is consistent with the investigator clinical records, the background data and concurrent medication are documented in the case report forms, and that there is an accurate account of the use of the study device in the treatment. The site Study Regulatory binder and other study documents will be reviewed. The subjects' clinical records will be reviewed to determine whether recording of adverse events has been omitted in the case report forms. If this is found to be so, the case report forms will be returned to the investigator and corrected to include this information. During the course of the study, the monitor shall be available to discuss, in person or by telephone, questions regarding adverse effects, removal of subjects from the study, conduct of the study, etc. At the completion or termination of this study a close-out visit will be conducted.

11. REGULATORY AND HEALTH AUTHORITY AUDITS

The European Union's authorities and/or the Food and Drug Administration (FDA) and/or the local state health authorities may request access to all study records, including source documents for inspection. The investigator and hospital staff are requested to cooperate with these audits. The investigator must notify the sponsor of any health authority audit as soon as notification of such audit is made. A representative or designee of the sponsor may also conduct similar audits and may be present during health authority audit.

12. RECORD RETENTION

It is required that a copy of all records (e.g., informed consent documents, source documents, safety reports, study device dispensing record, etc.) which support case report forms for this study, be retained in the files of the responsible investigator for a minimum of five (5) years following notification by the sponsor that all investigations (not merely the investigator's portion) are completed, terminated and/or discontinued. If the principal investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Smart Medical Systems Ltd. must be notified in writing of the name and address of the new custodian.

13. PROTOCOL MODIFICATIONS

An amendment to the protocol may be proposed by an investigator. The amendment will be prepared and approved by the sponsor according to the sponsor's relevant SOP. The amendment must be submitted to the EC. When applicable, the amendment's implementation will take place only once approved by the EC.

If for any unexpected reasons, there is any requirement to deviate from the treatments stated above, the protocol deviation should be discussed with a Smart Medical Systems Ltd. representative.

14. PUBLICATION POLICY

All information concerning this study that was not previously published is considered confidential information. This confidential information shall remain the sole property of Smart Medical Systems Ltd.; it shall not be disclosed to others without written consent of Smart Medical Systems Ltd. and shall not be used except in the performance of this study.

Any investigator involved with this study is obligated to provide the Sponsor with complete test results and all data derived from the study.

15. SUBJECT CONFIDENTIALITY

The subject's name and personal data will remain confidential and will not be published in any way. However, the sponsor's monitor or representative and regulatory representatives, auditors and inspectors may have access to medical files in order to verify authenticity of data collected.

16. SUBJECT / STUDY DISCONTINUATION (DROP OUT CRITERIA)

Subjects should be removed from the study whenever considered necessary for their welfare or when the subject expresses a desire to withdraw from the study. Non-compliance with the protocol, the occurrence of a Serious Adverse Event or any medical condition that, in the opinion of the investigator, warrants discontinuation from the study for the safety of the subject, may necessitate discontinuing a subject. If a subject is discontinued, the reason must be entered on the case report form and signed by the investigator. In case of any questionable situation, the study monitor or Smart Medical Systems Ltd. personnel should be consulted. When a subject is removed from the study as a result of Serious Adverse Event, a final physical examination must be performed. Subjects removed from the study because of an adverse event will be followed-up until the adverse event has been resolved.

In the case that the occurrence of adverse events is greater than anticipated, the clinical investigation will be suspended; in such a case, a safety committee will be arranged to decide if the study could be continued. The Ethics Committee will be notified and the results of the safety committee discussions will be brought for the EC review and decision.

Smart Medical Systems Ltd., reserves the right to discontinue any study for administrative reasons at any time, such as, but not limited to a decision to discontinue further clinical investigation with the device, improper conduct of the study by the investigator, inability to obtain the number of subjects required by the protocol, etc. Reimbursements for reasonable expenses will be made if such an action is necessary.

In the following cases, subjects will be withdrawn from the study:

- Technical error or device malfunction
- Inadequate bowel preparation (score <2 in one or more colon segments, according to BBPS). In such case patient can also be rescheduled for a secondary session. In such case patient will not be re-randomized.
- Any medical condition revealed during the examination that might require cease of treatment for medical reasons or affect study outcome
- Patient having more than 20 polyps

The following cases will be considered as screening failure and will also be withdrawn from the study:

- Polyposis that was revealed during the examination
 - Bowel obstruction
 - Any medical condition deemed too risky by the investigator
-

17. DEVICE ACCOUNTABILITY

Complete traceability records will be kept of all devices during the study. The NaviAid™ G-EYE™ system and relevant accessories will be provided by Smart Medical Systems Ltd., bearing required labeling. Device number will be documented in the center log.

Each clinical investigator will be responsible for the safe storage with restricted access of the investigational materials in their possession, thereby preventing use of any materials by any persons not participating in the study.

After completion of the study, all devices must be returned in their original package to Pentax Europe GmbH.

All investigators will be responsible for using the products according to the IFU and protocol and maintaining product inventory and records.

18. DATA MANAGEMENT

18.1 *Data handling procedure – Data review and Queries resolution*

18.1.1 eCRF

- An Electronic Case Report Form (eCRF) will be completed for each subject enrolled into the clinical study, to record and transmit all information collected in the study. The Investigator will review, approve and electronically sign/date each completed eCRF; the Investigator's signature serving as attestation of the Investigator's responsibility for ensuring that all clinical and laboratory data entered on the eCRF are complete, accurate and authentic. Access to the eCRF will be given by Smart Medical Systems to the PI through an dedicated iPad application.
 - It is the responsibility of the investigator to ensure that eCRFs are legible and completely filled in.
 - Errors must be corrected. History of changes including who performed the change and date of change will be kept in the study database. An investigator or any personnel signature authorized by the investigator is required to personally sign each eCRF on the appropriate pages to verify that the investigator has reviewed and concurs with the recorded data. No other person is permitted to sign for the investigator. The signature must be made at the time that the eCRF is reviewed by the investigator signing the eCRF. Patients will be identified only by ID number.
 - If an assessment is not done or not known or otherwise unavailable, indicate this by writing "Unknown" in the respective answer field of the eCRF. If the question is irrelevant (e.g. not applicable to the subject), indicate this by writing "N/A" (Not Applicable) in the respective answer field of the eCRF.
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- It is anticipated that relevant sections of the eCRF will be completed by the investigator or designee within 24 hours of the last data becoming available, but in no case later than 5 days. Similarly, when a subject completes a study, it is anticipated that all relevant eCRF pages will be completed within 24 hours of the last data becoming available, but in no case later than 5 days.
- 18.1.2 Source documents are the clinical findings and observations, laboratory and test data, and other information contained in Source Documents. Source Documents are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. Information recorded on the eCRF may be considered as Source Data only when Data is collected for trial purposes
- 18.1.3 For each Subject identifier code (patient code) will be given by the PI based on serial number. This code will be applied on documentation relating to each subject, namely, eCRF, Informed Consent form and CDs. Also, this will also be used for transferring, reporting processing and analysis of data. The investigator's iPad will include Subject identification list with the personal information of each Subject and will be accessible using a personal username and password. When printed, the list will be kept in closed envelop to protect subjects' confidentially.
- 18.1.4 Subject name or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes.
- 18.1.5 The PI will update the database upon receipt of new information for each patient. The CRA will issue query form when unclear information and/or significant deviation lab result or other information from previous visit occur.
- 18.1.6 The Study Coordinator will deal with the query form requirements no later than two weeks from date of query receipt and will send the query resolution to the CRA. Should new information becomes available the Study Coordinator will update the database accordingly.

18.2 Data retention

- 18.2.1 Smart Medical Systems and Investigator will maintain records in accordance with Good Clinical Practice guidelines; to include:
 - Clinical protocol, including copies of submitted Safety Reports and Annual Reports
 - Ethics Committee correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports.
 - Current and past versions of the EC-approved clinical protocol and corresponding EC-approved consent form(s).
 - Financial disclosure information (i.e., for the Sponsor-Investigator agreement and for sponsor-hospital agreement
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- Curriculum vitae of the Investigation team.
- Certificates of required training namely, physician training and protocol requirement training.
- Listing of printed names/signatures. (i.e., for the Sponsor-Investigator and for all sub-investigators who will be involved in the administration of the study drugs and/or the evaluation of research subjects [i.e., who will contribute significantly to the study data])
- Laboratory certification information
- Instructions for Use on-site preparation and handling of the G-EYE™ system and other study-related materials (i.e., if not addressed in the clinical protocol).
- Site Signature Log
- Signed informed consent forms
- Completed Case Report Forms; signed and dated by the Investigator
- Source Documents or certified copies of Source Documents § Monitoring visit reports
- Copies of Smart Medical Systems -Investigator correspondence (including notifications of safety information) to sub-investigators
- Subject screening and enrollment logs
- Subject identification code list
- Investigational device accountability records.
- Final clinical study report

19. APPENDIXES LIST

- A. Compliance with ISO 14155:2011(E) annex A
- B. Certificates-ISO 13485:2003+AC:2007, CE and AMAR

20. REFERENCES

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APPENDIX A

COMPLIANCE WITH ISO 14155:2011(E) ANNEX A

ISO section	Page/section in protocol
Introduction (A.1.1)	9-14/4
Identification of the CIP (A.1.2)	1
Sponsor details (A.1.3)	7/1
Investigators details (A.1.4)	Will be supplied in separate document
Synopsis (A.1.5)	7-8/2
Identification and description of the IP (A.2)	14-17/5
Justification for the study design (A.3)	12
Risks and benefits (A.4)	17-19/6
Objectives of CIP (A.5)	19/7.1
Design of clinical investigation – general (A.6.1)	21/7.4
Design of clinical investigation – subjects (A.6.3)	20/7.3
Design of clinical investigation – procedures (A.6.4)	22-24/7.6
Design of clinical investigation – monitoring plan (A.6.5)	35/10
Statistical considerations (A.7)	28/8
Data Management (A.8)	39-42/18
Amendments to the CIP (A.9)	37/13
Deviations from the CIP (A.10)	25/7.8
Device Accountability (A.11)	39/17
Statement of compliance (A.12)	2
Informed consent process (A.13)	25/7.9
AE (A.14)	28-35/9
Vulnerable population	NA
Suspension or premature termination (A.16)	38/16
Publication policy (A.17)	37/14
Bibliography	NA

APPENDIX B (DOCUMENTS WILL BE ADDED)

ISO 13485:2007+AC:2007 Certificate



The Certification Body

**MEDCERT Zertifizierungs- und Prüfungsgesellschaft für die Medizin GmbH
Pilatuspool 2 – 20355 Hamburg – Germany**

herewith confirms that the company

**Smart Medical Systems Ltd.
10 Hayetsira Str. – Raanana 43663
Israel**

has introduced and applies a Quality Management System in the area of

**Design, manufacture and final inspection of
endoscopic systems and medical devices
for performing endoscopic diagnosis and treatment**

A Quality Audit demonstrated compliance of the Quality Management System with

EN ISO 13485:2003 + AC:2007

The certification assumes that the company is applying and maintaining its
Quality Management System according to the above given standard.
The license of certification is subject to surveillance by MEDCERT.

This certificate is valid from 28 April 2011 to 27 April 2016

Hamburg, 11 February 2011

Process No.: QS - 3770

Certificate No.: 3770GB431110211



MEDCERT Certification Body
(Dr. Andreas Schich)

 Akkreditiert durch
Zentralstelle der Länder
für Gesundheitsschutz
bei Arzneimitteln
und Medizinprodukten
ZLG-ZQ-983.99.02-46



CERTIFICATE



This is to certify that the company

Smart Medical Systems Ltd.

10 Hayetsira St.
Ra'anana 43663
Israel

has implemented and maintains a **Quality Management System**.

Scope:

Design, manufacture and final inspection of endoscopic systems and medical devices for performing endoscopic diagnosis and treatment

Through an audit, documented in a report, performed by DQS Medizinprodukte GmbH, it was verified that the management system fulfills the requirements of the following standard:

ISO 13485 : 2003

Certificate registration No.	508646 MP23CMDR
Certificate unique ID	170586981
Effective date	2014-04-28
Expiry date	2017-04-27
Frankfurt am Main	2014-04-04



DQS Medizinprodukte GmbH

Frank Graichen
Managing Director

Maxim Shkolnikov
Product Manager

August-Schanz-Straße 21, 60433 Frankfurt am Main, Tel. +49 (0) 69 95427-263, medical.devices@dqs.de

DQS Medizinprodukte GmbH is a CMDCAS recognized registrar
(Canadian Medical Devices Conformity Assessment System).



CE Certificate



EC Certificate of Conformity

The Notified Body

MEDCERT Zertifizierungs- und Prüfungsgesellschaft für die Medizin GmbH
Pilatuspool 2 – 20355 Hamburg – Germany

herewith confirms that the company

Smart Medical Systems Ltd.
10 Hayetsira Str. – Raanana 43663
Israel

has introduced and applies a Quality Management System
for the products / product category

Endoscopic systems and medical devices
for performing endoscopic diagnosis and treatment

An Audit demonstrated compliance of the Quality Management System with

Annex II
excluding section (4)

of the **Council Directive 93/42/EEC concerning Medical Devices.**

The certification assumes that the company is applying and maintaining its Quality Management System according to the above given annex. The license of certification is subject to surveillance by MEDCERT.

This certificate is valid from 28 April 2011 to 27 April 2016

Hamburg, 11 February 2011

Process No.: QS - 3770

Certificate No.: 3770GB410110211

MEDCERT Identification No.: 0482


MEDCERT Certification Body
(Dr. Andreas Schich)



Akkreditiert durch
Zentralstelle der Länder
für Gesundheitsschutz
bei Arzneimitteln
und Medizinprodukten
ZLG-ZQ-983.94.13