Clinical validation of Artificial Intelligence in Polyp Detection

PIETER SINONQUEL

DATE: 26-05-2020

Version 1.8

SPONSOR:
UZ LEUVEN
HERESTRAAT 49
B-3000 LEUVEN

PRINCIPAL INVESTIGATORS:
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Protocol Signature Sheet

Name	Signature	Date
Principal investigator:		
Principal investigator		

Content

1. Synopsis

Title of clinical study	Clinical vAliDation of ARTificial Intelligence in POlyp Detection
Protocol Short Title/Acronym	CAD-ARTIPOD
Sponsor name	UZ Leuven
Principal Investigator	Prof dr Raf Bisschops dr Pieter Sinonquel
Medical condition or disease under investigation	Colonic polyps
Purpose of clinical study	Validation of the added clinical value of an automated endoscopic tool for polyp recognition and detection. Collect data for development and validation of an automated characterization tool for colorectal polyps.
Primary endpoint	Total polyp detection during single pass colonoscopy by the artificial intelligence tool in comparison to polyp detection by the endoscopist with endoscopic diagnosis as a gold standard.
Secondary endpoints	1. Number of extra detections made by artificial intelligence 2. The endoscopist's miss rate after single pass colonoscopy
Study Design	Interventional prospective multicenter study: Polyp detection by an automated endoscopic tool as second observer during routine diagnostic colonoscopy
Sample Size	2084 polyps (average of 2 polyps per patient)
Participating sites	1. Cesare Hassan - Nuovo Regina Margherita Hospital, Rome, Italy. 2. Raf Bisschops - University Hospitals Leuven, Leuven, Belgium. 3. Oliver Pech - Krankenhaus Barmherzige Brüder, Regensburg, Germany 4. Emmanuel Coron - Centre Hospitalier Universitaire de Nantes, Nantes, France 5. Michal Kaminski - Centrum Onkologii-Instytut im. Marii Skłodowskiej-Curie, Warschau, Poland 6. Pradeep Bhandari - Spire Portsmouth Hospital, Portsmouth, United Kingdom 7. Helmut Neumann - Universitäts Medizin, Mainz, Germany 8. Evelien Decker – University Medical Center, Amsterdam, The Netherlands (with reserve) 9. David Tate – University Hospitals Ghent, Ghent, Belgium
Summary of major selection criteria	1. ≥ 40 years 2. Diagnostic or screening colonoscopy 3. Ability to give informed consent by the patient or legal representative 4. Any contraindication for colonoscopy or biopsies of the colon 5. Therapeutic colonoscopy 6. Uncontrolled coagulopathy 7. Confirmed diagnosis of inflammatory bowel disease prior to the colonoscopy 8. Short bowel or ileostomy

	9. Lynch syndrome, FAP syndrome 10. Pregnancy
Period of evaluation of a subject in the study	Procedural time of one colonoscopy
Version and date of final protocol	Version 1.8 – 26.05.2020
Version and date of protocol amendments	NA

2. Introduction

Colorectal cancer is the second most frequent cancer in the general population. Accurate detection of precursor lesions, namely adenomas, is crucial for prevention of cancer related mortality. The detection and certainly the characterisation (i.e. differentiation between benign and malignant polyps) can be challenging with highly variable detection rates between different operators resulting in different rates of interval cancers.[1] Despite the increasing quality of endoscopy equipment, the miss rate for polyps has been reported to be as high as 21%.[2] The possible explanations for this high miss rate are multifactorial, but at least to a large extent operator dependent.

Over the past years, deep learning has revolutionized the field of computer-aided analysis and has also entered the medical world with results matching or even surpassing human-expert-level performance.[3]
For colorectal polyp detection, several pilot studies introducing automated systems for polyp segmentation and characterisation have recently been published, but they have never been tested in a clinical setting, are limited to one specific endoscopy system, and often biased in terms of image selection (only high quality images), weak ground truth or methodology.[4–7] There is a definite need to develop a system applicable for different endoscopy systems and that can be validated in a real-life clinical setting.

Due to a very close and successful collaboration with the multidisciplinary Medical Imaging Research Centre in Leuven, an improved artificial intelligence (AI) system was developed in-house and differs from the commercially available systems in the fact that this system is able to incorporate temporal information leading to a significant improvement in polyp segmentation as recently shown in the first pilot study, leading to an accuracy of 97% and only one false positive detection per minute. An illustration of what the AI-tool is able to is shown in figure 1.

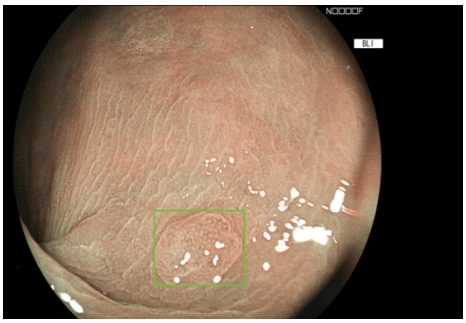

Figure 1 :
Example of current status for real time polyp detection; detected lesions are indicated with a green rectangle

In addition, since the introduction of a colorectal screening program, a steep increase in colonoscopies has occurred leading to a large amount of pathological examinations to differentiate between non-neoplastic (hyperplastic) and neoplastic (adenomas) lesions. This has significant cost implications, taking into account that in about 40-50% of the patients polyps are resected. To accommodate these costs, the NICE classification was developed to enable optical diagnosis of small polyps and to enable a resect and discard strategy what may improve the cost-effectiveness as shown by Hassan *et al*.[12] The latter uses optical diagnosis as a guide to determine the surveillance interval for colonoscopy instead of histology and is potentially cost-saving.[13]

After validation, the American Society of Gastrointestinal Endoscopy defined guidelines for Preservation and Incorporation of Valuable endoscopic Innovations (PIVI) for real time endoscopic assessment of the histology of diminutive polyps.[14] This guideline defines that a technique should have > 90% agreement for post polypectomy surveillance and a negative predictive value of > 90%. In expert hands, the NICE classification for polyps meets these PIVI criteria, however this could so far not be confirmed outside an expert setting.[15–17]

We are currently training a deep learning algorithm not only for polyp detection, but also for polyp characterization. Preliminary results show an accuracy of about 70% - 75%. To further optimize this system's performance, additional images and videos are necessary. Therefore, we would like to take the opportunity during the current study to collect images and videos of some of the detected polyps. With the obtained data we would like to further develop the AI tool for characterization of colonic polyps.

3. Aim

The primary aim of the current study is to further prospectively validate a computer-aided detection tool for colorectal polyp detection and evaluate its technical performance and feasibility in daily clinic. In addition, we want to use the obtained data for further development of an AI tool for characterization of colonic polyps.

4. Definitions

Positive detections:

- False positive detection: The AI-tool indicates a structure that is not a polyp (eg. Air bubbles, stools, tools, fold, …). We further specified three possible types of false positive detections:
  (1) Clinically irrelevant false positive detections
  These are detections that are obviously false and do not need further or close-by inspection by the endoscopists and can be readily recognized by the trained second observer.
  We defined this type of false positive detections in 6 subdivisions:
  1) Stool remnants: hard or soft stools, remnants of pills or vegetables
  2) Air bubbles
  3) Anatomical structures: ileocaecal valve, appendix
  4) Diverticulum: inverted or non-inverted
  5) Instruments: all possible accessory instruments (e.g. forceps, needle, snare, …)
  6) Vascular structures: all vascular structures (venes or arteries), hemorrhoids
  (2) Clinically relevant false positive detections
  These are detections that could not be classified as a an obviously false positive at first sight and which is indicated by the endoscopists as a side that needs further inspection. In case this is not spotted by the endoscopists, the second observer will ask the endoscopists to perform a second or close-by inspection for better evaluation, not showing endoscopic evidence of a polyp
  We subdivided this type of false positive detections in 3 subdivisions:
  1) (Thickened) fold
  2) Other: mucosal lesions different from normal colonic mucosa
  3) Not relocated: the detection could not be relocated for additional endoscopic inspection
  (3) Other false positive detections
  This is every other false positive detection that does not fit any other class and does not need a second or close-by inspection.
- True positive detection: The AI-tool detects a mucosal lesion that is endoscopically diagnosed to be a polyp at first sight (detected by the endoscopist) or after second and close-by look (if initially missed by the endoscopist).
  If in case of doubt the endoscopist takes a biopsy to rule out a polyp, this detection will be considered as a true positive detection by AI.

Negative detections:

- False negative detection: Every polyp that is found by the endoscopist and is not detected by the AI tool before the attempt of endoscopic optical diagnosis. On detection of a polyp, the endoscopist will use a standardized verbal action (ask “Did the system detect the polyp as well?”), to inform the second observer about the detection. Immediately the second observer hits the detection button on the AI system. This is a button that initiates time-limited indicator on the AI coupled screen for 1 second. If no detection is made by the AI system during that time, the endoscopically found polyp is to be considered as a false negative detection for the AI system.

5. Endpoints

Primary endpoint

Total polyp detection during single pass colonoscopy by the artificial intelligence tool in comparison to polyp detection by the endoscopist with endoscopic diagnosis as a gold standard.

Secondary endpoints

1. Total polyp detection during single pass colonoscopy by the artificial intelligence tool in comparison to polyp detection by the endoscopist with histological diagnosis as a gold standard.
2. The number of extra detected polyps by artificial intelligence with the endoscopic diagnosis as a gold standard.
3. The number of extra detected polyps by artificial intelligence with the histological diagnosis as a gold standard.
4. The endoscopist’s polyp miss rate defined as the additional detection of polyps during colonoscopy
5. The false positive rate during clean withdrawal.

Exploratory endpoints

1. Correlation between the Boston Bowel Preparation Score and the number of false positive detections during colonoscopy.
2. Correlation between the endoscopist’s historical adenoma detection rate and the number of extra detections and false negative detections by the artificial intelligence system.
3. Correlation between the polyp size and number of false negatives and additional detections.
4. Correlation between the Paris classification and the number of false negatives and additional detections.

5. Correlation between the total number of polyps per colonoscopy and additional detections.
6. Correlation between the experience of the endoscopist and additional detections.

6. Study Design

This is an investigator-initiated multicentre non-randomized prospective interventional trial to validate the performance of a novel state-of-the-art computer-aided diagnostic (CAD) tool in polyp detection implemented as second observer during routine diagnostic colonoscopy and to evaluate its feasibility in daily endoscopy. Consecutive patients referred for a screening, surveillance or diagnostic colonoscopy will be included. After standard bowel preparation with PEG based solutions, patients will undergo a standard colonoscopy performed by an endoscopist with moderate to high adenoma detection rate (ADR > 20% and < 50%). A second observer, who is not a trained endoscopist, but a person trained for recognition of polyps and endoscopic lesions (see section 8), will follow the procedure on a bedside AI-tool to count the number of detections made by the AI system and categorize the results into positive or negative results as follows (1) true positive, (2) false negative or (3) false positive (detailed description, see section 4).
When a detection is made by the AI system and this detection can clearly be categorized the endoscopist and second observer do not communicate. In case of a detection of the AI-system that was not seen by the endoscopist or is unclear to the second observer, the second observer will ask to re-evaluate the indicated region to determine whether after second look it is a true positive not detected by the endoscopist or a clinically relevant false positive detection of the AI system since it caused the endoscopist to take an extra action. Endoscopists will inspect perform a standard colonoscopy with a single withdrawal, inspecting each segment only once, except when the second observer asks to reinspect a certain area in case of a clinically relevant AI detection. The different timings in each segment will be separately measured with a built-in chronometer in the artificial intelligence tool. Time measurement will be initiated once withdrawal is initiated in the caecum and will be determined for every specific segment. In case of therapeutic actions, time registration will be paused and restarted after completion of this therapeutic act. Automated time calculation is integrated in the AI system and provides an overview of the real withdrawal time and the performed therapeutic time. The entire procedure is recorded. The practical set-up is shown in figure 2.

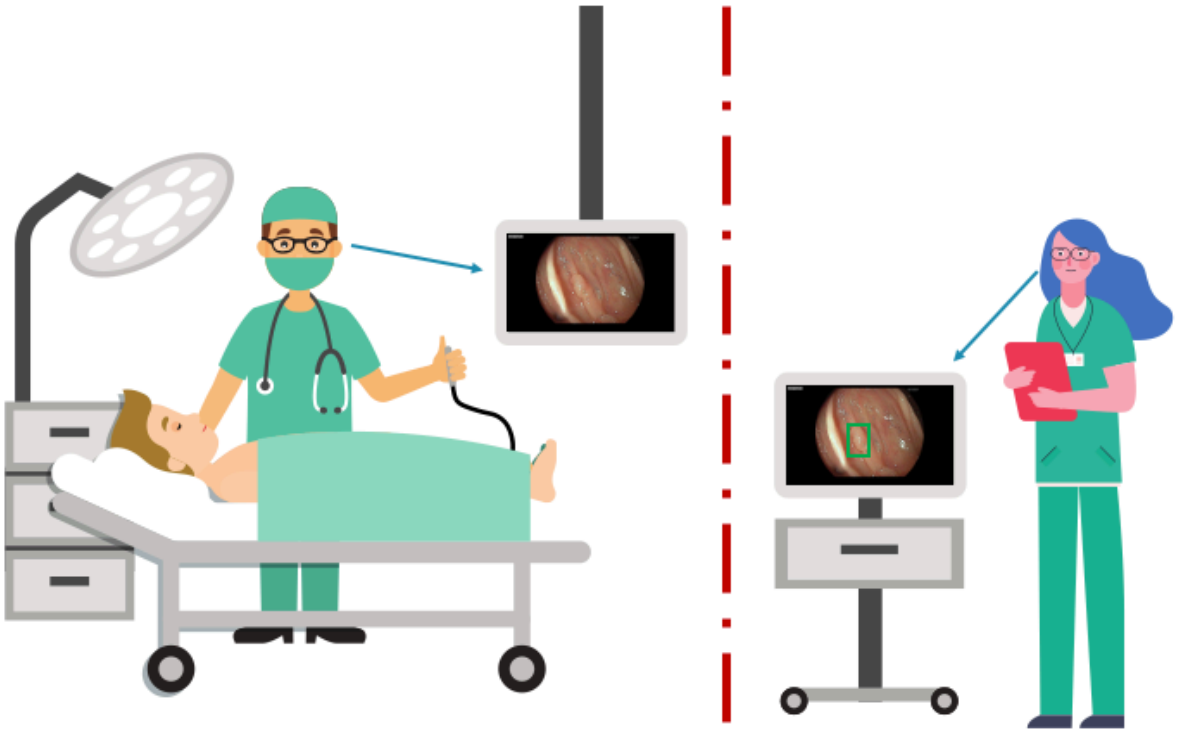

Figure 2: Basic set-up of the computer-aided diagnostic (CAD) tool as second observer during endoscopy. A patient undergoes a diagnostic colonoscopy performed by an experienced endoscopist (ADR > 20% and <50%), while a second observer watches the by the CAD-analyzed video to count and categorize the indicated detections. There is no communication between the endoscopist and the second observer unless a clinically relevant finding is found by the second observer or a polyp or clinically relevant finding is made by the endoscopists.

7. Study Population

Inclusion criteria

- Age ≥40 years
- Referral for screening, surveillance or diagnostic colonoscopy
- Able to give informed consent by the patient or by a legal representative

Exclusion criteria for study inclusion

- <40 years old
- Referral for a therapeutic colonoscopy
- Known Lynch syndrome or FAP syndrome
- Any contraindication for colonoscopy or biopsies of the colon

- Uncontrolled coagulopathy
- Confirmed diagnosis of inflammatory bowel disease prior to the scheduled colonoscopy
- Short bowel or ileostomy
- Pregnancy

Exclusion criteria for study analysis

- Colonic inflammation of > 30cm during colonoscopy
- Incomplete colonoscopy for any reason
- Incomplete recording or technical failure of the artificial intelligence system

8. Study Procedures

Bowel preparation

Before endoscopy patients will be prepared either at home either in hospital with standard bowel preparation according to local practice in the respective research centers, with an oral polyethylene glycol based regimen and if necessary, with an additional water enema.
During endoscopy, all residual stools will be removed from the colonic wall by rinsing with water with or without dimeticon. Every subject's bowel preparation will be scored using the Boston Bowel Preparation Scale (BBPS).

Endoscopy, video recording

Endoscopy will be performed in patients on the scheduled appointment as initially made after selection based on referral. Video recording of the procedure will be initiated to record the patient's number upon the case report form before the endoscope is introduced in the anal canal. Before withdrawal, a picture of the caecum needs to be taken. During withdrawal the bowel should be as maximal inflated as possible for a high-quality inspection. A single pass withdrawal will be applied during inspection.
If a polyp is found, it can be resected after an endoscopist's optical assessment. This endoscopist's optical assessment should include description of the polyp size, location, Paris classification and if possible endoscopic diagnosis of most probable histology (hyperplastic, sessile serrated, adenoma or carcinoma).
If more than 5 polyps with apparent hyperplastic morphology are found in the rectosigmoid, the first 5 polyps will be included for analysis of the AI tool performance and will be resected for histological assessment and inclusion in the study. Any additional apparent hyperplastic polyps in the rectosigmoid exceeding the number of 5 will be discarded from the study for practical reasons. Most of these polyps will be hyperplastic and are clinically irrelevant. Additional separate biopsies of these sometimes many polyps will incur unnecessary costs. The entire procedure needs to be recorded as one video.

Second observer

The second observer will undergo a standardized online training with at least 30-40 endoscopic videos (containing 10 clear videos of false positive detections and > 20-30 videos with difficult detections) for polyp recognition, before the start of the study, to correctly categorize the different detections and to be able to diagnose obvious clinically irrelevant false positive findings by the system.
In the ideal setting, this person has already a medical or endoscopic background (e.g.: endoscopy nurse, medical fellow, endoscopy researcher). Before a person can contribute in this study, this person will have to pass an online examination.
After proper training and passing the examination, this person is present during the entire colonoscopy to record the findings of the AI system. Before starting the procedure, the second observer fills in the patient's and institute characteristics onto the patient's individual case report form (CRF) and starts the bedside AI-system. Once the endoscopist starts, the exact time of insertion is noted on the CRF. During insertion the second observer does not count the AI-detections.

Once the endoscopist reaches the caecum and starts inspection during withdrawal, the second observer notes the time of start at the caecum on the CRF and starts to watch the AI detection system. Every detection made by the AI-system is counted and categorized as described above. When a polyp is resected, the number of the polyp, the number of its container and the description of the endoscopic diagnosis have to be noted on the backside of the CRF. Once endoscopy finishes, the second observer writes down the time of ending.

Histopathological assessment

Histopathological assessment will be done on-site by 2 local histopathologists to assess the type of polyp (hyperplastic, adenoma, sessile serrated or carcinoma in situ) and grade of dysplasia. In case of discrepancy between the two pathologists or between the pathological diagnosis and the endoscopic optical diagnosis a third local pathologist will review the tissue sample to come to a consensus diagnosis. When inconsistencies remain, a central pathologist will review and provide a definite diagnosis.

Baseline assessments

Of every patient entering this study the following characteristics and information will be collected by the principal investigator or one of the sub-investigators.

a. Informed consent

The requirements of the informed consent are described in Chapter 11. Informed consent must be obtained by the subject prior to entering the study, and before any protocol-directed procedures are performed. A unique subject identification number (subject number) will be assigned to each subject before starting endoscopy (see chapter 8); this subject number will be used throughout the study.

b. Demographics
Demographic information will include date of birth and sex described by the subject, BBPS and performing endoscopist.

c. Medical history
Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions.
Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 3 months prior to signing of informed consent.

9. Safety Reporting

The investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will make sure that all subjects are kept informed.

Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the procedure.
Adverse events (AEs) will be recorded from the moment the informed consent has been signed. AE's will be recorded based on interviews with the patient (asking open-ended questions) one hour after each procedure. Events will be graded as mild, moderate or severe and related or unrelated to the procedures. Relationship with other interventions (such as sedation, bowel preparation, coagulation, etc.) will also be recorded. Recording ends one week following the last procedure of the study.

Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is an adverse reaction, the nature or severity of which is not consistent with the information on the experiment, and, when a clinical trial is concerned, with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or the patient leaflet joined to the summary of product characteristics for an authorised product).

Timelines for reporting

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

- All AEs, SAEs and AESIs causally related to a study-related intervention will be reported until 7 days after the last study-related intervention or until last follow-up visit (whichever occurs first).

- All SAEs and AESI as defined in the protocol must be reported to the Sponsor within 24 hours of the trial staff becoming aware of the event. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by Trial identification.

SAE details will be reported by the Investigator to the Sponsor by completing the SAE form in the (e)CRF.

Follow-up

The Investigator must record follow-up information by updating the medical records and the appropriate forms in the (e)CRF. The worst-case severity and seriousness of an event must be kept throughout the trial.
SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported within 24 hours of the Investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

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

Pregnancy

Female subjects must be instructed to notify the Investigator immediately if they become pregnant during the trial. The Investigator must report any pregnancy in subjects during the trial to the Sponsor.

Death

All deaths will be reported without delay to the Sponsor (irrespective of whether the death is related to disease progression, study procedure or is an unrelated event). The sponsor will notify all deaths, as soon as possible after becoming aware, to the Central EC and the EC of the concerned site and provide additional information if requested.
Reporting requirements to Ethics Committee's (EC's) The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the Sponsor in accordance with instructions provided below.
The Sponsor will promptly evaluate all SAEs and AESIs against medical experience to identify and expeditiously communicate possible new safety findings to Investigators and based on applicable legislation.

Annual reporting

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

10. Statistical Consideration

Sample size calculation for a validation study on artificial intelligence in polyp detection.
The aim is to compare the accuracy of the detection by AI versus the endoscopist.

- The accuracy by AI is assumed to be 97% (pilot data). The accuracy by the endoscopist in the study setting of university hospitals is assumed to be 95%.
- The sample size is the number of polyps needed with an average of 2 polyps per patient (pilot data)

As polyps are clustered within patients, we need to take into account a clustering effect. Based on pilot data the intraclass correlation (ICC) was estimated as 0.003 which can be considered as negligible. (This means that there are no patient-effects, which would mean that probabilities of detection differ between patients).

The sample size calculations below are performed for the number of polyps needed, assuming independence.

- A sample size calculation was performed for a McNemar test for paired proportions.
- Sensitivity is assumed to be >90% (pilot data)
- Power = 90%
- A 5% two-sided significance level a difference in accuracy between AI and endoscopist, assuming respectively 97% and 95% of accuracy
- Indicating a total number of 2084 polyps is needed to prove superiority.

Statistical analyses will be performed according to the accuracy and extra detections. Descriptive statistics will be used for continuous variables and expressed as mean, median and range values. Association BBPS, ADR and location will be examined through logistic regression method, ROC curves, sensitivity and specificity.

11. Informed Consent

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC.
The subject must be given ample opportunity to:

a. Inquire about details of the study
b. Decide whether or not to participate in the study.

If the subject, determines he or she will participate in the study, then the informed consent form must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink.

The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form shall be given to the subject. In the

case of adolescents, a copy of the signed consent and assent will be given to both the parents/legal representative and the adolescent.
All revised informed consent forms must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

12. Data management

The data in the eCRF and the video database will be coded with a unique code to assure anonymization of the subject included in the study. The code for the eCRF is a 6-digit code based on the 3 digits site number and the 3 digits inclusion number. Exp: XXX / XXX. All data will be collected on an electronic web-based platform (REDCap). The videos will be centrally collected and uploaded on the secured platform with mention of the video format and inclusion number. The code for the videos consists of the 3 digits site number and the 3 digits inclusion number. In addition, all investigators should assure to omit all traceable data on the video such as hospital, date or patient name.

13. Authorship

Based on the Journal's guidelines, the maximum number of authors will be included. The order of the authorship will depend on individual contributions and be decided in agreement among the coordinating investigators. Pieter Sinonquel MD will be the first author. Raf Bisschops MD PhD, will be the last author.

14. References

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