STUDYPROTOCOL

OPTICAL II:

Implementation of optical diagnosis of T1 colorectal carcinoma in non-pedunculated polyps

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The OPTICAL II-STAR LNPCP study group

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1 Dutch Summary:

1.1 Achtergrond:

Na de invoering van het bevolkingsonderzoek naar darmkanker is er een toename van "vroege" darmkanker (T1 CRC). Ondanks lokale behandelmogelijkheden ondergaat een deel van deze patiënten een onnodige buikoperatie, wat kan leiden tot complicaties en in enkele gevallen zelfs tot overlijden.

De prognose van T1 darmkanker zonder lymfklieruitzaaiingen is gunstig. Een kleine groep patiënten heeft echter al lymfklieruitzaaiingen op het moment van diagnose. Voor deze groep leidt een buikoperatie met verwijdering van de tumor en nabije lymfklieren tot een verbeterde overleving. Bij de overige patiënten, zonder lymfklieruitzaaiingen, kan worden volstaan met een lokale endoscopische behandeling, mits de afwijking in zijn geheel verwijderd is.

Om een inschatting te maken welke patiënt wél of juist niet geopereerd dient te worden, maken we gebruik van kenmerken die (na verwijdering van de tumor) door de patholoog kunnen worden vastgesteld. Bij afwezigheid van deze kenmerken is het risico op lymfklieruitzaaiingen laag en is er geen aanvullende operatie nodig. Bij aanwezigheid van (één van) deze kenmerken is het risico op lymfklieruitzaaiingen hoog en adviseren de huidige richtlijnen om een aanvullende operatie te verrichten. Soms wordt de tumor in meerdere delen verwijderd, waardoor de patholoog onzeker is over volledige verwijdering en het risico op lymfklieruitzaaiingen. Deze patiënten ondergaan vaak een operatie hoewel het merendeel van hen uiteindelijk geen restafwijking of lymfklieruitzaaiingen blijkt te hebben.

Tot slot wordt er een grote groep patiënten onnodig geopereerd omdat er ten onrechte wordt gedacht dat er darmkanker speelt, terwijl de tumor achteraf goedaardig blijkt te zijn. Dit komt doordat het onderscheid tussen T1 darmkanker en goedaardige poliepen lastig kan zijn. Zulke onnodige buikoperaties zijn onwenselijk omdat deze altijd gepaard gaan met risico's voor de patiënt. Om in samenspraak met de patiënt tot een passend behandelplan te komen is het belangrijk om vooraf een inschatting te maken van de kans op (beginnend) darmkanker of een goedaardige poliep.

1.2 Probleemstelling

In de praktijk blijkt het onderscheid tussen een goedaardige poliep of beginnend darmkanker door de endoscopist lastig te maken. Hierdoor worden veel poliepen met een T1 darmkanker niet als zodanig herkent. Hierdoor wordt een verkeerde resectie techniek gebruikt waardoor in een later stadium alsnog operatie dient te volgen. Ondanks de stijging in het vóórkomen van T1 darmkanker komt de individuele endoscopist er niet vaak mee in aanraking. Door onjuiste diagnostiek

worden patiënten met verkeerd ingeschatte goedaardige poliepen of patiënten met niet adequaat herkende laag-risico T1 darmkanker ten onrechte geopereerd.

Het is echter mogelijk om een inschatting te maken op de kans op T1 darmkanker met behulp van geavanceerde lichttechnieken en een gestructureerde beschrijving van een poliep.

1.3 Doelstelling

Deze studie heeft tot doel om endoscopisten binnen een jaar bekwaam te maken en te houden in het herkennen van T1 darmkanker en binnen drie jaar het aantal onnodige operaties voor T1 darmkanker te verlagen.

1.4 Studieopzet

Het betreft een prospectieve observationele multicenter studie bij endoscopisten om grote niet-gesteelde poliepen gestructureerd te scoren. Endoscopisten worden getraind met behulp van een e-module waarin de uiterlijke kenmerken van T1 darmkanker uitvoerig worden belicht en getoetst. Vervolgens worden de grote poliepen gescoord volgens het aangeleerde model om in de klinische setting de inschatting van de endoscopist te vergelijken met de uiteindelijke diagnose (de gouden standaard is de PA diagnose). Tijdens de registratiefase worden de deelnemers blootgesteld aan actieve feedback om blootstelling te vergroten. Wij verwachten dat een gestructureerde benadering van grote poliepen gecombineerd met actieve feedback zal leiden tot een beter onderscheid in goedaardige poliepen en T1 darmkanker en zodoende zal resulteren in een afname van onnodige operaties.

2 Background

2.1 Problem

Unnecessary surgery is performed on patients for either incorrectly diagnosed colorectal carcinoma or inadequately resected T1 CRC despite the availability of minimal invasive endoscopic resection techniques. Besides, Western endoscopist show a lower sensitivity for diagnosing T1 CRC than Asian endoscopists. We believe we can improve the sensitivity of Dutch endoscopists by introducing an e-learning module based on systematically scoring optical features associated with T1 CRC, ultimately resulting in less unnecessary surgery.

2.2 Objectives

We aim to improve optical diagnostic accuracy during endoscopy for recognizing T1 CRC by combining an e-module with regular feedback.

2.3 Background

The introduction of the Dutch colorectal cancer screening program in 2014 has led to an increase in detected advanced adenoma and early stage colorectal cancer such as T1 colorectal cancer (T1 CRC) [1,2]. If no lymph node metastasis are present, most patients with T1 CRC can be cured with an endoscopic resection. However, it seems challenging to select the right patient by optically differentiating benign lesions from T1 CRCs and to subsequently choose the right resection technique.

Patients are referred to surgery for the removal of large (non)-pedunculated colonic polyps (LNPCP) [3] despite the existence of minimal invasive techniques such as endoscopic mucosal resection (EMR) for benign lesions [4,5] or endoscopic submucosal dissection (ESD) and endoscopic full-thickness resection (eFTR) for superficial invasive carcinomas [6]. Two recent Dutch retrospective studies evaluated the incidence of surgery for benign colorectal [7] or rectal [8] polyps over the past few years and showed that 21.7% and 34% of the surgical resections were performed on lesions suspected to contain adenocarcinoma respectively. Even more so, 73% of a subset of cases were thought to have been feasible for endoscopic resection techniques. Both studies emphasize the importance of optically differentiating (T1) CRC from benign lesions to prevent unnecessary surgical resections, especially because surgery may lead to adverse events. An analysis by the Dutch T1 CRC working group on patients with surgery for early (T1) or more advanced CRC (T2-T3) showed no significant difference in mortality or surgery complication rate between these stages [9].

However, endoscopic resection is only sufficient in T1 CRC when no residual disease is left: resection margins free of tumor and no lymph node metastasis. The risk on lymph node metastases is based on histopathological factors: tumor differentiation grade, submucosal invasion depth, lymphovascular invasion and tumor budding [10].

To adequately evaluate these risk factors and negative resection margins, the pathologist needs an en-bloc resection specimen. If resection margins are free of tumor and none of the histopathological risk factors are present, the risk for lymph node metastases is low (low-risk T1 CRC) and according to (inter)national guidelines follow-up without further intervention is warranted [11–13]. Oncologic resection with lymph node removal is reserved only for those patients with high risk for lymph node metastases or if endoscopic resection is incomplete. This strategy seems to be cost-effective in several studies [14,15], although adequate patient selection is important. In piecemeal resected lesions, such as with EMR, negative margins can often not be confirmed, leading to secondary surgery to ensure no residual disease is left behind. This underlines the importance of good optical diagnosis before proceeding to resection to be able to obtain an en-bloc resection.

The European Society of Gastrointestinal Endoscopy stated in 2016 that advanced endoscopic imaging can improve optical diagnosis but needs training and a classification system [16]. Until recently, most studies evaluating optical features in T1 CRC were performed in Asia [17], showing sensitivity of up to 85% when using Narrow-Band-Imaging (NBI) or magnifying chromoendoscopy [18]. A study in the Netherlands showed a pooled sensitivity of only 60% for gastroenterologists [19]. On the other hand, a recent study from the Dutch T1 CRC working group found a sensitivity of 78.7% for differentiating non-invasive from invasive large non-pedunculated colorectal polyps in a real-time assessment. The endoscopists were trained in scoring polyp characteristics attributed to T1 CRC as found in recent literature [17] indicating that better results are possible [20].

Although T1 CRC incidence has increased, individual exposure is still limited. Several recent studies have shown that e-learning modules can be used to improve optical diagnostic skills in endoscopists for recognizing early gastric cancer [21,22] and diminutive polyps [23,24]. The use of an e-learning module can increase exposure to T1 CRC features, even more so if followed by regularly sharing cases with feedback.

3 Strategy

3.1 Study design:

The study is designed as a prospective observational multi-center study in the Netherlands comparing trained optical diagnosis with histopathological outcome of large non-pedunculated colorectal polyps (LNPCP). The study consists of two phases: an e-module (phase 1) and a registration/feedback phase (phase 2). Phase 1 consists of a pre-test, a training-phase, a post-test and a confirmation test. In the second phase centers will receive monthly tests to maintain shared exposure to T1 CRC (active feedback). Also, for the duration of 1 year after the post-test all LNPCP will be registered as is advised by the Dutch guideline. Total duration of the study will be 1.5 years: participation in e-module and registration (1 years) and data collection and analysis (6 months).

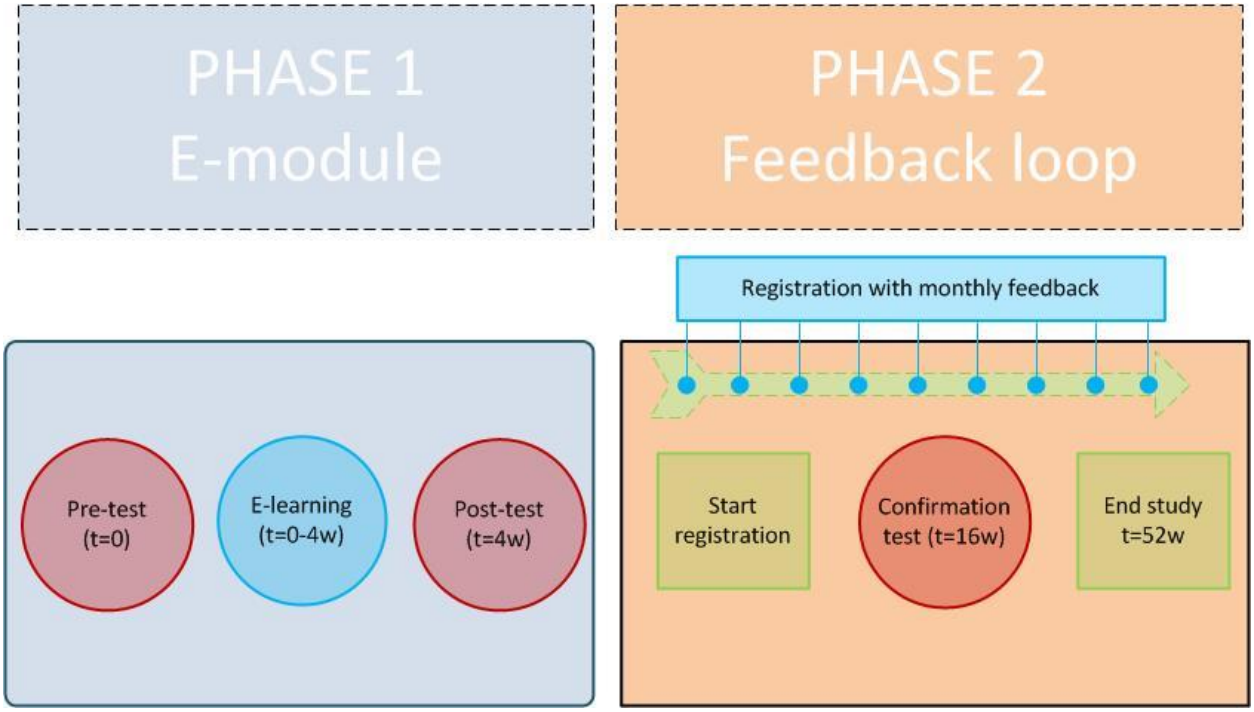

Figure 1: Study design

3.2 Population:

3.2.1 Inclusion criteria

Included in this study are all Dutch endoscopists with exposure to large colorectal polyps willing to partake. Both gastroenterologists, nurse endoscopist and residents can take part in this study, both with or without colon cancer screening exposure.

- gastroenterologists with or without colon cancer screening exposure
- nurse endoscopists with or without colon cancer screening exposure

- residents in gastroenterology

Participants will be actively invited by distributing information about this study via the Dutch T1 CRC working group. At this moment 45 hospitals (>50% of total Dutch hospital organizations [ref: RIVM 2016]) are participating in this working group. We expect to include multiple endoscopists per participating center. However, participation in this study is not restricted to the hospitals of the Dutch T1 CRC working group. Any endoscopist from any hospital or endoscopy unit can enroll.

During the registration, all non-pedunculated colorectal polyps ≥20mm diagnosed after completing the post-test are included in this study. Importantly, according to the Dutch guideline "Endoscopic polypectomy of the colon" it is currently already advised to register all colorectal polyps (>20mm) per center [25]. Participants are advised to use a reference tool of known size to estimate the size of the polyps during endoscopy. Although T1 CRC is not restricted to this group of polyps we know that the risk of T1 CRC in non-pedunculated polyps increases with larger size (≥20mm) (unpublished data Dutch T1 CRC working group). Moreover, lowering the threshold to 10 mm will increase registration burden drastically with only a small effect on non-missed T1 CRC (±20%). Restriction to non-pedunculated polyps is justifiable because pedunculated polyps are more easily resected en-bloc with conventional endoscopic techniques, with higher success rate for complete resection. Meaning that optical diagnosis is less important for treatment choice than in non-pedunculated polyps.

3.2.2 Exclusion criteria:

- Participants who do not complete the e-module and tests in time. Their characteristics will be recorded.
- Centers without availability of advanced endoscopic imaging.

- During registration: all polyps not fulfilling the criteria for non-pedunculated polyps ≥20mm.
- Lesions with known histopathological status due to prior biopsies before optical diagnosis.

4 Methods

4.1 Study parameters and endpoints

4.1.1 Primary endpoint:

- An increase of ≥ 10% in pooled sensitivity, comparing pre-test and first confirmation test after 16 weeks, for predicting T1 CRC optically in large non-pedunculated polyps, while maintaining specificity ≥95%.

4.1.2 Secondary endpoints:

- Pooled sensitivity and specificity for predicting invasive carcinoma optically before and after going through designed e-module (pre-test vs. post-test).
- Difference in pooled sensitivity and specificity at second confirmation test on center level after 1 year of registration.
- Incidence of separate scored polyp characteristics in benign polyps, T1 CRC and ≥T2 CRC.
- Real-time sensitivity and specificity outcome for each center.

4.2 Study parameters:

4.2.1 Optical polyp characteristics

Every large polyp will be scored on the following characteristics, thoroughly explained and tested in the e-module.

1. Proximal (proximal of splenic flexure) or distal location (distal of splenic flexure).
2. Spontaneous bleeding of polyp.
3. Vessel and surface pattern scored according to Hiroshima or JNET as described in the e-module [26].
4. Polyp morphology scored as:
    a. Paris classification. [27]
    b. Granular or non-granular, if granular:
        i. homogenous granular
        ii. granular with a depressed area
        iii. granular with a large nodule
        iv. granular with a non-granular erythematous area
    c. Presence of a depressed area.
5. Diagnosis estimation: Benign (low or high-grade dysplasia), superficial or deep-invasive T1 CRC or ≥T2 CRC.

4.2.2 Histopathological evaluation:

All resected lesions will be assessed by a pathologist with expertise in gastrointestinal pathology at the local hospital. Histopathologic assessment will be performed according to the 2010 WHO classification. Selected resection specimen will be reviewed centrally by organizing meetings for participating pathologists led by an expert gastrointestinal pathologist with high expertise in T1 CRC.

T1 CRC is defined as polyps with invasion through the muscularis mucosae and into, but not beyond, the submucosa. Deep submucosal invasion is defined as SM2-3 according to Kikuchi for surgically resected specimens, or invasion depth ≥1000 micrometers as measured from the muscularis mucosae to the deepest point of tumor invasion for endoscopically resected specimens. [28,29]

4.2.3 E-module (Phase I):

Endoscopists willing to participate in this study are enrolled in an E-module consisting of a pre-test, (t=0) an interactive e-learning (t=0-4 weeks), a post-test (t= 4 weeks) and a confirmationtest (t=16 weeks). The e-module will be developed according to the Kirkpatrick model to determine aptitude at four levels criteria: reaction, learning, behavior and results. The e-module will be tested by research students to assess the reaction level (e.g. satisfaction). Feedback will be used to adapt the e-module. The learning level will be analyzed by comparing the result of the pre-test with the post-test. To evaluate the level of change in behavior we will use the results of the registration phase to calculate the accuracy on clinical level. Also the confirmation tests at t=16 weeks will provide information about the lasting effect of the training. Finally, for the result level we will collect information about the used resection techniques after implementation of the e-learning and compare these with a retrospective analysis in a selection of centers with high exposure. The e-module and tests will be constructed in English.

To construct the four tests we will use images from a prospectively collected database of LNPCPs with known histopathological outcome. Preferably the tests should reflect the prevalence of real-time T1CRC (± 15% of >20mm LNPCPs). We will run sample size simulations with varying prevalence of 0.10 to 0.25. We will first select +/- 100 cases to reflect daily routine (both easy as difficult cases). From this database we will construct two tests by assigning cases to either test 1 (pre-/post-test) or test 2 (confirmation test). In these tests all above mentioned endoscopic features will be attributed, the participant has to fill the presence/score of (one of) the features and the suspected diagnosis (LGD, HGD, superficial or deep invasive carcinoma) combined with an expected risk percentage of carcinoma (0-100%). In the pre-test no feedback will be given. After the post-test, the participant will receive feedback on his/her answer. The optimal number of images to be used in the test and e-learning is limited by the attention span of participants. The number of images used in the tests are evaluated by scenario simulation (10-

40). The e-learning will consist of different chapters thoroughly explaining the above mentioned features with interactive pictures, videos and sample questions. Consensus will be reached for selecting endoscopic images/videos in the e-module to correctly display representable features during a meeting of expert endoscopists who have participated in the OPTICAL I study.

E-module chapters:

1. Why is optical diagnosis important for your practice:
2. The making of the OPTICAL model
3. Features of the OPTICAL model
4. How to apply the OPTICAL model

4.2.4 Registration (Phase II part 1):

To analyze if an improvement in testing for accuracy in optical diagnosis translates to improvement at clinical level, endoscopists will register all encountered LNPCPs. Therefore, after completing the e-learning and the post-test, all participants will score every non-pedunculated polyp ≥20 mm as explained during the e-learning and described as above. The original endoscopy report can be used to fill in all features. The report must include a conclusion: probable T1 CRC yes/no with high or low level of confidence. The endoscopy and pathology reports will be used to fill in the eCRF by the study coordinator along with a local storage of the endoscopic images of the polyps. Scored features will be compared with pathological report to calculate sensitivity and specificity of the endoscopist. The chosen resection technique will be retrieved from the patient file and/or pathology report. Additionally, in a select group of participating hospitals we will perform a retrospective analysis, looking at the chosen resection techniques for large non-pedunculated polyps from 6 months before training to the moment of registration of participating endoscopists.

4.2.5 Image library

All images of the LNPCPs registered in the registration phase will be collected in a central image database. A data transfer agreement will be made to support this transfer. Before transfer to the central database, the images will be anonymized. The images will be scored at the level of cleaning, sharpness, the use of zoom, the use of advanced imaging techniques, and adequacy (does it bring the area of interest in focus) on the basis of a standardized case record form (CRF). At least 5 observers will revise each individual case. The report will be checked at completeness (are all the 5 individual parameters of the OPTICAL I model recorded in the report?). The level of quality of the images and completeness of the report will be made available as feedback to the individual endoscopist. In the future, the collected images will be used for training of the endoscopists (Phase II part 2, next paragraph), aggregation of multiple observations to support decision making

(wisdom of the crowd), and making an artificial intelligence model for real life prediction of T1 CRC in the polyp.

4.2.6 Feedback loop (Phase II part 2):

After going through the e-learning and completing the first confirmation test, endoscopists will receive monthly feedback during the registration phase (active feedback). Active feedback will consist of selected images/videos of real-time encountered LNPCPs during the registration phase in the participating centers. The imagery will be sent out monthly to all endoscopists who completed the e-module. Participants are asked to score characteristics and diagnosis and are given direct feedback. The results of these interim tests will not be used for calculating sensitivity and specificity at those moments.

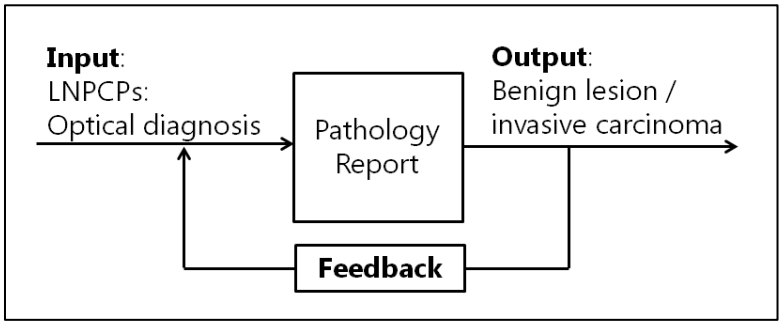

Figure 2: Feedback loop

5 Statistical analysis

5.1 Statistical analysis

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence intervals (CI) will be calculated as recommended in the Standards for Reporting Diagnostic Accuracy (STARD) statement, with histopathological diagnosis as the golden standard. Data will be analyzed using a mixed effect bivariate logistic regression model taking within reader clustering into account (random intercepts for pre/post-test sensitivity and specificity per reader). An increase of >10% between pre- and post-test is assumed to be of clinical importance.

The difference in frequency of chosen resection technique per pathological diagnosis for the selected hospitals before and after participating in this study will be displayed in a frequency distribution table. The chi-square test will be used to compare chosen treatment before and after the introduction of the e-module. Differences will be considered statistically significantly at $p<0.05$.

Results will be stratified by type of endoscopist and number of registered polyps. For piecemeal resections with possible invasive carcinoma but uncertainty about differentiating high grade dysplasia, T1 CRC or T2 CRC we will use latent class analysis.

Sample size is determined on simulation studies, varying:
- The number of readers (endoscopists) (varied between 30 and 100)
- The number of images (varied between 10 and 32)
- The prevalence of the outcome of interest (set at 0.25 or 0.10)
- The correlation between pre- and post-test sensitivity;
- The correlation between pre-test sensitivity and specificity

It is assumed that a reader's specificity will not change due to the training (i.e. pre-post-test correlation in specificity is 1.0). Scenario simulation shows a significant difference in sensitivity of at least 10% (from mean 60% to 70%) with a power set at 80% if we include at least 50 readers that score 32 images each test.

Our sample size calculation is based on a minimum number of readers to test. We will however invite as many Dutch participants as possible, resulting in a potential larger national effect. Also, in a trial like this study (without patient exposure) no ethical objection exists to limit exposure to participants. When 50% of the 45 hospitals affiliated with the T1 CRC working group are willing to participate we expect to include at least 75 endoscopists divided over 20 hospitals.

6 Ethical Considerations

6.1.1 Regulation statement

The study protocol will be presented to the Medical Ethics Review Committee of the University Medical Centre Utrecht. We expect this study to be non-WMO (Medical Research Involving Human Subjects Act). The study will be conducted according to the Code of conduct for medical research and data will be handled in accordance with EU General Data Protection Regulation.

6.1.2 Recruitment and consent

Phase 1: For the first phase this study is a non-medical study since patients are not involved. All participating endoscopists will do so voluntarily and agree with the use of their input by entering the e-module (a disclaimer is provided digitally).

Phase 2: For the second phase (registration of LNPCP) data will be collected anonymously to evaluate accuracy in daily practice. Of note, for quality registration purposed the current Dutch guideline "Endoscopic polypectomy of the colon (2019)" [25] already advises to systematically characterize and prospectively register all colorectal polyps >20mm and their treatment. Thus no additional information will be recorded or collected for the purpose of this study. If data has not yet been

registered by the participating center, the required data will be collected from standard care reports. The data will then be anonymously stored in an eCRF (Castor EDC). Patients are not recruited for this study, since the registration of the needed parameters are already collected in accordance with the Dutch guideline. Because data will be used anonymously, no informed consent will be asked for using this data. Access to data is restricted to the local investigator for its own center. Only the principal investigator has access to all data.

7 Administrative Aspects

7.1.1 Handling and storage of data and documents

Phase 1: All participating endoscopists will be assigned a pseudonym (code) based on center. For the analysis of test results data will be handled by code. We choose not to do this anonymously because we use three separate moments for testing and it is necessary to know which results belong to each participant to compare within participants. The code list will be stored in a secured folder by the principal investigator.

Phase 2: All scored polyps characteristics described in the endoscopy report by the endoscopist will be collected in an online Castor EDC database. The pathology report will be used to insert histopathological data in the same online Castor EDC database. Only the principal investigator will have access to all data. No personal data will be collected for the purpose of this study, all stored data will be anonymous.

Data will be analyzed (both for phase 1 and 2) with IBM SPSS Statistics version 25. The study will be carried out in accordance with EU General Data Protection Regulation. Data will be kept for 15 years. A data management plan is constructed for this study.

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