maison de la recherche en santé DRCI • CHU Nantes • CHD Vendée	*« NBI – COLON POLYPS »*

- Contribution of Narrow Band Imaging (NBI) to the Characterization of Scalloped Colon Polyps -

Minimal Risk, Minimal Constraint Interventional Research

Version 6.0 dated 14/12/2021

“NBI - POLYPES COLIQUES" project

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"*Contribution of Narrow Band Imaging (NBI) for the characterization of Scalloped Colon Polyps*".

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SIGNATURE PAGE

SPONSOR'S SIGNATURE

The person in charge of the research undertakes to carry out this study in accordance with all the legislative and regulatory provisions that may apply to the research and in accordance with the protocol.		
Name and position of signing representative : Mr Francis SAINT-HUBERT General Manager	**Date :**	**Signature :**

SIGNATURE OF INVESTIGATOR S

I have read all the pages of the protocol for the clinical trial for which the CHD Vendée is responsible. I confirm that it contains all the information required to conduct the trial. I undertake to carry out the trial in compliance with the protocol and the terms and conditions defined therein.
I am aware that this research falls within the scope of routine care research as defined by paragraph 2° of article L 1121-1 and article R 1121-3 of the French Public Health Code. The procedures are performed and the products are used in the usual way, but special monitoring procedures are provided for in this protocol.
I undertake to carry out the test in compliance with :

- the principles of the "Declaration of Helsinki",
- international (ICH) and French rules and recommendations of good clinical practice (rules of good clinical practice for biomedical research involving medicinal products for human use - decisions of November 24, 2006)
- national legislation and regulations governing clinical trials
- compliance with the current European Directive governing clinical trials

I also undertake to ensure that the investigators and other qualified members of my team have access to copies of this protocol and documents relating to the conduct of the trial to enable them to work in compliance with the provisions set out in these documents.

Coordinating investigator	**Name :** Dr. Vincent MACE CHD Vendée	**Date :**	**Signature :**
Principal investigator	**Name and address :**	**Date :**	**Signature :**

LIST OF ABBREVIATIONS

ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé (French Agency for the Safety of Medicines and Health Products)
AMM	Marketing Authorization
ARC	Clinical Research Associate
BPC	Good Clinical Practice
JRC	Colorectal cancer
CE	European conformity
CEC	Clinical Studies Coordinator
CNIL	Commission Nationale de l'Informatique et des Libertés (French Data Protection Authority)
PPC	Comité de Protection des Personnes
CRF	Case Report Form (observation booklet)
DM	Medical Devices
eCRF	Electronic Case Report Form (cahier d'observation électronique)
EMA	European Medicines Agency
EIG	Serious adverse effect
EIGI	Unexpected Serious Adverse Effect
EM	Medication error
EvIG	Serious Adverse Event
HAS	French Health Authority
ICH	International Conference on Harmonization
IRC	Clinical Research Nurse
LB	White Light
IBD	Chronic Inflammatory Bowel Disease
MR	Reference methodology (CNIL)
NBI	Narrow Band Imaging
NICE	Narrow band imaging International Colorectal Endoscopic
RCH	Hemorrhagic Rectocolitis
CPR	Summary of Product Characteristics
SUSAR (=EIGI)	Suspected Unexpected Serious Adverse Reaction
TEC	Clinical Study Technician
UFR	Training and Research Unit
WASP	Workgroup serrAted polypS and Polyposis
WHO	World Health Organization

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INTRODUCTION

This is a prospective bicentric study to assess the diagnostic performance of NBI (Narrow Band Imaging) characterization of scalloped colonic polyps less than 20mm in patients undergoing screening colonoscopy.

NBI is a "virtual" electronic staining technique available on conventional OLYMPUS and FUJIFILM endoscopes, with no additional intervention required.

The colonoscopy procedure for each patient will be no different from a conventional colonoscopy examination with excision of all polyps visualized and anatomopathological analysis, apart from a brief period of NBI analysis for each polyp detected prior to excision, enabling the polyp to be classified according to existing endoscopic classifications (i.e. NICE classification for adenomatous polyps and WASP classification for scalloped polyps).

This joint CHD-CHU project is original in that there are currently no data on the characterization of colonic polyps in NBI by large groups of "non-expert" endoscopists. Indeed, studies carried out to date on this subject, notably in the United States and England, have involved small numbers of NBI expert endoscopists. A recent "pilot" study carried out at Nantes University Hospital showed that NBI is becoming reliable, with a diagnostic accuracy of over 90%, for differentiating adenomatous polyps from typical hyperplastic polyps, but did not assess the contribution of NBI to the characterization of scalloped polyps, a still poorly understood entity. The technological improvement of endoscopes and the publication in 2016 of a classification (WASP) enabling the recognition of sessile scalloped polyps using NBI now necessitate evaluating the contribution of NBI for the recognition of these lesions. A study of this kind in general and university hospitals is essential to determine the feasibility of community implementation, with the ultimate aim of better detecting scalloped colonic lesions, which are often unrecognized but have a clearly demonstrated degenerative potential, and differentiating them from typical adenomatous polyps. The clinical gastroenterology departments of the CHD and CHU are very involved in clinical research, and collaborate on joint care and research projects. Both are equipped with the latest generation of Olympus and Fujifilm (for CHU de Nantes) systems with NBI, and have a significant endoscopic activity, notably in the field of colorectal cancer screening.

1. Justification of the study

1.1 Research positioning

Colorectal cancer is a major public health problem worldwide, particularly in industrialized countries. In France, the incidence of colorectal cancer ranked 3e among all cancers, with 40,500 new cases and an estimated 17,500 deaths in 2011. (1). Most sporadic colorectal cancers arise from pre-cancerous lesions, adenomatous polyps, according to a now well-known carcinological development sequence (2). Colonoscopy combined with resection of adenomatous polyps reduces the risk of colorectal cancer (3,4). In France, colonoscopy is the reference method for colorectal cancer screening in populations selected as being at risk, according to the recommendations of the French National Authority for Health (HAS), and in patients suspected of having a colorectal neoplastic lesion in the presence of suggestive symptoms. (5).

Although colonoscopy is effective overall in reducing the risk of colorectal cancer, it is an imperfect tool, with 15-27% of lesions 'missed' and left in place (6,7), which can lead to the occurrence of interval cancers. Interval cancers are cancers that occur between two colonoscopies, and could account for up to 10.5% of colon cancers. They occur within 6 to 60 months (7). Among the possible causes of missed lesions, the involvement of adenomatous scalloped polyps currently raises major questions, as these lesions are still a poorly understood entity, but have a demonstrated degenerative potential (8). Their involvement in interval cancers is suggested both by their preferential right-sided location (the protective effect of colonoscopy being much less for the right colon than for the left), and by their lack of relief, which makes them more difficult to detect. Moreover, until recently, there was no clear endoscopic description enabling the endoscopist to recognize them and treat them effectively. As a result, the rate of incomplete endoscopic resections of scalloped adenomatous polyps is estimated at 30% (9).

From an anatomopathological point of view, the situation has become relatively complex in recent years, with the description of new colonic polyp entities (8). Historically, only conventional adenomatous polyps (at risk of degeneration) and typical hyperplastic polyps (without risk of degeneration) were distinguished, which explains why endoscopic classifications have focused on the ability to distinguish these 2 anatomopathological entities. The new WHO anatomopathological classification describes scalloped polyps, which it subdivides into 4 different morphological entities constituting evolutionary lesion spectra. The histological appearance of these lesions distinguishes between 1) typical hyperplastic polyps (reclassified as non-adenomatous scalloped lesions, and accounting for some 80-90% of scalloped lesions overall), 2) sessile scalloped adenomas/polyps, 3) sessile scalloped adenomas with dysplasia, and 4) traditional scalloped adenomas. While typical hyperplastic polyps have virtually no degenerative potential, other scalloped (adenomatous) lesions may degenerate. Descriptively, typical hyperplastic polyps are generally small and occur throughout the colon. Sessile scalloped polyps/adenomas do not show cytological lesions of dysplasia in the basal state. They are essentially characterized by abnormalities in the maturation of colonic crypt cells. They share many morphological features with hyperplastic polyps of the microvesicular subtype, in particular their predominantly right-sided location. They are generally larger than hyperplastic polyps. Foci of dysplasia identical to that of "classic" adenomas may appear in sessile scalloped polyps/adenomas. Sessile scalloped lesions with dysplasia are thought to progress more rapidly to adenocarcinoma than classical adenomas of equivalent dysplasia grade. Traditional scalloped adenomas are different from sessile scalloped lesions. They generally appear in the left colon and rectum, and are of villeinous or filiform architecture. They are characterized by the presence of a dysplasia rich in cells with penicillate eosinophilic cytoplasm and ectopic crypts not anchored to the

muscularis mucosa. Many of them are associated with a classic adenomatous component, and their evolutionary kinetics are identical to those of classic adenomas.

As far as endoscopy is concerned, it is accepted that, in routine practice, it is relatively easy to distinguish typical hyperplastic polyps from classic adenomas, thanks to optical advances. On the other hand, it remains very difficult to recognize adenomatous scalloped polyps. This poses a real problem, since adenomatous scalloped polyps are probably responsible for around 30% of colorectal cancers, including interval cancers (9). The best way to detect adenomatous scalloped polyps is therefore to learn how to recognize these lesions, which requires a high-quality optical examination and the use of optical filters such as Narrow Band Imaging (NBI).

A major challenge is therefore to distinguish conventional adenomatous polyps from scalloped lesions, particularly sessile adenomatous scalloped polyps. These lesions have an increased risk of developing colorectal cancer and represent around 12% of colonic polyps in a population referred for screening colonoscopy, but are often missed at colonoscopy due to their very flat nature.

These strategies require highly reliable optical prediction techniques during the endoscopic examination. However, standard diagnostic colonoscopy using white light, as currently practised, does not effectively differentiate between different polyp subtypes. Indeed, the diagnostic efficiency of white light for histological prediction of colonic polyps is only around 60-80%. (10). The most promising advances concern so-called "virtual chromoendoscopy" techniques such as Narrow Band Imaging (NBI) (Olympus and Fujifilm, Japan). With NBI, the image can be colored simply and immediately, at the touch of a button on the endoscope handle, to enhance mucosal microarchitecture and vessels. In technical terms, this involves the activation of an optical filter limiting the light spectrum to 2 specific wavelengths, 415nm (blue) and 540nm (green) respectively. As the two absorption peaks of hemoglobin occur at these wavelengths, the NBI allows blood vessels to appear darker, enabling better visualization of both mucosal surface details and capillaries. Several studies have demonstrated the value of NBI for characterizing colonic polyps, particularly small ones, with very good diagnostic accuracy and a high degree of confidence on the part of endoscopists. Indeed, these studies show diagnostic efficacy rates in the order of 96 to 98% for colonic polyps of 6 to 9mm, and 91 to 92% for those under 5mm (11-14).

The population of gastroenterologists around the world who could potentially use NBI is extremely large, since NBI has been available on all Exera (Olympus) and 760 (Fujifilm) series video processors for around 5 years in routine practice. However, published scientific data comes mainly from expert centers, and has been acquired by endoscopists with considerable expertise in the interpretation of NBI images. Moreover, analysis of published data is confounded by the multiplicity of classifications used, whose diagnostic criteria can vary significantly (15-17). Thus, all the following classifications have been proposed: Vascular Pattern Intensity (VPI), Sano classification, Hiroshima, Showa, etc. In order to standardize diagnostic criteria and harmonize practices, Tanaka and Sano proposed a new classification in 2011 called the NICE classification (Narrow band imaging International Colorectal Endoscopic) (18)which has been validated by other groups from expert centers (19) which differentiates between typical hyperplastic polyps and conventional adenomatous polyps (Figure 1), but did not include recognition of adenomatous scalloped polyps. Recently, the WASP classification has been developed for the diagnosis of scalloped adenomatous polyps, and appears extremely promising (20). This classification was published in Gut in 2016 (Figure 2), but no external validation study is currently available, nor is it currently underway to our knowledge. It therefore seems particularly interesting to evaluate this new classification, all the more so as studies carried out in the field of learning NBI semiology in general are in favour of relatively short learning curves (21-24).

Our aim is to evaluate and compare, using the CONECCT classification, the diagnostic performance of NBI for histological prediction of the nature of colonic polyps (conventional

adenomatous *versus* scalloped polyps) during colonoscopy, compared with histological analysis (taken as the reference method), in a large population of "non-expert" NBI endoscopists, after rapid and simple training in the NBI technique.

The gastroenterology clinical departments of the CHD and CHU collaborate on joint care and research projects. They are both equipped with the latest generation of Olympus and Fujifilm systems with NBI, enabling the use of appropriate classifications, and have significant endoscopic activity, particularly in the field of colorectal cancer screening.

This study in no way alters the patient's clinical management or care pathway. During colonoscopy in the presence of polyp(s) <20 mm, an observation sequence and image acquisition are performed in NBI, which does not significantly alter the duration of the endoscopic examination. The NBI is integrated into the high-definition endoscope (Olympus, Fujifilm) and the transition from white light to NBI is instantaneous.

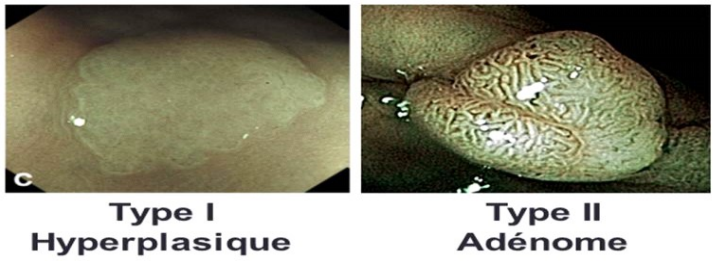


Figure 1: NICE (Narrow band imaging International Colorectal Endoscopic**) classification.** Diagnostic criteria in favor of a typical hyperplastic polyp (type I) are: a) absence of dark appearance of the polyp in relation to the adjacent mucosa, b) absence of brownish vessels, c) absence of oval structures within the polyp.
Conversely, the presence of one or more of the above-mentioned criteria is indicative of a conventional adenomatous polyp (type II).

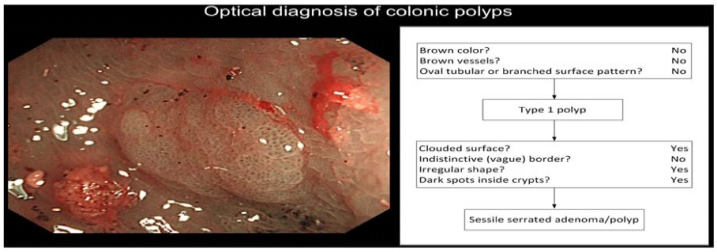


Figure 2: WASP (Workgroup Serrated PolypS and Polyposis) **classification.** Diagnostic criteria in favor of an adenomatous scalloped polyp are: a) the existence of a cloudy appearance of the polyp, b) an irregular shape, c) the presence of black spots within the colonic glands.

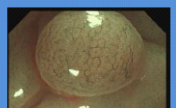
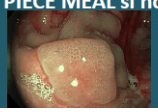
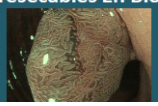
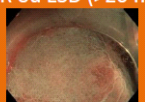
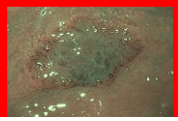
CONECCT	IH Hyperplasique	IS Lésion festonnée sessile	IIA Adénome simple	IIC Adénome à risque ou cancer superficiel	III Adénocarcinome profond
Macro	Souvent petits <10 mm Surélevé IIa	Paris IIa ou IIb Limites imprécises en nuage ou en plateau	Paris Ip, Is Ou IIa Rarement déprimé	Souvent IIc Ou IIa + IIc Ou LST Non granulaire Ou macronodule (> 1cm) sur LST Granulaire	Souvent III Ou IIc avec composant nodulaire dans la dépression **Saignements spontanés**
Couleur (NBI ou équivalent)	Claire ou équivalente au background	Variable Mucus jaune (rouge en NBI)	Foncée par rapport au background	Foncée souvent	Hétérogène, foncées ou très claires par zones
Vaisseaux (NBI ou équivalent)	Absence de vaisseaux ou vaisseaux fins ne suivant pas les cryptes	Absents parfois Spots noirs au fond des cryptes rondes	**Réguliers** Suivant les cryptes allongées	**Irréguliers mais persistants** Pas de zone avasculaire	Irréguliers Gros vaisseaux interrompus Ou absents (zones avasculaires)
Cryptes (chromo virtuelle ou réelle)	Rondes Blanches	Cryptes rondes points noirs (NBI)	Allongées Ou Branchées Cérébriformes **régulières**	**Irrégulières mais conservées** Pas de zone amorphe	**Absentes** **Détruites** Ou irrégulières dans une zone délimitée (démarcation nette)
Résection	Pas de résection 	**EN BLOC R0 si possible** **PIECE MEAL si non résécables En Bloc**  		**EN BLOC R0** (EMR ou ESD (>20 mm) 	**CHIRURGIE** avec curage 

Figure 3: CONECCT classification (Colorectal Neoplasia Classification to Choose the Treatment**).**

1.2 Benefits and risks for research subjects

1.2.1 Benefits

The results of this research will contribute to the development of knowledge in the field of pathology.

1.2.2 Risks

- NBI prediction: poor lesion targeting, erroneous use of NBI methodology and tests (despite learning) leading to misdiagnosis.

- The risk associated with **histological analysis** is not specific to this study, but applies to all procedures for processing, reading and interpreting histological specimens. It relates to malfunctions and quality defects at various stages (preparation, staining....), and can lead to misdiagnosis.

- Associated procedures: the risks of colonoscopy and biopsies are those incurred when these examinations and techniques are carried out as part of everyday practice, i.e. pain, bleeding, perforation and infectious risks.

- Added to this are the risks associated with **drugs administered for colonic preparation** and those administered for **anesthesia/analgesia** during and after the examination. These risks are described in the SPCs of the drugs concerned, administered within the scope of their marketing authorization.

- Pathology under study: colorectal cancer screening/risk monitoring: risk of underdiagnosis and latent progression.

1.2.3 Justification for positioning as research with minimal risks and constraints

The person in charge of the research qualifies it in first intention as **interventional research with minimal risks and constraints**, since :

- All procedures are routinely performed (colonoscopy) and defined in the order of April 12, 2018 set by the Ministry.

Research does not focus on innovative or obsolete techniques or strategies.

Apart from the transition to NBI, all patient management will be identical to usual practice. In particular, the date of discharge will be decided by the doctor in charge of the patient, independently of the study, but will be recorded in the patient file and the research CRF.

As a result, the particular conditions under which the research is carried out represent negligible constraints for the person undergoing the research. (Article R 1121-3 of the French Public Health Code (CSP), decree no. 2006-477 of April 26, 2006)

Before any research is carried out, the person in charge of the research will submit the study protocol to the Comité de Protection des Personnes Ouest III de Poitiers for a favorable opinion and confirmation of the research's qualification, in accordance with article L 1121-1 of the French Public Health Code (CSP), as amended by laws no. 2004-806 of August 9, 2004 and no. 2006-450 of April 18, 2006 relating to public health policy.

Bibliographical references are appended to the document.

2. Objectives and endpoints

2.1 Objective and primary endpoint

2.1.1 Primary objective

To evaluate the diagnostic performance of the NBI for the characterization of scalloped colonic polyps of all types [typical hyperplastic and adenomatous scalloped; i.e. CONECCT IH and CONECCT IS] versus conventional adenomatous [i.e. CONECCT IIA] during colonoscopy in a population of "non-expert" endoscopists.

2.1.2 Primary endpoint

Sensitivity of NBI compared with histological analysis (=reference method).
Number of polyps characterized as scalloped (CONECCT IS) on reading by NBI compared with the number of polyps characterized as scalloped on standard histology.

2.2 Objectives and secondary endpoints

2.2.1 Secondary objectives

- Measurement of diagnostic performance indices (specificities, PPV, NPV) using NBI and white light alone for characterization of polyps CONECCT IH and IS versus CONECCT IIA

Within scalloped polyps (according to pathological analysis results), diagnostic capabilities (sensitivities, specificities, PPV, NPV) of NBI and white light alone to characterize CONECCT IS polyps.

- Comparison of the diagnostic performance of NBI and white light alone for the characterization of polyps CONECCT IH and IS versus CONECCT IIA
- Diagnostic performance by degree of certainty in NBI.
- Evaluation of the role of endoscopist seniority in polyp characterization in NBI.
- Assessment of the role of polyp size in polyp characterization.

2.2.2 Secondary endpoints

1-2 Polyp characterization using white light according to CONECCT classification
Polyp characterization using NBI according to CONECCT classification
Polyp characterization using standard histology according to CONECCT classification

3- Evaluation of the degree of certainty of characterization after examination by: strong or weak

4- Endoscopist seniority: junior or senior: <2000 vs ≥ 2000 colonoscopies performed.

5- Polyp size defined on NBI examination: 1-5mm vs 6-9mm vs 10-20mm

3. Study population

3.1 Description of the population

- Any adult patient having a colonoscopy scheduled in one of the participating hospitals.

The expected number of patients is around 690, with the aim of characterizing at least 690 polyps. The average number of polyps per patient is estimated at between 1 and 2.
A limit of 4 polyps per patient will be set for data collection. Data collected for the study should relate to the first 4 polyps removed.

3.2 Pre-inclusion criteria

- Patients over 18 having a colonoscopy scheduled in one of the participating hospitals (CHD Vendée and CHU de Nantes).
- Patient having agreed to participate in the study and having given express consent
- Patient affiliated with or benefiting from a social security system

3.3 Inclusion criteria

- Patients with 1 or more polyps smaller than 20mm observed during colonoscopy

3.4 Non-inclusion criteria

- Patient undergoing emergency colonoscopy for ongoing GI bleeding or occlusion symptoms
- Patients with chronic inflammatory bowel disease (IBD): UC, Crohn's disease or unclassified colitis
- Patients with familial adenomatous polyposis
- Pregnant or breast-feeding women
- Minor patient
- Patients under guardianship or deprived of their liberty
- Patient unable to understand protocol and/or give express consent
- Patient not affiliated to a social security system or beneficiary of such a system
- Patients hospitalized or treated without their consent

4. Conduct of the study

4.1 General research methodology

The research has the following characteristics:

- Type of research: **Interventional research with minimal risks and constraints** (Study of electronic staining techniques (also known as 'virtual chromoscopy') during colonoscopy, without the addition of contrast media or specific intervention).
- **Bicentric** study**: CHD Vendée, CHU de Nantes**
- **Prospective** study

4.2 Study and analysis techniques

4.2.1 Detailed description of evaluation parameters

Parameters assessed :

- Characterization of polyps, using different analysis techniques: conventional adenomatous versus typical hyperplastic or scalloped adenomatous.

4.2.2 Description of techniques and analyses

Study diagram :

- All endoscopists participating in the study will receive an initial one-hour training course in NBI polyp characterization, delivered by an expert endoscopist in image analysis (Dr. Guillaume VELUT, graduate of the DIU 'Endoscopie Diagnostique Avancée').

- A verification test (rate of correct answers >95%) will be carried out before each operator is authorized to take part in the study, based on an independent set of images of 30 colonic polyps.

- Each patient corresponding to the pre-inclusion criteria and agreeing to take part in the study is "pre-included". During colonoscopy, the presence of any polyp(s) smaller than 20mm is determined. The right colon, which is the preferred site for adenomatous scalloped polyps, will be examined with particular attention by a second pass under white light. This 2ème pass is routinely performed in standard practice, for example to check fast-moving areas during colonoscopy, and will only increase examination time by around 2-3 minutes. Patients without a polyp smaller than 20 mm are not included in the study.

- Each polyp measuring less than 20mm will be analyzed in white light and NBI, as follows:

1) White-light image analysis
2) Switch to NBI mode by simply pressing the 'NBI' button on the endoscope handle (immediate acquisition of the NBI image with photographic recording in LB and NBI). A prediction of the histological type of polyp according to the CONECCT classification is made by the endoscopist and noted in the CRF, together with the degree of certainty (strong or weak).
The study is limited to 4 polyps per patient. Only data from the first 4 polyps removed will therefore be collected.

- All polyps detected and analyzed by NBI are then removed by excision (forceps excision, mucosectomy) according to the usual procedure and analyzed by conventional histology (gold standard).

- If it is impossible to characterize a polyp by NBI (image of poor quality or diagnosis impossible), the examination will be considered a technical failure of NBI, but the polyp will be removed for histological analysis in accordance with current recommendations.
- If the polyp is not recovered for histological analysis, or if interpretation is impossible (coagulation artifacts after standard resection, for example), the examination will be considered a technical failure of standard histology.
- Anatomopathology departments will be involved and will collaborate between the 2 centers to ensure standardized interpretation of polypectomy specimens.

4.3 Study schedule

A one-hour training session on the NBI technique, based on clinical cases and commented image analysis for the characterization of colonic polyps, will be given by an expert endoscopist (Dr. VELUT) at Nantes University Hospital and La Roche Sur Yon Hospital for all endoscopists taking part in the study. Dr. VELUT is a graduate of the DIU "Endoscopie Diagnostique Avancée" (Advanced Diagnostic Endoscopy) and will be taking over the "colonic polyps" course of this training program. The training course will therefore not call on the services of an outside consultant, and will not require a specific budget.

The inclusion period is 48 months.

For patients :

- Inform patients about the study when they schedule their endoscopy examination in consultation or during hospitalization before the examination is performed.
- Each patient corresponding to the pre-inclusion criteria and having the presence of at least one polyp of less than 20 mm at colonoscopy will be included.
- Colonoscopy with white-light analysis and NBI for each patient.
- Polyp excised for standard histological analysis.

4.4 Identification of source data not included in the medical record

- Total number of polyps
- Total number of polyps <2cm
- Quality of colonic preparation according to Boston classification
- Suggested monitoring interval per patient after polyp analysis (by NBI and pathology)
- Endoscopist seniority
- Information on polyps (Paris classification, prediction in white light and NBI, CONECCT classification, image quality in white light and NBI, degree of certainty of prediction)

4.5 Rules for terminating a person's participation

4.5.1 Criteria for premature termination of a person's participation in research

For details of how and for how long people who left the study prematurely were followed up, please refer to the statistics section.

-Patient consent can be withdrawn at any time during the study, before results are published.

Right to object to data processing at any time during the study, before publication of results s.

4.5.2 Procedure for premature termination of a person's participation in research

Please refer to the statistics section for details of how to use data from people who left the study prematurely.

4.5.3 Criteria for discontinuing all or part of a research project (excluding biostatistical considerations)

Part or all of the study may be stopped permanently or temporarily by decision of the ANSM, the CPP or the study sponsor.

A written confirmation will be sent to the study coordinating investigator (specifying the reasons for premature termination) and to the principal investigator of each center, if applicable.

5. Data management and statistics

5.1 Study data collection and processing

5.1.1 Data collection

An electronic case report form (eCRF) will be created for each patient. All information required by the protocol must be provided in the eCRF. It must include the data needed to confirm compliance with the protocol and all the data required for statistical analysis, and to detect major deviations from the protocol.

Data will initially be collected on paper in an observation notebook, with a form for each polyp visualized, filled in by the endoscopist.
All data are then entered into the eCRF by investigators, clinical study coordinators (CECs) or clinical research nurses (CRNs).

The people responsible for filling in the eCRF (investigator, CEC, IRC, etc.) must be identified and their responsibilities defined in each center's table of delegated responsibilities (kept in the investigator binder).

5.1.2 Data coding

By signing this protocol, the principal investigator and all co-investigators undertake to keep confidential the identities of the patients who have participated in the study.

The transmission of a person's data for research purposes will therefore only be possible if a coding system is used; the presentation of research results must exclude any direct or indirect identification.

Patients (and polyps) will be identified in order of inclusion by a number automatically assigned by the Clinsight software (eCRF), then completed by the patient's initials.

This code will be the only information on the eCRF that can be used to link the eCRF to the patient.
The person in charge of the research is also required to code patient data on any documents in his/her possession (reports of imaging or biological examinations, etc.) which may be attached to the CRF.

A correspondence table will be set up at each center. This table will be kept in a secure place by the center's principal investigator, and will contain the patient code and nominative data, so that it can be traced back to the patient file in the event of missing or erroneous data. No clinical data will be collected in these correspondence tables.

5.1.3 Data processing

The collection of clinical data will be based on the creation of a clinical database and the creation of data entry masks in the image of the observation notebook, in compliance with the protocol and regulations currently in force.
The structure of the database and input screens will be approved by the research manager.

5.2 Statistics

Responsible for statistical analysis: Ms Lucie PLANCHE

5.2.1 Description of planned statistical methods, including schedule of planned interim analyses and statistical justification of number of inclusions

Analysis of primary endpoint:

Sensitivity of the NBI technique to pathological findings for the characterization of colonic polyps (conventional adenomatous [CONECCT IIA] versus scalloped [CONECCT IS]) at colonoscopy will be calculated with its 95% confidence interval.

Secondary endpoints :
- The diagnostic performance (specificity, positive predictive value, negative predictive value, RV+, RV-, diagnostic accuracy (corresponding to the rate of correct responses)) of NBI for the characterization of colonic polyps (conventional adenomatous [CONECCT IIA] versus scalloped [CONECCT IS]) compared with standard histology will be estimated with their 95% confidence interval.

- The sensitivity and specificity of white light compared with standard histology results will be estimated with a 95% confidence interval and compared with those obtained by NBI using a McNemar test.

- If numbers permit, sensitivity analyses will be carried out:
  - The sensitivity of NBI for the characterization of CONECCT IH and IS polyps versus CONECCT IIA will be estimated according to the certainty of the polyp characterization in NBI: strong or weak. These 2 sensitivities will be compared using a Chi2 test.
  - The same analysis will be carried out on the seniority of the endoscopist: junior or senior.
  - The same analysis will be performed according to polyp size: 1-5mm vs. 6-9mm vs. 10-20mm or 1-5mm vs. 6-20mm depending on numbers.

Number of subjects required :
Over 48 months, we plan to include 690 patients at Nantes University Hospital and the CHD de Vendée, with the aim of characterizing at least 690 polyps measuring less than 20 mm. About 50% of these will be CONECCT IIA polyps, 40% CONECCT IH and 10% CONECCT

IS. In addition, a majority of these polyps will be <5 mm in size (≈60%), ≈30% between 6-9 mm and ≈10% >10mm.
Assuming that 5% cannot be analyzed, and that the sensitivity of the NBI is 90%, we can estimate our sensitivity with a confidence interval of ±3%.

5.2.2 Expected statistical significance

A p-value < 0.05 is considered statistically significant.

5.2.3 Method for taking into account missing, unused or invalid data

All missing data will be described in terms of numbers and percentages.
No imputation will be performed on the primary endpoint.

5.2.4 Managing changes to the initial strategy analysis plan

NA

5.2.5 Choosing the people to include in analyses

All polyps < 20mm characterized by NBI and standard histology of included patients will be analyzed.

6. Vigilance and management of undesirable events

6.1 Definitions

Vigilance	This is the monitoring of drugs, medical devices and other healthcare products. It also involves preventing the risk of undesirable effects resulting from their use, whether these risks are potential or proven,
Adverse events (AE)	Any harmful event occurring in a person undergoing research involving the human body, whether or not the event is related to the research or to the product to which the research relates.
Adverse reactions (AR)	An adverse event occurring in a person undergoing research involving the human body, when this event is related to the research or to the product to which this research relates.
Effects/ Serious adverse events (SAE)	Any adverse effect/event that : * results in death, * is life-threatening, * results in temporary or permanent disability, * requires or prolongs the patient's hospital stay, * causes a congenital or neonatal anomaly, * is medically important (the list of medically important effects/events is defined by the EMA).
Unexpected adverse events	Any undesirable effect whose nature, severity or course is not consistent with the information on the products, procedures and methods used in the research.
New fact	Any new data that could lead to a reassessment of the risk-benefit ratio of the research or the product under investigation, to changes in the use of the product, in the conduct of the research, or in the documents relating to the research, or to the suspension, interruption or modification of the research protocol or similar research. For trials involving the first administration or use of a health product in people with no medical condition: any serious adverse reaction.
Abuse	Intentional, persistent or sporadic excessive use of a drug accompanied by harmful physical or psychological reactions.
Overdose	Administration of a quantity of drug, given at one time or cumulatively, which is above the maximum recommended dose according to the rules of compliance or use of the product. Clinical judgment should always be applied. (actual overdose: due to too large a raw quantity / relative overdose: due to predisposing factors such as renal insufficiency, hypo-albuminemia...)
Misuse or off-label use	Situation where the product is intentionally used in a way that does not comply with the product's specifications for use (e.g. route of administration/posology or indication different from that listed in the reference document).

Medication error (ME)	Corresponds to any proven (or potential) omission or unintentional performance of an act during the care process, *in the circuit (from manufacture to administration)* involving a product, which may be the cause of a risk or undesirable event for the patient. The risk of error or potential error concerns situations where the error has not occurred, has been intercepted but could have occurred.

6.2 List of expected adverse events

Associated processes :
- Colonoscopy AEs
    - aches and pains
    - uneasiness
    - bleeding, digestive bleeding
    - perforations
    - black stools
    - fever
    - chills
    - spleen hematoma
    - infectious risks

- Biopsy AEs
- pain,
    - uneasiness
    - bleeding, hemorrhage
    - perforations
    - fever
    - chills
    - infectious risks ;

The histological analysis process can generate Evl and situations that interfere with the result and therefore the quality of the data required for the study:
- failure in the sample transport and storage process,
- faulty sample preparation
- slide reading/interpretation error

AEs from **drugs administered** for colonic preparation and those administered for anesthesia/analgesia during and after the examination. These risks are described in the SPCs of the drugs concerned, administered within the scope of their marketing authorization.

Evl of pathology under study (suspicion - search for colorectal cancer) :
- Signs suggestive of, or aggravated by, bleeding, anemia and/or signs of martial deficiency.
- Abnormalities or changes in intestinal transit
- Modification of a known polyp

AEs concerning any **ancillary treatments**: expected AEs are listed in the RCP for medicinal products used within the scope of the AMM, or in the instructions for use for DM used in accordance with the CE marking indication, and in the therapeutic procedures implemented in accordance with professional recommendations and good practice.

6.3 Adverse events management

6.3.1 Collection of AE

In the context of this minimal-risk, minimal-constraint research study, the protocol does not involve any change in the usual management of patients, so any adverse events or effects observed will be unrelated to the study.

AE related to the intervention, the pathology studied, co-pathologies and their respective treatments do not need to be entered in the vigilance section of the CRF, nor do they need to be notified to the sponsor if a severity criterion is present.
Under the investigator's responsibility, and following the example of care, the notification of complications arising from these examinations comes under regulated systems: AEs linked to drugs and DMs transmitted to pharmacovigilance systems, materialovigilance, complications of procedures and examinations integrated into the establishments' risk management system.

In this study, which aims to evaluate the diagnostic performance of NBI for the characterization of colonic polyps, only complications and AEs of techniques that could have a potential impact on the protocol objective will be collected and reported if a severity criterion exists.
For this purpose, investigators will be asked to provide the sponsor with an anonymized copy of their declaration made in the appropriate regulated declaration system.

The sponsor therefore wishes to receive :
- All new facts arising in the course of the study
- Any unexpected SAEs arising from the protocol procedure (for both types of analysis: white light/NBI and conventional histology)
- Pregnancy reports

6.3.2 Notification of SAE

SAE are notified to the appropriate vigilance circuits (a copy is kept in the patient's clinical file).

For the purposes of this protocol, the complications required to analyze the objective (see paragraph 6.3.1) are collected in the CRF and will be analyzed according to the study schedule (end of study).
When a severity criterion exists, in the context of RIRCM, it is not necessary to send a notification to the sponsor (entry on the CRF is sufficient).

Only "new facts" that may interfere with the research (new information on the technique, etc.), any SUSAR linked to protocol procedures and pregnancy reports must be transmitted to the sponsor as soon as possible after the investigator has become aware of them.
All correspondence between the investigator and the vigilance cell must be copied to the sponsor at the same time.

6.3.3 Notification period to sponsor

The investigator is responsible for collecting and reporting to the appropriate vigilance system the various complications presented by patients.
It is the investigator's responsibility to note and report all AEs, SAEs, special situations or new facts, with the exception of those previously excluded, whether expected or not, occurring during the entire study:

-from the start of the examination (colonoscopy)
-and up to histological analysis

6.4 Methods and duration of follow-up care following the occurrence of undesirable events

All events, particularly serious ones, must be monitored until recovery, consolidation or death (closed event).
NB: If a pregnancy occurs during the course of the study, it should be monitored until the child is born or reaches the age of majority.

7. Administrative and regulatory aspects

7.1 Right of access to source data and documents

Each patient's medical data will only be transmitted to the sponsor or any person duly authorized by the latter, and, where applicable, to the authorized health authorities, under conditions guaranteeing confidentiality.
The sponsor and the regulatory authorities may request direct access to medical records for verification of clinical trial procedures and/or data, within the limits authorized by laws and regulations.

7.2 Data confidentiality

Persons having direct access will take all necessary precautions to ensure the confidentiality of information relating to the persons concerned, in particular as regards their identity and the results obtained.
These people, like the investigators themselves, are bound by professional secrecy (under the conditions defined by articles 226-13 and 226-14 of the French penal code).
During or at the end of the research, the data collected on the subjects and transmitted by the participants will be rendered anonymous.
Under no circumstances may the names or addresses of the persons concerned appear in clear text.
Only the first two letters of the subject's last name and the first letter of his or her first name will be recorded, along with a coded number specific to the study, indicating the order of inclusion of subjects.

7.3 Computerized data and submission to CNIL

This study falls within the scope of the "Reference Methodology" (MR-001) in application of the provisions of article 54 paragraph 5 of the amended law n°78-17 of January 6, 1978 relating to information technology, files and freedoms. This change was approved by decision dated August 14, 2016. The CHD Vendée de La Roche sur Yon, sponsor of the study, has signed a commitment to comply with this "Reference Methodology".

7.4 Trial monitoring

Monitoring will be carried out by the Promotion Department of the Research Division. A Clinical Research Associate (CRA) will visit each investigator site to check the quality of the data reported in the case report forms.

The monitoring plan is defined in consultation between the research team and the institution in charge, according to the objectives of the study.

On-site monitoring visits will be organized by appointment with the investigator. The CRAs must have access to each site:
- data collection notebooks for included patients,
- patient medical and nursing records,
- investigator's binder.

7.5 Inspection / Audit

In the context of this study, an inspection or audit may take place. The sponsor and/or participating centers must be able to provide inspectors or auditors with access to data.

7.6 Ethical considerations

7.6.1 Informed consent express

The investigator undertakes to obtain the person's free, informed and express consent, given orally, after having provided information on the protocol (information note and consent form in appendix). He will give the person a copy of the information note. The person can only be included in the study after having read the information note and given oral consent, after having had time to reflect, if necessary.

The patient's information and agreement to participate in the research must be recorded in his or her medical file.

7.6.2 Personal Protection Committee

The person in charge of the research undertakes to submit the study project for prior authorization by a Comité de Protection des Personnes (CPP). The information provided covers the nature of the research and the safeguards provided for patients taking part in the trial.

7.6.3 Informing the competent authorities

The ANSM will be informed of this protocol.

7.7 Protocol amendments

Requests for substantial modifications will be sent by the sponsor to the relevant CPP for its opinion, in accordance with the law in force and its implementing decrees.

An updated, dated version of the modified protocol is required.
The information form will be modified if necessary.

7.8 Financing and insurance

The sponsor finances the study and takes out an insurance policy covering the financial consequences of its civil liability, in accordance with regulations.

7.9 Publication rules

The 1er author will be the doctor from the CHD de la Roche/Yon who wrote the article (Dr. Macé), with a place as second author for the Nantes doctor who included the most patients in Nantes. The last author will be the Nantes University Hospital doctor who supervised the study at the Nantes University Hospital (Pr Coron), with a possible penultimate author slot for the La Roche/Yon hospital doctor who supervised the study at the hospital (Dr Faroux). The other places will be allocated according to the number of patients recruited in the 2 centers, alternating between the centers (1 author/2). A co-author position (unspecified) will be reserved for the person in charge of biostatistical analysis.

7.10 Archiving source data

The investigator must keep all information relating to the study for at least 15 years after the end of the study.
At the end of the study, the investigator will also receive a copy of each patient's data from his or her center, via a CD-ROM sent by the institution responsible for the research.