Imperial College London

LumenEye during CovID-19 (LuCID study)

Study Protocol

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Study Coordination Centre: Imperial College NHS trust
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Protocol authorised by:

Name & Role	Date	Signature

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Clinical Queries

Clinical queries should be directed to James Kinross who will direct the query to the appropriate person

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
Imperial College London & Imperial College Healthcare NHS Trust
2nd Floor Medical School Building
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Funder

SurgEase Innovations Ltd

This protocol describes the LUCID study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Contents

Study Summary

TITLE	LumenEye during CovID-19 (LuCID study)
DESIGN	Prospective, observational pilot study, medical device
AIMS	The main hypothesis is that digital rectoscopy (using the LumenEye system) is safe and acceptable to clinicians including general practitioners and can significantly reduce the burden of endoscopy referral to and within secondary care centres. The secondary objectives are: 1. To assess the safety and acceptability of the LumenEye and CHiP system in primary and secondary care. 2. To establish the clinical utility of the CHiP software system for performing remote telemedicine assessment of the rectum and colon. 3. To provide pilot data for the diagnostic accuracy of the LumenEye system for colitis severity, cancer, rectal polyps and benign disease of the rectum and anus.
OUTCOME MEASURES	Primary outcome: Both safety and patient and clinical acceptance of the LumenEye device with specialist consultation over the CHiP platform. Secondary outcomes: 1. To establish the clinical utility of the CHiP software system for performing remote telemedicine assessment of the rectum and colon. 2. To provide pilot data for the diagnostic accuracy of the LumenEye system for colitis severity, cancer, rectal polyps and benign disease of the rectum and anus.
POPULATION	Adult patients presenting to either their primary care physician or to secondary care services because of a change in bowel habit, rectal bleeding or assessment for symptoms of established or suspected ulcerative colitis
ELIGIBILITY	Patients aged 18 and over Patients presenting to primary or secondary care settings With any of: i) rectal bleeding ii) established ulcerative colitis requiring assessment iii) Positive Faecal occult blood test / Faecal immunochemical test (FIT) or faecal calprotectin iv) any symptom that would warrant referral on the 2WW cancer referral pathway
DURATION	1 year

Reference Diagrams

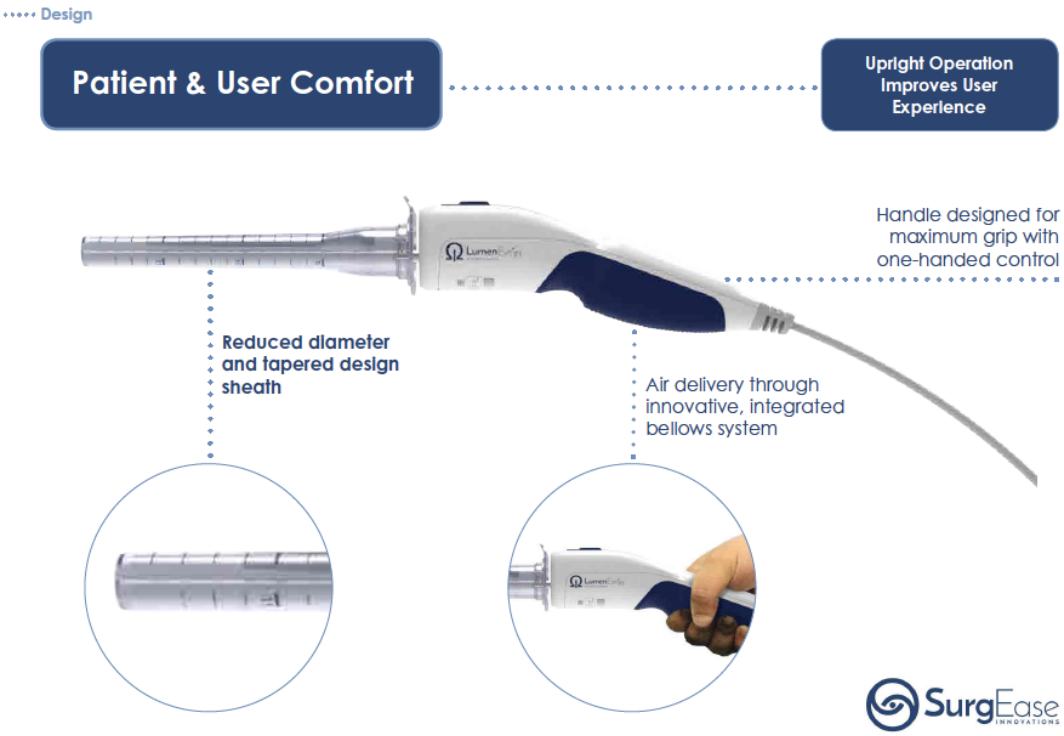

Figure 1: The LumenEye is a CE Marked digital rectoscope

Figure 2: The CHiP software system

1 Introduction

1.1 Background

Rigid sigmoidoscopy (RS) is an established diagnostic procedure used by clinicians worldwide. In the modern context, RS is typically used to make a luminal assessment of the distal gastrointestinal tract; up to 25 centimetres from the anal verge. The typical instrument arrangement consists of four main components: a light source, a rigid tube, a light head (sealed viewing window and fibre optic light connection) and an insufflation bellows. A standard RS also permits the introduction of forceps, needles, and other instruments. Increasingly, RS sets are disposable single use systems, self-lubricating and scope lengths average between 20-25 centimetres with diameters of up to 2 centimetres. The tube is inserted via the anus and has been reported to reach the distal sigmoid flexure in some series.(1)

Anorectal symptoms are a common complaint in both primary and secondary care. These include haematochezia, pruritus ani, proctalgia, anorectal swellings, discharge, change in bowel habit and incontinence. Rigid sigmoidoscopy is therefore typically performed in outpatient clinics in an unprepared bowel by healthcare professionals; particularly: gastroenterologists, general surgeons, primary care physicians and nurses.(2) RS provides clinical value through the early detection of polyps and malignant lesions within the rectum; but it also contributes to therapy and improved patient experience through the detection and management of benign disease.(3) It can be easily deployed for longitudinal assessment of pathology and treatment response and ultimately if used correctly it avoids the requirement for repeat visits for more costly investigations such as flexible sigmoidoscopy. But despite the common use and simplicity of RS as a diagnostic tool, its use is declining as it is replaced by flexible scopes despite is broad range of applications for patient benefit.

We have systematically reviewed this literature as part of this ethical approval process. Of 2,086 citations reviewed, 35 were eligible for analysis which included 27,369 episodes of rigid sigmoidoscopy. RS was used most commonly in secondary care in the assessment of symptomatic patients. It was also used in the screening of asymptomatic patients and in the surveillance and monitoring of patients with anorectal disease. The mean distance reached ranged from 12 to 22.4cm (n=5552). The average time taken was 4 minutes 30 seconds. Adverse events were reported in 11 articles (n= 19,632), the pooled complication rate was 0.01%. Of the three studies to discuss the risk of cross-contamination (n=145 two confirmed a theoretical risk due to bacterial harbouring in reusable components of the device. No patient preparation was used in 8 studies, enemas/suppositories were used in 15 studies and preparation was not reported by 12 studies. General anaesthetic and analgesia were used in children and in patients undergoing another procedure (e.g. laparoscopy, colonoscopy). This is therefore a safe and highly applicable technology.

1.1.1 Colitis assessment

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a condition in which the gastrointestinal immune system responds inappropriately. IBD is therefore often treated with immunosuppressing medications to control inflammation and prevent 'flares', a worsening of symptoms, which may be unpredictable.
While it is known that 0.8% of people in the UK currently have IBD (approximately 524 000 patients), only 44% have been to a clinic in the past 3 years. The greatest risks during Covid-19 relate not only to the infection itself, but also the emergency reorganisation of hospital and general practice services to deal with the pandemic. This has resulted in significant changes to routine IBD services. A combined approach covering both primary and secondary care is therefore required to keep vulnerable patients with IBD out of hospital as much as possible.

Current guidance from the BSG states: "Patients who may require hospitalisation will need to continue to be assessed in a timely manner. Consider the most appropriate location to do this that is away from COVID-19 assessment areas. Daily 'flare clinics' (virtual where possible) with limited numbers of patients who are at high risk of imminent hospitalisation should be considered. Where possible, limit visits to hospital and limit the patient journey around the hospital geographically.(4)

1.1.2 Bowel Cancer Screening and 2-week wait referrals

Approximately 1,240,000 new cases of colorectal cancer (CRC) were diagnosed globally in 2008, making it a lethal and highly prevalent disease. There are 16,000 deaths and 41,000 new cases are diagnosed in the UK each year from bowel cancer, affecting 1 in 14 men and 1 in 19 women. 20% of patients present as an emergency and over 50% will have advanced disease, and significantly worse outcome. The number of patients diagnosed with bowel cancer in the UK is set to increase and there is no feasible methodology for prevention. The disease carries a significant cost to the NHS of approximately £1.6 billion annually. A national bowel cancer screening program has thus been developed based on a screening faecal occult blood test. Uptake of the screening programme ranges between 55 to 60% and 2.5% of men and 1.5% of women have an abnormal test. 98% of patients have a colonoscopy as their first investigation. Colonoscopy remains the gold standard for CRC screening despite its associated morbidity and economic cost. Cancer (n=1772) and higher risk adenomas (n=6543) were found in 11.6% and 43% of men and 7.8% and 29% of women investigated, respectively. 71% of cancers were 'early' (10% polyp cancer, 32% Dukes A, 30% Dukes B) and 77% were left-sided (29% rectal, 45% sigmoid) with only 14% being right-sided compared with expected figures of 67% and 24% for left and right side from UK cancer registration.(4) However, several studies have demonstrated the efficacy of flexible sigmoidoscopy as a first line screening test, and this is now employed in the UK. The Flexiscope trial reduced the incidence of colorectal cancer by 23% and mortality by 31%. The Incidence of distal colorectal cancer (rectum and sigmoid colon) was reduced by 50%.(5) Therefore, there is a significant need for biomarkers that can support decision making in the selection of the correct definitive follow up investigation(6) and there is an urgent requirement for an office based endoscopy service that can provide the ability to detect rectal cancers during the covid-19 pandemic.

1.1.3 Covid19 and endoscopy services

Despite staff infection rates from endoscopy remaining low during the Covid-19 pandemic (7), staff safety from aerosol transmission remains concern.(8) All but emergency and essential endoscopy has been stopped in response to Covid-19 in the UK, so service provision for the symptomatic and screening populations can be reviewed and reorganised. Data from the National Endoscopy Database shows that the total numbers of endoscopic procedures fell in just 2 weeks in March from 33 000 to 7000 and has fallen further since. When endoscopy services resume, capacity will be significantly reduced due to the additional novel covid-19 cleaning requirements and the significant waiting times that are likely to be present.

1.1.4 LumenEye and CHiP

The intervention: The LumenEye X1 (SurgEase Innovations Ltd, UK) is a CE Marked novel point of care rigid digital endoscope which provides High-Definition views of the rectum up to 20cm from the anal verge. It permits endoscopic biopsy under view (figure 1) and maintains pneumorectum sufficiently with as little as 100ml of air. Air delivery is in a closed system thereby significantly reducing aerosol transmission relative to formal endoscopy. This feature is particularly attractive in the current Covid-19 pandemic. A removable disposable manifold and a chemical clean with Tristel™ Trio is the only requirement for reprocessing

which is more cost-effective than automated washing & sterilisation. All images and videos are displayed on a HD screen, supplied alongside the scope, which can be captured and stored securely on the cloud platform (called CHiP, Figure 2) which allows retrospective review of images and data taken during rectoscopy from any device. The technology permits high quality endoscopy at the bedside and outside of traditional tiers of care which is particularly attractive during the current Corona pandemic. An additional feature of CHiP includes telemedicine functionality with live video sharing of the camera feed; a proctor can be invited over WIFI into a session who can then view the live feed from the scope and offer advice and guidance. The technology can offer cost-effective, immediate tumour visualisation, critical measurement, opportunity for biopsy and virtual diagnostic support.

1.2 Rationale for current study

The LumenEye scope and CHiP platform will be piloted in a number of clinical settings including remote colorectal clinics. The rationale is to perform an initial pilot study to determine the clinical utility of the LumenEye device for use in primary and secondary care settings.
The main hypothesis is that digital rectoscopy is safe and acceptable to clinicians including general practitioners and can significantly reduce the burden of endoscopy referral to and within secondary care centres.

1.3 Study Objectives

Primary objective:

To assess both safety and patient and clinical acceptance of the LumenEye device with specialist consultation over the CHiP platform.

Secondary objectives:

1. To establish the clinical utility of the CHiP software system for performing remote telemedicine assessment of the rectum and colon.
2. To provide pilot data for the diagnostic accuracy of the LumenEye system for colitis severity, cancer, rectal polyps and benign disease of the rectum and anus.

2 Study Design

We propose a multi-centre prospective observational pilot study of the LumenEye and CHiP system. The experimental design is pragmatic and designed to permit the recruitment of patients in a timely fashion necessary for a prospective, confirmatory analysis during the Covid-19 pandemic. The study outline is provided in figure 3.

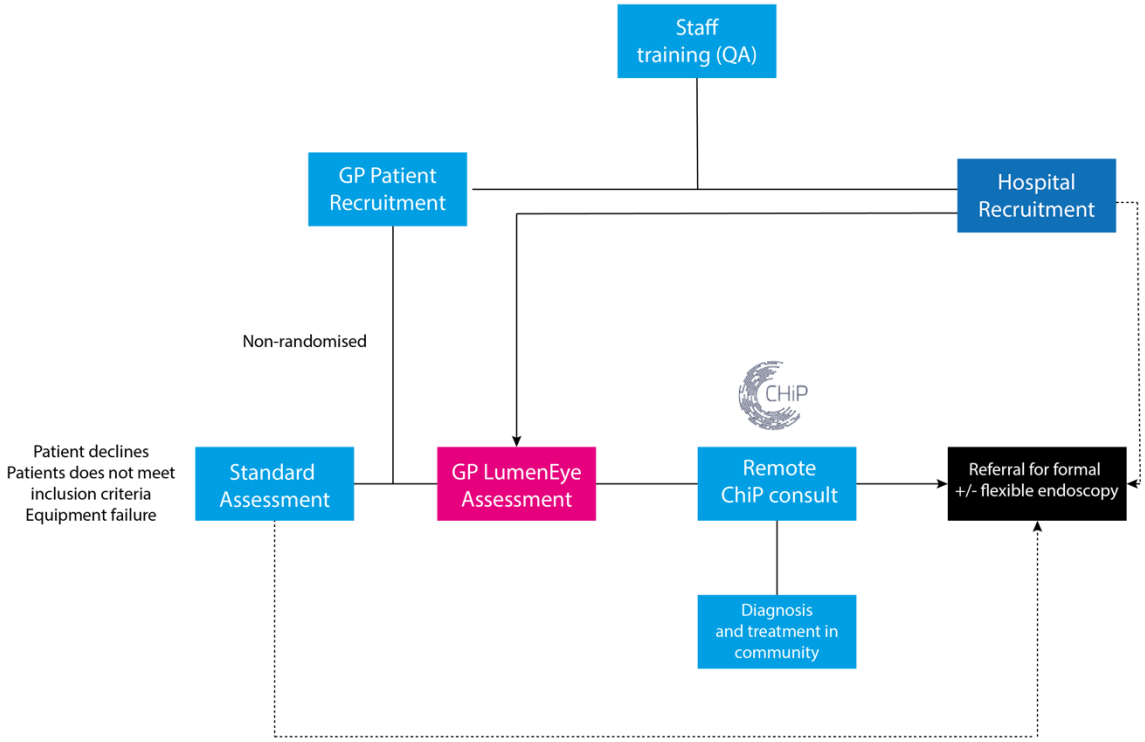

Figure 3. Overview of study protocol

2.1 Recruitment

Patients will be identified for recruitment via two routes:

1. Patients with an established diagnosis of inflammatory bowel disease who have been identified as being 'at risk' by either their secondary care doctor or GP and now require endoscopic assessment for ongoing disease symptoms but are unable to access endoscopy services urgently.

2. Patients presenting directly to their GP practice with symptoms of anorectal disease (e.g. rectal bleeding or pain) or symptoms that would warrant referral to a hospital under a 2WW appointment according to NICE criteria

All patients will be provided with written information about the study and an online website will be created to provide this information. The study aims to recruit 100 patients into the pilot study.

2.2 Quality assurance and training

All clinicians will be provided with an onboarding protocol and a LumenEye SOP for standardised use, which include recommendations for use during the Covid-19 pandemic will be created. All clinicians performing investigations with the LumenEye will undergo training and quality assurance assessment. The first 5 procedures will be performed with a proctor to ensure that this is performed safely using appropriate PPE according to Public Health England Recommendations.
The primary study site will be based at Imperial College NHS trust which is a recognized National Bowel Cancer Screening (NBCS) Centre of excellence. The Imperial endoscopy suite performs over 10,000 endoscopic procedures each year. Additional primary sites will be located at:

King's College Hospital NHS Foundation Trust- Dr. Bu Hayee
NHS Frimley Health Foundation Trust – Dr. Henry Tilney

All patients enrolled into the study will be asked to have either an enema or glycerine suppository prior to the examination. They will be examined by the primary care physician in the clinic as per a standard rigid sigmoidoscopy assessment. Physicians may take biopsies if required but only if the physician feels this is warranted for clinical use. There is no requirement for research specimens in this study.

All doctors using the LumenEye will asked to record images showing standard anatomical locations including:

1. The rectosigmoid junction
2. Each rectal haustral fold
3. Exit from the rectum.

Videos will also be recorded for any pathology identified.

Virtual clinics will be coordinated by the CI and Co-Is. During these clinics, a secondary care physician or surgeon will be available to discuss the case with the GP. These could be performed in real time with the patient present during a live examination or they could be performed retrospectively as part of a multidisciplinary team meeting.

2.3 Analysis

Clinicians will be asked to provide qualitative feedback data with each use concerning device performance. This will be in the form of a short questionnaire, split into technical performance, views achieved, diagnostic yield, quality of the telemedicine interaction, patient outcome (discharged or referred to formal endoscopy) and adverse events.

Local users of the LumenEye system will undergo nasal swab assessments every 4 weeks for a covid-19 PCR test to ensure staff safety is maintained during the study. If a swab tests positive, the physician will be asked to follow standard PHE advice on isolation, contact tracing and further treatment.

All LumenEye devices will undergo at least one random post-cleaning swab test for Covid-19 to confirm the Tristel Trio cleaning system sufficiently eradicates SARS-COv-2 from the LumenEye. (An analysis of this has been performed outside of the study which confirms the efficacy of the Tristel Trio system against SARS-COV-2).

Patient feedback will be requested through a validated questionnaire..

All clinicians providing advice and guidance via CHiP will be asked to provide data on the quality of the views, the stability of the platform and to provide information on the diagnosis. For flare patients, both clinicians will be asked to report Mayo flare scores based on observed

data. For adenomas, clinicians will be asked to report anatomical location, morphology, and Paris endoscopy assessment scores. All data pertaining to follow up colonoscopy or flexible sigmoidoscopy will be used as a comparator group for a diagnostic sensitivity / specificity analysis.

2.4 Study Outcome Measures

Primary outcome:

Both safety and patient and clinical acceptance of the LumenEye device with specialist consultation over the CHiP platform.

Secondary outcomes:

1. To establish the clinical utility of the CHiP software system for performing remote telemedicine assessment of the rectum and colon.
2. To provide pilot data for the diagnostic accuracy of the LumenEye system for colitis severity, cancer, rectal polyps and benign disease of the rectum and anus

3 Participant Entry

3.1 Pre-registration evaluations

All IBD patients requiring urgent flare assessment, patients presenting to their GP with anorectal symptoms, rectal bleeding, change of bowel habit or with a diagnosis that warrants an endoscopy,

3.2 Inclusion Criteria

- Patients aged 18 and over
- Patients with any of the following:
    - Positive Faecal occult blood test / Faecal immunochemical test (FIT)
    - Positive faecal calprotectin.
    - Established history of polyps and/or adenomas
- 2WW patients referred to a colorectal clinic
- Known IBD patients with flare symptoms
- Patients with a suspected new diagnosis of IBD

3.3 Exclusion Criteria

- Inability to consent
- Inability to communicate effectively in English
- Pregnancy
- Unfit for bowel preparation
- Anal stricture
- Allergy to plastic
- Inability to lie flat for more than 10 minutes

3.4 Withdrawal Criteria

Consent will be withdrawn at the patient's request. In the event that consent is removed, the images will be removed from the analysis.

4 Adverse Events

4.1 Definitions

Adverse Event (AE):

Any untoward medical occurrence in a patient or clinical study subject. This may include the diagnosis of Covid-19 that is found to have been transmitted during the procedure

Serious Adverse Event (SAE):

Any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

4.2 Reporting Procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

4.2.1 Non serious AEs

All such events, whether expected or not, will be recorded.

4.2.2 Serious AEs

Medical judgement will be exercised in deciding whether an adverse event is serious in other situations. Important adverse events that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a subject or may require intervention to prevent an adverse outcome should also be considered serious.

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to complication from subsequent investigations such as colonoscopy and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the Chief Investigator or Ruth Nicholson, where in the opinion of the Chief Investigator, the event was:

'related', i.e. resulted from the administration of any of the research procedures; and
'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

4.2.3 Contact details for reporting SAEs

Email:	j.kinross@imperial.ac.uk
Please send SAE forms to:	Mr James Kinross, Department of Surgery and Cancer, 10th Floor QEQM Building, St Mary's Hospital, Praed Street, London, W2 1NY

5 Assessment and Follow-up

We will record clinical outcome data in patients with a new diagnosis of IBD or colon cancer, and we will record if they underwent medical therapy, surgery or endoscopic therapy. The aim is to determine if the LumenEye improves the time to diagnosis and treatment, and ultimately outcome. The study will end when the 100th patient has been assessed and undergone any further investigation warranted by their presentation. Any incidental findings will be noted on the case report form and investigated as per the usual clinical pathways.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

6 Statistics and data analysis

This is a feasibility study. The aim is to establish whether the device is acceptable and to establish the initial diagnostic performance of this device. This data will be used to form the basis of a power calculation for future studies. All data will be analysed using SPSS v. 20 and will be analysed using standard univariate statistical models.

7 Regulatory issues

7.1 Ethics approval

The Study Management Committee will obtain all relevant approvals from the Health Regulatory Authority (HRA), NHS Research Ethics Committee (NHS REC) and local organisations as required. The study will also receive confirmation of capacity and capability from each participating organisation. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

7.2 Consent and Confidentiality

Individual informed consent for the capture, storage and analysis of LumenEye data and inclusion in the digital CHiP platform will be obtained from all participants. It will be the responsibility of local collaborators to obtain written informed consent from each participant after adequate explanation of the project, potential hazards and process for data capture and storage. The original copy of the signed and dated informed consent must be retained at the participating organisation and is subject to inspection by representatives of the Sponsor, or representatives from Regulatory Authorities. The standardised patient information sheet and consent form is included in this protocol.

7.3 Data Storage and Retention

All data will be stored for a minimum of 10 years (or according to changes in regulatory requirements). Data generated by this work will be processed in accordance with the Data Protection Act 1998. Retention and analysis will be conducted with regard to all local policies relating to the collection, holding and disclosure of data relating to individuals. The Principal and Co-applicants will act as custodians of the data and be responsible for its security. The PI will ensure the continued storage of all relevant data and documentation, even if they leave the clinic/practice or retire before the end of the required storage period. Delegation will be documented in writing.

7.4 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study/ Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study (delete as applicable)

7.5 Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

7.6 Funding

SurgEase Innovations will provide some funding towards the project and supply all diagnostic equipment and CHiP software for free.

7.7 Audits

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

8 Study Management

The day-to-day management of the study will be coordinated through the Study Management Committee (SMC) which will also function as the Scientific Advisory Board. The SMC will be convened including the Chief Investigator, co-investigators, and key collaborators. The committee will be responsible for day-to-day conduct of the trial and operational issues.

Quality Control will be performed according to Imperial College London internal procedures. The study may be audited by a Quality Assurance representative of the Joint Research Compliance Office (JRCO) at Imperial College London. All necessary data and documents will be made available for inspection. The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care.

8.1 Data Management Committee

The SMC will form a Data Management Committee (DMC) that will be responsible for oversight and assurance of all data capture, storage, and analysis.

9 Publication Policy

The COVID pandemic has created a new paradigm for the conduct and dissemination of research. We will provide dynamic, interactive and real-time learning and dissemination of knowledge through a dedicated website. We will also employ non-traditional routes, such as social media platforms (e.g. Twitter, Facebook, LinkedIn), in order to ensure that there is rapid dissemination of the pertinent study findings. In addition to leveraging online dissemination strategies, we will also target the following groups in a more specific fashion:

Policymakers:

At regular intervals throughout the project, and upon completion, we will produce an executive summary of our findings, which is to be distributed to relevant policy makers (e.g. NHS Digital) so that the relevant results may be rapidly disseminated globally through official and well-respected sources.

Clinicians and Health Managers:

The main findings will be submitted for publication in peer-reviewed scientific journals and presented in national and international conferences. We will provide updated information concerning the publication of study results to all stakeholders. The study results will also be presented to healthcare commissioners and policy makers at appropriate meetings and in publications.

Patients and the Public:

We will produce a short, easy to understand summary of our research findings that will be available from our website or that can be sent to interested stakeholders.

Academics:

We will make our intervention methodology and results available through presentations, workshops, conferences, the website, working papers and journal articles. We will provide an interactive framework on a web-based platform to facilitate the adoption of our model and methodology in clinical practice. We will seek to publish and present our results in high impact peer-reviewed journals and at relevant international conferences.

10 References

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