NRG Oncology is considering the development of a study to evaluate the use of surveillance colonoscopy in patients with 1-2 non-advanced adenomas and we would like your help to evaluate the feasibility of conducting the trial.

The study is currently undergoing review, but we have included for your consideration the current rationale and design of the concept.

**Rationale for Proposed Study:**

Colorectal cancer is the third leading cause of cancer death among men and women in the United States (US). The lifetime risk of colorectal cancer in both men and women in the US is approximately 6%. About 93% of colorectal cancer diagnoses are in patients older than 50 years. Randomized controlled trials show that screening for colorectal cancer significantly decreases colorectal cancer incidence and mortality. CRC screening has received a Grade A recommendation from the US Preventive Services Task Force.

In the U.S., colonoscopy is the most utilized screening modality for CRC. On a population basis, screening rates, which were around 40-50%, have now increased to 65%, and a goal to increase to 80% compliance is being promoted.
Adenomatous polyps are the acknowledged precursors of colorectal cancer. Identification and removal of adenomas is the mechanism by which screening is effective in reducing CRC incidence and subsequent mortality. “Advanced” adenomas are adenomas which are ≥ 1 cm, or have a “villous” component (tubulovillous or villous) or have foci of high grade dysplasia. Advanced adenomas are associated with increased long term risk of cancer, even years after colonoscopy. The prevalence of advanced adenomas at screening colonoscopy is 5-10%. Non-advanced adenomas are adenomas <1cm with neither villous components nor high grade dysplasia. Non-advanced adenomas are much more common than advanced adenomas, present in around 30% of colonoscopy exams.

After detection of adenomas, patients are advised to return periodically for surveillance colonoscopy. Patients with 1-2 non-advanced adenomas are recommended by guidelines to return in 5 – 10 years for follow up surveillance colonoscopy. However, there are no guidelines on how to triage individuals to 5 as opposed to 10 years. Furthermore, there is no strong evidence supporting the effectiveness of surveillance colonoscopy in reducing CRC incidence. The only randomized trial of surveillance colonoscopy was reported in the early 1990’s, when participants were randomized to 3 vs. 1 and 3 year surveillance. No difference in advanced adenoma detection was observed when comparing participants examined at the two screening intervals, and as a result, guidelines were modified with participants advised to return every 3 years after adenomatous polyp detection. The recommended interval for non-advanced adenomas was gradually lengthened to the current standard, but there is no randomized, controlled data to support that interval. Observational data of surveillance colonoscopy practice in the U.S. demonstrate that recommended intervals are often not adhered to, and individuals return for repeat testing well ahead of guideline recommendations.

Retrospective, natural history studies of non-advanced adenomas do not support the association of non-advanced adenoma with a higher risk of subsequent colorectal cancer. In a classic study from the United Kingdom, patients with small rectosigmoid adenomas, even if multiple, did not have an increased risk of CRC compared to the general population, over a 14 year mean follow up time. In a recent observational study from Norway, participants with a low risk adenoma followed over a median of 7.7 years (maximum 19 years) without subsequent surveillance colonoscopy, had a lower CRC mortality than the general population, implying that although the initial colonoscopy may be protective, subsequent follow up colonoscopy was not required.

Another recent major development affecting screening is that practitioners of colonoscopy are now recommended to monitor and insure their adenoma detection rates are high. Data from Poland and Kaiser Permanente in California have demonstrated that a higher adenoma detection rate (ADR) is associated with a lower long term risk of interval CRC, or cancer occurring after colonoscopy. Our understanding of these observations is premised on the notion that leaving pre-neoplastic tissue (adenomas) in situ, (such as what occurs with a lower ADR), increases the chance that an adenoma left behind will subsequently transform into cancer. The concern over interval cancers has stimulated quality concerns about the practice of colonoscopy. Guidelines for a recommended ADR at screening colonoscopy are rising, from the initial targets of 15% in women and 25% in men to 20% in women and 30% in men or 25% overall. ADRs in clinical studies are now commonly over 30% and some practitioners report rates exceeding 50%. However, adenomas that are detected when the ADR is high or as it increases over time are generally small, non-advanced adenomas.
Current clinical practice favoring colonoscopy based screening with increased emphasis on detection of adenomas, most of which will turn out to be small, non-advanced adenomas will greatly increase demand for utilization of surveillance colonoscopy exams in the coming decades. Yet, the evidence for determining the benefit, optimal timing, and recommended frequency of surveillance colonoscopy is unknown. A randomized, clinical trial to demonstrate the difference in yield between 5 or 10 year surveillance for participants with non-advanced adenoma is needed to guide clinical practice. Only a randomized trial will be authoritative enough to define good clinical practice and directly influence clinical care.

| No polyps, or hyperplastic polyps in rectum/sigmoid | Repeat in 10 years |
| Neoplasia found | |
| **Serrated polyps/lesions** | **High risk adenomas** | **Low risk adenomas** |
| Serrated polyposis \ Repeat in 1 year | > 10 Adenomas \ Repeat in less than 3 years | |
| ≥ 10 mm or With dysplasia or traditional serrated adenoma \ Repeat in 3 years | 3–10 Adenomas \ Repeat in 3 years | 1–2 Tubular adenomas < 10 mm \ Repeat in 5–10 years |
| < 10 mm in Proximal colon and without dysplasia \ Repeat in 5 years | Villous adenoma(s) or tubular adenoma(s) ≥ 10 mm \ Repeat in 3 years | Adenoma(s) with high grade dysplasia \ Repeat in 3 years |

These recommended intervals assume a complete exam to cecum, adequate bowel prep, and complete removal of polyps at the baseline exam.

**Significance of the Study:**

As the practice of colonoscopy expands to include the vast majority of adults and the detection of an adenoma at colonoscopy increases, the inconvenience, medical risk, and resources associated with and devoted to surveillance colonoscopy will greatly increase. Research to determine the benefit and yield of surveillance colonoscopy in patients with non-advanced adenomas is a high priority.

**Study Objectives and Hypotheses**

Hypothesis: For participants with 1-2 non advanced adenomas, CRC incidence will not be significantly increased in participants randomized to surveillance colonoscopy at 10 years compared to participants randomized to surveillance colonoscopy at 5 and 10 years.
1. We propose a non-inferiority trial design comparing CRC incidence in participants with 1-2 non-advanced adenomas randomized to recommendation for a 5 and 10 year surveillance colonoscopy exam vs. a 10 year surveillance colonoscopy exam.

Secondary Endpoints:

1. Examination of advanced adenoma incidence. Advanced adenomas are the higher risk adenoma precursor of colorectal cancer. Tracking advanced adenomas will enhance understanding of the natural history of adenoma development over time.
2. Examination of CRC mortality. CRC incidence is subject to lead time bias. The duration of follow up mitigates that concern, but tracking of mortality is a useful adjunct to understanding the impact of different surveillance intervals.

Study Design:

We propose a randomized, non-inferiority clinical trial set within the NRG Oncology group. Participants with 1-2 non-advanced adenomas would be randomized to the recommendation for 5 vs. 5 and 10 year surveillance colonoscopy. Randomization will be 1:1, stratified by study center, age, and gender. The endpoint will be a comparison of the cumulative incidence of colorectal cancer between the two arms.

Eligibility:

1. Healthy adults ≥ 50 years of age with a first time diagnosis of 1-2 non-advanced tubular adenomas (< 10mm without tubulovillous or villous changes or high grade or severe dysplasia)
2. Complete colonoscopy with adequate cleansing.
3. Complete excision of all polyps at baseline colonoscopy.

Ineligibility:

1. Prior history of colorectal cancer or adenomas.
2. Incomplete colonoscopy.
3. Incomplete endoscopic excision of polyps.
4. Participants at increased heritable risk for colorectal cancer (FAP, HNPCC defined by Amsterdam criteria or by known germline genetic testing)
5. Inflammatory bowel disease
6. Life expectancy less than 10 years due to co-morbid conditions
7. Significant medical or psychosocial disorder which precludes provision of adequate informed consent or compliance with the protocol

We recognize that a study such as this is not part of the conventional trial portfolio for NRG or for any of the cooperative groups. Entering 15,000 participants in a timely fashion and following them for at least 11 years will be challenging. NRG has begun to prepare for the study if it is approved. In May 2015, during Digestive Disease Week, NRG protocol representatives met with 12 key opinion leaders in the field of colon adenoma research and senior representatives of the NCI's Division of Cancer Prevention. The proposal was presented and discussed in detail. The group all agreed that the study was scientifically and clinically important and should move forward.