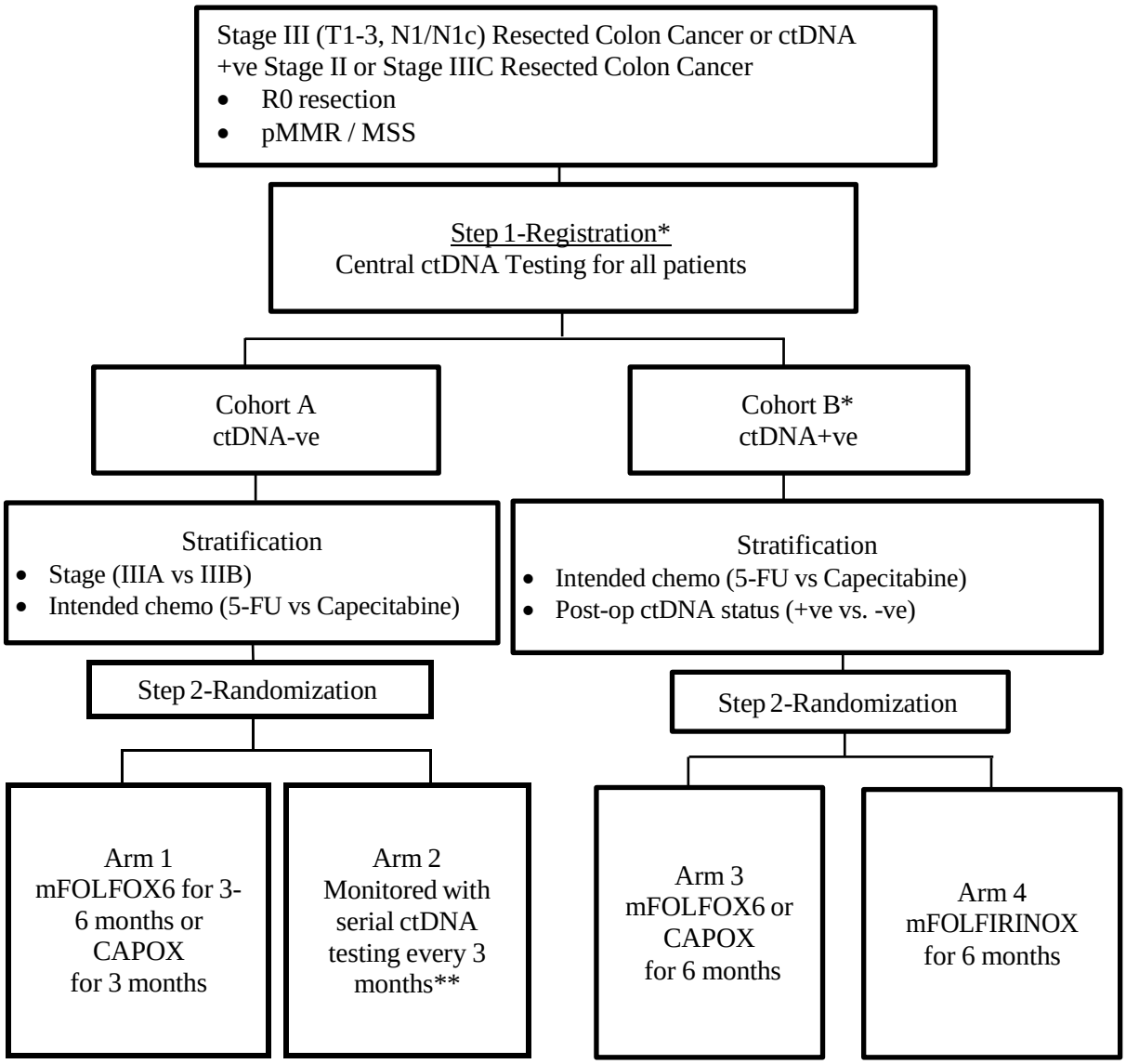
Figure 1.
NRG-GI008 SCHEMA



*Patients with completely resected stages II or IIIC colon cancer who are ctDNA +ve as determined by a Signatera™ ctDNA test performed outside of the trial through routine clinical care and who otherwise meet all eligibility criteria for Step 1-Registration are eligible for enrollment into Cohort B.

**Patients in Cohort A (Arm 2) who develop a ctDNA +ve assay during serial monitoring may transition to the ctDNA+ve cohort (Cohort B) and undergo a second randomization.

3.1 ELIGIBILITY AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Clinical Coordinating Department (CCD [see protocol cover page]).

Investigators should consider all relevant factors (medical and non-medical), as well as the risks and benefits of the chemotherapy, when deciding if an individual patient is an appropriate candidate for this trial.

Investigators should check with their site Pathology department regarding release of tumor tissue before approaching patients about participation in the trial.

3.2 Patient Entry and Randomization

The following sections outline procedures for Study Entry and Randomization.

3.2.1 Step 1: Study Entry and ctDNA assay testing.

- The authorized site staff must obtain signed informed consent from the potential patient before any study specific procedures are performed.
- The authorized site staff must determine patient eligibility by completing the assessments on Table 1 that are required prior to study entry. See Sections 3.2 and 3.3.
- Step 1 Entry in OPEN: Patients will be assigned a unique patient identifier which will be used to identify the blood and tumor samples to be sent for central Signatera™ ctDNA testing for patients who have not had ctDNA testing performed using the Signatera™ assay as routine care outside the study and for those patients who already have had a ctDNA status performed using the Signatera™ assay as routine care outside of the study, the eCRFs in Medidata RAVE, and any other trial-related communications.

3.2.2 Step 2: Randomization

- Following ctDNA assay testing, the authorized site staff will randomize the patient using OPEN. For the patients who had their ctDNA status checked with the Signatera™ assay as routine care outside of the study, the ctDNA test result from the central testing will be the result used to place the patients in Cohort A or Cohort B. When the result of the central ctDNA testing is not the same as the result of the Signatera™ assay done as routine care outside of the study, the patient/physician may choose not to proceed with participation in the study.
- OPEN will randomly assign treatment by cohort (ctDNA-ve or ctDNA+ve).

3.2.3 Second Randomization (Cohort A-Arm 2 patients who convert to ctDNA +ve)

- Cohort A-Arm 2 patients who develop a positive ctDNA assay during serial monitoring will transition to the ctDNA+ ve cohort (Cohort B) and undergo a second randomization to Arm 3 or Arm 4 treatment.
- The authorized site staff must determine patient eligibility (see Section 3.4).
- Patients must reaffirm their willingness to be enrolled in Cohort B and randomized to Arm 3 or 4 after review of the current consent form and signing a reaffirmation form.
- OPEN will randomly assign patient to Arm 3 or Arm 4.

3.3 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.3.1 The patient must have signed and dated an IRB-approved consent form that conforms to federal and institutional guidelines.

3.3.2 The patient must be ≥ 18 years old.

3.3.3 The patient must have an ECOG performance status of 0 or 1 (see Appendix A).

3.3.4 Patients must have histologically/pathologically confirmed Stage IIIA or Stage IIIB colon adenocarcinoma (T1-3, N1/N1c) with R0 resection accordingly to AJCC 8th edition criteria.
NOTE: Patients with pathologic stages II or IIIC colon adenocarcinoma with R0 resection who have a commercially obtained Signatera™ ctDNA+ve assay result post-operatively meeting all timelines and eligibility requirements otherwise, are eligible for enrollment and inclusion in Cohort B.

3.3.5 No radiographic evidence of overt metastatic disease within 28 days prior to study entry (CT with IV contrast or MRI imaging is acceptable and **must** include chest, abdomen, and pelvis).

3.3.6 The distal extent of the tumor must be ≥ 12 cm from the anal verge on colonoscopy or above the peritoneal reflection as documented during surgery or on pathology specimen (i.e., excluding rectal adenocarcinomas warranting treatment with chemoradiation).

3.3.7 The patient must have had an en bloc complete gross resection of tumor (curative resection). Patients who have had a two-stage surgical procedure, to first provide a decompressive colostomy and then in a later procedure to have the definitive surgical resection, are eligible.

3.3.8 The resected tumor specimen and a blood specimen from patients with Stage IIIA or Stage IIIB colon cancer must have central testing for ctDNA using the Signatera assay by Natera.

> **NOTE**: Patients with stage IIIA or IIIB colon cancer who otherwise meet eligibility criteria and have had ctDNA status checked with the Signatera™ assay as routine care outside of the study, are allowed to be enrolled, and will be retested and placed in either Cohort A or Cohort B depending on the ***central ctDNA testing result***.
>
> **NOTE**: Patients with stage II or IIIC colon cancer who otherwise meet eligibility criteria and have had ctDNA status checked with the Signatera™ assay as routine care outside of the study **AND** have a ctDNA+ve result, are allowed to be enrolled. Patients will have ***central ctDNA testing***, confirmed to be ctDNA+ve, and placed in Cohort B.

3.3.9 Tumor must be documented as microsatellite stable or have intact mismatch repair proteins through CLIA-approved laboratory testing. Patients whose tumors are MSI-H or dMMR are excluded.

3.3.10 The treating investigator must deem the patient a candidate for all potential agents used in this trial (5FU, LV, oxaliplatin and irinotecan).

3.3.11 The interval between surgery (post-operative Day 7) and study entry must be no more than 60 days.

3.3.12 Availability and provision of adequate surgical tumor tissue for molecular diagnostics and confirmatory profiling.

3.3.13 Adequate hematologic function within 28 days before study entry defined as follows:

- Absolute neutrophil count (ANC) must be ≥ 1500/mm^3;
- Platelet count must be ≥ 100,000/mm^3; and

- Hemoglobin must be ≥ 9 g/dL.

3.3.14 Adequate hepatic function within 28 days before study entry defined as follows:
- total bilirubin must be ≤ ULN (upper limit of normal) for the lab *and*
- alkaline phosphatase must be < 2.5 x ULN for the lab; *and*
- AST and ALT must be < 2.5 x ULN for the lab.

3.3.15 Adequate renal function within 28 days before study entry defined as serum creatinine ≤ 1.5 x ULN for the lab ***or*** measured or calculated creatinine clearance ≥ 50 mL/min using the Cockroft-Gault formula for patients with creatinine levels > 1.5 x ULN for the lab.

For Women

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

For Men

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

3.3.16 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.3.17 Pregnancy test (urine or serum according to institutional standard) done within 14 days before study entry must be negative (for women of childbearing potential only).

3.3.18 Patients receiving a coumarin-derivative anticoagulant must agree to weekly monitoring of INR if they are randomized to Arm 1 or Arm 3 and receive capecitabine.

3.4 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.4.1 Colon cancer histology other than adenocarcinoma (i.e., neuroendocrine carcinoma, sarcoma, lymphoma, squamous cell carcinoma, etc.).

3.4.2 Pathologic, clinical, or radiologic overt evidence of metastatic disease. This includes isolated, distant, or non-contiguous intra-abdominal metastases, even if resected.

3.4.3 Tumor-related bowel perforation.

3.4.4 History of prior invasive colon malignancy, regardless of disease-free interval.

3.4.5 History of bone marrow or solid organ transplantation (regardless of current immunosuppressive therapy needs). Bone grafts, skin grafts, corneal transplants and organ/tissue donation are not exclusionary**.**

3.4.6 Any prior systemic chemotherapy, targeted therapy, or immunotherapy; or radiation therapy administered as treatment for colorectal cancer (e.g., primary colon adenocarcinomas for which treatment with neoadjuvant chemotherapy and/or radiation is warranted are not permitted).

3.4.7 Other invasive malignancy within 5 years before study entry. Exceptions are colonic polyps, non-melanoma skin cancer or any carcinoma-in-situ.

3.4.8 Synchronous primary rectal and/ or colon cancers.

3.4.9 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

3.4.10 Sensory or motor neuropathy ≥ grade 2, according to CTCAE v5.0.

3.4.11 Blood transfusion within two weeks before collection of blood for central ctDNA testing.

3.4.12 Active seizure disorder uncontrolled by medication.

3.4.13 Active or chronic infection requiring systemic therapy.

3.4.14 Known homozygous DPD (dihydropyrimidine dehydrogenase) deficiency.

3.4.15 Patients known to have Gilbert's Syndrome or homozygosity for UGT1A1*28 polymorphism.

3.4.16 Pregnancy or lactation at the time of study entry.

3.4.17 Co-morbid illnesses or other concurrent disease that would make the patient inappropriate for entry into this study (i.e., unable to tolerate 6 months of combination chemotherapy or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens or prevent required follow-up).

3.5 **Eligibility Criteria for Cohort A Arm-2 patients on Second Randomization**

3.5.1 Patient must have developed a ctDNA +ve assay during serial monitoring.

3.5.2 Patient's willingness to be re-randomized affirmed.

3.5.3 The patient must continue to have an ECOG performance status of 0 or 1 (see Appendix A).

3.5.4 No radiographic evidence of overt metastatic disease.

3.5.5 Pregnancy test (urine or serum according to institutional standard) done within 14 days before second randomization must be negative (for women of childbearing potential only).

3.5.6 Adequate hematologic function within 28 days before second randomization defined as follows:
- Absolute neutrophil count (ANC) must be ≥ 1500/mm^3;
- Platelet count must be ≥ 100,000/mm^3; and
- Hemoglobin must be ≥ 9 g/dL.

3.5.7 Adequate hepatic function within 28 days before second randomization defined as follows:
- total bilirubin must be ≤ ULN (upper limit of normal) for the lab *and*
- alkaline phosphatase must be < 2.5 x ULN for the lab; *and*
- AST and ALT must be < 2.5 x ULN for the lab.

3.5.8 Adequate renal function within 28 days before second randomization defined as serum creatinine ≤ 1.5 x ULN for the lab ***or*** measured or calculated creatinine clearance ≥ 50 mL/min using the Cockroft-Gault formula for patients with creatinine levels > 1.5 x ULN for the lab.

For Women

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

For Men

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

3.6 **Ineligibility Criteria for Cohort A Arm-2 patients on Second Randomization**

3.6.1 Pregnancy or lactation at the time of second randomization.

3.6.2 No longer a candidate for systemic chemotherapy (FOLFOX, CAPOX, and mFOLFIRINOX) in the opinion of the treating investigator.