PROTOCOL TITLE: A pragmatic, single-arm clinical trial of a novel dose adjustment algorithm for preventing cytopenia-related delays during FOLFOX chemotherapy

D-HH IRB OVERSIGHT:

One of the following must be true in order to submit to the D-HH IRB. Please check all that apply:

☒ The Principal Investigator is employed by D-H
☒ The study will utilize any D-H data or specimens
☒ The study will enroll D-H patients or recruit from D-H sites
☒ The study will utilize any D-H resources, e.g. study procedures will occur at D-H locations and/or use of D-H equipment or shared resources

PROTOCOL TITLE:

A pragmatic, single-arm clinical trial of a dose-adjustment algorithm for preventing cytopenia-related delays during FOLFOX chemotherapy (**NCT04526886**)

PRINCIPAL INVESTIGATOR:

Gabriel A. Brooks, MD, MPH
Medicine (Section of Medical Oncology)
603-650-9474
gabriel.a.brooks@hitchcock.org

CO-INVESTIGATOR / BIOSTATISTICIAN:

Tor D. Tosteson, ScD
Biomedical Data Science
603-653-3677
Tor.d.tosteson@dartmouth.edu

VERSION NUMBER/DATE:

Version 4.0: September 30, 2022

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1.1	July 15, 2020	Revisions made in response to comments from the CCRC review (prior to DHH IRB review).	N/A
1.2	July 28, 2020	Revisions made in response to 7/27/20 comments from CCRC review	N/A
2.0	Aug. 20, 2020	Revised to include plan to collect DHH billing data for participants.	N/A
3.0	June 15, 2021	Revisions to protocol to include clarification of eligibility criteria and dosing algorithm	N/A
4.0	September 30, 2022	Revision to increase accrual goal from 50 to 53 patients, to allow for a greater-than-anticipated number of inevaluable patients.	N/A

PROTOCOL TITLE: A pragmatic, single-arm clinical trial of a novel dose adjustment algorithm for preventing cytopenia-related delays during FOLFOX chemotherapy

Table of Contents

1.0 Study Summary

Study Title	A pragmatic, single-arm clinical trial of a novel dose adjustment algorithm for preventing cytopenia-related delays during FOLFOX chemotherapy
Study Design	Single-arm clinical trial (single-stage phase II design)
Primary Objective	To evaluate the effectiveness of an adaptive chemotherapy dose adjustment algorithm for reducing unplanned delays during cycles 2-6 of FOLFOX chemotherapy
Secondary Objective(s)	• To confirm the safety of the FOLFOX dose adjustment algorithm • To evaluate the relative dose intensity of FOLFOX chemotherapy in patients managed according to the investigational dose adjustment algorithm • To estimate out-of-pocket costs associated with chemotherapy treatment visits and unplanned chemotherapy delays
Research Intervention(s)/ Investigational Agent(s)	Implementation of an investigator-developed chemotherapy dose adjustment algorithm to guide chemotherapy dose reductions and delays related to neutropenia or thrombocytopenia
IND/IDE #	Not applicable
Study Population	Adult patients with gastrointestinal cancer receiving first-line chemotherapy with FOLFOX-type regimens at the Norris Cotton Cancer Center
Sample Size	53 patients (45 evaluable patients)
Study Duration for individual participants	Approximately 12 weeks
Study Specific Abbreviations/ Definitions	FOLFOX: 5-fluorouracil, folinic acid, and oxaliplatin ANC: Absolute neutrophil count RDI: Relative dose intensity

2.0 Objectives*

- We will test an intervention of an investigator-developed chemotherapy dose adjustment algorithm, with the **long-term goal** of reducing unplanned cytopenia-related treatment delays during FOLFOX chemotherapy.
- The **primary objective** of this study is to evaluate the effectiveness of the investigator-developed chemotherapy dose adjustment algorithm for reducing unplanned delays in patients receiving FOLFOX-type chemotherapy. In a historical cohort, 40% of patients experienced at least one delay in cycles 2-6 of FOLFOX chemotherapy.[1] If the study intervention is successful, this proportion should be 20% or less.
- The **secondary objectives** of this study are:
    - To confirm the safety of the investigator-developed dose adjustment algorithm, by demonstrating that study algorithm is associated with a low rate of cytopenia-related adverse events.
    - To evaluate the dose intensity of FOLFOX chemotherapy in patients managed according to the investigational dose adjustment algorithm, relative to the standard dose intensity (RDI).
    - To estimate out-of-pocket costs associated with chemotherapy treatment visits and unplanned chemotherapy delays

3.0 Background*

Unplanned chemotherapy delays are a common and disruptive event during cancer treatment.[1,2] Unplanned delays are disruptive for patients and their caregivers because they can lead to additional travel, clinic visits, blood draws, copays, and time away from home and work. Unplanned delays are also costly and inefficient for the health care delivery system, resulting in unused capacity at the time of the delay in addition to duplicative future clinic visits and laboratory testing. The most frequent cause of unplanned delays are cytopenias—reduced counts of white blood cells and/or platelets.

The modified FOLFOX (mFOLFOX) chemotherapy regimen is a key component of treatment for colorectal and gastroesophageal cancers,[3,4] and unplanned delays due to cytopenias are common among patients receiving this regimen.[2] In a retrospective, multi-site analysis of 214 patients with colorectal cancer—including over 100 patients from the Dartmouth Cancer Center (DCC)—we found that 43% of patients experienced one or more unplanned delays during the first six cycles of treatment.[1] The majority of these delays were attributed to asymptomatic neutropenia or thrombocytopenia. eDH reporting shows that over 100 patients are treated with the mFOLFOX regimen each year at NCCC (Lebanon campus), highlighting the relevance of developing patient-centered approaches to prevent cytopenia-related treatment delays while maintaining the effectiveness of cancer treatment.

The justification for delaying chemotherapy treatment in the face of reduced blood counts is to reduce risk for infection or bleeding. Clinical trial protocols have historically mandated both a one-week treatment delays and a chemotherapy dose-reduction for patients with grade ≥3 neutropenia (absolute neutrophil count < 1000/mm^3) or grade ≥2 thrombocytopenia (platelet count < 75,000/mm^3).[3] This approach has been widely adopted in clinical practice; however, with nearly two decades of experience with the mFOLFOX regimen it is increasingly apparent that this reactive "delay and dose-reduce" approach is highly conservative and is associated with very low rates of fever and neutropenia (generally <5%).[2,3,5-7]

In order to maximize benefits (e.g. cure in the adjuvant treatment setting, and prolonged survival in the palliative setting) and minimize harms of chemotherapy, new approaches are needed for more adaptive, individualized chemotherapy dose adjustment. We propose to test a strategic care delivery intervention—a chemotherapy dose adjustment algorithm—with the primary objective of demonstrating that the dose adjustment algorithm leads to a reduction in the proportion of patients with one or more delays prior to the completion of cycle 6 of mFOLFOX chemotherapy. The long-term research objective is to use the dose adjustment algorithm to safely increase on-time delivery of mFOLFOX chemotherapy in real-world clinical practice, reducing cytopenia-related treatment delays and the attendant burdens and costs while maintaining treatment effectiveness.

4.0 Study Endpoints*

- The primary study end point is the incidence of any unplanned chemotherapy treatment delay prior to delivery of cycle 6 of chemotherapy. This will be assessed as a binary endpoint for each evaluable subject.
    - The standard cycle length for mFOLFOX chemotherapy is 14 days.
    - A treatment delay is defined as any interruption of therapy leading to a cycle length of >18 days; the 18-day interval allows for minor schedule-related variations in treatment intervals.
    - An unplanned treatment delay is any treatment delay that is not premeditated as of day 3 of the preceding treatment cycle (the day on which the 5-FU ambulatory infusion pump is disconnected).
- Secondary endpoints will include:
    - A composite safety endpoint of the occurrence of any of the following:
        - Febrile neutropenia (CTCAE grade 3 or 4)
        - Major bleeding[8] with concurrent grade CTCAE grade ≥3 thrombocytopenia (platelet count <50,000/mm^3)
        - CTCAE grade 4 neutropenia (ANC <500/mm^3)

- CTCAE grade 4 thrombocytopenia (platelet count <25,000/mm^3)

- Relative dose intensity (RDI) of chemotherapy. RDI is defined as (planned cumulative dose/cumulative administered dose)*(actual duration/planned duration).[2]
- Patient out-of-pocket costs associated with attendance at a chemotherapy treatment visit (from a patient survey). Survey-reported out-of-pocket costs will be used to estimate out-of-pocket costs associated with cytopenia-related chemotherapy treatment delays, as visit-related out-of-pocket costs are similar whether or not a patient receives a scheduled treatment.

- Additional study end points will include:
  - Days elapsed from day 1 of cycle 1 to day 1 of cycle 6.
  - Clinician acceptance of the dose modification algorithm. Clinician acceptance will be assessed by identifying deviations from the algorithm-recommended dosing, and identifying the reason for the deviation.

5.0 Study Intervention/Investigational Agent

The study intervention will involve implementation of a clinical algorithm to guide chemotherapy dose reductions and treatment delays in patients with neutropenia and/or thrombocytopenia during treatment with FOLFOX-type regimens. The clinical algorithm (see **Appendix A**) was developed by the principal investigator, Dr. Gabriel Brooks, based on clinical experience and published evidence regarding the safety of mFOLFOX administration in the setting of neutropenia and thrombocytopenia.[2,6] Dr. Brooks and colleagues have previously implemented many of the algorithm's features at DCC in the course of routine care, and Dr. Brooks has iteratively revised the algorithm over time based on experiences from clinical use.

Features of the dose adjustment algorithm that differ from criteria used in clinical trial protocols and routine care include:

- At presentation for cycle 2 and 3 – the algorithm employs proactive chemotherapy dose reductions, without treatment delay, in patients with mild cytopenias (ANC 1000-1499/mm3 and/or platelet count 75,000-99,000/mm3).

  - *In usual care, mild cytopenias during early treatment cycles do not trigger a chemotherapy dose reduction, but these early cytopenia events often lead to more severe cytopenias and subsequent delays in later treatment cycles.*

- At any cycle – the algorithm employs chemotherapy dose reductions without treatment delay in patients with moderate cytopenias (ANC 750-999/mm3 and/or platelet count 50,000-74,000/mm3).

    - *In usual care, moderate cytopenias trigger both a chemotherapy treatment delay AND a subsequent dose reduction, whereas the study algorithm will introduce a dose reduction without a treatment delay.*

Participating clinicians will be educated regarding the rationale and evidence support for the clinical algorithm as part of study initiation. Decisions about dose modifications and delays for reasons other than neutropenia and/or thrombocytopenia will be made at the discretion of the treating clinician, as per standard-of-care treatment.

6.0 Procedures Involved*

The proposed study is a pragmatic, single arm clinical trial. The study will enroll patients with gastrointestinal cancer (including cancers of the colorectum, stomach, esophagus, appendix, and small bowel) receiving mFOLFOX chemotherapy. Eligible patients may receive chemotherapy with either adjuvant (curative) or palliative intent, and concomitant monoclonal antibody therapy with bevacizumab, cetuximab, panitumumab, or trastuzumab is permitted (these concomitant therapies do not meaningfully increase risk of treatment-related cytopenias). The key inclusion criterion will be the treating oncologist's recommendation for standard-dose mFOLFOX chemotherapy.

All study participants will undergo cycle 1 of mFOLFOX chemotherapy as per standard chemotherapy doses (defined below). Accordingly, study subjects may be recruited at any time up to (and including) the day of presentation for the planned day 1 of cycle 2 of chemotherapy, when the adaptive dose adjustment algorithm would first take effect. Patients will undergo a standard-of-care clinical informed consent procedure outlining the risks of chemotherapy prior to initiation of cycle 1 of mFOLFOX. Patients may provide consent for study participation on any day up to and including planned day 1 of cycle 2 of mFOLFOX chemotherapy. Specifically, patients may provide consent prior to meeting the final inclusion criterion of completing day 1 of cycle 1 of mFOLFOX chemotherapy. Eligible patients will be registered after documentation of informed consent, and only after meeting the final inclusion criterion of completing day 1 of cycle 1 of mFOLFOX chemotherapy.

The DCC institutional standard dosing for mFOLFOX is oxaliplatin 85mg/m2 over 85-120 minutes, 5-fluorouracil bolus 400mg/m2 (push), leucovorin 350mg (fixed dose), and 5-fluorouracil infusion of 2400mg/m2 over 46 hours (via ambulatory infusion pump). mFOLFOX chemotherapy cycles will be administered every 14 days.

Study visits will occur as per usual care during cycles 2 through 6.. The complete blood count will be assessed on the day of treatment or in the two days preceding treatment with cycles 2 through 6, consistent with DCC institutional standards.

For each chemotherapy treatment in cycles 2-6, any chemotherapy delays or dose-reductions will be guided by 1) neutrophil and platelet counts, with dose reductions as indicated by the study dose adjustment algorithm, and 2) other symptoms and treatment-related adverse events, with dose reductions as determined by the treating clinician. Where relevant, clinically appropriate dose reductions or treatment changes for bevacizumab, cetuximab, panitumumab, or trastuzumab shall also be made as per the discretion of the treating clinician.

Use of G-CSF (*e.g.* filgrastim or pegfilgrastim) is not permitted during protocol therapy. An exception to the prohibition on G-CSF use is made for patients who have already incurred an unplanned delay (the primary study outcome) in conjunction with an ANC of less than 750 cells/mm^3 on day 1 of any cycle. In such a case, G-CSF agents may be used at the discretion of the treating clinician. . Relevant chemotherapy dose adjustments from the investigational dose adjustment algorithm shall be applied regardless of G-CSF use.

Subject participation in the study will not generate any additional office visits or blood draws. The electronic health record (eDH, Epic Systems) will serve as the primary source for all data collection, excepting the use of a patient survey for collection of information about patient and caregiver time costs, travel, and out-of-pocket costs (see **Appendix B**).

Data collection will include the following information:

- Demographic information including age, sex, race, height, weight, and body surface area, and medical insurance type (*e.g.* Medicare, Medicaid, private) – at baseline only
- *DPYD* gene variant testing result (normal, abnormal, or not done – pharmacogenetic variant collected in routine care, relating to 5-fluorouracil metabolism) – at baseline only
- Cancer diagnosis, and treatment goal (e.g. “palliative” or “adjuvant”) – at baseline only
- Treatment dates and doses of mFOLFOX chemotherapy agents, with reasons for any chemotherapy dose reductions or delays – cycles 1-6
- Use of G-CSF agents (e.g. pegfilgrastim) – cycles 1-6
- White blood count, absolute neutrophil count, and platelet count – cycles 1-6 (values associated with any planned treatment day)
- Specified adverse events related to chemotherapy (in addition to cytopenias identified through laboratory data alone):
    - Fever and neutropenia (fever > 100.6 F with ANC <1000/mm^3])
    - Major bleeding with concurrent grade CTCAE grade ≥3 thrombocytopenia (platelet count <50,000/mm^3)
- Clinician deviation from dosing algorithm, with reasons for deviation
- Incidence of unplanned chemotherapy delays (see definition of unplanned delay in Section 4.0).

In addition to the information noted above, patients will complete a survey regarding time costs and out-of-pocket monetary costs associated with chemotherapy treatment visits (see **Appendix B**). This survey will be administered once per patient at the clinic visit for the 3rd, 4th, or 5th treatment cycle. We will also obtain DHH billing statements from chemotherapy treatment visit dates occurring during the study period (to augment survey data regarding patient out-of-pocket costs associated with chemotherapy treatment).

7.0 Data and Specimen Banking*

N/A – see data management plan in Section 17.

8.0 Sharing of Results with Subjects*

A summary of the general study findings will be shared with research participants at the conclusion of the trial. Results will be shared with participants in a short letter, to be mailed to the home address of surviving subjects.

9.0 Study Timelines*

Subjects will be monitored from day 1 of cycle 2 through day 1 of cycle 6 of FOLFOX chemotherapy (roughly 12 weeks). We anticipate accruing participants over the course of 12 months, based on historical DCC volumes of treatment with FOLFOX-type regimens (>120 patient treated with FOLFOX-type regimens at DCC-Lebanon in 2019.) The estimated date of study completion, inclusive of patient enrollment, data collection and analysis, is December 2021.

10.0 Inclusion and Exclusion Criteria*

Potential study subjects will be identified through the GI oncology group's weekly team meetings. Once potential study subjects are identified, a member of the study group will assess the patient's potential eligibility. If determined to be eligible, study subjects will be consented by a delegated member of the study team.

Inclusion criteria:

- Age greater than 18
- Diagnosis of adenocarcinoma of the gastrointestinal tract (to include cancers of the colorectum, stomach, esophagus, appendix, and small bowel) or squamous cell carcinoma of the esophagus
- The treating oncologist's recommendation must be for six or more cycles of standard-dose mFOLFOX chemotherapy (with or without concurrent bevacizumab, cetuximab, panitumumab, trastuzumab, and/or checkpoint inhibitor immunotherapy agents [including but not limited to nivolumab, pembrolizumab, or atezolizumab]). Intent of treatment may be either curative or palliative in nature.

- Completion of day 1 of cycle 1 of standard-of-care FOLFOX chemotherapy, with standard chemotherapy doses of bolus 5-FU (400 mg/m2), oxaliplatin (85 mg/m2), and infusional 5-FU (2400 mg/m2)

Exclusion criteria:

- Prior receipt of systemic chemotherapy in the 12 months prior to day 1 of cycle 1 of mFOLFOX (other than radiation-sensitizing chemotherapy)
- History of baseline neutropenia; defined as neutrophil count <1500 in the 30 days preceding planned day 1 of cycle 1 of mFOLFOX
- Patients known to be carriers of pathogenic *DPYD* gene variants (as standard dosing of fluoropyrimidine chemotherapy would be contraindicated in this setting). Prospective *DPYD* genotyping is encouraged but not required for study eligibility.
- History of baseline thrombocytopenia; defined as platelet count <100,000) in the 30 days preceding planned day 1 of cycle 1 of mFOLFOX
- Patients with a history of an uncorrected bleeding condition that would preclude safe use of the dose adjustment algorithm, in the judgement of the enrolling investigator
- Patients who have started a new prescription anticoagulant (e.g. warfarin, heparin derivatives, or direct oral anticoagulants) in the 14 days preceding day 1 of cycle 1 of mFOLFOX
- Patients who are unable to provide informed consent
- Pregnant women

11.0 Vulnerable Populations*

N/A

12.0 Local Number of Subjects

All study subjects will be recruited and enrolled at DCC sites. The planned study accrual is 45 evaluable patients. We will allow for the accrual of a total of 53 patients, to account for subjects inevaluable for the primary endpoint due to 1) withdrawal of consent, 2) permanent discontinuation of therapy for reasons other than chemotherapy toxicity, or 3) planned interruption of FOLFOX chemotherapy for greater than 6 weeks (42 days), for any reason. Sample size justification is described in Section 17.

Patients who sign consent for study participation but who are determined to be ineligible (see Section 10, Inclusion and Exclusion Criteria) prior to the planned day 1 of cycle 2 of chemotherapy will be considered screen failures, and will not be counted toward study accrual targets.

13.0 Recruitment Methods

Potential research subjects will be identified in the population of the GI oncology clinic at the DCC Lebanon campus, including through weekly medical oncology team meetings and weekly meetings of the DCC GI Tumor Board. Additionally, potential research subjects may be recruited from the general patient population of DCC satellite clinics where the study protocol has been activated. Participants will not receive compensation for study participation.

14.0 Withdrawal of Subjects*

Study participants may choose to withdraw from the study at any time for any reason. The Investigator may choose to remove a patient from the study if he/she is unable to comply with the study procedures or has experienced unacceptable toxicity. Should a subject choose to withdraw from the study, standard care will be provided during subsequent management. In the case of withdrawal of consent, no further study data will be collected after the date of consent withdrawal.

15.0 Risks to Subjects*

While we do not anticipate that the study's chemotherapy dosing algorithm will contribute to increased risk of adverse events, there is a theoretical increased risk of symptomatic neutropenia and/or thrombocytopenia.

Another theoretical risk related to study participation is that the investigational dose adjustment algorithm could lead to reduced treatment effectiveness. The study team considers it very unlikely that the investigational dose adjustment algorithm would have a material negative impact on the effectiveness of treatment. Despite limited corroborating evidence, chemotherapy relative dose intensity (RDI) is widely considered to be a surrogate marker of treatment effectiveness. Unplanned treatment delays contribute directly to reduced chemotherapy dose intensity, as the treatment interval serves as the denominator of the dose intensity calculation. By evaluating an intervention to reduce unplanned delays in chemotherapy, the study team expects that dose-intensity of treatment will be similar to historical standards, or improved, in patients treated according to the investigational dose adjustment algorithm. Chemotherapy relative dose intensity (RDI) will be evaluated as a secondary endpoint of the course of the study to better appraise the theoretical risk that the study intervention could impact anti-cancer treatment effectiveness.

Any adverse event will be evaluated and treated by the patient's primary oncologist in combination with the principal investigator as deemed appropriate in light of the medical situation. All pertinent observations and treatments will be recorded and reported to the appropriate entity.

16.0 Potential Benefits to Subjects*

Unplanned delays in chemotherapy are disruptive for patients and their caregivers because these delays lead to additional travel, clinic visits, blood draws, copays, and time away from home and work. Treatment according to this protocol may alleviate these burdens and result in fewer treatment delays.

17.0 Data Management* and Confidentiality

Data analysis plan

The ***primary analysis*** will consist of evaluation of the proportion of study patients experiencing one or more unplanned treatment delays prior to cycle 6 of chemotherapy. Exact methods for binomial data will be used to provide 95% confidence intervals. A chi-squared test will be performed to compare this proportion to the estimate of 40% found in a historical cohort of patients from DCC and the University of Colorado.[1]

The study will enroll a total of 50 participants in order to accrue 45 evaluable participants (accounting for a drop-out rate of 10%). This sample size of 45 participants provides power of 0.90 to detect a proportion of 20% or lower than the historical control of 40%, based on an exact chi-squared test with a one-sided significance level of 0.05.

Analyses of secondary endpoints will include reporting of the incidence of the events making up the composite safety outcome, calculation of the RDI (relative dose intensity, as previously defined in section 4.0) of mFOLFOX chemotherapy, and reporting of survey findings regarding patient out-of-pocket costs related to chemotherapy treatment visits (as a surrogate for out-of-pocket costs associated with cytopenia-related chemotherapy delays).

We will calculate RDI for each of the individual component drugs of the mFOLFOX regimen (oxaliplatin, 5-FU bolus, and 5-FU 46-hour infusion). We will report values of the mean, standard deviation, and 95% confidence intervals for the RDI of each drug. Bootstrap 95% confidence intervals for each RDI (*Statistical Science 1996, Vol. 11, No. 3, 189–228*) will be performed using the *boot* package in R.

We will report descriptive findings from the survey of patient out-of-pocket costs associated with chemotherapy treatment visits. Descriptive information will include patient-reported estimates of mean patient out-of-pocket costs for chemotherapy treatment visits related to travel, copayments, lost income, and child care, elder care, or pet care.

Data management

Electronic information about study participants will be kept in a secure, password-protected research database at Dartmouth-Hitchcock Medical Center (DHMC). The information collected for this study will be used only for the purposes of conducting this study. Every effort will be made to protect the identities of the participants and the confidentiality of the research data used in this study. As described above data will be collected from the patient's electronic chart and stored on a password protected DHMC server. This information will be maintained for no more than 2 years after the study is published in case of audits or inquiries regarding the study.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

The PI and collaborating physicians will be involved in monitoring the safety of the study interventions. The PI and key personnel will monitor study patient progress on an ongoing basis to identify possible adverse events.

Adverse events of interest for this study will be graded as described in the CTCAE (version 5). Because the adverse effects associated with mFOLFOX chemotherapy are well known, safety monitoring will focus on a short list of specified adverse events that potentially related to the dose adjustment algorithm. The occurrence of any component of the composite safety endpoint (secondary endpoint) that is attributable or potentially attributable to the dose adjustment algorithm will be considered unacceptable toxicity. These components are:

(1) grade 4 neutropenia
(2) grade 4 thrombocytopenia
(3) febrile neutropenia (grade 3 or 4)
(4) major bleeding with grade 3 or higher thrombocytopenia

Major bleeding is defined according to the criteria of the International Society for Thrombosis and Haemostasis.[8] Criteria for defining major bleeding are:

(1) Bleeding causing a >2 g/dL drop in hemoglobin or leading to transfusion of > 2 units of pRBCs
(2) Bleeding in a critical area (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial or intramuscular with compartment syndrome)
(3) Fatal bleeding

In the event that any component of the safety endpoint occurs, physicians and nurse practitioners managing care for enrolled subjects will notify the PI (or his/her designate) within 2 business days of the event. Other study data elements will be abstracted from the primary source record (eDH) on a periodic basis. Participants will be removed from the study protocol if they experience the primary safety endpoint or any other unacceptable toxicity (as determined by the treating clinician). The study will be discontinued for safety concerns if more than 3 patients experience any component of the safety endpoint.

Reports of unexpected adverse events occurring with any patient participating in this clinical trial will be submitted promptly to the IRB and the Data Safety Monitoring and Accrual Committee (DSMAC) according to institutional reporting policy and procedures. This study will be monitored by the Data Safety Monitoring and Accrual Committee (DSMAC) of the Norris Cotton Cancer Center. The Clinical Cancer Review Committee (CCRC) determines the frequency of DSMAC review. The DSMAC meets quarterly to review accrual rates and information of studies that have accrued participants. The DSMAC has the authority to suspend or to recommend termination to the CCRC of all research activities that fall within its jurisdiction. In the event that a study is suspended or terminated, that information will be forwarded to the D-HH IRB (Dartmouth IRB) office.

Adverse event (AE) reporting is conducted in accordance with the guidelines provided in the NCI Investigator Handbook (https://ctep.cancer.gov/investigatorResources/investigators_handbook.htm). Investigators and research teams receive electronic notification from the electronic medical record and the CTMS of participant admissions, changes in inpatient status, and emergency department visits. Unexpected, serious, and at least possibly related AEs are promptly reported to the DH-H IRB. The DSMAC and the IRB have the authority to suspend accrual in response to a safety concern. The IRB and the CCRC have the authority to immediately close a study due to an unacceptable level of risk to participants.

19.0 Provisions to Protect the Privacy Interests of Subjects

Electronic information will be kept in a secure, password-protected research database, utilizing REDCap at DHMC. The information collected for this study will be used only for the purposes of conducting this study. Every effort will be made to protect the identities of the participants and the confidentiality of the research data used in this study. Personal and medical information about subjects will be kept in a secured file. This information will be coded with a study ID number so that subjects cannot be identified. Utmost effort will be made to protect participant identity and the confidentiality of the medical information obtained from their charts. No identifying information will be used in any publication or presentation which may result from subject participation in the study.

20.0 Compensation for Research-Related Injury

There are no plans to provide compensation for injury related to research participation. Given the nature of chemotherapy, even the current standards of care carry considerable risk to the patient and may result in harm to patients. As such, it would be infeasible to determine if injury was a direct result in participation of our protocol.

21.0 Economic Burden to Subjects

There will be no additional cost to subjects to participate in this study.

22.0 Consent Process

All subjects will provide written informed consent prior to participating in the study. Consent will be obtained on or before the planned day 1 of cycle 2 of chemotherapy. Consent will typically be obtained during routine office visits related to oncologic care of potential study participants.

23.0 Process to Document Consent in Writing

The study will follow SOP: Written Documentation of Consent (HRP-091). Consent will be documented in writing.

24.0 Setting

The study will be activated initially at the DCC-Lebanon and DCC-St. Johnsbury sites. The study may also be activated at other DCC satellite campuses where eDH is the primary source for clinical documentation, where routine oncologic care is directed by an DCC medical oncologist, and where trained, credentialed, and delegated research staff are available to implement study procedures (as per DCC standard operating procedures for clinical research). Potential satellite locations for study activation include DCC clinics in Nashua and Manchester.

25.0 Resources Available

Based on historical data collected by the principal investigator, we expect that we will be able to enroll 50 evaluable patients over the course of 12 months. We plan to dedicate an additional 6 months to data collection and analysis. To ensure that all persons assisting with the research are adequately informed about the protocol, we will dedicate time to reviewing our study intermittently during the GI oncology group meetings.

Funding for the study will come from institutional start-up funds available to the PI, Dr. Brooks.

26.0 Multi-Site Research*

N/A

27.0 References

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PROTOCOL TITLE: A pragmatic, single-arm clinical trial of a novel dose adjustment algorithm for preventing cytopenia-related delays during FOLFOX chemotherapy

Appendix A. Algorithm for cytopenia-related delay and dose-reduction of mFOLFOX chemotherapy

ANC and/or Platelet count	**Action at time of cytopenia**	**Action at subsequent cycle**, *if ANC ≥1.5 and platelets ≥100*
- *Planned Day 1 of Cycle 2*		
ANC 1.00 – 1.49 *and/or* Platelets 75-99	Reduce oxaliplatin to 75mg/m2 (dose level -1). Reduce 5-FU bolus to 200mg/m2 (dose level -1).	May re-escalate doses by 1 dose level (discretion of treating physician).
ANC 0.75 – 0.99 *and/or* Platelets 50-74	Reduce oxaliplatin to 65mg/m2 (dose level -2). HOLD 5-FU bolus. Reduce 5-FU infusion to 1800mg/m2 (dose level -2).	Escalate 5-FU infusion to 2100mg/m2. May escalate oxaliplatin by 1 dose level (discretionary). May resume 5-FU bolus at 200mg/m2 (discretionary).
ANC <0.75 *OR* Platelets <50	HOLD chemotherapy until ANC ≥ 0.75 and platelets greater than 50, then dose reduce as for ANC 0.75 – 0.99 and/or platelets 50-74.	May escalate oxaliplatin and 5-FU infusion doses by 1 dose level (discretionary). Permanently discontinue 5-FU bolus.
- *Planned Day 1 of Cycle 3‡*		
ANC 1.00 – 1.49 *and/or* Platelets 75-99	Reduce oxaliplatin by one dose level. Reduce 5-FU bolus by one dose level. Maintain 5-FU infusion.	May re-escalate doses by 1 dose level (discretionary).
ANC 0.75 – 0.99 *and/or* Platelets 50-74	Reduce oxaliplatin to 65mg/m2, or by 1 dose level (whichever is lower). HOLD 5-FU bolus. Reduce 5-FU infusion to 1800mg/m2, or by 1 dose level (whichever is lower).	Escalate 5-FU infusion by 1 dose level. May escalate oxaliplatin by 1 dose level (discretionary). May resume 5-FU bolus at 200mg/m2 (discretionary).
ANC <0.75 *OR* Platelets <50	HOLD chemotherapy until ANC ≥ 0.75 and platelets greater than 50, then dose reduce as for ANC 0.75 – 0.99 and/or platelets 50-74.	May escalate oxaliplatin and 5-FU infusion doses by 1 dose level (discretionary). Permanently discontinue 5-FU bolus.
- *Planned Day 1 of Cycles 4 or higher‡*		
ANC 1.00 – 1.49 *and/or* Platelets 75-99	Reduce 5-FU bolus by 1 dose level. Permanently discontinue 5-FU bolus in patients receiving palliative therapy.	Maintain previous doses.
ANC 0.75 – 0.99 *and/or* Platelets 50-74	Reduce oxaliplatin by 1 dose level. HOLD 5-FU bolus. Reduce 5-FU infusion dose by 1 dose level.	Permanently discontinue 5-FU bolus in patients receiving palliative intent therapy. Otherwise, may re-escalate doses by 1 dose level in future cycles (discretion of treating physician).
ANC <0.75 *or* Platelets <50	Permanently discontinue 5-FU bolus. HOLD oxaliplatin and 5-FU infusion until ANC ≥ 0.75 and platelets > 50, then dose reduce as for ANC 0.75 – 0.99 and/or platelets 50-74.	May re-escalate oxaliplatin and 5-FU infusion doses by 1 dose level in future cycles (discretionary). Do not escalate oxaliplatin higher than 75mg/m2 (dose level -1).

‡ For patients who received protocol-mandated dose-reduction(s) in a prior treatment cycle: if ANC and platelets are stable (by category/table row), then maintenance of chemotherapy dose levels from the previous cycle is permitted at the discretion of the treating clinician.

PROTOCOL TITLE: A pragmatic, single-arm clinical trial of a novel dose adjustment algorithm for preventing cytopenia-related delays during FOLFOX chemotherapy

Dose levels (doses expressed in mg/m2):

Drug	*Level 0*	*Level -1*	*Level -2*	*Level -3*	*Level – 4*
Oxaliplatin	85	75	65	55	discontinue
5-FU bolus	400	200	discontinue	*n/a*	*n/a*
5-FU infusion	2400	2100	1800	1200	discontinue

*Dose reductions for symptoms and adverse events other than cytopenias are at the discretion of the treating physician. Dose reductions for management of other treatment-related adverse events take priority over recommendations in this table.
** Use of G-CSF (e.g. filgrastim or pegfilgrastim) is not permitted during protocol therapy. An exception to the prohibition on G-CSF use is made for patients who have already incurred an unplanned delay (the primary study outcome) in conjunction with an ANC of less than 750 cells/mm3 on day 1 of any cycle. In such a case, G-CSF agents may be used at the discretion of the treating clinician. The algorithm for dose delay and dose-reduction shall be applied regardless of G-CSF use.