TrACER: Trial Assessing Colony Stimulating Factor (CSF) prescribing Effectiveness and Risk (S1415CD)

ORDER ENTRY CHANGE PROTOCOL

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I. GENERAL INFORMATION

Dates of Study: 9/1/2015-9/30/2020

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Collaborating Institutions:

- Hutchinson Institute for Cancer Outcomes Research (HICOR), Fred Hutch
- University of Washington
- Columbia University
- SWOG
- CRAB
- NCI

Intervention Component Sites: (n=18)

Main Component	CTEP ID	NCORP Name	Arm
Billings Clinic Cancer Center	MT002	Montana Cancer Consortium NCORP	4
Bozeman Deaconess Cancer Center	MT019	Montana Cancer Consortium NCORP	4
Cancer Care Specialists of Central Illinois	IL185	Heartland NCORP	3
Columbia University/ Herbert Irving Cancer Center	NY024	Columbia NCORP-MU	4
Contra Costa Regional Medical Center	CA463	Bay Area NCORP	3
Essentia Health Cancer Center	MN024	Essentia NCORP	3
Illinois CancerCare- Peoria	IL101	Heartland NCORP	3
John H. Stroger Jr Hospital of Cook County	IL042	SHCC NCORP-MU	3
Lewis Cancer and Research Pavilion at St. Joseph's/ Candler	GA106	Georgia NCORP	4
Louisiana State University Health Science Center	LA002	Gulf South NCORP-MU	4
Presbyterian Kaseman Hospital	NM005	New Mexico NCORP- MU	3
St. Joseph Mercy Hospital	MI013	Michigan NCORP	4
St. Luke's Hospital of Kansas City	MO028	Kansas City NCORP	4
Self Regional Healthcare	SC015	Medical University of South Carolina NCORP-MU	3
Tripler Army Medical Center	HI010	Hawaii NCORP-MU	3
Queen's Medical Center	HI005	Hawaii NCORP-MU	4
University of New Mexico Cancer Center	NM004	New Mexico NCORP- MU	4
William Beaumont Hospital- Troy	MI128	Beaumont NCORP	3

HICOR Support Team:

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EHR Technical Consultants: Contact HICOR Support Team to request consulting services

Funding: Provided by the Patient-Centered Outcomes Research Institute (PCORI).

Key Terms and Abbreviations:

- Component: A hospital, cancer center, physician practice or other institution where patients/participants are enrolled on a regular and ongoing basis on NCI-approved clinical trials available to the NCORP Community Site. Each participating hospital/clinic location listed above under **Intervention Component Sites** is a unique component for this project. The process of adding protocol-indicated order sets for this study will occur at each listed component location.
- Computerized physician order entry (CPOE): the process of a medical professional entering medication orders or other physician instructions electronically (vs. on paper].
- Febrile Neutropenia (FN): The development of a fever, suggesting infection, in patients with a suppressed white blood cell count.
- Order entry system (OES) or Electronic Health Record (EHR) system: The primary software or tool used to order treatments for patients. (e.g. EPIC is used in components to order chemotherapy, while others use paper orders)
- Primary prophylactic colony stimulating factor (PP-CSF): a drug commonly prescribed alongside chemotherapy regimens with an elevated risk of Febrile Neutropenia. Functions to promote the body's production of white blood cells.

II. STUDY OBJECTIVES AND HYPOTHESES

Primary Objectives:

a) To compare the use of primary prophylactic colony stimulating factor (PP-CSF) according to recommended clinical practice guidelines among patients registered at Intervention components versus Usual Care components.

b) To compare the rate of febrile neutropenia (FN) among patients registered at Intervention components versus Usual Care components.

c) To compare the rate of FN among intermediate risk patients registered at Intervention components by component treatment assignment (administer PP-CSF to intermediate risk patients versus not).

Primary Hypotheses**:**

H1 (Primary Objectives a and b): At the practice level, the CSF standing order intervention will, as compared to Usual Care:

1. Reduce the overall rate of FN
2. Increase the use of PP-CSFs per FDA label and as recommended by clinical practice guidelines;
3. Decrease the use of PP-CSFs that are not FDA label indicated and not recommended by clinical practice guidelines

For secondary objectives and hypotheses, see approved complete study protocol, sections 1.0 and 10.0.

III. RATIONALE AND BACKGROUND INFORMATION

Colony-Stimulating Factors (CSFs) can be used to maintain a patient's white blood cell count, and are commonly used to reduce the risk of FN, as well as its severity and duration. Clinical practice guidelines recommend the use of prophylactic CSFs with the first cycle of chemotherapy—termed primary prophylactic CSF (PP-CSF) use—for patients receiving chemotherapy that carries a high risk (>20%) of FN and suggest "consideration" of PP-CSFs in conjunction with chemotherapy that has an intermediate risk (10-20%) of FN (Table 1).

Table 1: ASCO recommendations for Primary Prophylactic CSF use in patients receiving chemotherapy

Recommend use	Consider use	Do not recommend use
High-risk of FN (>20%)	**Intermediate**-risk of FN (10-20%)	**Low**-risk of FN (<10%)

Although evidence-based clinical practice guidelines for CSF have been available for nearly two decades, multiple studies show that the gap between best scientific evidence and clinical practice is wide for PP-CSF prescribing: between 55% and 95% of PP-CSFs prescribing is inconsistent with guidelines.[1-9] Inappropriate prescribing occurs in both directions: underuse for high FN risk regimens (where PP-CSF is recommended); and overuse of PP-CSF for patients receiving low-risk chemotherapy (where PP-CSF is not recommended).

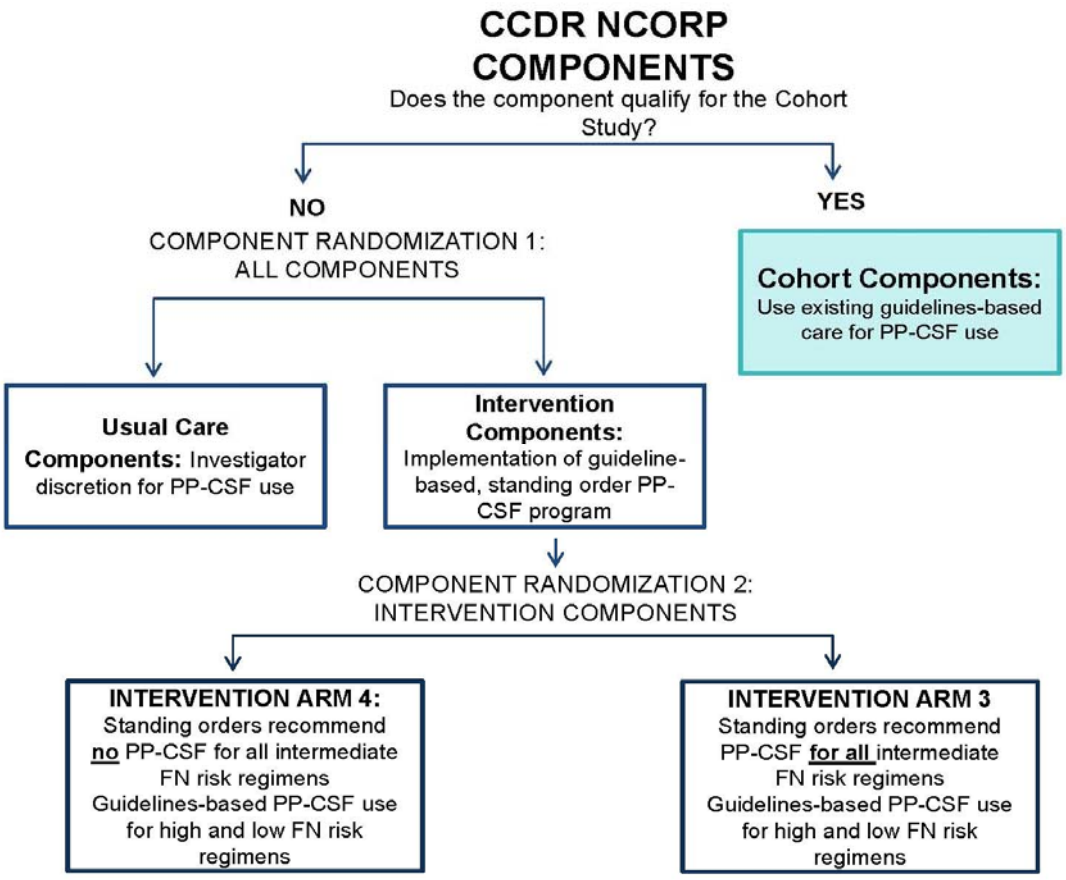
This pragmatic study is designed to compare outcomes of PP-CSF use in community practice as currently managed by physicians and clinic staff (usual care) with care that includes a protocol-based, guideline-informed standing PP-CSF order system. The intent of the first study aim is to align PP-CSF prescribing with clinical evidence, where the benefit to patients is likely to be highest. The second specific aim will evaluate the

effectiveness of PP-CSF in *modern*, intermediate-risk chemotherapy regimens, for which there is currently an evidence gap. The design of this study is innovative in that it generates evidence on an important patient-level clinical question within the context of evaluating the effectiveness of a system-level cancer care delivery intervention. Given the documented variation in CSF prescribing and the resulting impact on patient outcomes, this pragmatic trial has the potential to provide substantial benefit to many of the 275,000 breast, lung and colorectal cancer patients who receive myelosuppressive chemotherapy each year. [(10-12)]

For more information on the background of the study, see Section 1.0 of the approved complete study protocol.

IV. STUDY DESIGN & METHODOLOGY

Chart 1. Component Schema



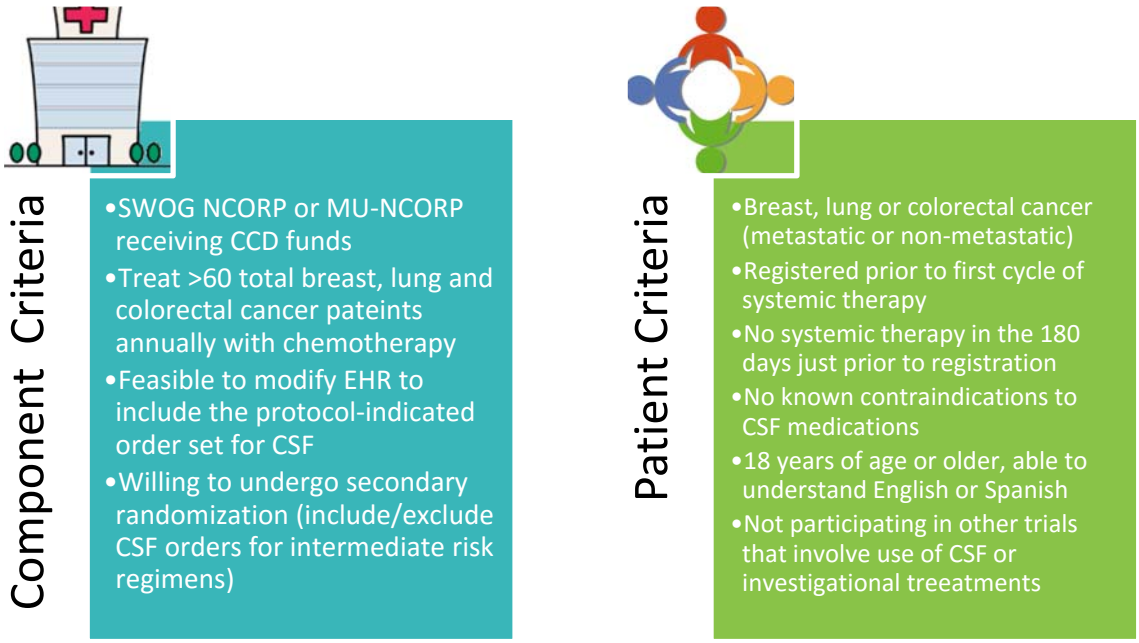
Primary prophylactic CSF (PP-CSF) is defined as CSF administered with the first cycle of systemic therapy, within 24 to 72 hours after the initial systemic therapy dose. PP-CSF and general CSF use is observed and reported.

The study uses a cluster-randomized design: the study intervention is administered at the component level, rather than the patient level. All patients at a given component will be subject to the same order system, regardless of study participation; only registered patients will have their data reported to the study. As shown in Chart 1, at each intervention component an automated order entry system for CSF prescribing will be integrated into existing clinic processes for prescribing CSF prophylaxis at the onset of the first cycle of myelosuppressive chemotherapy, as indicated in the FDA product label and based on the myelosuppressive risk of each regimen.

Individual clinicians will be able to override orders based on clinical expertise and patient factors. This system-oriented, clinic-level intervention will be complemented with academic detailing for clinic staff.

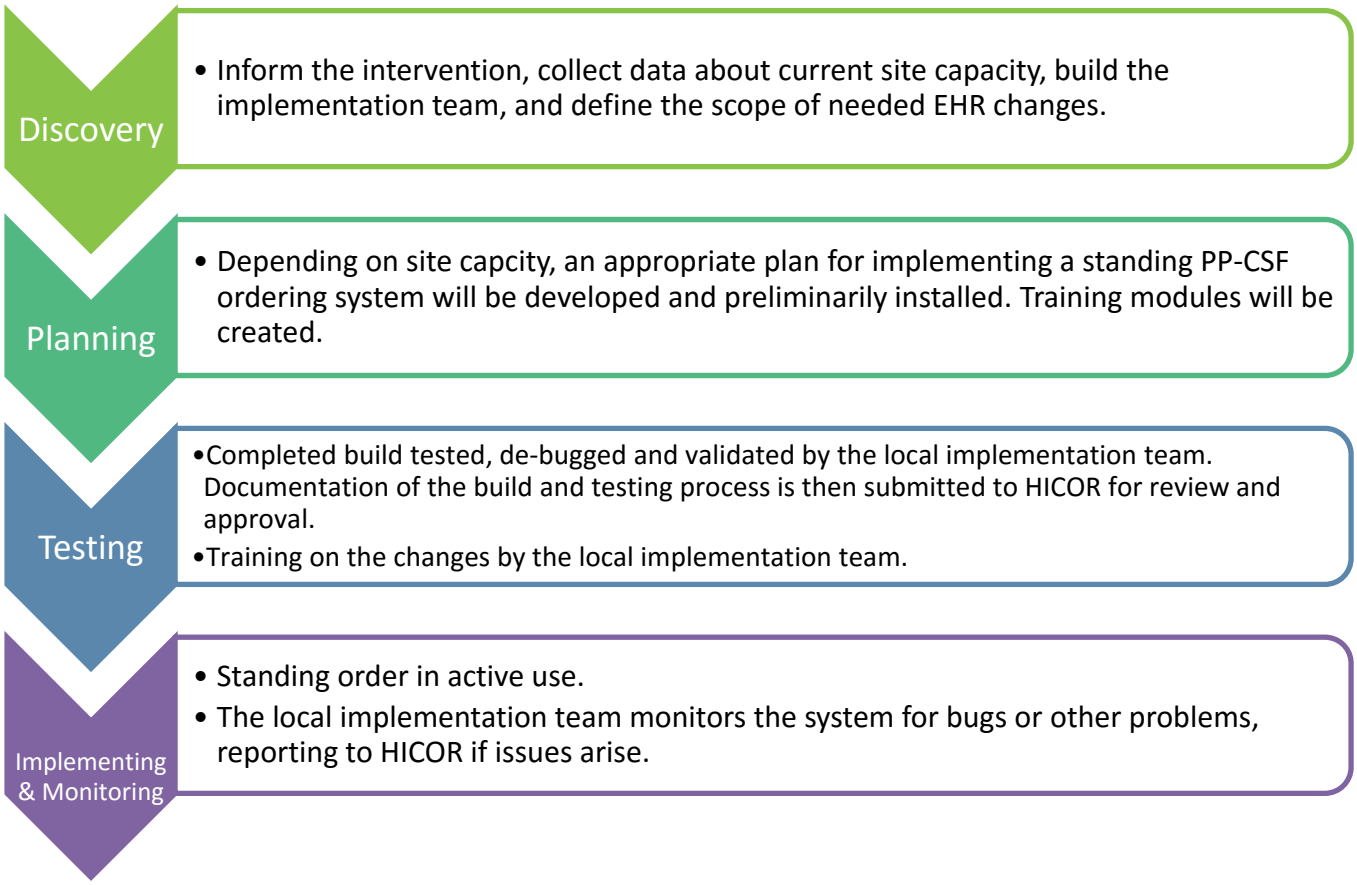
Chart 2 lists the separate eligibility criteria for participating component practices and patients. Patient eligibility requirements are the same for all participating components, regardless of component treatment assignment (Cohort, Intervention and Usual Care). This study is only looking at PP-CSF use in patients diagnosed with breast, colorectal or non-small cell lung cancer.

Chart 2. Component and Patient Eligibility



Changing a component's order entry system to include the protocol-indicated intervention is broken down into four major steps (**Chart 3**). The HICOR Support Team will be available at each step to provide guidance and technical expertise as needed, and oversee the process of intervention implementation at each of the 24 components. The HICOR Support Team must approve each component's final build before it can be rolled out into the live, clinic environment.

Chart 3. Overview of TrACER Orders Change Process



A. Step 1: Discovery

The purpose of Step 1 is to gather relevant information to inform the intervention. Component leadership will determine the makeup of their local implementation teams and collect the data needed to define the scope of the modifications that should be made to their existing electronic health record (EHR) systems to comply with the study protocol. The study coordinating center at the Hutchinson Institute for Cancer Outcomes Research (HICOR) will monitor and support this process by:

1) Hosting a project kickoff meeting and monthly calls with members of the component leadership,
2) Answering questions and meeting with individual components as needed
3) Providing technical expertise as needed from EHR consultants hired for their expertise in the different EHR systems found at the 24 participating intervention components.

The size and makeup of the local implementation team should be determined by the local study leadership and will vary based on local differences in the process for requesting order entry system changes, who makes those changes, and the end-users at each clinic.

It is recommended that the component leadership select at least one representative from the following groups to serve on the local implementation team:

- Systems Analysts/IT Professionals
- Clinical Pharmacists
- Prescribers (Clinician, Nurse Practitioner)

A list of the local implementation team members and their contact information should be provided to HICOR. The local implementation team and other key clinic staff as identified by the component leadership will be invited to attend a formal, brief overview of the project hosted by HICOR (kickoff meeting). HICOR will provide background information from the complete study protocol regarding the risks of febrile neutropenia by chemotherapy regimen and the over- and under-utilization of CSF. Local implementation teams will be given the opportunity to ask questions and discuss the intervention. Potential forums for this discussion include conference calls, webinars, staff meetings, among others as appropriate. Due to scheduling conflicts, multiple opportunities to participate in the academic detailing may be provided. Printed materials summarizing the presentations may be e-mailed to staff at each clinic.

To determine the scope of the necessary modifications, the local implementation team and HICOR will need to gather information about the type of EHR currently in place and how widely it is used across the component, and if there are any plans to make significant upgrades or migrate to a new system that could affect the chemotherapy and CSF ordering process (**Table 2**). Detailed information about the process for placing chemotherapy and CSF orders and the process for requesting changes to those systems should also be collected. Some of this information may already be available on the component's application to participate in the trial. HICOR will administer and share results of a Clinic Characterization Survey to components randomized to the intervention arm of the trial soon after randomization. This survey will collect additional data used to inform the orders change process. Any remaining information will be gathered via interviews or other communication between the local implementation team and the appropriate representatives at their practices.

Table 2. Summary of Variables to Inform Implementation Planning

Variable of interest	Method of collection	Collected By
Type of existing EHR (e.g. software name, paper)	Study application	HICOR Support Team
How widely used is this EHR across the component?	Component interview	Local Implementation Team
Are there imminent plans to significantly modify the existing EHR or change to a new system?	Clinic Characterization Survey	HICOR Support Team
Detailed description of the existing process for submitting chemotherapy and CSF orders	Application, Clinic Characterization Survey, Component interview	HICOR Support Team, Local Implementation team
Regimen details such as does the component use CPOE, are regimens easily identifiable within the EHR, how widely is automatic inclusions or exclusion of PP-CSF for different regimens already used	Application, Clinic Characterization Survey	HICOR Support Team
Detailed description of the existing process for submitting changes to the EHR, including the expected length of time for the changes to be made and the types of system tools used	Component interview	Local Implementation Team
Who approves changes to your prescription ordering system?	Clinic Characterization Survey	HICOR Support Team
Who is responsible for making changes directly to the prescription ordering system?	Clinic Characterization Survey, Component interview	HICOR Support Team, local Implementation Team
What types of CSF medications do you prescribe? (e.g. injection vs. on body injector)	Application, Clinic Characterization Survey	HICOR Support Team

B. Step 2: Planning

Per sections 7.3 and 18.1 of the study protocol, an automated order entry system for CSF prescribing will be integrated into existing clinical processes for prescribing CSF prophylaxis. This may be integrated into the computerized order entry system (CPOE) or into pre-printed paper order sets, depending on site capacity. Individual clinicians will be able to override the order entry system based on clinical expertise and individual patient factors. Clinicians may change an individual patient's orders from what is specified by following local standard procedures for changing a prescription order when adding or removing CSF.

Charts 3 and 4 present the general framework for guideline-integrated automated ordering systems, both electronic and paper. Note that CSF is always automatically included with orders for high risk regimens, and always excluded from orders for low risk regimens. This is the same across both secondary randomization arms. The difference between these arms lies with the prescribing practice for intermediate risk regimens. In Intervention Arm 3 (Chart 3), actions for both **intermediate and high risk** regimens are identical. In Intervention Arm 4 (Chart 4), actions for both **intermediate and low risk** regimens are identical. The language on the order will be customized based on whether the regimen is high, intermediate or low risk. A summary of implementation details can be found in **Table 3**. Pragmatically, modifications from this general framework may be necessary due to variations at the different components.

Chart 3: Schema for electronic or paper intervention Arm 3- PP-CSF for Intermediate Risk

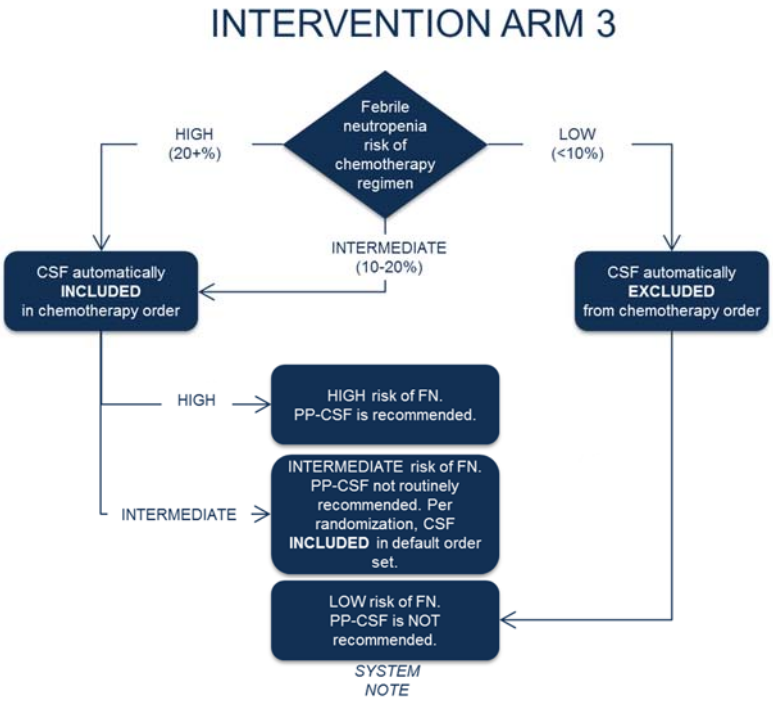


Chart 4: Schema for electronic or paper intervention Arm 4- <u>NO</u> PP-CSF for Intermediate

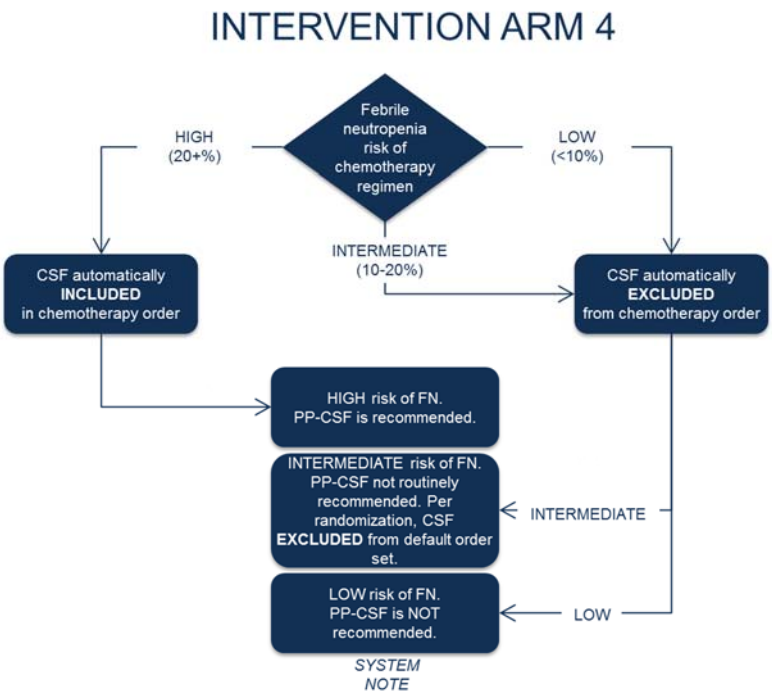


Table 3: Implementation of automated order entry system

Regimen FN Risk Category	Default Setting	Example System Note
High	CSF automatically **included** in prescription order.	HIGH risk of FN per guidelines. Primary prophylactic CSF is RECOMMENDED.
Intermediate – Intervention Arm 3	CSF automatically **included** in prescription order.	INTERMEDIATE risk of FN per guidelines. Primary prophylactic CSF is not routinely recommended. Per your practice's ASSIGNED S1415CD STUDY ARM, CSF is INCLUDED by default in the order set.
Intermediate – Intervention Arm 4	CSF automatically **excluded** from prescription order.	INTERMEDIATE risk of FN per guidelines. Primary prophylactic CSF is not routinely recommended. Per your practice's ASSIGNED S1415CD STUDY ARM, CSF is EXCLUDED by default from the order set.
Low	CSF automatically **excluded** from prescription order.	LOW risk of FN per guidelines. Primary prophylactic CSF is NOT recommended.

The algorithm defining the levels of risk associated with breast, lung, and colon chemotherapy regimens was built based on National Comprehensive Cancer Network (NCCN) guidelines, templates, and designations as the primary source. In the absence of NCCN data, guidelines were derived from the following sources: European Organisation for Research and Treatment of Cancer (EORTC), American Society of Clinical Oncology (ASCO), and peer-reviewed publications of clinical trials. This algorithm has been vetted through leading experts in CSF risk categorizations that serve as project investigators or as part of our external stakeholder advisory group.

EHR build specifications are available upon request from HICOR for the more commonly used systems in this study: EPIC Beacon, Aria and Mosaiq. The study is prepared to support other systems as well and HICOR should be notified as soon as it is determined that additional guidance or technical assistance is required to complete the local blueprint as they can connect the local implementation team with appropriate consultants and resources as needed. EHR consultants for TrACER are available on an as needed basis to assist the local implementation teams with the orders change modification planning, build, and testing phases. Consultants may need access to a test environment on your platform in order to build order set templates or assist with testing and debugging. Contact HICOR to request consultant services for your component.

The local implementation team will develop a plan that describes how order-entry system end-users will be notified of the protocol-indicated changes and trained on their proper use. The specifics of this training will vary by component, and can follow the component's standard procedure for physician and staff notification and training for new EMR features and procedures. The video available for download as part of the Study Toolkit (at TrACER web page on SWOG.org and FredHutch.org) provides an overview of the intervention process and may also be helpful for training purposes.

The training plan and final blueprint should be reviewed and approved by the local implementation team and well-documented. The build should be executed by qualified professionals with sufficient experience updating and modifying the local order sets/CPOE. If needed, the study team can provide additional guidance and technical expertise.

C. Step 3. Testing and Validation

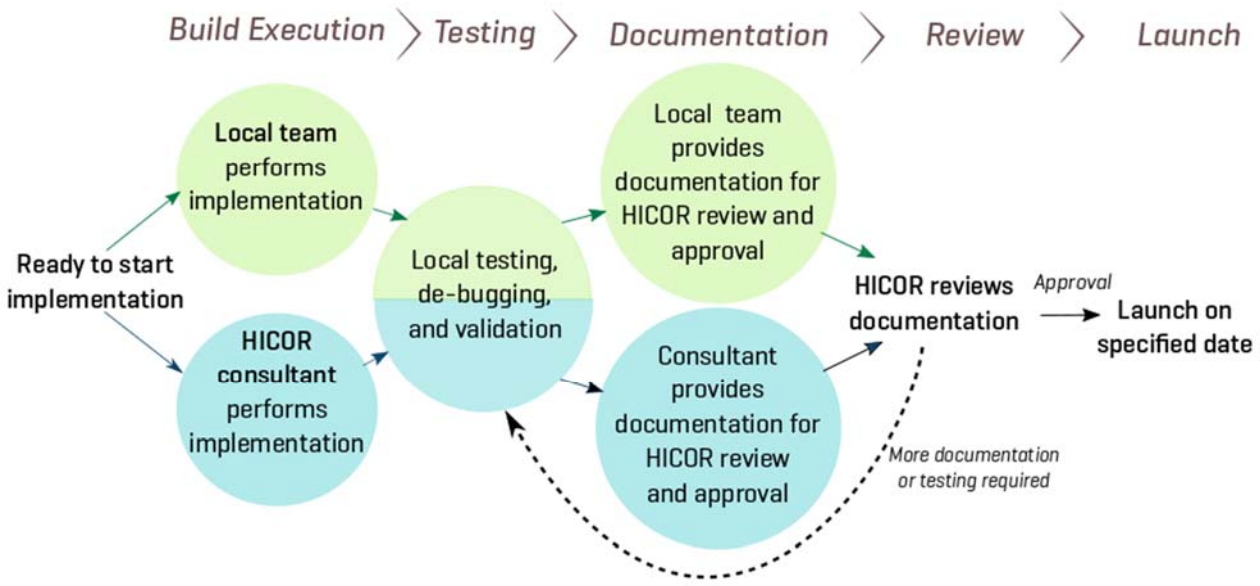
The overall process for testing and validation of the protocol-indicated build is described in Chart 6. The completed build should be tested, de-bugged and validated first by the local implementation team and/or the appropriate pharmacy and IT personnel, using the local process for testing order set/CPOE changes. When this initial testing is complete, documentation of the build and testing process will be submitted to HICOR for review and approval. If the build was done by the local implementation team, they are responsible for providing this information directly to HICOR. If the build was done by the HICOR-provided consultant, he/she is responsible for providing the proper documentation. The documentation requested will include but is not limited to the following:

- Screenshots of each step of the ordering process for a high, intermediate, and low-risk regimen
- System report showing study-recognized regimens and corresponding CSF defaults

The specific documentation required is determined by HICOR and will vary slightly depending upon the type of platform (EHR vs. paper) and amount of consultant involvement.

A HICOR review team consisting of the Project Manager, Data Operations Coordinator, and Pharmacists will review the submitted documents and notify the local implementation team that they are approved to implement the changes in the production clinical system environment. Components may not implement the changes until they have received approval from HICOR. The HICOR support team may need to gather additional information from the local implementation team or request design modifications before approval is issued.

Chart 6. Overview of Testing and Validation Step



D. Step 4. Implementation and Monitoring

Before full launch of the updated protocol, the local implementation team is expected to provide training related to the system changes to their physicians and staff.

After full implementation and launch of the new standing order protocol, the local implementation team should monitor the system for bugs or other problems. If such issues do occur, HICOR should be notified within 3 business days and told the nature of the problem and the steps planned to resolve it by contacting the HICOR Support Team. HICOR and their consultants are available to assist with troubleshooting as needed. HICOR will track all reported bugs and other problems related to the protocol intervention and make that information available to other sites as a resource.

Questions or problems with study implementation that are unrelated to the intervention system changes, such as those involving patient eligibility and study procedures, should be directed to the SWOG Data Operations Center by phone or email: 206.652.2267, cancercontrolquestion@crab.org. For question unrelated to patient eligibility, site requirements or data submission, contact CTSU: 888.823.5923, ctsucontact@westat.com.

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APPENDIX A: List of Protocol Recognized Regimens, FN Risk and Supporting Evidence