A Pragmatic Trial to Improve Colony Stimulating Factor Use in Cancer
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Principal Investigator: Scott Ramsey, MD, PhD
Co-Principal Investigator: Gary Lyman, MD, MPH

Partners:
• SWOG
• NCI Community Oncology Research Program (NCORP)
• Columbia University
• Cancer Research and Biostatistics (CRAB)
• University of Washington (UW)

Sponsor: pcori
Background

- Colony-Stimulating Factor (CSF) is prescribed to patients undergoing chemotherapy which carries a high risk of febrile neutropenia (FN).

- FN is a serious, life-threatening complication which can result in hospitalization and death, and disrupt treatment, compromising the likelihood of remission or cure.

ASCO* recommendations for Primary Prophylactic CSF use in patients receiving chemotherapy.

*American Society of Clinical Oncology

<table>
<thead>
<tr>
<th>Recommend use</th>
<th>Consider use</th>
<th>Do not recommend use</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk of FN (&gt;20%)</td>
<td>Intermediate-risk of FN (10-20%)</td>
<td>Low-risk of FN (&lt;10%)</td>
</tr>
</tbody>
</table>
Study Rationale

• Between 55%-95% of CSF use is inconsistent with clinical practice guidelines including over- and underuse.

• CSF is costly to patients and the healthcare system
  – In 2010, the Centers for Medicare and Medicaid Services (CMS) paid $888 million for CSF

• This pragmatic trial is designed to test an intervention to increase compliance with guidelines, and generate evidence to assess effectiveness of Primary Prophylactic CSF (PP-CSF) on reducing rates of FN for patients receiving intermediate-risk chemotherapy regimens.
Specific Aims

**Aim 1:** With input from diverse stakeholders, design and conduct a pragmatic randomized trial comparing the effectiveness of a guideline-based, standing PP-CSF order entry intervention to usual clinical practice on:

- Rates of FN
- Adherence to clinical practice guidelines
Specific Aims

The trial will include the following two arms:

1. **Intervention Arm:** Standing orders for delivering CSF prophylaxis within 24-48 hours following the first cycle of myelosuppressive chemotherapy, based on FN risk of each regimen, as specified by the National Comprehensive Cancer Network (NCCN) Guidelines.

2. **Usual Care Arm:** CSF prescribing as currently managed by the physician and their practice staff.
Specific Aims

**Aim 2:** Compare the impact of PP-CSF vs. no PP-CSF on rates of FN, FN-related ED visits and hospitalizations, health-related quality of life, and short-term mortality among patients receiving intermediate risk chemotherapy
Study Setting

• This trial will be conducted by the **SWOG research base** through the NCI Community Oncology Research Program (NCORP).

• NCORP consists of three major components: Research Bases, Community Sites, and Minority/Underserved Community Sites.
  
  – **Research Bases**: design and conduct NCORP multi-center cancer prevention, control, screening and post-treatment surveillance clinical trials, and **cancer care delivery research (CCDR) studies**.
  
  – **Community Sites**: consortia of community hospitals and/or oncology practices and integrated healthcare systems participating in NCORP studies.
  
  – **Minority/Underserved (MU) Community Sites**: Community sites with patient populations of at least 30% racial/ethnic minorities or rural residents.
  
  – **394** community site practices including 45 at MU-NCORP sites are able to participate in CCDR studies.
Pragmatic Trial Design

Practice Eligibility and Selection
- All NCORP practices:
  - Oversample minority-based clinics
  - Exclude very low volume clinics

Primary Randomization (Practice Level)
- Usual Care
- Secondary Randomization (Practice Level – All intermediate risk patients within the practice)
  - No Prophylactic CSF
  - Prophylactic CSF

Cohort Study

Intervention:
- Guideline-based, standing PP-CSF order program
- Usual Care

Existing guideline-informed CSF order entry system?
- Yes
  - Cohort Study
- No
  - Intervention: Guideline-based, standing PP-CSF order program

Prophylactic CSF

No Prophylactic CSF
Cohort Study

The cohort study includes 8 practices that are ineligible for the randomized trial because they have already implemented a CSF order system. It has several purposes.

1. Compare existing, implemented order entry systems to our approach
2. Track trends in CSF prescribing and outcomes; compare against our trial population
3. Understand factors that may influence post-randomized, controlled trial implementation
4. Compare adherence and outcomes in the cohort practices and the trial populations using exploratory, comparative, analyses
Hypotheses

• Primary - Aim 1. A protocol-based standing order program of CSF use as primary prophylaxis for patients receiving high or intermediate risk myelosuppressive chemotherapy 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

• Primary - Aim 2. Among patients receiving intermediate risk chemotherapy, the rate of FN will be lower in patients who receive PP-CSFs in the first cycle compared to those who do not.
Hypotheses

• **Secondary - Aim 1:**
  • Total FN events and FN-related health-related quality of life (HRQOL) for low risk patients will be no different for those who receive CSFs as prophylaxis during the initial cycle of chemotherapy vs. those who do not
  • Adherence to PP-CSF orders will be greater in the standing order intervention group than the usual care group
  • Patient knowledge of the indications for, efficacy, and side effects associated with PP-CSF will improve between the initiation and conclusion of the first cycle of myelosuppressive chemotherapy
  • The proportion of patients completing the initial chemotherapy regimen: a) at planned duration; and b) at planned dose intensity will be higher in the intervention vs. usual care
  • Use of antibiotics, both as prophylaxis and as treatment for FN, will be lower in the protocol-based standing order program group
Hypotheses

**Secondary - Aim 2:**
- Among patients receiving intermediate risk chemotherapy, the rate of FN, FN-related ED visits, and hospitalizations will be lower in patients who receive PP-CSFs in the first cycle compared to those who do not.

- FN-related HRQOL for intermediate risk patients will be greater at 3-5 weeks for those who receive PP-CSF during the initial cycle of chemotherapy vs. those who do not.

- Short-term mortality will be the same for intermediate risk patients who receive PP-CSFs vs. no prophylaxis (no use or other use) during the initial cycle of chemotherapy.
Pragmatic Trial: Practice Eligibility

**Inclusion:** NCORP or MU-NCORP oncology practices affiliated with SWOG

**Exclusion:**
- Very low volume (<100 breast, non-small cell lung, and colorectal total cancer patients received chemotherapy in 2013)
- Unwilling to undergo secondary randomization
- Implemented or will implement PP-CSF order entry system (these clinics may enroll in the cohort study)
Pragmatic Trial: Patient Inclusion Criteria

• Over 21 years of age
• Non-metastatic or metastatic breast cancer, non-small cell lung cancer, or colorectal cancer
• Scheduled to receive first course of neoadjuvant, adjuvant or palliative cytotoxic chemotherapy regimen. Includes newly diagnosed and recurrent disease.
Pragmatic Trial: Patient Exclusion Criteria

Exclusion:

• Age of 21 years or below
• Pregnant or breastfeeding
• Scheduled to receive dose dense chemotherapy, defined as repeating chemotherapy cycles every 14 days. PP-CSFs are already included with dose dense chemotherapy protocols.
• Enrolled in a therapeutic clinical trial
• Contraindication to CSFs, specifically prior hypersensitivity to Escherichia coli-derived proteins, filgrastim, or pegfilgrastim, or tbo-filgrastim
• Other severe acute or chronic medical or psychiatric condition that would impart, in the judgment of the recruiting physician, excess risk associated with study participation or study drug administration, or which, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
• Inability to complete survey and consent form in either Spanish or English
Stakeholder Engagement

The study has been designed and will be conducted with active engagement of key stakeholders: clinicians, patient advocates, payers, guidelines groups and delivery systems. Individual representatives of these groups will comprise our External Stakeholder Advisory Group (ESAG).

The aims of stakeholder engagement for this project are four-fold:

**Aim 1**
To refine the research question and study protocol to ensure that the question is of maximal relevance to key decision makers, the outcomes being measured are meaningful to these decision makers, the patient population includes all important subgroups of interest, the comparators and their definitions reflect primary real world alternatives, and any other factors relevant to the analysis or interpretation of the data are considered up front.

**Aim 2**
To help interpret the study results.

**Aim 3**
To develop a dissemination strategy tailored to the information needs and decision context of patients, clinicians, and policymakers.

**Aim 4**
To evaluate the impact of stakeholder engagement in the context of this project.
Stakeholder Engagement

• The ESAG currently has 14 confirmed members: an ethicist, guideline group representatives from NCCN and ASCO, an NCORP PI, a nurse, patient advocates (4), representatives from Aetna and Anthem, a representative of the Hematology/Oncology Pharmacy Association, and the SWOG Pharmacy Committee Chair.

• During the grant writing phase, the ESAG actively participated in the design of the intervention and provided feedback on other key components of the trial via individual solicitation and group webinars. Their input was systematically collected and incorporated into the final funded proposal.

<table>
<thead>
<tr>
<th>Representative Group</th>
<th>Topic</th>
<th>Question/Comment/Issue</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Site/Clinician</td>
<td>Comparators</td>
<td>Heterogeneous prescribing protocols in control arms will make comparison difficult</td>
<td>Cohort arm was added to provide additional opportunity for comparison.</td>
</tr>
<tr>
<td>Payer</td>
<td>Clinical significance</td>
<td>50% reduction in FN rate would work out to 5-8% in absolute terms. Discuss in grant what rate of FN reduction is clinically meaningful.</td>
<td>Addressed in proposal text</td>
</tr>
<tr>
<td>Patient Advocate</td>
<td>Costs to Patients</td>
<td>Patients should be trusted with financial implications of their treatment choices.</td>
<td>Added out-of-pocket costs and reasons for no CSF use to patient reported outcomes</td>
</tr>
</tbody>
</table>
Future Stakeholder Engagement

- Active involvement in writing the protocol
- Annual face-to-face meetings
- Twice yearly webinars
- Special consumer- and patient-focused webinars
- Online surveys at critical junctures for decision making
- Dedicated SharePoint site
- Individual consultation as needed
Timeline, Aug 2015-June 2020

- PCORI contract finalized, funding begins (Aug, 2015)
- First Patient Partner and full ESAG meetings (Aug, 2015)
- Study kick-off at SWOG Group Meeting (Fall, 2015)
- Clinic recruitment and randomization (Fall-Winter, 2015)
- Training and implementation of order-entry systems (Spring, 2016)
- Patient recruitment begins (Summer, 2016)
- Patient recruitment complete (Fall, 2018)
- Patient data collection complete (Winter, 2019)
- Prepare and disseminate final reports and manuscripts (Spring, 2020)
Investigator Team

**Fred Hutchinson**
- Scott Ramsey
- Gary Lyman
- Bernardo Goulart

**University of Washington**
- Sean Sullivan
- Jeannine McCune
- Aasthaa Bansal

**SWOG**
- Charles Blanke
- Bill Barlow

**Columbia University**
- Dawn Hershman
Thank You