No relevant disclosures

IMPACT
Improving the Management of symPtoms during And following Cancer Treatment

Consortium Overview

- An initiative designed to improve symptoms and side effects of cancer and its treatment through routine monitoring and management of patient-reported symptoms
- Supported by the National Cancer Institute with funding provided through the Cancer Moonshot[SM]
- Research centers are testing symptom management interventions integrated in the electronic health record (EHR) that collect patient-reported outcomes and trigger clinical responses consistent with guidelines in patients across the cancer continuum
- Examines intervention effects on symptom control, physical functioning, treatment delivery, and healthcare utilization
- Implementation science approaches are being used to examine the interventions' feasibility, acceptability, scalability and sustainability
- Pooled consortium-wide data will evaluate intervention effects across symptoms, the cancer continuum, and in underserved populations

For more information about IMPACT visit https://www.rti.org/impact/impact-consortium

IMPACT
Improving the Management of symPtoms during And following Cancer Treatment

IMPACT CONSORTIUM

IMPACT Research Center Descriptions: Pragmatic, cluster randomized trials

E2C2

- 1 health system
- 21 oncology care teams
- Patients on treatment, monitored, or survivorship care for solid tumors
- Recruit from rural populations, target older adults with cancer in MN, IA, and WI

MAYO CLINIC

SIMPRO

- 6 health systems
- GI, GYN, lung cancer patients receiving surgery or chemotherapy for advanced disease
- Recruit from diverse populations in community and rural settings in ME, WV, NH, VT, TN, MS, and MA

DANA-FARBER CANCER INSTITUTE
BAPTIST
Maine Medical Center MaineHealth
WVU Cancer Institute
Dartmouth-Hitchcock NORRIS COTTON CANCER CENTER
Lifespan Cancer Institute
Rhode Island Hospital • The Miriam Hospital Newport Hospital
Delivering health with care®

NU IMPACT

- 1 health system
  - 7 geographical/organizational clusters of 32 clinical practices
  - Embedded enhanced care individual-level randomized trial
- English and Spanish-speaking patients receiving treatment with curative or non-curative intent or disease-free survivors
- Recruit from racially and ethnically diverse populations in metropolitan Chicago

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IMPACT
Improving the Management of symPtoms during And following Cancer Treatment

Consortium Members

Research Triangle Institute **Coordinating Center** **Principal Investigator:** Barbara Kroner Grant No. U24CA232980	**Northwestern University IMPACT (NU IMPACT)** **Research Center** **Principal Investigator:** David Cella Grant No. UM1CA233035	**Symptom Management Implementation of Patient Reported Outcomes in Oncology (SIMPRO)** **Research Center** **Principal Investigators:** Michael Hassett, Deborah Shrag, Sandra Wong, Raymond Osarogiagbon, Grant No. UM1CA233080	**Enhanced, Electronic Health Record-Facilitated Cancer Symptom Control (E2C2)** **Research Center** **Principal Investigator:** Andrea Cheville Grant No. UM1CA233033	**National Cancer Institute, Division of Cancer Control and Population Sciences, Healthcare Delivery Research Program** **Program Director:** Lynn Adams
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We gratefully acknowledge our study participants and patient representatives

SIMPRO Research Center

Integration and Implementation of PROs for Symptom Management in Oncology Practice

Hajime Uno, PhD

Division of Population Sciences

Dana-Farber Cancer Institute

May 22, 2023

2023 SCT annual meeting

Disclosure

No relevant disclosures

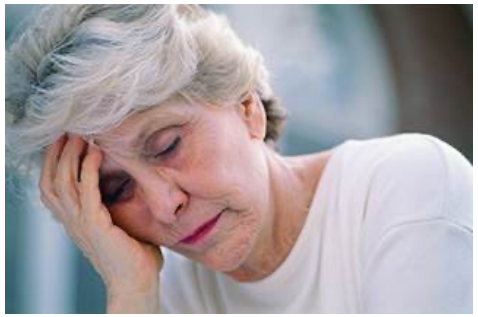
OUTLINE

- Background
  - SIMPRO Research Center
  - SIMPRO Project overview
- Intervention: eSyM
- Type II hybrid effectiveness-implementation SW-CRT to deploy and assess eSyM
  - Study Outcomes
  - Design features
  - Statistical Analysis Plan
- Challenges

Background

Current Problem

High symptom burden



Cancer patients

- Healthcare in the USA is reactive, not proactive
- Doctor-patient communication is often suboptimal (sparse)

Symptomatic patients may suffer between clinic visits

Promising approach

Research has shown that systematic assessment of **electronic patient-reported outcomes (ePROs)** coupled with clinical responses can *ease symptom burden, improve quality of life, reduce acute care needs, and extend survival.*

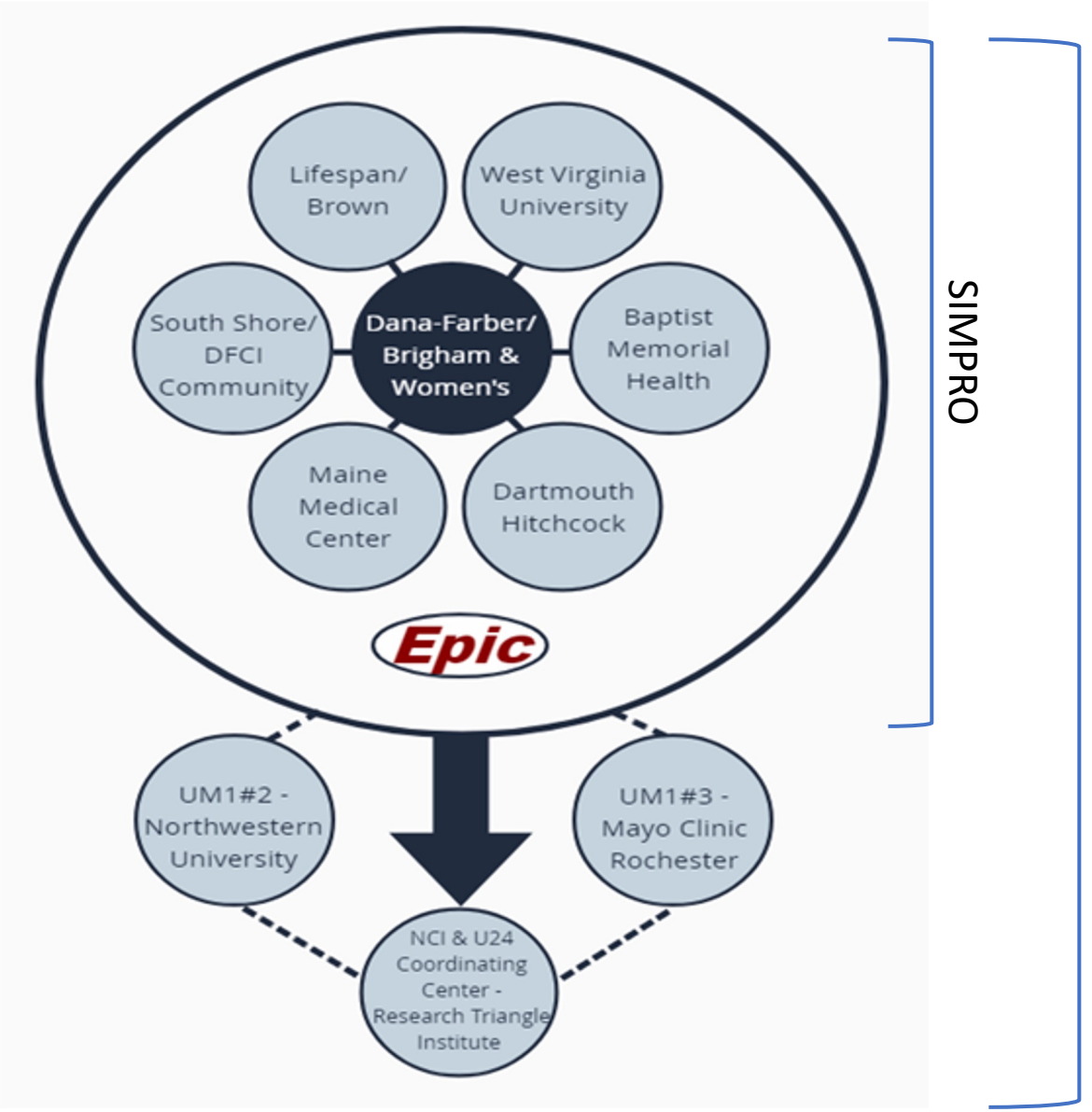
Challenge

Implementing ePRO-based symptom management programs in routine care is challenging because of workflow, staffing, and technical barriers.

eSyM Electronic Symptom Management

SIMPRO Research Center

- SIMPRO (***S***ymptom Management ***IM***plementation of ***P***atient ***R***eported Outcomes in ***O***ncology) is 1 of 3 research centers funded by the National Cancer Institute that together comprise the IMPACT Consortium (**I**mproving the **M**anagement of sym**P**toms during **A**nd following **C**ancer **T**reatment)
- SIMPRO includes **6 US health systems** that care for patients from many states
- SIMPRO **implementation** focus:
  - Community and rural cancer centers
  - Work directly with ***Epic*** (a HIPAA-compliant EHR)



eSyM Electronic Symptom Management

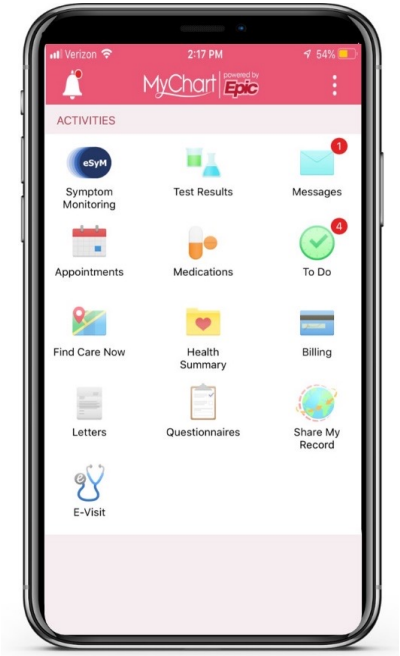
SIMPRO Project Overview

eSyM
Electronic
Symptom
Management

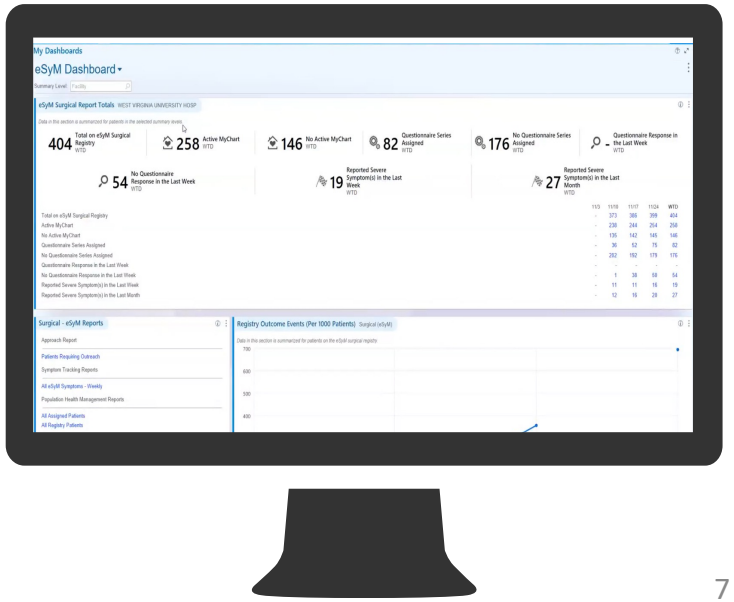
What is eSyM?

- **eSyM** is a coordinated set of tools within Epic which allow patients to **report** and clinicians to efficiently **track and react** to patients' symptoms during treatment or after surgery
- The primary purpose is to decrease emergency department visits and admissions during chemotherapy and after surgery, thereby improving quality of life
- Tracking patient symptoms supports communication, increases patient engagement, optimizes information collection, and leads to improved symptom management

Available to patients through MyChart



Available to staff and clinicians through Epic Hyperspace®



eSyM Electronic Symptom Management

Who is eSyM for?

eSyM focuses on two patient groups:

1. Surgery
   - Patients who have had a qualifying operation (based on CPT codes)

2. Medical Oncology
   - Patients starting a new chemotherapy or immunotherapy regimen (based on ICD-10 codes)

eSyM starts with focus on 3 cancer types:

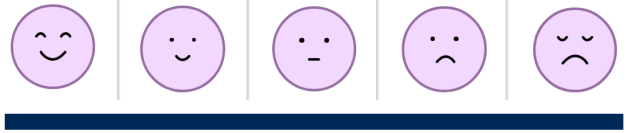
- eSyM Surgery focus: patients undergoing surgery for suspected **GI, GYN or thoracic malignancy**

- eSyM Medical Oncology focus: patients starting a new chemotherapy regimen for **GI, GYN, or thoracic malignancy** of any type

eSyM can easily be extended to other patient groups for research and non-research purposes

eSyM Electronic Symptom Management

What does eSyM ask patients to report?

Core Symptoms		Other Symptoms (Optional Pick List)		*Study-Developed Questions* (Items below were developed for eSyM)
Anxiety	Rash*	Bleeding	Hand Foot Syndrome	**Overall Wellbeing**
Constipation	Numbness & Tingling*	Cough	Headache	*In the last 7 days, how did you feel overall?*
Decreased Appetite	Diarrhea*	Insomnia	Heart Palpitations	
Fatigue	Wound Discharge**	Depression	Heartburn	**Physical Function**
Nausea	Wound Redness**	Difficulty Concentrating	Itching	*In the last 7 days, which best describes your activity level?*
Overall Wellbeing	Painful Urination**	Difficulty Swallowing	Mouth or Throat Sores	
Pain		Dizziness	Swelling	
Physical Function		Feeling Discouraged	Wheezing	
Shortness of Breath		Fever		
Trouble Drinking Fluids				
Vomiting				

* medical oncology patients only
** surgery patients only

- Patients answer standardized and validated symptom reporting questionnaires (PRO-CTCAE)
- Patients report on the severity, frequency, and interference of their symptoms
- No free text option
- Summary scores are generated: **0=none**, **1-2=mild/moderate**, **3= severe**

eSyM Electronic Symptom Management

When are patients asked to report?

- eSyM **automatically assigns** questionnaires to eligible patients (**no manual enrollment**)

Medical Oncology Version:

- Patients receive their first eSyM questionnaire the day after their D1C1
- Patients receive reminder MyChart messages to complete their eSyM questionnaire **on day 4 and 7** after chemotherapy
- Patients receive questionnaires for up to 180 days

Surgical Version:

- Patients receive their first eSyM questionnaire the day after discharge
- eSyM is assigned on a tapered schedule:
  - Weeks 1-2 → 3 questionnaires per week
  - Weeks 3-4 → 2 questionnaires per week
  - Weeks 5-8 → 1 questionnaire per week
- Patients receive questionnaires for up to 60 days

eSyM Electronic Symptom Management

SIMPRO SW-CRT & Outcomes

The eSyM program is being deployed through a type II hybrid effectiveness-implementation stepped wedge cluster randomized trial (SW-CRT). As such, we have clinical outcomes and implementation outcomes being assessed:

Outcome		Data Source
Primary Outcome	Emergency Department Treat/Release (EDTR) event within 30-days post-chemotherapy start or post-surgical discharge.	EHR
Key Secondary Clinical Outcomes	ED-hospitalization event occurrence within 30 days of eSyM trigger event	EHR
	Number of ED-hospitalization event occurrences during one-year follow-up	EHR
	Number of EDTR event occurrences during one-year follow-up	EHR
	Occurrence of 1st chemotherapy discontinuation during one-year follow-up	EHR
	Occurrence of 1st admission during one-year follow-up	EHR
	Occurrence of 1st re-operation during one-year follow-up	EHR
	Death during one-year follow-up	EHR
Key Secondary Implementation Outcomes	Evaluate facilitators and barriers to implementation of an EHR-integrated ePRO symptom management system from the patient, clinician and organizational perspectives.	Qualitative and quantitative methods (ERIC/CFIR)
	Evaluate **patient adoption, clinician utilization**, and their perspectives on appropriateness and acceptability	EHR and Survey
	Evaluate sustainability of ePRO symptom management within a health system	Qualitative and quantitative methods (CSAT survey)
	Evaluate penetration and scalability of ePROs for symptom management	Qualitative and quantitative methods (SASS qnrs + stakeholder interviews)
	Evaluate adaptation of ePRO systems over the course of the implementation process	Qualitative and quantitative methods (stakeholder interviews)

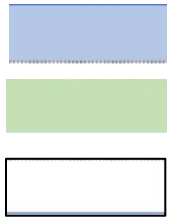
eSyM Deployment Schedule and Key features of SW-CRT

Sequence	Group	Site	eSyM version	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7
				Mar '19 - Aug '19	Sep '19- Feb '20	Mar '20- Aug '20	Sep '20 – Feb '21	Mar '21- Aug '21	Sep '21- Feb '22	Mar '22- Aug '22
Med Onc live Before Surgery	Southern	BAPT	Med	Pre-live	Live					
			Surg	Pre-live						Live
	Northern	MMC	Med	Pre-live		Live				
			Surg	Pre-live					Live	
	Metro-politan	DFCI	Med	Pre-live			Live			
			Surg	Pre-live				Live		
Surgery live Before Med Onc	Metro-politan	LCI	Med	Pre-live				Live		
			Surg	Pre-live			Live			
	Northern	DHMC	Med	Pre-live					Live	
			Surg	Pre-live		Live				
	Southern	WVU	Med	Pre-live						Live
			Surg	Pre-live	Live					

Notes:

1. No active recruitment
2. Eligible patients must be at least 18 years old and have an active patient portal account
3. Timing of the transition from the control condition to the intervention condition is different between Medical Oncology and Surgery
4. Possibly multiple data points will be collected from one patient since some patients may experience multiple trigger events

- Number sequences: 6 for each (Medical Oncology, Surgery)
- Number periods: 7
- Number clusters: 6 total (1 cluster per sequence)
- Period duration (step length): 6 months



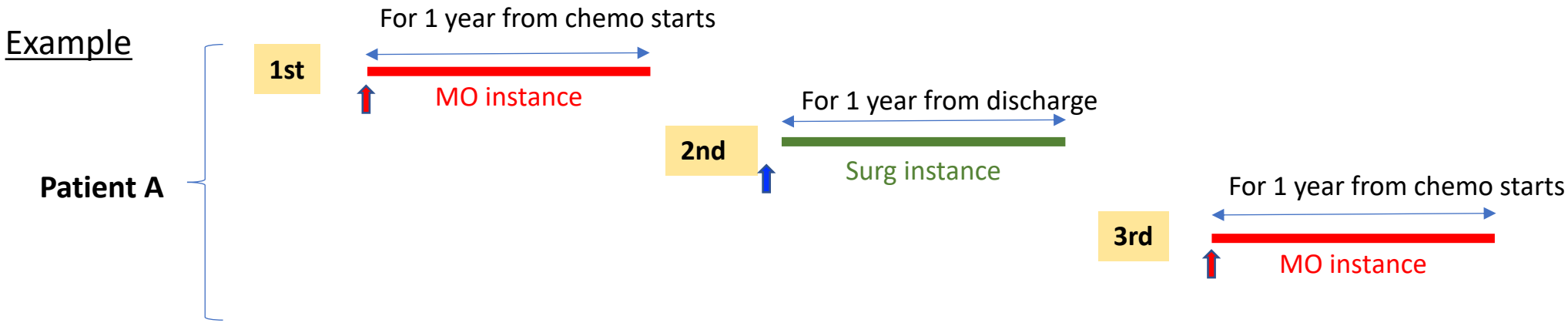
Intervention condition

Control condition

Definition of trigger event

Trigger event

- **Medical Oncology (MO):** a new chemotherapy treatment plan ⬆
- **Surgery (Surg):** a qualifying surgical procedure ⬆



Notes:

- Because each patient possibly experiences multiple episodes during the study period, the analysis data will include multiple data points from the same subject

eSyM Electronic Symptom Management

Conservative estimates of study sample size of the SW-CRT

Site	MO/Surg	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7	Total
BAPT	Med Onc	72	72	72	72	72	72	72	504
	Surgery	72	72	72	72	72	72	72	504
MMC	Med Onc	72	72	72	72	72	72	72	504
	Surgery	72	72	72	72	72	72	72	504
DFCI	Med Onc	72	72	72	72	72	72	72	504
	Surgery	72	72	72	72	72	72	72	504
LCI	Med Onc	72	72	72	72	72	72	72	504
	Surgery	72	72	72	72	72	72	72	504
DHMC	Med Onc	72	72	72	72	72	72	72	504
	Surgery	72	72	72	72	72	72	72	504
WVU	Med Onc	72	72	72	72	72	72	72	504
	Surgery	72	72	72	72	72	72	72	504
Total	**Med Onc**	**432**	**432**	**432**	**432**	**432**	**432**	**432**	**6048**
	Surgery	**432**	**432**	**432**	**432**	**432**	**432**	**432**	

Intervention condition (Medical Oncology)

Intervention condition (Surgery)

Control condition

eSyM Electronic Symptom Management

Statistical Analysis Plan

Multilevel generalized linear regression models (or GLMM)

- Link function
  - For binary outcomes (eg, ED visit yes/no within 30 days), the logit-link will be used. (Logistic regression)
  - For count outcomes (eg, # of ED visits), the log-link will be used, and the follow-up time will be included as the offset in the model. (Poisson regression)
- Secular trend
  - Primary: Time of the trigger event will be included as a continuous variable with natural cubic spline
  - Secondary: 7 periods will be included as a categorical variable.
- Site (cluster)
  - Primary: Due to a small number of cluster (i.e., 6 sites), sites will be included as fixed effects
  - Secondary: Sites will be included as random-effects with a small sample adjustment (the Kenward-Roger method)
- Subjects (cluster)
  - We will potentially have more than one data point from one subject in this study. Subjects will be included as random effects

eSyM Electronic Symptom Management

Challenges

1. Medical Oncology and Surgery Heterogeneity
2. Small number of clusters
3. Censoring by a new trigger event

1. Medical Oncology and Surgery Heterogeneity

- The intervention effect in Medical Oncology (MO) may be different from that in Surgery (Surg)
- Symptoms collected by eSyM are different between MO and Surg

- Interested in estimating an overall intervention effect of eSyM

<u>Planned analysis</u>

- Primary: The GLMM will include an indicator variable (MO vs. Surg)
- Secondary: We will analyze the data from MO and Surg separately and estimate the intervention effect for each

2. Small number of clusters

SIMPRO SW-CRT study

- The number of clusters is **only 6** (1 cluster per step)
- **The cluster size is >500**. (>1000 when MO and Surg are combined)

Planned analysis

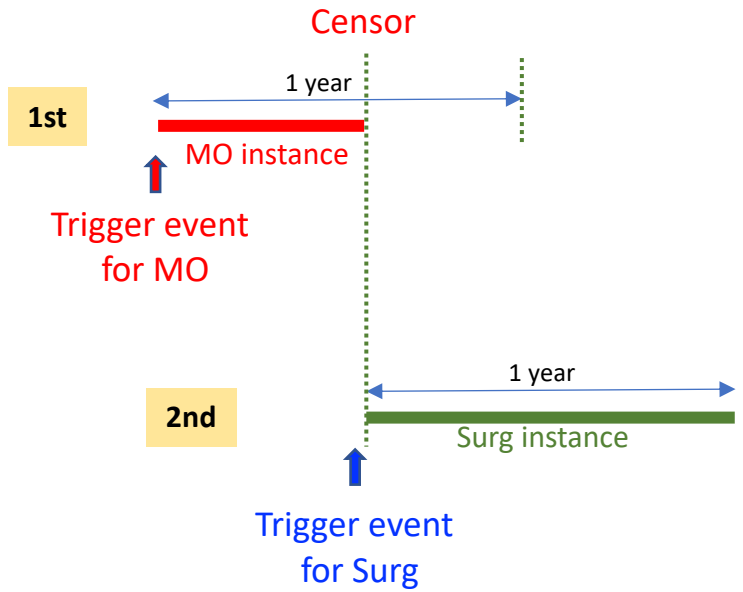
	Fixed Effect (FE) [primary analysis]	Random Effect (RE) [secondary analysis]
Model assumption	Weaker	Stronger
Robustness	Better preserved	Less preserved
Efficiency	Less efficient (if the RE model is valid)	More efficient (if the RE model is valid)
When the number of clusters is small	Will not have a problem unless the cluster size is small	Will have a problem Remedy: permutation test, correction of DF methods (the Kenward-Roger method will be used in SIMPRO)

eSyM Electronic Symptom Management

3. Censoring by a new trigger event

The follow-up of one instance may be censored by the occurrence of a new trigger event during the follow-up time

Example



- The primary endpoint is ED visit status yes/no at Day 30. We have confirmed that the cases where another trigger event occurred within 30 days follow-up is rare and negligible.

Planned analysis

- Binary outcomes: We will ignore censoring and use the event status at a specified time point (eg, Day 30)
- Count outcomes: We will take the length of the follow-up time of each instance into account via Poisson regression models.

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- Baptist Memorial Health Care Corporation, Memphis, TN
- Dana-Farber Cancer Institute, Boston, MA
- Dartmouth Hitchcock Medical Center, Lebanon, NH
- Lifespan Health System, Providence, RI
- Maine Medical Center, Portland, ME
- West Virginia University, Morgantown, WV

Trial registration:
ClinicalTrials.gov: NCT03850912
Registered on February 22, 2019.

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- Karla Hemming

Questions?

The SIMPRO Research Center website:
https://www.esymcancermoonshot.org/

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NU IMPACT: Design and Analysis Challenges

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Professor, Department of Preventive Medicine

Director, Northwestern University Data Analysis and Coordinating Center (NUDACC)

No relevant disclosures

NU IMPACT: Study Goals and Design

Primary goals: To study **clinic-level implementation outcomes** and **patient-level effectiveness outcomes** for an EHR-integrated oncology symptom assessment (cPRO) and management program across a multi-site healthcare delivery system

- Two interventions being evaluated: clinic-level and patient-level
  - **Clinic-level:** 'cPRO' symptom monitoring and management system across 7 regional clusters within the healthcare system using a cluster randomized modified stepped-wedge trial design
    - Evaluated using clinic-level 'implementation outcomes'
  - **Patient-level:** evidence-based symptom-management content on cancer-related concerns and approaches to enhance quality of life, using a web-based tool ('MyNM Care Corner')
    - Evaluated using patient-level 'effectiveness outcomes'

cPRO System

NU IMPACT Clinic-level Intervention

Multicomponent package of cPRO implementation strategies:

-Smart phrases for clinician ease of access to cPRO results
-Patient-facing education print materials
-In-clinic assistance with cPRO

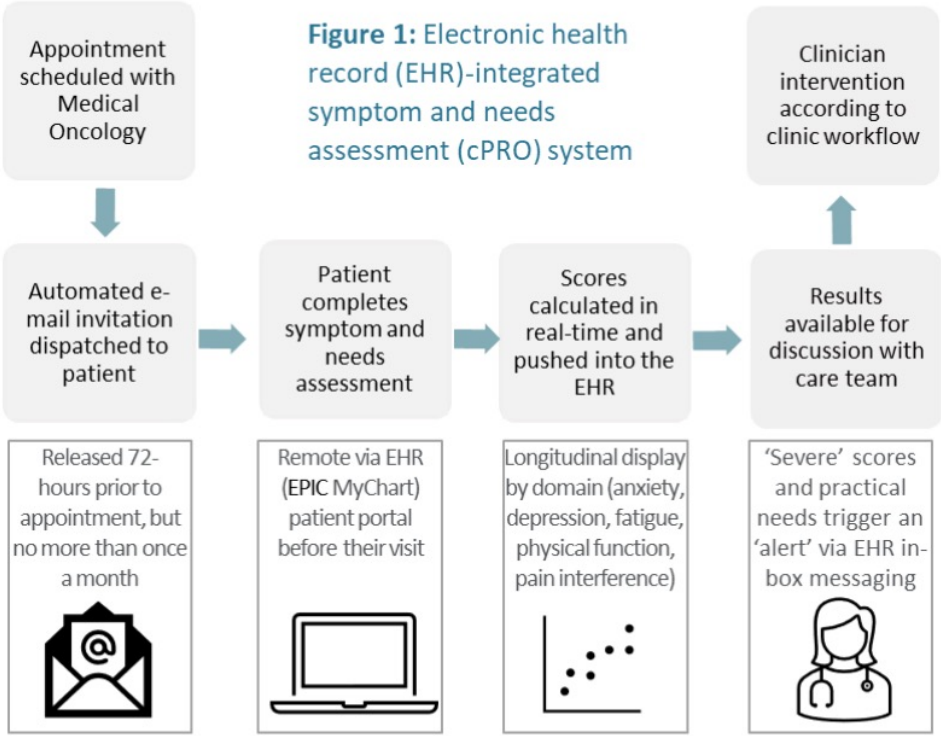

Figure 1: Electronic health record (EHR)-integrated symptom and needs assessment (cPRO) system

Figure published in Garcia SF, et al. BMJ Open. 2022;12(5):e059563. PMID: 35504641.

Intervention described in Cella D et al. Contemporary Clinical Trials. 2023;128:107171. PMID: 36990275.

NU IMPACT: Clinic-level Intervention SW Trial

Clinic-level intervention implemented across 32 clinics in 7 regional/ operational clusters (median 5 clinics per cluster) within the healthcare system using a cluster randomized stepped-wedge trial design.

First cluster was not randomized.

		Year 3				Year 4				Year 5				Year 6	
Cluster	Clinic	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
1	1	pre	pre	post	post	post	post	post	post	post	post	post	post	post	post
1	…	pre	pre	post	post	post	post	post	post	post	post	post	post	post	post
1	n_1	pre	pre	post	post	post	post	post	post	post	post	post	post	post	post
2	1	pre	pre	pre	post	post	post	post	post	post	post	post	post	post	post
2	…	pre	pre	pre	post	post	post	post	post	post	post	post	post	post	post
2	n_2	pre	pre	pre	post	post	post	post	post	post	post	post	post	post	post
3	1	pre	pre	pre	pre	post	post	post	post	post	post	post	post	post	post
3	…	pre	pre	pre	pre	post	post	post	post	post	post	post	post	post	post
3	n_3	pre	pre	pre	pre	post	post	post	post	post	post	post	post	post	post
4	1	pre	pre	pre	pre	pre	post	post	post	post	post	post	post	post	post
4	…	pre	pre	pre	pre	pre	post	post	post	post	post	post	post	post	post
4	n_4	pre	pre	pre	pre	pre	post	post	post	post	post	post	post	post	post
5	1	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post	post	post
5	…	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post	post	post
5	n_5	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post	post	post
6	1	pre	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post	post
6	…	pre	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post	post
6	n_6	pre	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post	post
7	1	pre	pre	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post
7	…	pre	pre	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post
7	n_7	pre	pre	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post

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MyNM Care Corner

NU IMPACT Patient-level Intervention

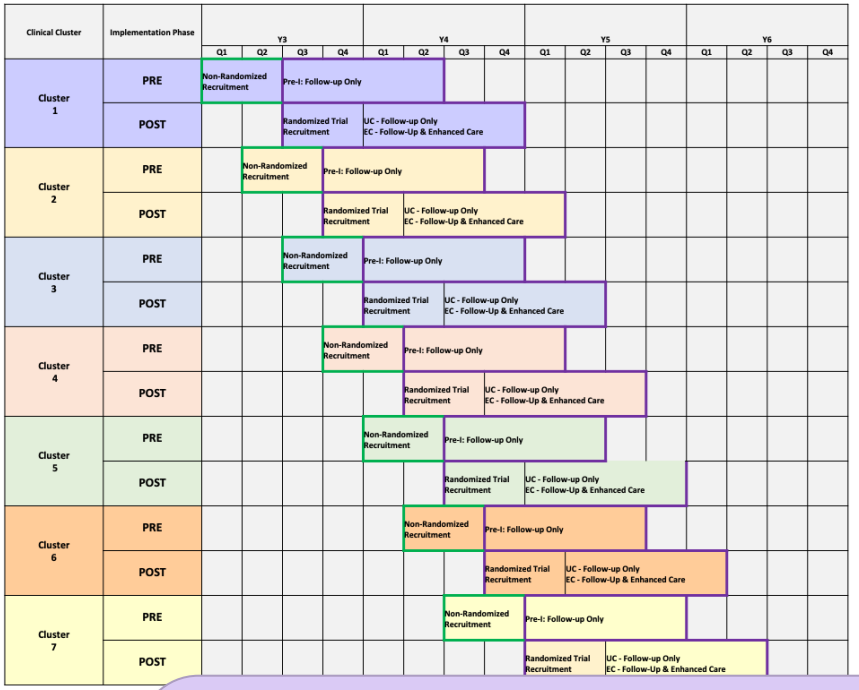
Intervention: 'Enhanced Care (EC)' additional self-management information through a patient-centered website/smartphone app called MyNM Care Corner

Comparator: 'Usual Care (UC)' cPRO

A subset of participants consent to complete monthly PROs during Pre-I. Another subset is randomized to EC:UC (1:1) during Post-I and completes the same monthly PROs.

Primary Outcomes

- PROMIS Anxiety v1.0, Depression v1.0, Fatigue v1.0, Pain Interference v1.1, Physical Function v1.2 (monthly for 12 months)



Statistical Analysis Plan:
Traditional RCT analysis methods
Not the focus of this presentation

Consented Pre-I and Post-I patients will be removed from implementation outcome analyses.

NU IMPACT: Implementation Outcomes

- **Primary**
  - **Patient-level adoption**: proportion of patients completing cPRO among those eligible

- **Secondary**
  - **Patient-level reach**: proportion of patients enrolled in cPRO among those eligible
  - **Patient-level reach**: proportion of patients who are referred for appropriate services from among those that trigger an alert in cPRO
  - **Provider-level adoption**: proportion of unique clinicians who use a cPRO dot phrase to follow up on triggers received from patients
  - **Survey outcomes** evaluating appropriateness, acceptability, feasibility, and sustainability of the implementation strategies package supporting cPRO
  - **Qualitative data** from focus group interviews concerning barriers/facilitators, acceptability, feasibility, and sustainability

Implementation Analysis Inclusion Criteria

- Cancer diagnosis in medical record (ICD-9/ICD-10 code on problem list or encounter diagnosis)
- Visit to the clinic during study period
- Still in care at NMHC (e.g., not deceased, care terminated, etc.)

Implementation Analysis Sample Size

- Estimated 12,000 patients (currently somewhat higher)
- Estimate based on sizes of clusters of clinics
- Prior years' metrics projected 18,000 unique patients across clinics, ranging 1500-4500 per cluster
- Estimated 2/3 patients would meet inclusion criteria
  - 30% treated for cure
  - 30% treated for life-extension
  - 40% disease-free survivors

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Implementation Analysis

- **Primary outcome: Reach**
  - Proportion of patients completing one or more (≥1) cPRO assessments among those eligible for cPRO
  - Clinic-level analysis using 6 randomized clusters
    - Clinics are nested within clusters, grouped by region and operational connections (e.g. shared leadership)
  - 1-month sampling periods
  - Outcome variable: proportion of patients who complete a cPRO assessment among those who are eligible within the clinic and the 1-month period

- Monthly proportion of patients completing one or more (≥1) cPRO assessments among those eligible for cPRO, depicted here for clinic 1 in cluster 2

		Year 3				Year 4				Year 5				Year 6	
Cluster	Clinic	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
1	1	pre	pre	post	post	post	post	post	post	post	post	post	post	post	post
1	…	pre	pre	post	post	post	post	post	post	post	post	post	post	post	post
1	n_1	pre	pre	post	post	post	post	post	post	post	post	post	post	post	post
2	1														
2	…	pre	pre	pre	post	post	post	post	post	post	post	post	post	post	post
2	n_2	pre	pre	pre	post	post	post	post	post	post	post	post	post	post	post
3	1	pre	pre	pre	pre	post	post	post	post	post	post	post	post	post	post
3	…	pre	pre	pre	pre	post	post	post	post	post	post	post	post	post	post
3	n_3	pre	pre	pre	pre	post	post	post	post	post	post	post	post	post	post
4	1	pre	pre	pre	pre	pre	post	post	post	post	post	post	post	post	post
4	…	pre	pre	pre	pre	pre	post	post	post	post	post	post	post	post	post
4	n_4	pre	pre	pre	pre	pre	post	post	post	post	post	post	post	post	post
5	1	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post	post	post
5	…	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post	post	post
5	n_5	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post	post	post
6	1	pre	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post	post
6	…	pre	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post	post
6	n_6	pre	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post	post
7	1	pre	pre	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post
7	…	pre	pre	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post
7	n_7	pre	pre	pre	pre	pre	pre	pre	pre	post	post	post	post	post	post

Outcome Data Points

- 30 clinics, 42 monthly proportions, 1260 data points

Clinics in…	Number of monthly Pre-I proportions	Number of monthly Post-I proportions
Cluster 2	9	33
Cluster 3	12	30
Cluster 4	15	27
Cluster 5	18	24
Cluster 6	21	21
Cluster 7	24	18

Implementation Outcome Statistical Analysis

- **Generalized least squares linear regression analysis**
  - Primary predictor: Post-I v. Pre-I [referent]
  - Autoregressive correlation structure (lag 1) among linear model residuals resulting from repeated measures within clinic
    - Other correlation structures evaluated using AIC and BIC
- **Effect estimates**
  - Identity link to estimate risk differences
  - Log-transformed proportion outcomes to estimate risk ratios
- **Clinic level covariate adjustment**
    - cluster; time (categorical variable for quarter); number of 1.0 FTE equivalent oncologists per clinic; number of unique patients per clinic; type of cancer care clinic (e.g., medical oncology, surgical oncology).

Implementation Outcome Statistical Analysis

- **Sensitivity analyses**
  - Weights based on number of eligible patients per clinic
  - No formal transition period, but will evaluate removing observations at the crossover point (2 1-month increments on either side of the post-I start up)
  - Test for cluster*treatment and time*treatment effects to test for lagged / delayed effect of the exposure
- **Computation**
  - Restricted maximum likelihood (REML) estimation
  - nlme R package

  - Similar approach specified for secondary outcomes

NU IMPACT: Challenges

- Analytic plan described here was developed in response to surprises as the trial was conducted
  - Far fewer patients consented to monthly PRO assessments and randomization to EC:UC than anticipated
  - Motivated an analytic plan with more ‘separation’ of system-wide versus patient-level interventions than originally intended

- Implementation outcomes
  - Clinic-level v. cluster-level v. patient-level definitions – much debate!
    - E.g. one alternative was individual level data using GLMM with random cluster or clinic effects.
  - Understanding correlation of observations within clinic – also much debate!
    - Many sources of correlation, including patients contributing to monthly summaries across Pre-I and Post-I phases.
    - The individual level GLMM analysis could allow more complicated correlation structures, but can suffer from convergence problems.

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Questions?

Northwestern Medicine®

E2C2

Society for Clinical Trials

22 May 2023

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MAYO CLINIC

IMPACT
Improving the Management of symPtoms during And following Cancer Treatment

Disclosures

No relevant disclosures

E2C2: Overview

E2C2 : Enhanced, EHR-facilitated Cancer Symptom Control

"…a pragmatic, stepped-wedge cluster-randomized clinical trial that will assess the impact of an intervention to control … symptoms among patients with cancer spanning the cure-directed, survivorship, and palliative phases of disease management, while also exploring factors relevant to its implementation."

MAYO CLINIC

E2C2 - Study design

Stepped Wedge Cluster-Randomized Trial

- Clusters = 15 cancer care teams
  - 11 at Mayo Rochester (RST)
  - 4 at other sites (SWWI, NWWI SWMN, SEMN
- Care teams were randomized to 5 sequences of 6 steps
  - Step 0 – 6 months baseline
  - Steps 1-5 – 8 months
- All patients treated by these 15 cancer teams are included
  - Followed for entire study period

Figure 1. Final allocation of 15 cancer care teams to 5 sequences.

		Step						Sequence
Cluster	Strata	0	1	2	3	4	5	
SWWI	2	0	1	1	1	1	1	011111
RST:Head/Neck	1	0	1	1	1	1	1	
RST:GU	4	0	1	1	1	1	1	
RST:Lung	2	0	0	1	1	1	1	001111
RST:Sarcoma	1	0	0	1	1	1	1	
RST:GI Blue	4	0	0	1	1	1	1	
RST:Breast	2	0	0	0	1	1	1	000111
NWWI	3	0	0	0	1	1	1	
RST:Gyn	1	0	0	0	1	1	1	
SWMN	3	0	0	0	0	1	1	000011
RST:GI Red	4	0	0	0	0	1	1	
RST:Brain	1	0	0	0	0	1	1	
RST:Melanoma	1	0	0	0	0	0	1	000001
RST:General/Endo	1	0	0	0	0	0	1	
SEMN	2	0	0	0	0	0	1	
		T1	T2	T3	T4	T5	T6	

Control condition
Intervention condition
T1 6 months
T2-T6 8 months

E2C2- Intervention and Outcomes

Intervention (key elements)

- Booklet describing general symptom self-management strategies
- Additional EHR-delivered educational materials to support self-management of problematic symptom(s)
- Phone call from a nurse symptom care manager if severe symptoms
- EHR-based clinical decision support, support for oncology providers

Comparator

- Usual care
  - + additional collection of PROMs

Primary outcomes

- SPPADE hexad symptoms
  - Sleep disturbance, Pain, Physical function decline, Anxiety, Depression, and Energy deficit scores
  - Self-reported measures using 0-10 numerical rating scales

Secondary outcomes

- Requests for guideline-concordant symptom management
- Rates of ED visits and hospitalizations
- Treatment adherence
- Vital status

E2C2- Measurements and Considerations

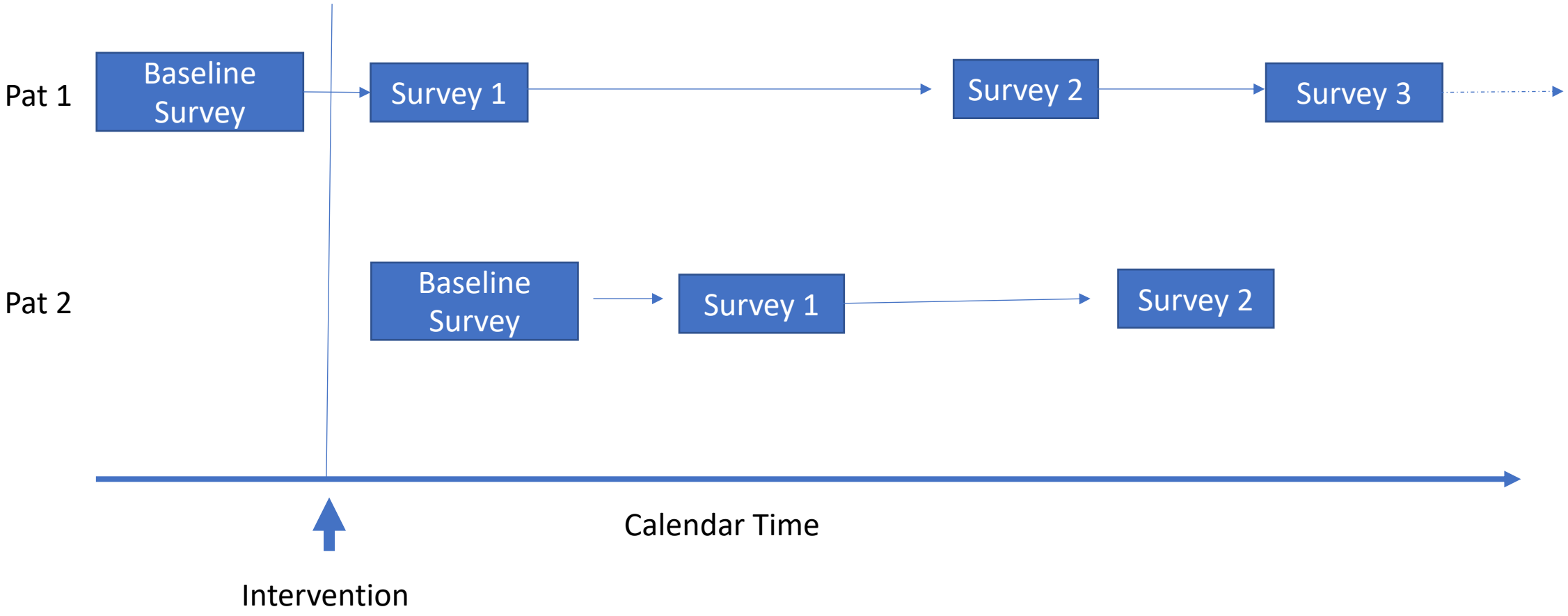
Measurement of Primary Outcomes

- Collected before a patient's visit
  - Collected electronically
  - On site or through the patient web portal
- Collected at all subsequent visits
  - No fixed schedule
  - On site or through the web portal

Considerations

- Patients clustered within care teams
- Repeated patient measures over time
- Patients may contribute control and intervention state data
- Individuals will have secular change in symptoms
  - Related to the cancer type (~ care team)
- Number or spacing of surveys may be associated with patient factors
  - Age, sex, severity of illness
  - Education, income, broadband access

E2C2- Patient measurement (single cluster)



E2C2 – model

Analyze at level of survey encounter

Model jointly using a multivariate linear mixed model with 6 dependent variables

- Adjust for calendar time (6 month indicators)
- Adjust Y_k for prior symptom score Y_{k-1}
- Random patient effects – capture mean patient effect
  - Time dependence of Y_k on prior symptom score Y_{k-1}
    => Lag as moderator approach, using L x Y_{k-1} to account for time between surveys
- Random cluster effects – capture mean cluster score in each time period
  - Discrete- step x cluster level effects
- Adjust for 6 key patient covariates that may be associated with survey completion

Fully Bayesian estimation

- Have successfully implemented this model in Stan using initial sample of 30k patients (without intervention indicator)
- Use a single posterior probability of 6 joint effects to test hypothesis

E2C2- Status

Final data collection in February 2023

- About 50,000 patients enrolled over 3 years.
- Median of 3 data points per patient (baseline + 2 followup).
- Currently in process of finalizing data.

Challenges

- Hypothesis
- Clusters

E2C2- Primary Hypotheses

Original

Intervention will reduce SSPADE scores relative to patients receiving usual care

Challenge

Intervention only impacts patients with elevated scores

- Patients with no elevated scores will be treated the same as control patients
- Initial data review found about 20% with no elevated scores, substantially diluting intervention effect.

E2C2- Primary Hypotheses

Solution

Two primary hypotheses

1a. Intervention will reduce SSPADE scores relative to patients receiving usual care

1b. Intervention will reduce SSPADE scores in patients **with at least one elevated symptom score**, relative to patients **with at least one elevated symptom score** receiving usual care.

Sample size adequate (50k patients, planned 40k)

E2C2 - Clusters

Two clusters are separate teams in the same unit

- Turns out they aren't that separate
- Intervention is 1 year apart

Figure 1. Final allocation of 15 cancer care teams to 5 sequences.

Cluster	Strata	Step 0	1	2	3	4	5	Sequence
SWWI	2	0	1	1	1	1	1	
RST:Head/Neck	1	0	1	1	1	1	1	011111
RST:GU	4	0	1	1	1	1	1	
RST:Lung	2	0	0	1	1	1	1	
RST:Sarcoma	1	0	0	1	1	1	1	001111
RST:GI Blue	4	0	0	1	1	1	1	
RST:Breast	2	0	0	0	1	1	1	
NWWI	3	0	0	0	1	1	1	000111
RST:Gyn	1	0	0	0	1	1	1	
SWMN	3	0	0	0	0	1	1	
RST:GI Red	4	0	0	0	0	1	1	000011
RST:Brain	1	0	0	0	0	1	1	
RST:Melanoma	1	0	0	0	0	0	1	
RST:General/Endo	1	0	0	0	0	0	1	000001
SEMN	2	0	0	0	0	0	1	
		T1	T2	T3	T4	T5	T6	

Control condition
Intervention condition
T1 6 months
T2-T6 8 months

E2C2 - Clusters

Solution

Assign ambiguous observations to the late cluster

- bias towards the null

Secondary analyses

- Drop ambiguous patients

Questions?

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ClinicalTrials.gov : NCT03892967

Navigating Stepped Wedge Cluster Randomized Trials: Unraveling the complexities

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Three Stepped Wedge CRTs

	NU IMPACT	E2C2	SIMPRO
Intervention	'cPRO' symptom monitoring and management system	EHR-faciliated cancer system control	Epic/MyChart-integrated symptom management system
Primary Outcomes	Proportion of patients completing ≥ 1 cPRO assessments	six symptom scores	yes/no (30-days ED visit)
Unit of analysis	clinic-level	survey encounter	patient level
Number of Randomization Units	6	15	6
Total Sample Size	12,000+	$\sim$ 50,000	6048
Analysis strategy	GLM	MLMM	GLMM
Some challenges	complex correlation structure	primary hypothesis	small number of clusters
Treatment effect heterogeneity	delayed effect	w./w.o. elevated scores	medical oncology vs. surgery

Model 1

- Model 1 (Hussey and Hughes 2007):

$$h\{E(Y_{kti} \mid X_{kt}, \alpha_k)\} = \mu + \beta_t + \theta X_{kt} + \alpha_t,$$

  - h is a link function
  - μ is the intercept
  - β_t is the fixed effect for time ($\beta_1 = 0$ for identifiability)
  - θ represents the treatment effect
  - $\alpha_k \sim N(0, \sigma_\alpha^2)$ is a cluster-level random intercept.

- Assumes that the treatment effect is instantaneous and constant: treatment is effective immediately, and the effect remains the same regardless how long the cluster has been under the exposure condition

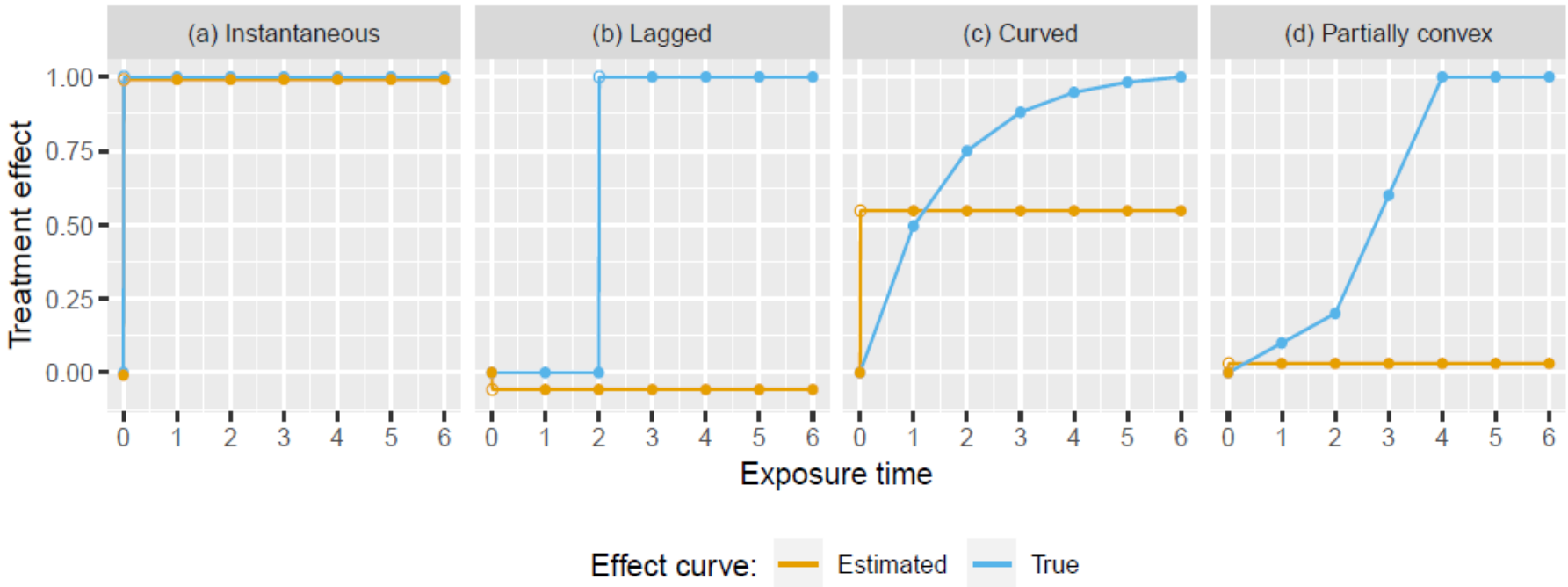
Constant treatment effect by exposure time

	t=1	t=2	t=3	t=4	t=5
k=1	0	θ	θ	θ	θ
k=2	0	0	θ	θ	θ
k=3	0	0	0	θ	θ
k=4	0	0	0	0	θ

Schematic of intervention effect for Model 1 for a SW-CRT with K=4 clusters and T=5 time periods

Treatment effect as a function of exposure time

Figure 2 of Kenny et al. (SIM, 2022) illustrates that, in the presence of treatment effect heterogeneity across exposure time, the resulting estimator from Model 1 does not necessarily represent the average of exposure-time specific treatment effect, even for a continuous outcome



Replacing θ with $\theta(E_{kt})$?

Linear treatment effect (Model 2)

$$\theta(E_{kt}) = \omega_0 + \omega_1(E_{kt} - 1)_+$$

	t=1	t=2	t=3	t=4	t=5
k=1	0	ω	2ω	3ω	4ω
k=2	0	0	ω	2ω	3ω
k=3	0	0	0	ω	2ω
k=4	0	0	0	0	ω

Schematic of intervention effect for Model 2 for a SW-CRT with K=4 clusters and T=5 time periods

Delayed treatment effect (Model 3)

$$\theta(E_{kt}) = \pi^{(1)} I(0 < E_{kt} \leq \ell) + \pi^{(2)} I(E_{kt} > \ell)$$

	t=1	t=2	t=3	t=4	t=5
k=1	0	π_1	π_2	π_2	π_2
k=2	0	0	π_1	π_2	π_2
k=3	0	0	0	π_1	π_2
k=4	0	0	0	0	π_1

Schematic of intervention effect for modelling a delayed-by-one treatment effect for a SW-CRT with K=4 clusters and T=5 time periods

General treatment effects (Model 4)

$$\theta(E_{kt}) = \theta_{E_{kt}}$$

	t=1	t=2	t=3	t=4	t=5
k=1	0	θ_1	θ_2	θ_3	θ_4
k=2	0	0	θ_1	θ_2	θ_3
k=3	0	0	0	θ_1	θ_2
k=4	0	0	0	0	θ_1

Schematic of intervention effect for Model 4 for a SW-CRT with K=4 clusters and T=5 time periods

A random effect model forumaltion (Model 5)

$$h\{E(Y_{kti} \mid X_{kt}, \alpha_k)\} = \mu + \beta_t + (\phi + \delta_{E_{kt}})X_{kt} + \alpha_t,$$

where $\delta_{E_{kt}}$ follows a distribution F and is independent of $\alpha_k \sim N(0, \sigma^2_\alpha)$.

	t=1	t=2	t=3	t=4	t=5
k=1	0	$\varphi + \delta_1$	$\varphi + \delta_2$	$\varphi + \delta_3$	$\varphi + \delta_4$
k=2	0	0	$\varphi + \delta_1$	$\varphi + \delta_2$	$\varphi + \delta_3$
k=3	0	0	0	$\varphi + \delta_1$	$\varphi + \delta_2$
k=4	0	0	0	0	$\varphi + \delta_1$

Schematic of intervention effect for Proposed Model 5 for a SW-CRT with K=4 clusters and T=5 time periods

Testing and Estimation

- Testing the null hypothesis of no treatment effect heterogeneity across exposure time
  - (Model 4) H_0: $\theta_1 = \theta_2 = \cdots = \theta_E = \theta$ (Likelihood ratio test)
  - (Model 5) H_0: $\sigma^2_\delta = 0$ (permutation test)

- Estimating the average and exposure-time specific treatment effects

Exposure time	Model 1	Model 2	Model 3	Model 4	Model 5
Average (Δ)	θ	$\frac{1}{E}\sum_{e=1}^{E} e\omega$	$\frac{1}{E}(\pi^{(1)} + (E-1)\pi^{(2)})$	$\frac{1}{E}\sum_{e=1}^{E} \theta_e$	ϕ
1	θ	ω	$\pi^{(1)}$	θ_1	$\phi + \delta_1$
2	θ	2ω	$\pi^{(2)}$	θ_2	$\phi + \delta_2$
⋮	⋮	⋮	⋮	⋮	⋮
E	θ	$E\omega$	$\pi^{(2)}$	θ_E	$\phi + \delta_E$

- All models fall under the generalized linear mixed model framework, standard software available (e.g., lme4 in R) for parameter estimation

- For variance estimation, we use the cluster bootstrap methods

Maleyeff L, Li F, Haneuse S, Wang R. Assessing exposure-time treatment effect heterogeneity in stepped-wedge cluster randomized trials, Biometrics, First published: 23 November 2022.

Different types of treatment effect heterogeneity

(a) *Model 5:* $\theta(t,k) = \phi + \delta_{E_{tk}}$

$k=1$	0	$\phi+\delta_1$	$\phi+\delta_2$	$\phi+\delta_3$	$\phi+\delta_4$
$k=2$	0	0	$\phi+\delta_1$	$\phi+\delta_2$	$\phi+\delta_3$
$k=3$	0	0	0	$\phi+\delta_1$	$\phi+\delta_2$
$k=4$	0	0	0	0	$\phi+\delta_1$

(b) *Hemming et al.:* $\theta(t,k) = \psi + \nu_k$

$k=1$	0	$\psi+\nu_1$	$\psi+\nu_1$	$\psi+\nu_1$	$\psi+\nu_1$
$k=2$	0	0	$\psi+\nu_2$	$\psi+\nu_2$	$\psi+\nu_2$
$k=3$	0	0	0	$\psi+\nu_3$	$\psi+\nu_3$
$k=4$	0	0	0	0	$\psi+\nu_4$

Hemming K, Taljaard M, and Forbes A. Modeling clustering and treatment effect heterogeneity in parallel and stepped-wedge cluster randomized trials. Statistics in Medicine, 37(6), 883-898.

Model extensions - different types of treatment effect heterogeneity

Incorporate treatment effect heterogeneity both at the exposure-time level and at the cluster level

(c) *Model 6:* $\theta(t,k) = \pi + \delta_{E_{tk}} + \nu_k$

$k=1$	0	$\pi+\delta_1+\nu_1$	$\pi+\delta_2+\nu_1$	$\pi+\delta_3+\nu_1$	$\pi+\delta_4+\nu_1$
$k=2$	0	0	$\pi+\delta_1+\nu_2$	$\pi+\delta_2+\nu_2$	$\pi+\delta_3+\nu_2$
$k=3$	0	0	0	$\pi+\delta_1+\nu_3$	$\pi+\delta_2+\nu_3$
$k=4$	0	0	0	0	$\pi+\delta_1+\nu_4$

Alternative Analysis Strategies

- Fully parametric: Likelihood-based inference (GLMM)
- Semi-parametric: Marginal mean specification (GEE) (Liang and Zeger, Biometrika, 1986)
  - Only requires the mean model to be correctly specified, valid inference is robust to the misspecification of the correlation structure
  - Correct specification of the correlation structure affects efficiency (Mancl and Leroux, Biometrics, 1996)
  - The number of clusters can not be too small (finite sample correction) (Fay and Graubard, Biometrics, 2001; Preisser et al., SIM, 2008; Scott et al., SMMR, 2017; Thompson et al., SMMR, 2020)
  - The use of GEE analyses in stepped wedge cluster randomized trials have been studied (see for examples, Li et al., Biometrics, 2018; Li, SIM, 2020; Ford and Westgate, SIM, 2020; Harrison and Wang, SIM, 2021)
  - Computational challenges when the cluster sizes are large may be addressed by stochastic gradient descent (Chen et al., JCGS, 2020)

Alternative Analysis Strategies

- Fully parametric: Likelihood-based inference (GLMM)
- Semi-parametric: Marginal mean specification (GEE)
- Non/Semi-parametric: Randomization-based inference
  - Testing the null hypothesis of no intervention effect is non-parametric (Ji et al., AoAS, 2017; Wang and De Gruttola, SIM, 2017)
  - Can be based on individual-level data or cluster-level data (Thompson et al., SIM, 2018; Kennedy-Shaffer et al., SIM, 2020; Hughes et al., Biometrics, 2020)
  - Randomization-based CIs based on individual-level data can be obtained leveraging the offset term in the model (Rabideau and Wang, SIM, 2021)
  - Faster algorithm to obtain randomization-based CIs is available (Garthwaite, Biometrics, 1996; Garthwaite and Jones, JCGS, 2009)
  - Can easily incorporate design features (stratified/constrained randomization)

Some Remarks

- Carefully consider the rationale of choosing stepped-wedge designs versus parallel designs (Hemming and Taljaard, IJE 2020)
- Unit of randomization and unit of analysis
- Analysis approaches: A review of conditional and marginal model variants and associated statistical software for estimating model parameters is provided in Li and Wang (2022; World Neurosurgery)
- Sample size calculation can be complex: varying cluster sizes (Martin et al., BMC Medical Research Methodology, 2019; Harrison et al., Biometrics, 2019), treatment effect heterogeneity along the exposure time scale (Maleyeff et al., Biometrics, 2022), targeting both the average treatment effect and/or confirmatory interaction effects

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