Title Page

Grant Number: 1R01OH010582-04
FAIN: R01OH010583
Principal Investigator(s): CHRISTOPHER R. FRIESE, PHD, RN, AOCN®, FAAN
UNIVERSITY OF MICHIGAN SCHOOL OF NURSING
400 North Ingalls Building, Room 1172
Ann Arbor, MI 48109-5482
(734) 647-4308, cfriese@umich.edu

Co-Investigator(s): MARJORIE C. MCCULLAGH, PHD, RN, APHN-BC, COHN-S, FAAOHN, FAAN
UNIVERSITY OF MICHIGAN SCHOOL OF NURSING
400 North Ingalls Building, Room 3182
Ann Arbor, MI 48109-5482
(734) 763-3450, mcculla@umich.edu

DUXIN SUN, PHD
UNIVERSITY OF MICHIGAN COLLEGE OF PHARMACY
North Campus Research Complex
1600 Huron Pkwy., Building 520, Room 3353
Ann Arbor, MI 48109-2800
(734) 615-8740, duxins@umich.edu

JAMES YANG, PHD
UNIVERSITY OF MICHIGAN SCHOOL OF NURSING
400 North Ingalls Building, Room 4336
Ann Arbor, MI 48109-5482
(734) 764-4143, jjyang@med.umich.edu

Project Manager: KARI MENDELSOHN-VICTOR**,** MPH
UNIVERSITY OF MICHIGAN SCHOOL OF NURSING
400 North Ingalls Building, Room 4344
Ann Arbor, MI 48109-5482
(734) 615-4017, karimend@umich.edu

Institution: Regents of the University of Michigan, 881 N University Ave, Ann Arbor, MI 48109

Project Title: Randomized Controlled Trial to Improve Oncology Nurses' Protective Equipment Use (also known as DEFENS: Drug Exposure Feedback and Education for Nurses' Safety)
7/1/2014 – 6/30/2019

Sponsor(s): National Institute of Occupational Safety and Health, Centers for Disease Control and Prevention, Department of Health and Human Services

Report: Final **Date of Preparation:** September 27, 2019

Table of Contents

List of Terms and Abbreviations

ASCO: American Society of Clinical Oncology
DEFENS: Drug Exposure Feedback and Education for Nurses' Safety
HIPAA: Health Insurance Portability and Accountability Act
IAA: IRB authorization agreement
ICC: Intraclass correlation coefficient
IRB: Internal Review Board
JITAI: Just-in-time adaptive intervention
LC-ESI-MS: Liquid chromatography-electrospray ionization-mass spectrometry
LLOQ: Lower limit of quantification
LOD: Level of detection
MRM-IDA-EPI: Multiple reaction monitoring-information dependent acquisition-enhanced production ion
NIOSH: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, United States
ONS: Oncology Nursing Society
PI: Primary investigator
PPE: Personal protective equipment.
RN: Registered nurse
RT: Retention time
USP: United States Pharmacopeia

Abstract

Randomized Controlled Trial to Improve Oncology Nurses' Protective Equipment Use

(also known as DEFENS: Drug Exposure Feedback and Education for Nurses' Safety)
Christopher R. Friese, RN, PhD, AOCN®, FAAN, Principal Investigator

University of Michigan School of Nursing cfriese@umich.edu

Objectives: Occupational exposure to hazardous drugs confers well-documented adverse health effects to health care workers. Nurses in ambulatory oncology settings are at high risk given the large volume of drugs administered. Extensive preliminary data show frequent hazardous drug exposure in the ambulatory oncology setting, low perceived risk of drug exposure, inadequate knowledge about personal protective equipment (PPE) use, and low PPE use by nurses, in addition to differences in organizational factors between exposed and unexposed nurses. Despite this knowledge, there is an absence of tested interventions aimed at increasing PPE use among nurses who handle hazardous drugs. This project was aligned with Goals 1 and 3 of the 2013 National Occupational Research Agenda for Healthcare and Social Assistance: to "promote safe and healthy workplaces and optimize safety culture in healthcare organizations," and "reduce or eliminate exposures and adverse health effects caused by hazardous drugs and other chemicals."

Methods: A cluster, randomized controlled design was used to evaluate the efficacy of a web-based audit and feedback intervention intended to increase risk perception, reduce barriers to PPE use, and ultimately improve adherence to recommended PPE. Sites randomized to the control condition received a one-hour continuing education module on hazardous drug handling. The primary endpoint of the trial was increased use of personal protective equipment when handling hazardous drugs. A second component of the project was to prospectively describe hazardous drug spills experienced by participants. Blood and plasma samples were obtained from all participants to develop methods to measure hazardous drug exposures among ambulatory oncology nurses. An innovative high performance liquid chromatography multiple reaction monitoring-information dependent acquisition-enhanced production ion analytical method was developed to simultaneously detect the presence of 18 hazardous drugs in human samples.

Results: From 2015 to 2017, the investigators partnered with 12 ambulatory oncology settings in the United States to enroll 396 nurses, 257 of whom completed baseline and primary endpoint surveys. Control and intervention sites had suboptimal PPE use before and after the intervention. No significant differences were observed in PPE use, knowledge, or perceived barriers. Participants reported high satisfaction with the study experience. Over 24 months, participants reported 73 unique hazardous drug spills, which ranged in volume from 1 to 200 mL. During spill response, nurses reported wearing disposable gowns (65% of the time), double gloves (52%), single gloves (41%), respirators (28%), and eye shields (26%). No detectable plasma concentrations were measured at baseline, post-intervention and in cases of spills.

Conclusions: Hazardous drug exposure confers notable health risks to health care workers. A novel feedback intervention targeted to oncology nursing clinicians did not result in improved personal protective equipment use. Standardized hazardous drug spill reporting and analysis is a promising quality improvement tool to identify and rectify practice gaps. Our project has contributed to the methodology to detect multiple hazardous drugs simultaneously through easily-reproducible methods. To improve the safety and health of oncology clinicians, occupational health care workers, health systems, and professional organizations should consider coordinated, multi-level efforts to implement policy and practice changes.

Keywords: Antineoplastic drugs, workplace exposure, registered nurses, randomized trials

Clinical Trials Registry: NCT02283164

Section 1 of the Final Progress Report

Significant or Key Findings

1. Despite numerous guidelines, standards, and policies, nurses in ambulatory oncology settings continue to not wear personal protective equipment as recommended. Our study identified that a majority of participants failed to wear two pairs of chemotherapy-tested gloves and a single-use, disposable gown when handling hazardous drugs. When spills occurred, the majority of respondents surveyed did not immediately don personal protective equipment before commencing clean up activities or assisting patients.

2. The intervention tested in this study – a theory-based, tailored feedback intervention – did not result in improved personal protective equipment use. Scores on the revised hazardous drug handling questionnaire did not change significantly between baseline and primary endpoint assessment, in either arm of the trial. None of the proposed mediator or moderator variables was significantly associated with PPE use.

3. Ambulatory oncology nursing practices experience acute hazardous drug exposure "drug spills" not infrequently. In the two-year reporting period, 73 unique spills were reported, involving 86 exposures to nurse participants. Over half (65%) of spills occurred during the use of a closed-system transfer device, yet respondents reported the device functioned properly only 20% of the time. Suboptimal use of PPE was reported during spill response.

4. After developing a novel, reproducible approach to screen biological samples from health care workers for commonly used hazardous drugs, we did not detect hazardous drugs in the study sample. Our colleagues at the Rogel Cancer Center Pharmacokinetics Core led an analysis of plasma samples obtained from all study participants and a small pilot sample of urine samples (to assure comparability across biological samples).

Translation of Findings

Key study findings suggest that direct and indirect hazardous drug exposures remain a pervasive problem in health care settings. Interventions targeted to individual health care workers may be less effective than group-based approaches or strategies that include partnerships between workers and management.

Closed-system transfer devices, a recognized engineering control to mitigate hazardous drug exposures, had a higher than anticipated failure rate. Our study would suggest that efforts to improve closed-system transfer devices are needed. Particular attention should be paid to end-user design features, integrating closed-system transfer devices into the myriad of intravenous tubing systems, and delivering evidence-based training modules to health care workers in the correct use, application, and troubleshooting of these devices.

Our team has been able to transfer findings from this study to develop and deliver a highly regarded interprofessional training course on chemotherapy safety, funded by the National Cancer Institute. A key module of this training program is hazardous drug exposure prevention. To date, faculty have led two workshops. 266 nurses and 72 pharmacists applied, and we accepted 77 (29%) and 30 (42%), respectively.

The data generated by this study have informed study consultant Dr. Martha Polovich's efforts to revise and subsequently validate the Hazardous Drug Handling Questionnaire, which was used to measure the study's primary endpoint. With our consultation, Dr. Polovich has revised the questionnaire and is currently conducting reliability and validity testing on a new sample of health care workers. This work will improve subsequent teams' ability to measure personal protective equipment use when handling hazardous drugs.

The data generated by this study support efforts by the United States Pharmacopeial Convention to revise its standards for hazardous drug preparation and administration (commonly referred to as USP General Chapter <800>). These revised standards codify current recommendations for clinical settings that store, prepare, and administer hazardous drugs.

The data generated by this study also reinforce the 2019 National Occupational Research Agenda for Healthcare and Social Assistance Objective 12:

> Develop and implement methods to identify, assess, control and prevent exposure to hazardous drugs, biological pharmaceuticals, reproductive hormones and other chemicals (e.g., cleaners, disinfectants, sterilants) in acute care human and veterinary healthcare settings and for difficult-to-access, low wage and underserved workers in home care, animal care, day care and other social services[1].

During our study, we identified several instances where pharmacy technicians, housekeeping personnel, and other workers had hazardous drug exposure. Yet most research studies (including ours), has focused on licensed clinicians. There remains an important opportunity to target monitoring and educational efforts to a broader category of workers and extend this area of inquiry outside of formal care settings (e.g., home care).

We have disseminated our findings through ten publications (five data-based, peer-reviewed publications, one book chapter, and four commentaries), two poster presentations, three podium presentations at participating Cancer Centers' Nursing Grand Rounds, and a webinar for all study participants. Two more papers are under review, and one is in preparation. We also prepared two-page summaries of study findings for the 12 participating Cancer Centers.

Research Outcomes/Impact

1. Potential Outcomes. We provided recommendations to the American Society of Clinical Oncology Work Group on Hazardous Drugs that closed system transfer devices, routine availability and training on personal protective equipment use, be part of any facility's hazardous drug program. We also recommended full implementation of USP General Chapter <800> as part of a suite of administrative controls to protect health care works.
2. Intermediate Outcomes. Data from the project were used to successfully receive a training grant from the National Cancer Institute for a chemotherapy training workshop, targeted to practicing oncology nurses and pharmacists. Study data are used as part of the workshop's training materials.
3. End Outcomes. Our study was not designed to measure a reduction in hazardous drug exposure or adverse health effects. Several participating sites have made changes to their equipment or training as a result of this study. Thus, the project has had an indirect effect on hazardous drug exposure prevention efforts across twelve high-volume cancer centers in the United States.

Section 2 of the Final Progress Report Scientific Report.

Background

For over four decades, scientists have documented the pernicious effects of handling hazardous drugs such as antineoplastics[2,3,4,5,6]. Reports have identified the following health effects: acute nausea and vomiting, reproductive difficulties, cancer, and myelodysplastic syndrome. In 2004, the National Institute for Occupational Safety and Health (NIOSH) issued an alert that summarized the evidence and recommended that health care settings and employees adopt practices to minimize the risk of handling potentially hazardous drugs[7]. The Oncology Nursing Society[8] and the American Society of Health-System Pharmacists[9] published guidelines on hazardous drug handling. The NIOSH 2004 recommendations are now included in the 2013 American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards[10].

Published guidelines include the use of personal protective equipment (PPE), comprised of two pairs of chemotherapy-tested gloves, single-use disposable gowns, eye protection during handling specific activities, and respiratory protection when vapor exposure is possible. However, adoption of these guidelines has been suboptimal in clinical settings[11]. A statewide survey revealed that 16.9% of ambulatory oncology nurses reported skin or eye exposure to chemotherapy in the past year[12]. Increased exposure has been associated with higher nursing workloads and poorer nurse practice environments. Oncology nurses deliver an astounding volume of chemotherapy; US estimates suggest over 18 million doses of chemotherapy are administered annually in the United States, primarily by nurses[13].

Audit and feedback is an established intervention to support clinician practice change. Successful audit and feedback interventions include education and periodic reminders[14]. Systematic reviews have identified improvements in clinician practice after feedback interventions[15]. Using a pre-post design, one Malaysian study reported increased scores on safe handling knowledge, beliefs, and observed practices for 96 inpatient nurses who completed an educational module on hazardous drug handling[16]. The absence of multi-site, controlled intervention studies to improve PPE use in ambulatory oncology nurses is surprising given the large volume of drugs handled and the potential health risks involved.

In this context, we conducted a cluster, randomized controlled trial to evaluate the efficacy of an audit and feedback intervention to improve nurses' use of personal protective equipment when handling hazardous drugs. The overall objective of this project was to measure and improve the safety of chemotherapy administration in ambulatory oncology settings. Study results will inform practicing nurses, cancer center administrators, and policymakers on optimal approaches to protect workers who handle potentially hazardous drugs.

Specific Aims

The trial had three specific aims:

1. **Evaluate the efficacy of an audit and feedback intervention to improve recommended use of personal protective equipment (PPE).**

2. **Determine whether the intervention effects on PPE use are mediated by knowledge about PPE use and perceived risk of hazardous drug exposure.**

3. **Determine whether the intervention effects on PPE use are moderated by personal (experience, education, and certification) and organizational factors (workloads, practice environments, and safety organizing behaviors).**

Methodology

A cluster randomized controlled trial design was chosen to compare an educational module on hazardous drug handling with the same educational module plus feedback from survey and biological data obtained from participants. Specifically, a clustered design reduced the likelihood for contamination bias between participants and facilitated measurement of the organizational context that we hypothesized moderated the effects of the proposed intervention. Participants provided baseline data upon study enrollment. After evaluation for the primary endpoint was completed, all participants received the feedback materials for the remainder of the 4-year study. These materials and study questionnaires were located on a user-authenticated website maintained by the investigative team. Table 1 shows the study procedures.

Table 1. Drug Exposure Feedback and Education for Nurses' Safety (DEFENS) Study procedures.

	Enrollment	Allocation	Post-allocation							Closeout
TIMEPOINT (Month)	1-5	6	7	9	12	15	18	21	24	25-30
ENROLLMENT										
Eligibility screen	X									
Informed consent	X									
Site Coordinator Training	X									
Cluster Allocation		X								
INTERVENTIONS										
Control: Web-based educational module			X							
Intervention: Audit and Feedback			X					X (both arms)	X	X
Quarterly Reminders				X	X	X	X	X	X	X
ASSESSMENTS										
Baseline Survey Demographics, PPE use, Plasma levels, PPE Knowledge, PPE Barriers, Moderators		X								
Primary Endpoint PPE use, Plasma levels							X			
Spill Assessments PPE use, Plasma levels			X	X	X	X	X	X	X	X

PPE: Personal protective equipment

Human subjects considerations

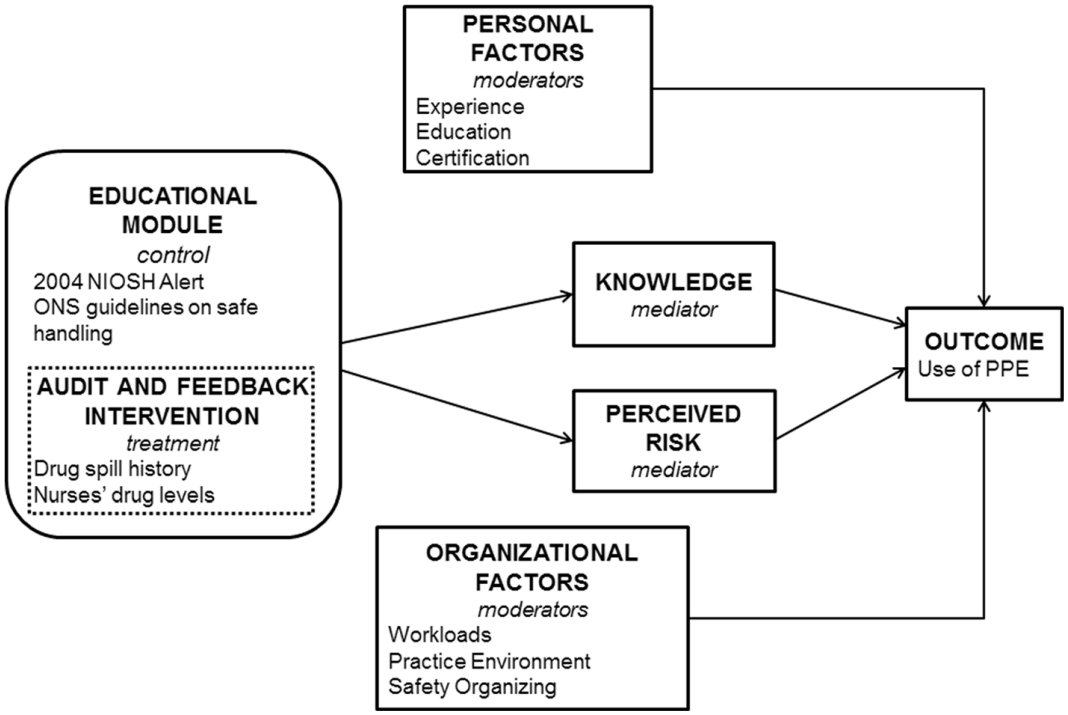
The University of Michigan Institutional Review Board approved the study (HUM00086541). All participants completed informed consent on the study website.

Conceptual framework

The study's conceptual framework integrated theoretical, empirical, and pilot work that spans occupational health, health promotion, and organizational studies (Figure 1)[17,18,19,20]. The

primary *outcome* of interest was PPE use using a valid and reliable measure described below[11]. The *interventions* were a 1-hour web-based educational module on hazardous drug safe handling with quarterly reminders about the educational content (control) or the web-based educational module with tailored messages plus quarterly feedback on hazardous drug spills and drug levels measured in the study population (treatment). Aim 1 compared the control and treatment groups on PPE use. Next, we hypothesized the interventions would result in a) increased *knowledge*[21] about PPE use and b) increased *perceived risk*[22] of hazardous drug exposure. We hypothesized the treatment intervention would result in higher knowledge and perceived risk than the control intervention. In Aim 2, knowledge and perceived risk were considered mediators of the intervention effect because they are likely influenced by the intervention received and in turn will likely influence PPE use. Finally, preliminary work suggested a relationship between the *personal factor* of years of experience and PPE use. We will explored additional personal factors, including nursing education and certification. Two *organizational factors* (nursing workloads and practice environments) were correlated to PPE use and hazardous drug exposure in prior work[12]. We also explored a third factor of safety organizing behaviors[23]. In Aim 3, personal and organizational factors were considered moderators in our framework because they may strengthen or weaken the observed effect of the interventions on PPE use.

Figure 1. Conceptual framework. NIOSH: National Institute for Occupational Safety and Health. ONS: Oncology Nursing Society



Settings and sample

Settings

Site inclusion criteria were ambulatory oncology infusion settings with at least 20 employees who met the individual participant eligibility criteria listed below. In addition, the chief nursing executive for cancer services in each facility provided endorsement of the study. Exclusion criteria were infusion areas that were not within easy access to the on-site study coordinator's office or lacked on-site phlebotomy services.

Individual Participant Sample

Primary inclusion criteria included registered nurses employed 16 hours or more per week in the ambulatory infusion area. To eliminate the chance of contaminated results in accordance with a previous protocol[24], exclusion criteria included treatment with an antineoplastic agent in the past year. Women who were pregnant were allowed to participate, but for safety reasons, did not have blood drawn.

Recruitment and retention

The principal investigator visited each site and offered a live presentation that reviewed study procedures. The presentation was recorded so off-shift workers could view the material at their convenience. Our recruitment strategy incorporated procedures supported by Dillman's Tailored Design Method[25]. Chief nursing executives for cancer services endorsed the study and co-signed all recruitment materials. Site leaders provided a list of all nurses who met employment criteria, and personalized emails were sent to each nurse by the site leader and co-signed by the principal investigator. An upfront $10 cash gift was provided during the enrollment period. Each site also had at least one study coordinator who was fully versed on the scientific protocol and could direct study questions to the coordinating center.

To promote retention, we planned quarterly electronic updates to all sites through personalized email messages from the coordinating center. The study website was developed by a professional vendor with expertise in user-centered design[26]. These efforts ensured study participants can navigate the website easily. At our post-intervention data collection point, participants received electronic and in-person cues to complete the survey, have blood draws performed, and receive a second $10 cash gift.

Randomization

Randomization occurred after participants had enrolled and completed the baseline survey. Randomization occurred at the site, rather than the participant level, to reduce the likelihood of contamination across study arms within one cancer center. We recognized that sites varied by size. To address this, sites were reordered by number of participants in decreasing order. The .ralloc command in Stata 12 (StataCorp, College Station, TX, USA) was used to perform random allocation in blocks of two so that one of the first two sites was in each condition. This helped ensure fairly equal sample size in the two groups.

Education versus audit and feedback

Both the control and treatment interventions were delivered to individual nurse participants. Table 2 compares the control and treatment interventions.

Table 2. Control and treatment interventions description

	Control	Treatment
Format	Web-based	Web-based
Duration	Forty-five minutes of audio/video content	Sixty minutes of audio/video content
Content	Review of 2004 NIOSH alert and recommendations for practice	Content from control video + video messages from practicing nurses on strategies to reduce barriers to PPE use
Tailored Messaging	No	Yes: tailoring variables are barriers to PPE use measure obtained at baseline
Fidelity Assessment	Completion of post test	Completion of post test; paradata to track that video messages were viewed
Reminders	Email reminders every 3 months of content	Email messages every 3 months with updates on spill data collected

NIOSH: National Institute for Occupational Safety and Health; PPE: personal protective equipment.

Control: hazardous drug safe handling web-based educational module with quarterly reminders

Participants viewed a 1-hour web-based educational module on safe handling procedures. Our study consultant presented a 1-hour informational webinar on principles of hazardous drug handling, consistent with Oncology Nursing Society chemotherapy guidelines[8] and recommendations from NIOSH[27] and the American Society of Health-System Pharmacists[9]. The module content included a summary of the 2004 NIOSH alert regarding the health effects of hazardous drug handling, a summary of the recommendations for PPE use, and resources to identify whether a drug is classified as hazardous. Participants completed a post test to measure knowledge of PPE and perceived risk of hazardous drug exposure. Continuing nursing education credit was provided. Every 3 months, short messages that summarize one of the main points presented during the webinar was posted to the study website.

Treatment: tailored web-based educational module plus quarterly audit and feedback on spills and drug levels

For the tailored educational module, participants viewed the 1-hour module on safe handling procedures plus additional short videos tailored on the barriers to PPE use they reported in the baseline survey[28]. The videos addressed each barrier individually and offered suggestions for overcoming them. For example, a nurse who scored highly on the item, 'PPE makes me too hot' on the barriers questionnaire viewed a video from an interviewed oncology nurse who has successfully addressed that barrier. The audit and feedback intervention was a video report prepared every 3 months during the study period. The report summarized: (1) the number of drug spills reported, (2) the context of the spill occurrences (when, activities performed, pertinent details, and use of PPE), and (3) drug levels obtained from participants' blood

samples. The reports were viewable from the study's secure website. Drug levels from our baseline assessment and from spills were reported using procedures described below.

Intervention fidelity assessment

Fidelity of the control intervention were assessed through the quiz required to receive a continuing education certificate. Fidelity of both treatments was expected to be high because delivery of content via a secure website assures consistent presentation. This mode of delivery offered greater fidelity than interventions delivered by a person, which can vary over time and with the person offering the intervention. Prior to accessing the site, participants logged on using their unique study identifier, allowing the study team to track the number of times each user accessed the site. Access (number of times) and duration (minutes viewed, longest time between keystrokes) data was used in the analyses to assess intervention effects. Because randomization occurred at the site rather than the individual, there was minimal opportunity for crossover contamination bias. The use of unique, secure user logins and passwords limited access to the intended recipients only.

Measures

Measures were selected for their fit to the conceptual framework of the study, their performance in previous studies, and documented validity and reliability (see Table 3).

Table 3. Measures table and timing

Concept	Measure	Description	When collected
Outcome	Revised Drug Handling Questionnaire	Five items, 0 to 5 (never to always) use selected PPE items	Baseline Primary endpoint
Mediator: Knowledge	Knowledge questionnaire	Twelve items, multiple choice, true/false about 2004 NIOSH alert and recommendations	Baseline After viewing module Primary endpoint
Mediator: Perceived Risk	Three items from Geer's dermal exposure survey	Three items, score 1 to 4 (strongly disagree - strongly agree) about health risks from exposure	Baseline Primary endpoint
Personal Factor	Experience	Number of years in nursing, oncology nursing, and in current position	Baseline
Personal Factor	Highest education degree completed	Diploma, Associates' Bachelors, Masters, or Doctorate	Baseline
Personal Factor	Completed certifications	ONS Chemotherapy certification, OCN, AOCN	Baseline
Organizational Factor	Workload	Number of patients cared for on shift	Baseline With a spill report Primary endpoint
Organizational Factor	Revised PES-NWI	Six subscales, 23 items, score range 0 to 5 (strongly disagree - strongly agree) about presence of favorable work features	Baseline Primary endpoint
Organizational Factor	Safety Organizing Scale	Nine items, score range 1 to 7 (not at all - to a very great extent) team performance of safety behaviors	Baseline Primary endpoint

AOCN: Advanced Oncology Certified Nurse; OCN: Oncology Certified Nurse; ONS: Oncology Nursing Society; PES-NWI: Practice Environment Scale of the Nursing Work Index.
Note. Baseline assessment began in Year 1 of the study; the Primary endpoint was assessed approximately 18 months later.

Outcome

The study's primary endpoint was optimal use of PPE, measured at the individual participant level using the Revised Hazardous Drug Handling Questionnaire originally developed by Martin and Larson[21] as modified by Polovich and Martin[11]. The items were mapped to the 2004 NIOSH alert recommendations[7]. Use of PPE was measured on a 6-point Likert scale (5 = always, 4 = 76 to 99% of the time, 3 = 51 to 75%, 2 = 26 to 50%, 1 = 1 to 25%, and 0 = never). A mean score was calculated for each participant across five items: use of chemotherapy gloves, double gloves, single-use disposable gowns, eye protection, and respirators. Higher scores reflected more frequent use of PPE elements. In the original study, test-retest Kappa was calculated at 0.80, and measure validity was established through direct observation of nurses who also completed the questionnaire. In a sample of 165 nurses who completed the revised scale, the Cronbach alpha was 0.83[11]. Although the original scale asks separate questions about drug preparation, drug administration, and drug disposal activities, this study focused on PPE use for drug administration only, an activity shared by all study participants. This measure was obtained with the baseline survey and at the post-intervention assessment.

Potential mediators

Both knowledge of PPE and perceived risk of hazardous drug exposure were hypothesized to mediate the potential effects of the intervention on PPE use. These measures were obtained at baseline at the individual participant level, after the educational module was viewed, and at the post-intervention assessment. The mediator analysis used the measures obtained after the intervention was delivered. Both measures were validated by expert panel review and discussion with two focus groups of at-risk workers. In prior work, both measures achieved a content validity index of 1 from 3 experts[11].

Knowledge of PPE was measured using a 12-item chemotherapy exposure questionnaire that assessed knowledge of the 2004 NIOSH alert. The measure was developed by a content expert and study consultant. Each item provided four answer choices with one correct answer for each question. The scale range was 0 to 12, with higher scores reflecting increased knowledge. Perceived risk of drug exposure was measured using a 3-item subscale from Geer's Occupational Dermal Survey[22]. A 4-point Likert scale (1 = *strongly disagree*, 4 = *strongly agree*) was used to assess nurses' perceptions of the risks of chemotherapy exposure and potential health effects. The score range was 1 to 4. The Cronbach alpha in a similar study population was 0.70[11].

Potential moderators

Three organizational factors (workloads, practice environments, and safety organizing) and three personal factors (experience, education, and certification) were proposed moderators. These measures were obtained on the web-based survey at baseline and the post-intervention

assessment. In contrast to our outcomes and potential mediators, the moderators were obtained from participants and aggregated to the cluster level.

Workloads was measured by asking participants: 'How many patients did you assume primary responsibility for on your last shift?' For spill reporting, the time referent was changed to 'the shift the drug spill occurred'. Workload measures correlated significantly with administratively-derived staffing levels and perceived staffing adequacy[29]. Workload was also significantly associated with patient mortality[30], nurse-reported needlesticks[31], and hazardous drug exposure[12].

Practice environments are workplace features that enable nurses to deliver high-quality care[32]. Items from the Practice Environment Scale of the Nursing Work Index, revised for ambulatory oncology, were scored on a 5-point Likert scale, where 1 = *strongly disagree* to 5 = *strongly agree* that the characteristic is present in the practice. The range of setting-level scores on a composite of the 6 subscales was 2.7 (disagree) to 5.0 (strongly agree). Previously analyzed for validity and reliability, acceptable fit was achieved in a structural equation model with a comparative fit index of 0.95 and a root mean-square error of approximation of 0.057, and subscale Cronbach alphas ranged from 0.80 to 0.90[33]. Our preliminary data showed lower scores (that is, poorer practice environments) for nurses who reported hazardous drug spills. We used the mean score of the 23-item composite measure for the proposed analyses (range = 1 to 5).

The Safety Organizing Scale[23] reflects behaviors employees perform in high-reliability organizations that avert operational failure. Nine items reflect the concept of a safety culture, and importantly, capture observable actions of clinicians. Each item was scored on a 7-point Likert scale (1 = *not at all*, 7 = *to a very great extent*) to reflect the degree to which the nurse and his/her co-workers engage in the behaviors on their work unit. The items identify safe performance as a function of five processes: preoccupation with failure, reluctance to simplify interpretations, sensitivity to operations, commitment to resilience, and deference to expertise. The scale has high internal reliability and discriminant validity[23].

Congruent with prior studies, the three potential moderators described above were aggregated to the cluster level. In this study, a cluster was considered each of the 11 participating cancer centers. For each cluster, the mean value for these three measures was calculated from the individual responses from each nurse in the cluster.

Three personal factors were collected from each participant with the baseline survey: oncology nursing experience (years), education (diploma, associate's degree, bachelor's degree, master's degree, post-master's degree), and certification (Oncology Nursing Society chemotherapy certification, Oncology Certified Nurse, Advanced Oncology Certified Nurse, other certification).

Baseline evaluation

After informed consent was obtained, participants completed a baseline questionnaire online at the secure study website. Baseline blood draws were performed on-site at the conclusion of

a participant's scheduled work shift. All plasma samples were shipped to the University of Michigan for processing and analyses for the detection of 20 commonly-used chemotherapy drugs.

Spill reporting

If a spill occurred in the ambulatory oncology infusion center throughout the 4-year study period, participants returned to the secure study website and completed a brief spill report. They also had blood drawn at the end of the shift to obtain drug levels. A second blood draw was performed 24 hours after the first one (or the next available business day) to obtain estimated peak and trough values, respectively.

Plasma analyses

Participants provided blood for plasma sampling at the baseline and post-intervention assessment, as well as with the occurrence of any reported drug spill during the study. The procedures below were used for all obtained samples. At the end of a nurse's shift, the nurse reported to the participating site's designated phlebotomy area. Trained and credentialed phlebotomy staff performed venipuncture using standard technique and placed whole blood into 5-mL heparinized tubes. Cells were removed from plasma by centrifugation for 10 minutes at 1,000 to 2,000 x g using a refrigerated centrifuge. Plasma were pipetted into a clean polypropylene tube and stored in a −20°C or lower freezer. After plasma samples were frozen, they were shipped by next-day air and on dry ice to the University of Michigan.

To measure levels of potentially hazardous drugs from the obtained samples, a specific and highly sensitive liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS) method was established. We focused efforts on the 20 drugs that are the most commonly administered agents in ambulatory oncology settings with chemical properties suitable for analysis. We also explored other drugs as they were reported in spill events. Signals from the test drug were monitored under the multiple reaction monitoring mode of the LC-ESI-MS for quantification[34]. Ionization mode, precursor to product ion transition, ion source parameters (potential, gas, temperature, and so on), mobile phase, and column were optimized and selected under direct infusion and flow injection analysis of the pure compound. The selection of extraction method, including protein precipitation, liquid-liquid extraction, and solid phase extraction, depended on the drug properties (for example, acidity content, lipophilicity, aqueous solubility and chemical stability). The most efficient and specific extraction method was used for sample preparation.

Drugs with similar properties and similar measurement methods (using the same column, same mobile phase, and similar extraction conditions) were grouped into one method to simultaneously detect several drugs in one injection. This technique greatly enhanced the screening throughput. Each sample batch processed included plasma samples from healthy, unexposed volunteers to ensure calibration. The established method for detecting multiple test drugs in one injection were evaluated for linearity, specificity, and sensitivity according to guidance from the Food and Drug Administration[35]. Results from the LC-ESI-MS analyses were provided to the investigative team. Specimens and survey data were linked by unique study identifiers.

Statistical analysis

Survey data were stored on the password-protected, user-authenticated encrypted server behind a firewall. Our hypotheses were focused on the efficacy of an audit and feedback intervention to nurse participants. 415 nurses were sampled from 12 sites. Each site was randomized into either control or intervention condition. Because the nurses within the same site were likely to show correlated outcomes, we used linear mixed-effects models to account for the intraclass correlation for the cluster randomized trial[36,37]. More specifically, we used a random intercept model in which a variable *site* was created to identify the sites, and then added *site* as a random effect to the mixed model.

Aim 1 evaluated the efficacy of audit and feedback to improve recommended PPE use (compared with an educational video). The outcome variable of the fixed-effect structure was the PPE use scores. The predictor of the fixed effect was the intervention indicator variable. The data from the PPE use questionnaire and demographics variables were included in the fixed-effect structure to increase the precision of estimates. The random effect in the model was the *site* variable. We assumed the *site* variable followed a normal distribution with mean zero and was independent of the error term in the mixed model. The hypothesis was that there will be a significant intervention effect such that nurses in sites who received the treatment, in addition to the web-based educational module, would report higher PPE use scores compared to nurses in sites randomized to receive only the control. Means within time were computed as descriptive statistics to help describe the effect.

Aim 2 examined whether knowledge about PPE use and perceived risk of drug exposure mediated the effect of the treatment intervention on PPE use. The hypothesis was that the effect of the treatment on PPE use would be at least partially mediated by knowledge and perceived risk. To measure the mediation effect, we fit two linear mixed models. The first model was the same model used in Aim 1. The second model added the two potential mediators in the first model. The mediator effect was measured as the difference in the coefficients of the intervention variable between the two models. A 95% confidence interval was calculated for the estimate. If the confidence interval does not cross zero, it would show that mediation effect was statistically significant.

Aim 3 determined whether the treatment intervention effect on PPE use was moderated (strengthened or weakened) by personal (experience, education, certification) and organizational factors (workloads, practice environments, safety organizing). We used mixed model analyses that include receipt of the treatment intervention, the moderator variables, and the products of treatment intervention receipt with the moderator variables as predictors of PPE use. Significance tests of the product terms between moderator and intervention variables indicated whether moderation is present[38]. We hypothesized that at least one of these moderator variables would interact significantly with the treatment intervention. When the product term was significant, we conducted a *post hoc* analysis by plotting the PPE use versus intervention at various levels of the moderator variables. Using graphical presentations, we

could show the size of the intervention effect and how the effects vary based on the values of moderate variables.

Sample size considerations and statistical power

The design and sample size for this study were determined in part by power analysis conducted by Optimal Design software[39] that is designed specifically for mixed models such as ours in which nurses are nested within sites that are treated as a random factor. We considered power for detecting a medium sized effect of the intervention and a medium sized multiple correlation (both as defined by Cohen)[40]. We considered scenarios with different numbers of clusters/sites, with different average numbers of nurses per site, and with different levels of the intraclass correlation coefficient (ICC) ranging from 0.01 to 0.03. The ICC was a measure of the extent that PPE use differs across sites. The higher the ICC, the greater the sample size needed. ICCs of up to 0.03 are common; therefore, we aimed to obtain 80% power for tests with a 2-tailed alpha of 0.05 to detect medium sized effects with this ICC. Analysis revealed that we would obtain this power if our sample includes 11 sites with a mean of 26 participating nurses. In reality, our 12 sites had a mean of 35 nurses (range of 20 to 90), which suggested that we would achieve 80% power even if we had a 25% decrease in the expected sample size (n = 287).

Human subjects considerations

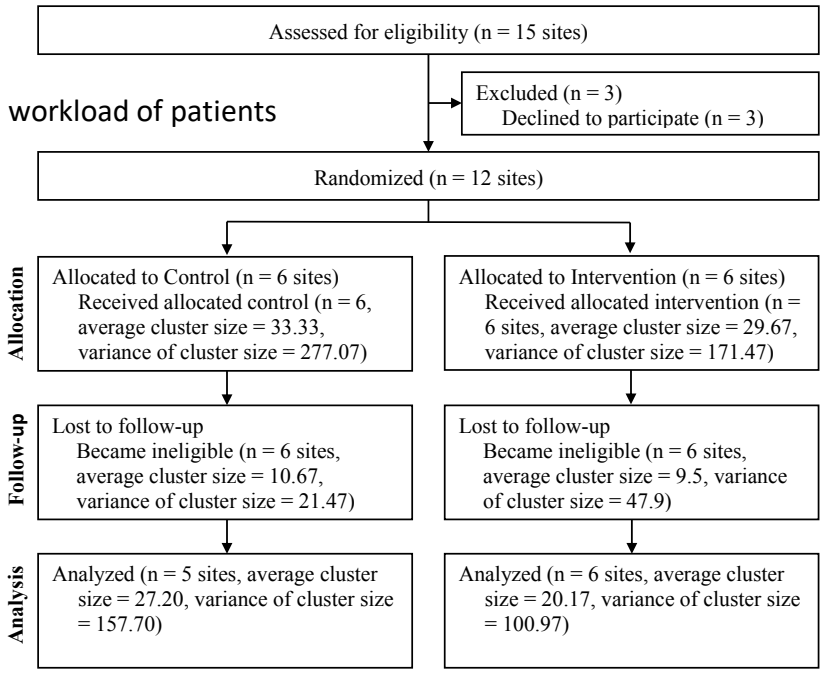
Potential participants were invited to the study website using their unique assigned study identifier and also completed informed consent. During the consent process, they had a yes/no option of providing additional plasma and whole blood samples for our biorepository. A data safety monitoring board comprised of three faculty members not involved in the project reviewed study progress and human subjects concerns on a quarterly basis. Study withdrawals and potential adverse events were reviewed at these meeting and reported to our Institutional Review Board.

Three sites identified challenges with accessing the project website from their setting, due to organizational-level privacy restrictions, outdated web browsers, or authentication challenges. To enable easier viewing of content, the coordinating center sent email messages to all participants with the content embedded directly in the message as well as a link to the website. The email distribution platform also enabled the coordinating center to track the number of participants who viewed educational materials directly from the email message. The change in quarterly video distribution was made starting with the second quarterly video.

Results and Discussion

Of 439 registered nurses eligible to participate across 12 practice sites, 415 (94.5%) enrolled in the study, 189 from practice sites assigned to the treatment arm and 226 from practice sites assigned to the control arm. Of enrolled participants, 378 (91.1%) completed baseline and 257 (61.9%) completed both the baseline and the primary endpoint survey; 121 participants were in treatment arm-assigned practices and 136 participants were in control arm-assigned practices. Table 4 shows the participant characteristics and Figure 2 summarizes the recruitment, enrollment, and participation data.

Figure 2. Participant Flow Diagram.



workload of patients control-assigned setting participants by race/ethnicity, years of experience, and receiving chemotherapy (see Table 4). There were more Asian nurses in the control arm (12.3% vs. 6.0% in the treatment arm), more Hispanic nurses in the control arm (9.2% vs 1.7%, respectively) and fewer white nurses in the control arm (78.5% vs 92.2%, respectively). Nurses in the control arm reported slightly more years in current role (mean [SD] of 6.7 [7.2] years vs. 5.1 [4.5] years in the treatment arm). Nurses in the treatment arm reported higher workloads of patients receiving chemotherapy than nurses in the control arm (6.2 patients on the last shift versus 5.0 patients). Initial fidelity intervention - defined as viewing the webinar – was 50.4% for the intervention arm and 72.8% for the control arm. Additionally, 57.3 % of intervention participants watched one or more feedback video.

Table 4. Participant Characteristics

	Control (N=136)	Experimental (N=121)	Total (N=257)	P-value
Oncology nursing experience				.52
N	136	121	257	
Mean (SD)	12.7 (9.4)	12.0 (8.2)	12.4 (8.8)	
Education (bachelors or higher)				.49
Diploma	5 (3.7%)	5 (4.1%)	10 (3.9%)	
Associates Degree	21 (15.4%)	19 (15.7%)	40 (15.6%)	
Bachelors in Nursing	102 (75.0%)	90 (74.4%)	192 (74.7%)	
Bachelors in Other Field	4 (2.9%)	3 (2.5%)	7 (2.7%)	
Master's degree in Nursing	4 (2.9%)	1 (0.8%)	5 (1.9%)	
Master's degree in other field	0 (0.0%)	3 (2.5%)	3 (1.2%)	
Race/Ethnicity				.01
Missing	6	5	11	
Asian	16 (12.3%)	7 (6.0%)	23 (9.3%)	

	Control (N=136)	Experimental (N=121)	Total (N=257)	P-value
Hispanic	12 (9.2%)	2 (1.7%)	14 (5.7%)	
White	102 (78.5%)	107 (92.2%)	209 (85.0%)	
Gender				.78
Male	6 (4.4%)	7 (5.8%)	13 (5.1%)	
Female	130 (95.6%)	114 (94.2%)	244 (94.9%)	
Chemotherapy Workload				.01
N	136	119	255	
Mean (SD)	5.0 (2.6)	6.2 (4.4)	5.5 (3.6)	
Fidelity: Viewed control module				<.01
No	37 (27.2%)	60 (49.6%)	97 (37.7%)	
Yes	99 (72.8%)	61 (50.4%)	160 (62.3%)	
Viewed at least one educational module				N/A
No	0	45 (37.2%)	45 (37.2%)	
Yes	0	76 (62.8%)	76 (62.8%)	

For both the intervention and control arms, differences in PPE use score did not change between study initiation and primary endpoint assessment (see Table 5). At baseline, the mean (SD) five-item PPE use score was 2.4 (0.8) in the treatment arm and 2.4 (0.7) in the control arm. At one-year follow up, the PPE use score was similar in both treatment and control arms (2.3 [0.9] in both groups). Hazardous drug knowledge scores and reported barriers to PPE use did not change significantly between baseline and follow up for nurses in either arm.

Table 5. PPE Knowledge, Barriers, and Use Scores before and after the Intervention

			Setting[a]			
Characteristics	Full Sample N= 257		Assigned to Treatment Intervention n=121		Assigned to Control Intervention n=136	
	Pre	Post	Pre	Post	Pre	Post
PPE Knowledge Score	6.5 (1.7)	6.7 (1.5)	6.4 (1.5)	6.5 (1.6)	6.7 (1.8)	6.9 (1.5)
Barriers to PPE Use	1.9 (0.5)	1.9 (0.5)	1.8 (0.4)	1.8 (0.5)	2.0 (0.5)	1.9 (0.5)
PPE Use Score – 5 items	2.4 (0.7)	2.3 (0.9)	2.4 (0.8)	2.3 (0.9)	2.5 (0.7)	2.3 (0.9)
PPE Use Score – 3 items	3.6 (1.0)	3.5 (1.2)	3.5(1.1)	3.6(1.2)	3.6(1.0)	3.5(1.2)

Results from a linear mixed model show that PPE use scores between baseline and follow up did not change significantly in the intervention arm, after adjustment for PPE use at baseline (β = 0.1, SE 0.4, p = .75, see Table 6).

In sensitivity analyses using the three-item PPE use score (chemotherapy-tested gloves, double gloves, and single-use disposable gowns), results obtained did not differ appreciably from those reported above when all five PPE items were considered (see Table 6). Results reported above also did not change appreciably when analyses were restricted to participants who had viewed the web-based materials at least once during the study period.

Table 6. Association between Study Variables and PPE Use[a]

	Model I (5-items)		Model II (3-items)	
Variable	Beta (SE)	*p*	Beta (SE)	*p*
Intercept	1.7(-0.5)	<.001	3.2 (0.8)	<.001
Setting assigned to Treatment Intervention	0.1 (0.4)	.75	0.1 (0.6)	.85
Baseline Use of PPE	0.2 (-0.1)	<.001	0.1 (0.1)	.07
Personal Factors				
-Oncology nursing experience	<.01 (<.01)	.92	<.01 (<.01)	.35
-Education (bachelors or higher)	0.03 (0.06)	.56	0.05 (0.08)	.53
-Oncology nursing certification	-0.01(0.11)	.91	0.09 (0.15)	.56
-Race (Asian vs. White)	0.61(0.15)	<.001	0.61 (0.20)	<.01
Organizational Factors				
-Workload	<0.01(0.01)	.63	<0.01(0.01)	.85
-Practice Environment Scale of the Nursing Work Index	0.11 (0.08)	.19	0.12 (0.11)	.30
-Safety Organizing Scale	<0.01(0.05)	.96	<0.01(0.07)	.57
Knowledge				
-Hazardous drug handling knowledge	-0.05(0.03)	.05	-0.06(0.04)	.09
-Perceived risk score	-0.02(0.07)	.78	-0.02(0.10)	.83

[a]Coefficients, standard errors, and *p* values were derived from two linear mixed models: Model I used the five-item PPE use measures. Model II used the three-item PPE use measure.

We conducted post-hoc descriptive and correlational analysis to identify variables potentially associated with personal protective equipment use. Table 7 shows the most-frequently reported barriers to PPE use among the sample and correlation coefficients between barrier items and PPE use scores. While the most frequently reported barrier was heat, the barrier most highly-correlated with PPE use was other colleagues' use, suggesting an important peer effect.

Table 7. Nurse-Reported Barriers to Wearing Personal Protective Equipment (PPE)

Barrier	% Reporting	Correlation with PPE use
PPE makes me feel too hot	67%	0.14*
PPE is uncomfortable to wear	59%	0.09
Others around me don't use PPE	**45%**	**0.45****
PPE makes it harder to get the job done	35%	0.12

*$p < .05$; ** $p < .01$.

In our process evaluation, 71.4% reported they were satisfied/very satisfied with participating in the study, 4.7% were dissatisfied/very dissatisfied, and 23.9% endorsed a neutral assessment. Just under two-thirds (64.6%) agreed/strongly agreed that the educational content was useful to their clinical practice, 2.0% disagreed/strongly disagreed, and 23.4% endorsed a neutral assessment. Over three-quarters (80.8%) would be willing to receive future invitations for study participation. Thirty-nine nurses provided open-text feedback; 59.0% of which was positive (principally focused on importance of the topic and feedback received), 30.8% was negative (principally focused on time involved and website difficulties), and 10.2% was neutral.

Study Limitations.

A key limitation to the project was the reliance on a self-report measure of PPE use as the primary endpoint. Resource constraints and the frequent application of PPE prohibited us from measuring PPE use through direct observation. However, the primary endpoint was validated in the original study with direct observation. A second limitation was our selection of elite cancer centers, as opposed to community-based oncology settings, which biased our results toward conservative exposure rates. The participating facilities were high-volume cancer centers that currently provide training and PPE to their staff. For an efficacy trial, larger samples of participants per cluster are needed. It is our goal to move from efficacy to effectiveness in a larger, more diverse sample of oncology practices that includes nurses and other health care workers who are at risk for drug exposure.

Despite high participation and response rates for nurses, coupled with a controlled experimental design informed by a theory-based framework, the study has several limitations worthy of comment. First, the study took place in a convenience sample of academic health centers with high-volume cancer programs. Results may not generalize to smaller or community-based oncology settings.

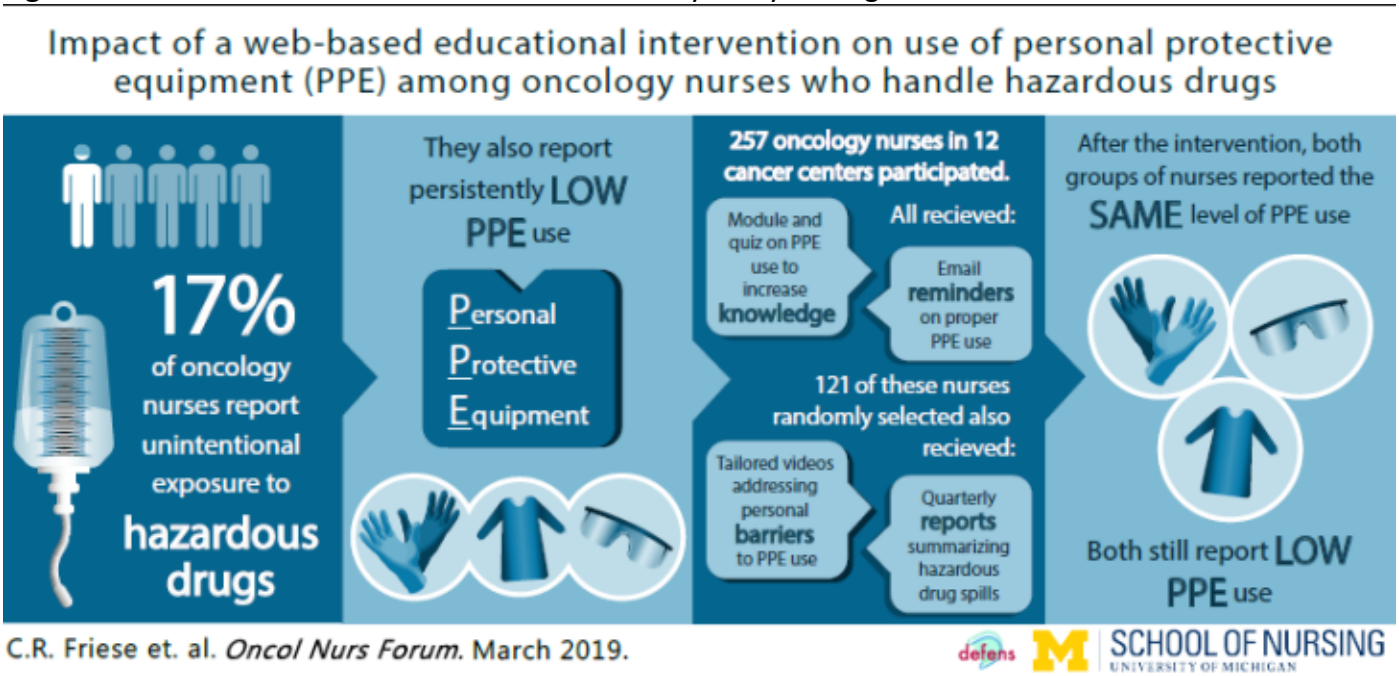
The calculated reliability of the outcome measure in our sample was relatively low (0.46 for the three-item measure and 0.50 for the five-item measure considered in the sensitivity analysis).

Our team is currently collaborating with Dr. Martha Polovich to revise and validate measures of PPE use. Fidelity to the intervention was high soon after study activation and decayed over time. Thus, assessing the primary endpoint one year after study activation may have limited the ability to detect meaningful changes in PPE use. Future research efforts would benefit from development and testing novel measures of PPE use and evaluating optimal measurement times after delivering educational interventions and delivering study reminders.

Novel study designs, such as sequential multiple assignment randomized trials, may address the ongoing challenges of reaching non-engaged participants and titrating interventions based on behavioral response. Implementation science techniques could elucidate factors associated with increased adherence to study protocols and/or PPE recommendations. Participants' knowledge of chemotherapy administration safety was measured using a team-designed instrument. Psychometric testing of the instrument in diverse samples will increase confidence in measure validity. The study focused on nurses who handle hazardous drugs but did not include other workers exposed to hazardous drugs routinely in their workplaces.

Conclusions

Figure 3 shows a visual abstract to summarize our key study findings.



Our study findings have important implications for nursing from various perspectives: individual health systems, professional organizations, and regulatory efforts. The challenges that characterize influencing nurse's use of PPE found in this and previous studies underscore the importance of higher-order hazard control strategies, such as engineering and administrative controls [41]. During the enrollment period, we noted inconsistencies in existing institutional policies on hazardous drug handling across participating institutions, despite similar patient populations and care processes. Nursing leaders could standardize educational content and

policies on PPE use across oncology settings – with leadership endorsement and accountability – to address existing confusion among health care workers. While nursing and other professional organizations have attempted to address this issue, differences in opinion remain across these organizations [42,43], and recent efforts to strengthen oversight of hazardous drug handling across cancer settings have been delayed to 2019 [44]. These delays will hamper efforts to improve PPE use. While several states have passed legislation aimed to improve hazardous drug handling, delayed implementation has hampered effectiveness [45]. When placed in the context of our study findings, it is clear that education and engagement of nursing personnel is not sufficient to improve PPE use; systematic approaches may result in improved practice.

Despite four decades of evidence to suggest adverse health effects for workers who handle hazardous drugs, nurses persistently do not wear PPE as recommended. An educational intervention tailored to address documented barriers and targeted to practicing nurses did not improve PPE use. When considering the hierarchy of controls, efforts should focus on developing novel and reliable engineering controls, improving existing engineering controls, strengthening clinician adherence to efficacious engineering controls, and developing and evaluating system-level interventions to address pervasive gaps in hazardous drug handling practice. To minimize the risk of hazardous drug exposure, health care workers must receive adequate training and equipment. Policymakers, clinical experts, and health system leaders should encourage clinical settings to adopt guideline-concordant PPE policies and activities.

The primary results of the trial were published in *Oncology Nursing Forum* in 2019.[46]

Lessons Learned

Leadership Engagement

Congruent with the implementation science literature [47], as well as organizational change theory [48], our team identified that endorsement and ongoing support by the senior nursing executive was crucial for success. Senior nursing leadership engagement facilitated timely protocol activation and encouraged clinical nurses to participate. Engagement began before the proposal was submitted and continued throughout the project.

Before the original grant proposal was submitted, the principal investigator (PI) contacted senior nurse executives from National Cancer Institute-designated comprehensive cancer centers. He presented an overview of the proposed project at their annual meeting. He led one-hour informational webinars that reviewed the study team's preliminary data and outlined the proposed research project. He prepared 5-page executive summaries for these leaders to share with their institution's senior leadership. On several occasions, feedback from these executives led to important study protocol changes. For example, one leader recommended reviewing the policies of all participating institutions for differences in hazardous drug handling policy. Another leader identified strategies for nurses in satellite locations to participate.

After a favorable peer-review process by NIOSH's study section, the PI re-engaged with interested leaders to plan for study activation. Re-engagement enabled leaders to identify key contacts, budgetary considerations, and information technology needs for participation. After

re-engagement, several supportive leaders declined participation, principally due to major organizational changes in cancer care services and/or electronic health record implementation. The PI was able to replace these sites by contacting chief nursing officers from other cancer centers.

To demonstrate leadership support of the project to potential participants, we drafted study letter endorsements that would be sent to eligible staff nurses on behalf of the nurse leaders. The study team and the nursing leaders agreed that study participants would remain anonymous to the nurse leaders in the institution to promote trust in the study and ensure confidentiality of responses as well as of personal health information from employers.

Human Subjects Protections

Institutional review boards (IRBs) have extensive experience in protecting human subjects who are patients in a health care facility. They have less experience when employees are participants, and the interventions are not of a clinical nature. Timely, thorough, and efficient human subjects review was a critical priority for the study team. In partnership with leaders of our institution's IRB, we carefully reviewed the criteria in place during our study for "not-engaged" status for participating sites. An institution can be considered "not engaged" if the involvement of their employees or their agents is limited, among other things, to the following criteria:

a. the services performed do not merit professional recognition or publication privileges;
b. the services performed are typically performed by those institutions for non-research purposes; and
c. the institution's employees or agents do not administer any study intervention being tested or evaluated under the protocol [49].

The advantage of not-engaged status meant that our protocol would be reviewed, critiqued, and approved centrally, that informed consent documents would be standardized, and administrative workloads would be reduced for participating sites. Another option to retain centralized control was to have site IRB cede control to the University by completing an IRB Authorization Agreement (IAA) form [50].

Our initial approach was to review our IRB's determination of not-engaged status with each site, provide requisite documentation, and ask them to confer with their IRB. We offered to speak with IRB staff, and highlight that participants were employees, not patients, the intervention was behavioral in nature, and a data safety monitoring board was in place at the primary institution in the event of an adverse event. In six cases, the participating sites' IRBs agreed with our interpretation. In three cases, participant sites' IRBs ceded authority to our institution's IRB. In three cases, the participating institution required full review by their IRB. In the three latter cases, the study team provided as much assistance in preparing documents for review as possible. The time between initial IRB approval and final IRB approval at the last research site was 11 months.

The shift to not-engaged status required the team to modify several study procedures from our original plan. The coordinators at each site were no longer responsible for direct participant recruitment. Their role shifted to study facilitation, as they provided information, resources, and assisted participants with website navigation. Informed consent took place on the study website. Questions regarding consent and the study protocol were directed to the study personnel at the primary site. The downside of this approach is study coordinators did not know which nurses were enrolled in the study and couldn't provide personal reminders to complete study activities. A full-time project manager at the primary site was essential to manage participant inquiries.

Benefits of On-Site Study Coordinators

We asked each site to name at least one registered nurse to serve as a study coordinator. In most cases, the grant provided financial resources to the institution to partially subsidize the hours coordinators spent. These individuals provided information about the study to participants and clinic leaders, coordinated logistics of site visits, identified where and how blood would be drawn at each site, and directed participants to complete surveys and have blood drawn, when applicable.

To support these study coordinators, the project manager prepared a binder with all study materials, including the full protocol, a clean copy of the consent form, and a document of frequently asked questions. These materials were updated as necessary, based on feedback from the study coordinators. The primary site also held 4 recorded webinars to review study procedures, answer questions, and address concerns. The primary site has held webinars approximately quarterly to keep study coordinators informed on study progress, address any ongoing challenges, and maintain enthusiasm for the project. Finally, the PI and/or project manager conducted visits to all 12 sites at the time of study activation; another site visit occurs close to the primary endpoint collection time point. This visit enabled the PI and project manager to educate staff and engage nurses at each site in the study. It was also an opportunity to connect with study coordinators and outline logistics of study accrual and intervention procedures. Study coordinators were instrumental in arranging these visits and encouraging staff to attend information sessions with the study personnel.

Study coordinators assisted the project by troubleshooting reasons for low participation rates in educational video viewing. Study coordinators identified technology challenges and time constraints as barriers to timely completion. Coordinators also challenged our assumption that staff members would complete study activities after hours at home. They suggested communal "viewing parties" during scheduled work breaks with refreshments to facilitate completion. We also modified delivery of the materials to facilitate easy viewing based on their feedback. These suggestions were associated with improving our participation rate from 17.4% to 60.8% at the time of this publication.

Internet Access and Browser Compatibility

Advantages of Web-based study platforms include the capacity to standardize delivery, monitor access, and adjust content as needed. Our team experienced substantial challenges with the variation in informational technology and security restrictions across twelve participating sites. Despite substantial user testing before the project website launched, several institutions continued to use outdated and unsupported web browsers during the study period. This required unplanned modifications to the website design and scaled-down versions of materials for participants in affected sites. In addition to website browser incompatibility, several sites restricted the kinds of files staff members could access on clinic computers. Although we provided each site's informational technology departments with web addresses in advance, several sites blocked viewing of video materials, regardless of source. For participants unable to access the videos, our team created one-page handouts that summarized the video content. To reduce the burden of using the website, we used Qualtrics™ (Provo, UT) software to deliver videos and handouts directly to participants' email accounts.

A paper summarizing lessons learned was published in *Journal of Nursing Scholarship.* [51]

Ancillary Analysis: Analysis of Hazardous Drug Spills

We included a prospective reporting system to capture hazardous drug spills among our study participants. This was collected as part of our feedback intervention as well as to inform the field about the patterns and correlates of hazardous drug exposures across twelve diverse cancer centers.

When drug spills occurred, participants completed brief questionnaires to describe the spill event, protective equipment worn during the spill, and spill containment efforts. Descriptive statistics were used to describe equipment use and spill events.

Over 24 months, 73 unique spills were reported involving 86 nurse participants. Spilled drug volumes ranged from 1 to 200 mL. Despite published evidence-based guidelines from professional organizations and institutional policies, a troubling underuse of PPE was reported during routine handling of hazardous drugs and when managing spills. PPE use during routine administration was somewhat worse than during unanticipated spills, especially for double glove use. Only 54% of nurses involved in a spill wore two pairs of chemotherapy-tested gloves, 63% wore a single-use, disposable gown, and on 29% wore respiratory protection, despite the high likelihood for vapor transmission during a spill. An uneven distribution of PPE use across study sites was found, suggesting differences in institutional response to hazardous drug exposures. Respondents reported using a closed-system transfer device – an engineering control – in 65% of the spills. Yet nurses reported that the device functioned properly in only 20% of the spills.

A paper from this work is under review at *Clinical Journal of Oncology Nursing*.

Ancillary Analysis: Development of a High-Throughput Assay to Detect Hazardous Drugs with plasma and/or urine.

Simple, multi-target and specific analytical methods are needed so that acute exposures to hazardous drugs in the health care setting can be assessed rapidly. Our aim was to develop an analytical method for simultaneous detection and quantification of widely-used hazardous drugs handled by health care workers.

We examined the feasibility of alternate high-performance liquid chromatographic-tandem mass spectrometry methods to simultaneously detect eighteen chemotherapy analytes in plasma and urine. The linear concentration ranges tested during assay development were 0.1-50 ng/mL. After development of a multi-analyte assay protocol, plasma samples (n=743) from a multi-center cluster-randomized clinical trial (n=12 sites) of an educational intervention were assayed. Samples were obtained at baseline and with any hazardous drug spill event that occurred during the study period (acute spill). Confirmatory assays were performed based on the individual acute-spill case-histories.

An innovative high performance liquid chromotography-multiple reaction monitoring-information dependent acquisition-enhanced production ion (MRM-IDA-EPI) analytical method was developed to simultaneously detect: cytarabine, gemcitabine, dacarbazine, methotrexate, topotecan, mitomycin, pemetrexed, irinotecan, doxorubicin, vincristine, vinblastine, ifosamide, cyclophosphamide, vinorelbine, bendamustine, etoposide, docetaxel, and paclitaxel. The retention times ranged from 4 minutes to 13 minutes for the analytical run. The limit of detection and limit of quantitation was 0.25 ng/mL and 0.1 ng/mL, respectively for most analytes. No detectable plasma concentrations were measured at baseline, post-intervention and in cases of documented acute spills. Use of a secondary tandem mass spectrometry approach was able to successfully rule out false positive results.

Development of a sensitive high throughput multi-analyte cancer chemotherapy assay is feasible using a MRM-IDA-EPI method. This method can be used to rapidly rule out systemic exposure to accidental acute chemotherapy spills in health care workers.

A paper from this work was published in *Journal of Oncology Pharmacy Practice*.

Future Directions

In partnership with other laboratories, we have analyzed our existing plasma samples taken at baseline, follow-up, and during spill events to measure Anti-Müllerian hormone and oxidative stress. These two biomarkers are hypothesized to correlate with reproductive difficulties and a host of immune, inflammatory, and metastatic processes, respectively. This is exploratory work to inform subsequent confirmatory work. Our hypothesis is that workers with increased exposure to hazardous drugs will have lower levels of Anti-Müllerian hormone and higher levels of oxidative stress than sex and age-matched controls who do not handle hazardous drugs as part of routine work.

Additionally, our team is exploring novel study design approach to address the limitations reported in this project. Specifically, just-in-time, adaptive interventions (JITAI) hold promise when investigators face the challenge of participants who do not complete study interventions and/or do not appear to benefit from interventions. Real-time adjustment of study procedures to engage participants and/or alter the dosage or format of behavioral interventions is a promising avenue, particularly in busy health care settings.[52]

Additional strategies to improve adherence to hazardous drug handling guidelines include multi-level interventions, targeted to both health care facility leaders and front-line clinicians, as well as brief motivational interviewing techniques.

Informed by our finding that heat during PPE use was the most-often cited barrier, we have conducted pilot work with our colleagues in the College of Engineering to empirically measure body heat and thermal comfort among health care workers who don PPE used for hazardous drug handling.

Data from this project were used to apply and receive a grant from the National Cancer Institute to develop and deliver interprofessional workshops on chemotherapy safety (R25CA214227). This hybrid learning program combines online modules, in-person didactic lessons, and high-fidelity simulations to provide practicing oncology nurses and pharmacists with enhanced knowledge and skills. Explicit content is provided on hazardous drug handling. To date, over 100 clinicians have completed the training and there is a wait list with over 200 names.

References

1. Centers for Disease Control and Prevention. National Occupational Research Agenda for Healthcare and Social Assistance (HCSA). https://www.cdc.gov/nora/councils/hcsa/agenda.html. Published 2019. Accessed May 31, 2019.
2. Stellman JM, Aufiero BM, Taub RN. Assessment of Potential Exposure to Antineoplastic the Health Care Setting. *Prev Med (Baltim)*. 1984;255(3):245-255.
3. Connor TH, McDiarmid MA. Preventing occupational exposures to antineoplastic drugs in health care settings. *CA Cancer J Clin*. 2006;56(6):354-365. doi:10.3322/canjclin.56.6.354
4. Fransman W, Roeleveld N, Peelen S, de Kort W, Kromhout H, Heederik D. Nurses with dermal exposure to antineoplastic drugs: reproductive outcomes. *Epidemiology*. 2007;18(1):112-119. doi:10.1097/01.ede.0000246827.44093.c1
5. Valanis B, Vollmer WMWBM, Steele P. Occupational Exposure to Antineoplastic Agents : Self-Reported Miscarriages and Stillbirths Among Nurses and Pharmicists. *J Occup Environ Med*. 1999;41(8):632-638. doi:10.1097/00043764-199908000-00004
6. Fransman W, Peelen S, Hilhorst S, Roeleveld N, Heederik D, Kromhout H. A pooled analysis to study trends in exposure to antineoplastic drugs among nurses. *Ann Occup Hyg*. 2007;51(3):231-239. doi:10.1093/annhyg/mel081
7. National Institute for Occupational Safety and Health (NIOSH), Alert N. *Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Healthcare Settings. 2004.*; 2004. http://stacks.cdc.gov/objectView!getDataStreamContent.action?pid=cdc:6030&dsid=DS1&mimeType=application/pdf. Accessed April 2, 2013.
8. Polovich M. *Safe Handling of Hazardous Drugs*. 2nd ed. Pittsburgh, PA: Oncology Nursing Press, Inc.; 2011.
9. American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs. *Am J Heal Pharm*. 2006;63(12):1172-1191. doi:10.2146/ajhp050529
10. Neuss MN, Polovich M, McNiff K, et al. 2013 updated american society of clinical oncology/oncology nursing society chemotherapy administration safety standards including standards for the safe administration and management of oral chemotherapy. *Oncol Nurs Forum*. 2013;40(3):225-233. doi:10.1188/13.ONF.40-03AP2
11. Polovich M, Martin S. Nurses' use of hazardous drug-handling precautions and awareness of national safety guidelines. *Oncol Nurs Forum*. 2011;38(6):718-726. doi:10.1188/11.ONF.718-726
12. Friese CR, Himes-Ferris L, Frasier MN, McCullagh MC, Griggs JJ. Structures and processes of care in ambulatory oncology settings and nurse-reported exposure to chemotherapy. *BMJ Qual Saf*. 2012;21(9):753-759. doi:10.1136/bmjqs-2011-000178
13. Centers for Disease Control and Prevention. National Ambulatory Medical Care Survey: 2010 summary tables. http://www.cdc.gov/nchs/data/ahcd/namcs_summary/2010_namcs_web_tables.pdf. Published 2010. Accessed April 4, 2015.
14. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of

change in patients' care.[see comment]. *Lancet*. 2003;362(9391):1225-1230.
15. Ivers N, Jamtvedt G, Flottorp S, et al. Audit and feedback: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev*. 2012;Art. No.:(6):CD000259. doi:10.1002/14651858.CD000259.pub3
16. Keat CH, Sooaid NS, Yun CY, Sriraman M. Improving safety-related knowledge, attitude and practices of nurses handling cytotoxic anticancer drug: pharmacists' experience in a general hospital, Malaysia. *Asian Pac J Cancer Prev*. 2013;14(1):69-73. http://www.ncbi.nlm.nih.gov/pubmed/23534806.
17. Kamimura A, Schneider K, Lee CS, Crawford SD, Friese CR. Practice environments of nurses in ambulatory oncology settings: a thematic analysis. *Cancer Nurs*. 2011;35(1):E1-7. doi:10.1097/NCC.0b013e31820b6efa
18. Vogus T, Sutcliffe K, Weick K. Doing No Harm: Enabling, Enacting, and Elaborating a Culture of Safety in Health Care. *Acad Manag …*. 2010:60-77. http://amp.aom.org/content/24/4/60.short. Accessed May 3, 2013.
19. McCullagh M, Lusk SL, Ronis DL. Factors Influencing Use of Hearing Protection Among Farmers. *Nurs Res*. 2002;51(1):33-39. doi:10.1097/00006199-200201000-00006
20. Michie S. Making psychological theory useful for implementing evidence based practice: a consensus approach. *Qual Saf Heal Care*. 2005;14(1):26-33. doi:10.1136/qshc.2004.011155
21. Martin S, Larson E. Chemotherapy-handling practices of outpatient and office-based oncology nurses. *Oncol Nurs Forum*. 2003;30(4):575-581. doi:10.1188/03.ONF.575-581
22. Geer L a, Anna D, Curbow B, et al. Survey assessment of worker dermal exposure and underlying behavioral determinants. *J Occup Environ Hyg*. 2007;4(11):809-820. doi:10.1080/15459620701612722
23. Vogus TJ, Sutcliffe KM. The Safety Organizing Scale: development and validation of a behavioral measure of safety culture in hospital nursing units. *Med Care*. 2007;45(1):46-54.
24. Connor TH, DeBord DG, Pretty JR, et al. Evaluation of antineoplastic drug exposure of health care workers at three university-based US cancer centers. *J Occup Environ Med*. 2010;52(10):1019-1027. doi:10.1097/JOM.0b013e3181f72b63
25. Dillman DA. *Mail and Internet Surveys: The Tailored Design Method*. 2nd ed. New York: Wiley and Sons; 2007.
26. Cato J. *User-Centered Web Design*. Boston, MA: Addison Wesley Longman; 2001.
27. NIOSH. Hazardous drug exposures in healthcare. http://www.cdc.gov/niosh/topics/hazdrug/. Accessed April 4, 2015.
28. Polovich M, Clark PC. Factors influencing oncology nurses' use of hazardous drug safe-handling precautions. *Oncol Nurs Forum*. 2012;39(3):E299-309. doi:10.1188/12.ONF.E299-E309
29. Kalisch BJ, Friese CR, Choi SH, Rochman M. Hospital Nurse Staffing: Choice of Measure Matters. *Med Care*. 2011;00(00):1-5. doi:10.1097/MLR.0b013e318222a6df
30. Friese CR, Lake ET, Aiken LH, Silber JH, Sochalski J. Hospital Nurse Practice Environments and Outcomes for Surgical Oncology Patients. *Health Serv Res*. 2008;43(4):1145-1163. doi:10.1111/j.1475-6773.2007.00825.x
31. Clarke S. Organizational climate, staffing, and safety equipment as predictors of

needlestick injuries and near-misses in hospital nurses. *Am J Infect Control*. 2002;30(4):207-216. doi:10.1067/mic.2002.123392
32. Lake ET. The nursing practice environment: measurement and evidence. *Med Care Res Rev*. 2007;64(2 Suppl):104S-22S.
33. Friese CR. Practice environments of nurses employed in ambulatory oncology settings: measure refinement. *Oncol Nurs Forum*. 2012;39(2):166-172. doi:10.1188/12.ONF.166-172
34. Guitton J, Cohen S, Tranchand B, et al. Quantification of docetaxel and its main metabolites in human plasma by liquid chromatography/tandem mass spectrometry. *Rapid Commun Mass Spectrom*. 2005;19(17):2419-2426. doi:10.1002/rcm.2072
35. U.S. Department of Health and Human Services. Guidance for the industry: bioanalytical method validation. http://www.fda.gov/downloads/Drugs/Guidances/ucm070107.pdf. Accessed April 4, 2015.
36. Li Y, Baron J. *Behavioral Research Data Analysis with R.* New York: Springer; 2011.
37. Brown, H., Prescott R. *Applied Mixed Models in Medicine*. 2nd ed. West Sussex: Wiley; 2006. 978-0-470-02356-3.
38. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. Inc E, ed. *J Pers Soc Psychol*. 1986;51(6):1173-1182. http://www.ncbi.nlm.nih.gov/pubmed/3806354.
39. Spybrook J., Bloom H., Congdon R., Hill C., Martinez A. Raudenbush S. Optimal design plus empirical evidence: documentation of the "Optimal Design" software. http://hlmsoft.net/od/. Accessed April 4, 2015.
40. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale: Lawrence Erlbaum Associates; 1988.
41. Hon C-Y, Abusitta D. Causes of Health Care Workers' Exposure to Antineoplastic Drugs: An Exploratory Study. *Can J Hosp Pharm*. 2016;69(3):216-223. doi:http://dx.doi.org/10.4212/cjhp.v69i3.1558
42. Connor TH, Celano P, Frame JN, Zon RT. Summary of the Workshop on the Safe Handling of Hazardous Drugs Cohosted by the National Institute for Occupational Safety and Health and the American Society of Clinical Oncology. *J Oncol Pract*. 2017;13(3):199-205. doi:10.1200/JOP.2016.017384
43. Zon RT. USP 3 : United in Safeguarding Patients , Personnel , and Providers. 2018;13(3):145-148. doi:10.1200/JOP.2016.020453
44. United States Pharmacopeial Convention. USP General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings. http://www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare. Published 2017. Accessed June 11, 2018.
45. Walton AL, Eisenberg S, Friese CR. Hazardous Drugs: Legislative and Regulatory Efforts to Improve Safe Handling . *Clin J Oncol Nurs*. 2017;21(2):254-256. doi:10.1188/17.CJON.254-256
46. Friese CR, Yang J, Mendelsohn-Victor K, McCullagh MC. Randomized Controlled Trial of an Intervention to Improve Nurses' Hazardous Drug Handling. *Oncol Nurs Forum*. 2019;46(2):248-256. doi:10.1188/19.ONF.248-256
47. Yevchak AM, Fick DM, McDowell J, et al. Barriers and facilitators to implementing delirium rounds in a clinical trial across three diverse hospital settings. *Clin Nurs Res*.

2014;23(2):201-215. doi:10.1177/1054773813505321
48. Tropman JE, Wooten L. Executive leadership: A 7C approach. *Probl Perspect Manag*. 2010;8(4):47-57.
49. US Department of Health and Human Services Office of Human Research Protections. Engagement of institutions in human subjects research (2008). http://www.hhs.gov/ohrp/policy/engage08.html. Published 2016. Accessed August 2, 2016.
50. National Academies of Science, Engineering, and Medicine. Federal Demonstration Partnership: Subaward Agreement Forms. http://sites.nationalacademies.org/PGA/fdp/PGA_063626. Published 2016. Accessed August 2, 2016.
51. Friese CR, Mendelsohn-Victor K, Ginex P, McMahon CM, Fauer AJ, McCullagh MC. Lessons Learned From a Practice-Based, Multisite Intervention Study With Nurse Participants. *J Nurs Scholarsh*. 2017;49(2):194-201. doi:10.1111/jnu.12279
52. Lei H, Nahum-Shani I, Lynch K, Oslin D, Murphy SA. A "SMART" design for building individualized treatment sequences. *Annu Rev Clin Psychol*. 2012;8:21-48. doi:10.1146/annurev-clinpsy-032511-143152

Publications

1. Shu P, Zhao T, Wen B, Mendelsohn-Victor K, Sun D, Friese CR, Pai, MP. Application of an innovative high-throughput liquid chromatography-tandem mass spectrometry method for simultaneous analysis of 18 hazardous drugs to rule out accidental acute chemotherapy exposures in health care workers. *J Oncol Pharm Practice*. In Press.
2. Friese CR, Yang J, Mendelsohn-Victor K, McCullagh M. Randomized controlled trial of an intervention to improve nurses' hazardous drug handling. *Oncol Nurs Forum*. 2019;46(2):248-256. doi:10.1188/19.ONF.248-256.
3. Friese CR, Mendelsohn-Victor K, Ginex P, McMahon CM, Fauer AJ, McCullagh MC. Lessons learned from a practice-based, multisite intervention study with nurse participants. *J Nurs Scholarsh*. 2017;49(2):194-201. doi:10.1111/jnu.12279.
4. Friese, C.R. & McCullagh, M.C. (2017). The hazardous drug handling policy landscape. In Polovich, M., & Olsen, M.M. (Eds.). *Safe handling of hazardous drugs*. (3rd. Ed). Pittsburgh, PA: Oncology Nursing Society.
5. Walton AL, Eisenberg S, Friese CR. Hazardous drugs: legislative and regulatory efforts to improve safe handling. *Clin J Oncol Nurs*. 2017;21(2):254-256. doi:10.1188/17.CJON.254-256.
6. He B, Mendelsohn-Victor K, McCullagh M, Friese C. Personal protective equipment use and hazardous drug spills among ambulatory oncology nurses. *Oncol Nurs Forum*. 2017;44(1):60-65. doi:10.1188/17.ONF.60-65.
7. Friese C. Friese: Health workers need protection from chemo meds. *Detroit News*. http://www.detroitnews.com/story/opinion/2015/06/30/protect-michigan-health-workers/29480417/. Published June 30, 2015.
8. Friese CR, Mendelsohn-Victor K, Wen B, et al. DEFENS - Drug exposure feedback and education for nurses' safety: Study protocol for a randomized controlled trial. *Trials*. 2015;16(1):171. doi:10.1186/s13063-015-0674-5.
9. Friese CR, McCullagh MC, Sutcliffe KM. Handle with care: The known and unknown risks to nurses who handle hazardous drugs. *Am Nurse Today*. 2015;10(1):41-42.
10. Friese CR, McArdle C, Zhao T, et al. Antineoplastic drug exposure in an ambulatory setting: a pilot study. *Cancer Nurs*. 2014;38(2):1-7. doi:10.1097/NCC.0000000000000143.

Addenda

1. Cumulative Inclusion Enrollment Table.
See attached
2. Inclusion of Gender and Minority Study Subjects
See attached
3. Inclusion of Children
Children (persons aged up to 21 years) were not enrolled in the study because the phenomena examined in this study (occupational exposure to hazardous drugs) are not expected to occur in this population. All members of our study population were over the age of 21.

4. Materials available for other investigators.
A de-identified file containing the pre- and post-intervention data only along with data dictionary has been prepared for deposit at the Inter-university Consortium for Political and Social Research (ICSPR), a publically accessible data archive. Requests for use will be sent to the PI for approval.