BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-097127
Article Type:	Protocol
Date Submitted by the Author:	26-Nov-2024
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Keywords:	Patient Reported Outcome Measures, Radiation oncology < RADIOTHERAPY, Implementation Science, Surveys and Questionnaires, STATISTICS & RESEARCH METHODS, QUALITATIVE RESEARCH

Enhancing representativeness of patient-reported outcomes in routine radiation oncology care: a quality improvement protocol to address nonresponse

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Running Title: Nonresponse of Patient-reported Outcomes

Figures: 2; **Tables:** 2

Abstract: 299/300

Main Text: 3,422/4,000

Abstract

Introduction: Nonresponse significantly undermines the representativeness of patient-reported outcome (PRO) data, thereby compromising its utility for facilitating high-value, equitable, patient-centered care in cancer clinics. Quality improvement studies are needed to assess the representativeness of PRO data collected in routine care, identify the underlying causes of nonresponse, and develop novel methods to ensure data representativeness. Using a multilevel framework and a mixed-methods approach, this project has three aims: (1) characterize the nonresponse of the Global-10 across clinic, provider, and patient levels; (2) identify multilevel causes of nonresponse and potential strategies to improve representativeness in PRO collection; and (3) develop effective modifications to missing-data methods to enhance the representativeness of pre-existing PRO data.

Methods and analysis: Our primary data source is the Patient Reported Outcomes Measurement Information System Global-10, collected as part of routine care at the Radiation Oncology clinics within the Mass General Brigham (MGB) healthcare system. Other data sources include (1) Harvard Catalyst for provider-specific data, (2) MGB administrative data, (3) public Centers for Medicare & Medicaid Services data, and (4) the National Plan and Provider Enumeration System. We will conduct quantitative analyses to assess variations in Global-10 nonresponse across multilevel factors. Additionally, we will use qualitative interviews with patients and clinical professionals to understand the causes of nonresponse and to formulate strategies to expand the reach of PRO collection to underrepresented cancer patients, improve their PRO completions, and enhance overall PRO data representativeness. Finally, we will integrate

implementation science knowledge and findings from the first two aims into missing-data methods to manage nonresponse in the pre-existing Global-10 data and to evaluate their performance in preserving representativeness.

Ethics and dissemination: The study protocol was reviewed and approved by the Institutional Review Board at the Dana-Farber/Harvard Cancer Center (24-225). We will publish the findings in peer-reviewed scientific journals and present the findings at national and international conferences.

Strengths and Limitations

- This project will dissect nonresponse using a multilevel framework which has been widely applied in dissemination and implementation science but not yet commonly applied to nonresponse research.
- We will examine patient reported outcome (PRO) data, collected as part of routine care at Radiation Oncology clinics within Mass General Brigham healthcare system in Massachusetts, United States.
- Our project introduces methodological innovation by integrating implementation knowledge from PRO data collection experiences into missing-data methods.
- This is a cross-sectional study, so causal relationships cannot be determined.

Introduction

Patient-reported outcome (PRO) measures, or PROMs, are powerful tools in cancer care to enhance clinician-patient communication, identify problematic symptoms and treatment priorities, facilitate shared decision-making, and prolong survival.[1, 2] Aggregated PRO data can also generate patient-centered real-world evidence to inform clinical practice and are increasingly incorporated into national public reporting and value-based healthcare initiatives as measures of care quality.[3, 4] Regardless of their purpose, PRO data can exist only when patients participate, and nonresponse emerges as a significant challenge to data representativeness.

Compared to clinical trials, collecting PROMs in clinical care involves large-scale implementation and is susceptible to significant heterogeneity due to the absence of standardization, limited resources, variable leadership buy-in, and diverse patient populations, resulting in heterogeneity in the collected data.[5, 6] Furthermore, studies have shown that minoritized groups, such as racial/ethnic minorities and non-English speakers, are less likely to complete PROMs.[7-12] Using PRO data that do not represent the patient population to generate evidence or evaluate care delivery threatens the validity of such efforts and can worsen healthcare disparities.[13-16] For PROMs to continue to promote high-quality and equitable patient-centered cancer care, it is crucial to identify the underlying causes of nonresponse and to develop novel methods to ensure data representativeness.

Research into the implementation of PROMs in clinical care has revealed many patient-, provider-, and clinic- level factors that can affect PROM completion rates, such as provider engagement and infrastructure support.[17-21] Although identifying the barriers

and facilitators to PROMs collection is important, higher collection rates do not necessarily imply better data representativeness. Strategies aimed at increasing collection may differ from those designed to enhance representativeness. Yet, most current research focuses on methods to increase collection instead of methods to enhance PRO data representativeness. Multilevel frameworks can help to not only characterize nonresponse but to also identify determinants that can improve the representativeness of routinely collected PRO data.[22-25] These structured frameworks can simultaneously be used to develop mitigation strategies to target the identified determinants, thereby addressing PRO data representativeness efficiently and effectively.[22-25]

The overarching goal of this project is to delineate potential causes of nonresponse and to devise mitigation strategies to improve the representativeness of PRO data collected as part of routine radiation oncology care. To achieve this, we will examine Patient Reported Outcomes Measurement Information System (PROMIS) Global-10 (Global-10) data, collected as part of routine care at the Radiation Oncology clinics within the Mass General Brigham (MGB) healthcare system, a large, integrated health system in Massachusetts. Using a multilevel framework and a mixed-methods approach, this project aims to:

- Aim 1: Characterize the nonresponse of the Global-10, collected as part of routine care, across clinic-, provider-, and patient- levels.
- Aim 2: Identify multilevel causes of nonresponse and potential strategies to improve representativeness in PROMs collection.

- Aim 3: Develop effective modifications to missing-data methods to enhance the representativeness of pre-existing PRO data.

Methods and Analysis

Project Overview

The approach consists of a multilevel framework derived from the Consolidated Framework for Implementation Research (CFIR) and a mixed-methods strategy. Figure 1 displays the project overview. In Aim 1, we will assess variations in nonresponse of Global-10 across multilevel factors to identify key areas of concern and organize our findings. In Aim 2, we will use qualitative interviews to understand the causes of nonresponse across the key areas identified from Aim 1, and to formulate strategies that can expand the reach of PROMs collection to underrepresented cancer patients, improve their PROMs completions, and enhance overall PRO data representativeness. In Aim 3, we will incorporate implementation science knowledge and findings from the first two aims into missing-data methods to manage nonresponse of the pre-existing Global-10 data and to evaluate their performance in preserving representativeness. In the final stages of Aim 3, we will compare the results yielded from different missing-data methods. This comparison will not only validate the robustness of our findings but also highlight the most effective modifications to missing-data methods to protect representativeness in PRO data with nonresponse.

[INSERT FIGURE 1 HERE]

Conceptual Framework

To ensure thorough investigations into nonresponse and to facilitate the development of actionable mitigation strategies, this project draws from the CFIR, which

has been used to guide the systematic evaluation of determinants in the design and implementation of PROMs collection in clinical care.[23] The CFIR encompasses five major domains: Intervention Characteristics, Outer Setting (e.g., patient needs, external policies), Inner Setting (e.g., institute characteristics, implementation climate, and accessible information and technology), Characteristics of the Individuals Involved, and Implementation Process.[23-25] Our project focuses on the Inner Setting and Characteristics of the Individuals Involved (i.e., patients and providers) domains. We perceive the Inner Setting to include factors at the clinic level, such as facility characteristics and implementation climate, which are associated with leadership engagement, available resources, and accessible knowledge essential for PROMs collection in diverse populations and problem-solving.[20, 21] Providers' clinical workload and annual PROMs collection affect their willingness and ability to collect PROMs, address nonresponse, and reach minority groups.[19, 21] Patients' demographic characteristics, socioeconomic status, and health status influence their motivation to complete PROMs.[7-11] The multilevel framework will guide the design of quantitative analyses (Aims 1 and 3) to uncover the landscape of nonresponse and aid in the development of qualitative interview guides (Aim 2) to solicit knowledge on improving representativeness in data collection across clinic-, provider-, and patient- levels.

Study Setting

We will use Global-10 data collected as part of routine care in MGB Radiation Oncology clinics. MGB is an integrated health system comprised of two academic medical centers as well as eight community hospitals and a large network of community-based physician office practices. In 2012, MGB initiated a standardized

PROMs collection program for routine clinical specialty care, offering participating physician practices and clinics the necessary technical infrastructure, personnel training, continuous education, and operational resources for successful implementation.[20, 26, 27] To date, the MGB PROMs Program accrues more than 6 million PROMs per year across more than 475 clinics from more than 80 medical, behavioral health, and surgical specialties, representing the largest repository of multispecialty PRO data in the US.

The MGB Radiation Oncology practices uniformly implemented PROMs collection across all clinic sites and remain active today. Because radiation therapy is a fundamental component of cancer care across nearly all cancer types for curative or palliative purposes, Radiation Oncology serves as a prime specialty from which to conduct our analyses to yield generalizable results applicable across the cancer care continuum. Furthermore, MGB Radiation Oncology clinics are in different settings (e.g., academic vs. community) and geographical locations and serve a diverse patient population, allowing for better capture of variations in sex, race/ethnicity, and socioeconomic status.

Data Sources

Multiple data sources will be merged to conduct this study (Table 1).[28-30] Our primary data source is MGB Enterprise Data Warehouse (EDW), a system-wide data resource that contains harmonized medical, billing, claims and financial data, including PROMs data.

[INSERT TABLE 1 HERE]

Aim 1: Characterize the nonresponse of the Global-10 across clinic-, provider-, and patient- levels

Study Design and Data Analysis: Preliminary data show Global-10 completions from a total of 34,516 patients with 68,933 submissions representing 70% of the individuals who were assigned the Global-10 in the MGB Radiation Oncology clinics since the start of data collection in January 2015, with the lowest rate during the COVID-19 pandemic. Given that all patients are assigned the Global-10 as part of their initial visit to Radiation Oncology clinics, we will conduct a cross-sectional study focusing on the characterization of Global-10 nonresponse. Additionally, due to the probable differences in nonresponse mechanisms between children and adults, this proposal will focus only on adult patients (those aged 18 years or older). In the MGB Radiation Oncology clinics, patients must complete all assigned items (i.e., 10 items on Global-10) to finalize their submissions and obtain the summary scores (i.e., global physical and mental health).[31] Therefore, we will classify the completion to the assigned Global-10 as *response* and *nonresponse*. *"Response"* is defined as patients who completed all 10 items on Global-10. *"Nonresponse"* includes patients who missed at least one of the 10 items on Global-10. Within each clinic, we will calculate the overall frequencies and percentages for respondents and nonrespondents, respectively. Furthermore, we will describe the distributions of respondents and nonrespondents by factors at patient- and provider- levels for the overall sample and by each clinic, with a specific focus on underrepresented populations such as racial/ethnic minorities, older age, less-educated individuals, non-English speakers, etc. (Table 1).

We will identify the predictors of nonresponse. Our primary hypothesis is that there are significant relationships between nonresponse and patients' demographic characteristics (e.g., being a racial/ethnic minority, being of an older age, being a non-English speaker, and having a low income), providers' data collection proficiency, and the history of the PROMs program in the clinics.[7-11, 18-21] Using bivariate analyses, we will assess the differences in distributions among respondents and nonrespondents across multilevel factors. Factors with p-values less than 0.20 will enter the multivariable model. For factors outside this threshold, we will refer to existing literature to determine their appropriateness for inclusion in multivariable analyses. We will use multinomial logistic regression and stepwise selection to identify significant predictors of nonresponse, adjusting for the random effects of clinics and providers.

Summary: By analyzing Global-10 data from the MGB Radiation Oncology clinics, we will characterize the heterogeneity in nonresponse of routinely collected PRO data across clinic-, provider-, and patient- level factors. This will not only facilitate our understanding of critical areas of concern but also guide our research in developing strategies to improve representativeness for both PROMs collection and PRO data analysis.

Aim 2: Identify multilevel causes of nonresponse and potential strategies to improve representativeness in PROMs collection

Study Design and Semi-structured Interview Guides: We will conduct 2 separate focus groups with clinical professionals (i.e., clinic leaders and providers) and approximately 25 1:1 in-depth interviews with cancer patients in Radiation Oncology clinics. Clinic leaders and providers will be purposively recruited. Eligible clinic leaders

include chief-level executives, administrative leaders, PROMs directors, and clinician leaders.[18] Provider participants must have been actively involved in PROMs collection in the past year. Regarding patients, we will recruit adults aged 18 years or older who are receiving care. We will employ quota sampling to ensure the inclusion of sex, race, ethnicity, and other minority groups. Patients will be recruited with the help of radiation oncology providers or through electronic communication. We will exclude patients with documented cognitive impairment or those unable to provide informed consent.

Building on the findings from Aim 1 and in accordance with our multilevel framework (Figure 2 and Table 1), we will develop semi-structured interview guides tailored for clinical professionals (i.e., clinic leadership and providers) and patients. For clinical professionals, we will explore (1) their perceived issues and causes of nonresponse and (2) potential strategies to enhance representativeness in data collection. For patients, we will solicit their insights regarding (1) PROMs collection overall, (2) the main challenges they face when deciding whether to complete PROMs, and (3) potential solutions from their perspectives (e.g., technology, rationale, etc.). Both interview guides will be pilot tested with 3 clinical professionals and 3 patients before their use.

[INSERT FIGURE 2 HERE]

Data Collection and Analysis: For clinical professionals, we will collect demographic characteristics, such as age, sex, job titles, years of experience in their respective fields, and history of PROMs collection. We will conduct focus groups separately to foster open discussion and gather a rich variety of perspectives. We plan to recruit 7 clinic leaders and 10 providers, specifically from clinics exhibiting the lowest

and highest rates of nonresponse. We believe that 2 focus group interviews, with at least 5 clinical professionals in each, will achieve information saturation.[32]

For cancer patients, we will collect demographic characteristics and medical information (e.g., cancer stage, treatment type, and comorbidities) through the MGB EHR and pre-interview surveys as needed. The research team will conduct 1:1 in-depth interviews with cancer patients to understand their experiences and insights. We estimate that each interview will last 45-60 minutes and approximately 25 patient interviews will be sufficient to reach thematic saturation.[33] A $50 gift card will be provided to each patient for remuneration.

Quantitative data will be summarized descriptively. All interviews will be professionally transcribed. The research team will analyze qualitative data using the content analysis approach, independently and in conference to facilitate rigor. Discrepancies in coding between team members will be discussed and arbitrated by a third party as necessary to reach consensus. Deductive coding will be used to map the themes to the components of our multilevel framework (Figure 2 and Table 1), and strategies addressing the causes of nonresponse across clinic-, provider-, and patient-levels. Inductive coding will be used for new themes. We will use NVivo software for data analysis and management and follow consolidated criteria for reporting qualitative research to draft results.

Summary: The qualitative study in Aim 2 will deepen our understanding of the issues and causes of nonresponse from both clinical professionals' and patients' perspectives to uncover mitigation strategies. Importantly, these strategies can effectively address the issue of "missing not at random (MNAR)." [34] The MNAR

mechanism is the most difficult to address as it assumes that nonresponse is related to both observed (e.g., patients' characteristics) and unobserved factors.[34] Unlike other types of missing-data mechanisms which will be evaluated in Aim 3, nonresponse operated under MNAR cannot be fixed with *post hoc* statistical maneuvers, thus uncovering its potential causes during data collection will provide valuable information.

Aim 3: Develop effective modifications to missing-data methods to enhance the representativeness of pre-existing PRO data.

Aside from MNAR, the most probable mechanism for nonresponse of PRO data collected in routine cancer care is "missing at random (MAR)," given the established relationships between nonresponse and the demographic and clinical characteristics recorded in patients' medical records. MAR assumes that nonresponse is related to observed variables.[34] Advanced missing-data methods, such as Hot-deck imputation, multiple imputation (MI), and inverse probability weighting (IPW), are recommended for addressing MAR-based nonresponse.[34-37] However, these methods can sometimes result in extreme values or unbalanced weights, making it challenging to fully establish representative data for analysis.[38-41] We will seek to improve upon these approaches by incorporating multilevel factors based on our multilevel framework. A notable feature of Hot-deck imputation and MI is their ability to incorporate auxiliary variables – those related to outcomes or nonresponse but not part of the main analyses – to enhance their performance, making them well-suited to modification based on multilevel factors.[35-37, 42] IPW adjusts for nonresponse bias using complete cases without imputation.[40] Another mechanism for nonresponse is "missing completely at random (MCAR)", which assumes that nonresponse is unrelated to any variables.[34] MCAR is an

unrealistic assumption in routinely collected PRO data as we know nonresponse bias exists. Therefore, in Aim 3, we will explore the solutions to MAR that incorporate the multilevel factors inherently influencing PROMs data collection.

Study Design and Data Analysis: We will integrate determinants of nonresponse, derived from (1) our multilevel framework and (2) findings from the first two aims, into the missing data analysis. The goal is to modify missing-data methods to improve their performance in preserving the representativeness of routinely collected PRO data. We will employ six missing-data methods to address the nonresponse of pre-existing Global-10 data (Table 2). Under the MCAR assumption, listwise deletion will be used as a standard approach for comparison, while Hot-deck imputation, MI, and IPW will be used for MAR. Specifically, when applying Hot-deck imputation, MI, and IPW, multilevel factors of nonresponse will be integrated into the analyses. This integration enables us to investigate whether the performance of these methods in achieving representativeness can be enhanced. Notably, although Hot-deck imputation, MI, and IPW are primarily recommended for nonresponse under the MAR assumption, they also effectively address nonresponse under the MCAR assumption and thus we will examine both assumptions in this proposal for completeness.[34, 35]

[INSERT TABLE 2 HERE]

Performance Evaluation: We aim to rigorously assess the performance of various missing-data methods to enhance the representativeness of Global-10 data, in both scenarios where information from successful PROMs collection is available and where it is absent. Our assessment will comprise a comprehensive comparative analysis focusing on (1) demographic characteristics, (2) summary scores, and (3) predictive

validity between the complete cases and the overall sample after adjustment for each missing data technique.[31, 43-45] *For demographic characteristics*, we will compare the distributions of sex, age, race, ethnicity, language, education, employment status, and financial insurance type. Our goal is to determine whether the sample post-adjustment reflects the demographic distributions observed in the overall population who have been assigned the Global-10.[43, 45] *For physical and mental health summary scores*, we will describe and compare their distributions (e.g., mean, standard deviation, minimum, and maximum) between complete cases and the post-adjustment sample. Favorable missing-data methods should produce summary scores with fewer outliers, smaller standard deviations, and lower mean values, especially since we account for the nonresponse in minority groups and cancer patients with advanced diseases and poor health status.[44, 46, 47] *Regarding the predictive validity*, we will use logistic regression to evaluate the ability of physical and mental health summary scores to predict healthcare utilization (e.g., urgent care visits, hospitalizations, etc.) or death.[44] Our hypothesis is that after accounting for the nonresponse, the adjusted summary scores will have stronger correlations with healthcare utilization or death than the scores from the complete cases.

Summary: By developing and examining modifications to statistical methods for handling missing data, Aim 3 can identify effective strategies to address nonresponse and increase representativeness in the analysis of pre-existing, routinely collected PRO data. Given the large volume of such data and significant heterogeneity in its quality, the findings from Aim 3 can guide the selection of appropriate statistical approaches and key determinants of nonresponse to improve representativeness to the extent possible

when utilizing pre-existing PRO data for quality improvement and patient-centered cancer care.

Potential Challenges and Considerations

There are several potential obstacles to successful completion of the study aims. First, recruiting clinical professionals for qualitative interviews may pose a challenge due to their demanding schedules. To address this, we will liberally conduct focus group interviews via secure teleconferencing platforms outside of normal business hours. Second, recruiting underrepresented cancer patients may also be challenging, with some minority groups potentially reluctant to participate. If this occurs, we will increase the incentives. Third, there might be a lack of direct data sources for some aggregated level factors in our multilevel framework. In such cases, we will collect information through MGB administrative or human resources data or direct contact with clinical professionals. Finally, our currently developed multilevel framework may not cover all potential factors. We will continue to add additional variables based on available databases and current evidence as the project ensues.

Ethics and dissemination

This study has been approved by the Dana-Farber/Harvard Cancer Center (DF/HCC) IRB (24-225). The research team will take all necessary steps possible to protect participants from the few minimal risks potentially associated with the study. All patient identifiers will be removed prior to the analysis. Throughout all project activities, the study team members will adhere to all MGB policies, standards, and procedures, as well as any Data Use Agreements related to specific data sources. We will continue to protect confidentiality and prevent inappropriate access, use or disclosure of data.

Focus group interviews with clinical professionals will be conducted via a secure video-conferencing platform. In-depth interviews with patients will be conducted in a private room or conducted remotely using a secure video-conferencing platform or telephone, according to participant preference. All audio/video recordings, transcripts, surveys, and demographic forms for qualitative studies will be stored on secure, encrypted servers on password-protected computers, accessible only by the study research staff. The qualitative data will be collected using password-protected digital recorders. During transcription, all identifying information that could be used to link the data with the participant will be de-identified. Audio files will be destroyed once transcribed, and no personal identifiers will be linked to the transcripts. Study participants will not be identified in any reports, presentations, or publications resulting from this study. All quantitative and qualitative data will be stored on encrypted study computers, and all analyses will be conducted at Brigham and Women's Hospital, where the study database will be hosted.

We will publish the findings in peer- reviewed scientific journals and present the study findings at national and international conferences. The completion of this project will elucidate the characteristics of nonresponse and its intricate associations with multilevel factors of successful, large-scale PROMs collection in diverse patient populations. Insights from this endeavor will guide the evolution and development of PROMs collection programs to expand their reach to underrepresented cancer patients and improve data representativeness. This, in turn, enables the utility of PRO data for quality improvement and high-quality, equitable patient-centered cancer care.

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Authors' contributions: CZ and JBL are the principal investigators of this project and led the study design. CZ, JBL, and MOE contributed to the conception and design of the study. CZ led the writing of this protocol manuscript. JBL, MOE, ALP and NEM contributed significantly to the editing of this manuscript. All authors reviewed and provided comments to improve the manuscript. All authors contributed to the editing and final approval of the protocol.

Funding: CZ, JBL, and MOE are supported by the National Cancer Institute of the National Institutes of Health under Award Number R03CA292987. The funders had no role in the conceptualization, analysis or presentation of findings of this study.

Competing interests: Outside of the submitted work, ALP is co-developer of the Q-Portfolio measures and receives royalties when used for commercial purposes. ALP, CZ, and MOE are supported in part by the National Cancer Institute for unrelated work. All other authors have nothing to disclose.

Patient and public involvement: Patients and/or the public were not involved in the development of the protocol.

Table 1. Proposed Multilevel Factors for the Domains of Inner Setting and Individual Characteristics

DOMAINS	LEVELS	VARIABLES	DATA SOURCES
Inner setting	Clinic	• Administrative mode of PROMs (e.g., paper, tablet) • Average outpatient volume per week • Average years of training in providers • Average years in practice in providers • Average PROMs collection per week • Clinical level (community- or academic-) • Early adoption (PROMs program launched from March 2014 to December 2016) • History of PROMs program • Institute characteristics (e.g., total employees)	EDW, MGB administrative data, direct contact
Individual characteristics	Provider	• Average number of clinical patients per week • Average PROMs collection per week • Providers' characteristics (e.g., sex) • Years of training • Years in practice	EDW, MGB administrative data, Harvard catalyst, CMS, NPPES, direct contact
	Patient	• Age • Cancer diagnosis • Cancer stage at PROM submission • Comorbidity • Education • Employment status • Ethnicity • Financial insurance • Language • Race • Sex	EDW

Notes: PROMs: Patient-reported outcome measures; EDW: Enterprise data warehouse; MGB: Mass General Brigham; CMS: Center for Medicare & Medicaid Services; NPPES: National Plan & Provider Enumeration System

Table 2. Missing-Data Mechanisms and Proposed Methods

MISSING-DATA METHODS	MCAR	MAR
Listwise deletion	√	□
Single imputation		
Hot-deck imputation	√	√
Hot-deck imputation with auxiliary variables	√	√
Multiple imputation (MI)	√	√
MI with auxiliary variables	√	√
Inverse probability weighting	√	√

Notes: MCAR: Missing completely at random; MAR: Missing at random.

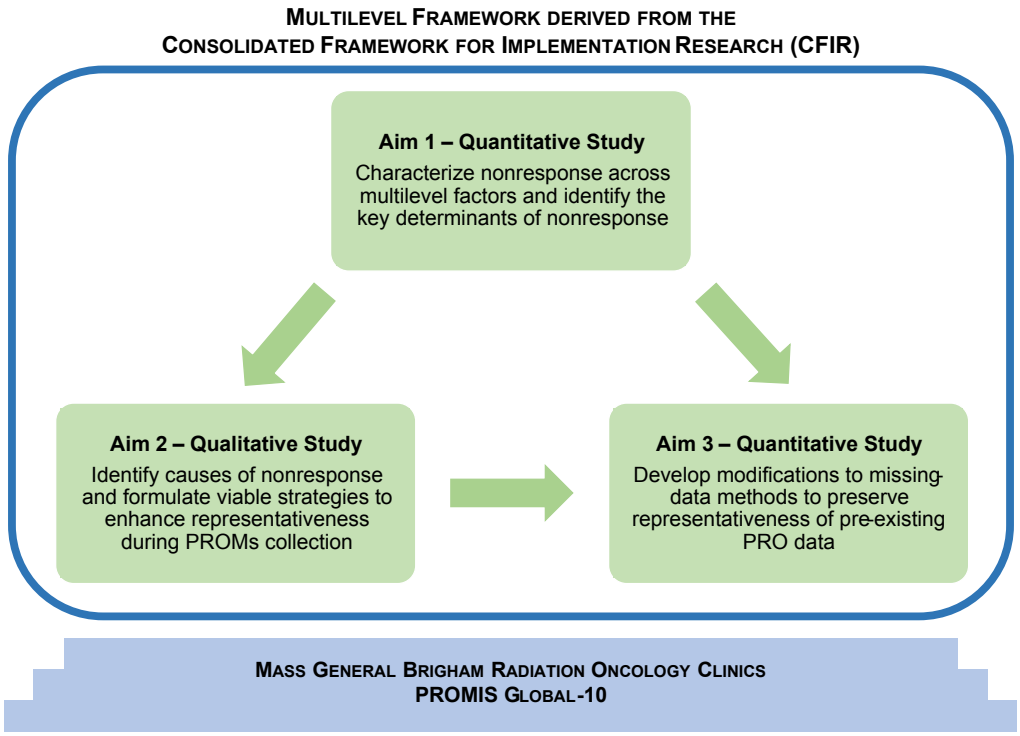

Figure 1. Project Overview

Notes: PROMs: Patient-reported outcome measures

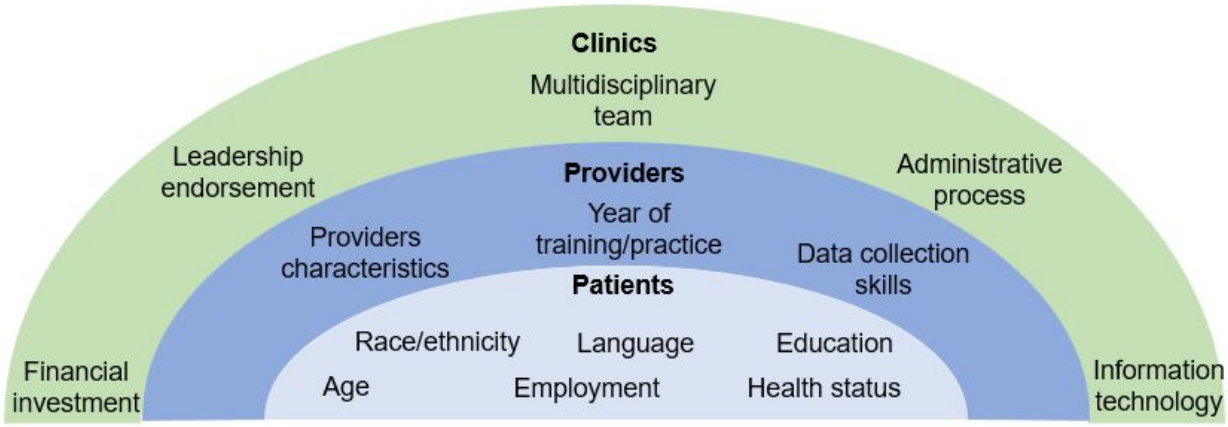

Figure 2. Multilevel Framework of PROMs Nonresponse

Notes: PROMs: Patient-reported outcome measures

BMJ Open

Enhancing representativeness of patient-reported outcomes in routine radiation oncology care: a quality improvement protocol to address nonresponse

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-097127.R1
Article Type:	Protocol
Date Submitted by the Author:	26-Nov-2024
Complete List of Authors:	Zeng, Chengbo; Brigham and Women's Hospital, Patient Reported Outcomes, Value and Experience (PROVE) Center, Department of Surgery; Harvard Medical School Martin, Neil E.; Brigham and Women's Hospital, Department of Radiation Oncology; Harvard Medical School; Dana-Farber Cancer Institute, Department of Radiation Oncology Pusic, Andrea; Brigham and Women's Hospital, Patient Reported Outcomes, Value and Experience (PROVE) Center, Department of Surgery; Harvard Medical School; Brigham and Women's Hospital, Division of Plastic and Reconstructive Surgery, Department of Surgery Edelen, Maria O.; Brigham and Women's Hospital, Patient Reported Outcomes, Value and Experience (PROVE) Center, Department of Surgery; Harvard Medical School; RAND Corporation Liu, Jason B.; Brigham and Women's Hospital, Patient Reported Outcomes, Value and Experience (PROVE) Center, Department of Surgery; Harvard Medical School; Brigham and Women's Hospital, Division of Surgical Oncology, Department of Surgery
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Oncology, Patient-centred medicine, Qualitative research
Keywords:	Patient Reported Outcome Measures, Radiation oncology < RADIOTHERAPY, Implementation Science, Surveys and Questionnaires, STATISTICS & RESEARCH METHODS, QUALITATIVE RESEARCH

Enhancing representativeness of patient-reported outcomes in routine radiation oncology care: a quality improvement protocol to address nonresponse

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Running Title: Nonresponse of Patient-reported Outcomes

Figures: 2; **Tables:** 2

Abstract: 300/300

Main text: 3,785/4,000

Abstract

Introduction: Nonresponse significantly undermines the representativeness of patient-reported outcome (PRO) data, thereby compromising its utility for facilitating high-value, equitable, patient-centered care in cancer clinics. Quality improvement studies are needed to assess the representativeness of PRO data collected in routine care, identify the underlying causes of nonresponse, and develop novel methods to ensure data representativeness. Using a multilevel framework and a mixed-methods approach, we have three aims: (1) characterize the nonresponse of the Global-10 across clinic-, provider-, and patient- levels; (2) identify multilevel causes of nonresponse and potential strategies to improve representativeness in PRO collection; and (3) develop effective modifications to missing-data methods to enhance the representativeness of pre-existing PRO data.

Methods and analysis: Our primary data source is the Patient Reported Outcomes Measurement Information System Global-10, collected as part of routine care at the Radiation Oncology clinics within the Mass General Brigham (MGB) healthcare system. Other sources include (1) Harvard Catalyst for provider-specific data, (2) MGB administrative data, (3) public Centers for Medicare & Medicaid Services data, and (4) the National Plan and Provider Enumeration System. We will conduct quantitative analyses to assess variations in Global-10 nonresponse across multilevel factors. Additionally, we will use qualitative interviews with patients and clinical professionals to understand the causes of nonresponse and to formulate strategies to expand the reach of PRO collection to underrepresented cancer patients, improve their completions, and enhance overall data representativeness. Finally, we will integrate implementation

science knowledge and findings from the first two aims into missing-data methods to manage nonresponse in the pre-existing Global-10 data and to evaluate their performance in preserving representativeness.

Ethics and dissemination: The study protocol was reviewed and approved by the Institutional Review Board at the Dana-Farber/Harvard Cancer Center (24-225). Written informed consent will be obtained from participants. Study findings will be disseminated through peer-reviewed publications and presentations at national and international conferences.

Strengths and limitations of this study

- This project will dissect nonresponse using a multilevel framework which has been widely applied in dissemination and implementation science but not yet commonly applied to nonresponse research.
- We will examine patient reported outcome (PRO) data, collected as part of routine care at Radiation Oncology clinics within Mass General Brigham healthcare system in Massachusetts, United States.
- Our project introduces methodological innovation by integrating implementation knowledge from PRO data collection experiences into missing-data methods.
- This is a cross-sectional study, so causal relationships cannot be determined.

INTRODUCTION

Patient-reported outcome (PRO) measures, or PROMs, are powerful tools in cancer care to enhance clinician-patient communication, identify problematic symptoms and treatment priorities, facilitate shared decision-making, and prolong survival.[1, 2] Aggregated PRO data can also generate patient-centered real-world evidence to inform clinical practice and are increasingly incorporated into national public reporting and value-based healthcare initiatives as measures of care quality.[3, 4] Regardless of their purpose, PRO data can exist only when patients participate, and nonresponse emerges as a significant challenge to data representativeness.

Compared to clinical trials, collecting PROMs in clinical care involves large-scale implementation and is susceptible to significant heterogeneity due to the absence of standardization, limited resources, variable leadership buy-in, and diverse patient populations, resulting in heterogeneity in the collected data.[5, 6] Furthermore, studies have shown that minoritized groups, such as racial/ethnic minorities and non-English speakers, are less likely to complete PROMs.[7-12] Using PRO data that do not represent the patient population to generate evidence or evaluate care delivery threatens the validity of such efforts and can worsen healthcare disparities.[13-16] For PROMs to continue to promote high-quality and equitable patient-centered cancer care, it is crucial to identify the underlying causes of nonresponse and to develop novel methods to ensure data representativeness.

Research into the implementation of PROMs in clinical care has revealed many patient-, provider-, and clinic- level factors that can affect PROM completion rates, such as provider engagement and infrastructure support.[17-21] Although identifying the barriers

and facilitators to PROMs collection is important, higher collection rates do not necessarily imply better data representativeness. Strategies aimed at increasing collection may differ from those designed to enhance representativeness. Yet, most current research focuses on methods to increase collection instead of methods to enhance PRO data representativeness. Multilevel frameworks can help to not only characterize nonresponse but to also identify determinants that can improve the representativeness of routinely collected PRO data.[22-25] These structured frameworks can simultaneously be used to develop mitigation strategies to target the identified determinants, thereby addressing PRO data representativeness efficiently and effectively.[22-25]

The overarching goal of this project is to delineate potential causes of nonresponse and to devise mitigation strategies to improve the representativeness of PRO data collected as part of routine radiation oncology care. To achieve this, we will examine Patient Reported Outcomes Measurement Information System (PROMIS®) Global-10 (Global-10) data, collected as part of routine care at the Radiation Oncology clinics within the Mass General Brigham (MGB) healthcare system, a large, integrated health system in Massachusetts. Using a multilevel framework and a mixed-methods approach, this project aims to:

- Aim 1: Characterize the nonresponse of the Global-10, collected as part of routine care, across clinic-, provider-, and patient- levels.
- Aim 2: Identify multilevel causes of nonresponse and potential strategies to improve representativeness in PROMs collection.

- Aim 3: Develop effective modifications to missing-data methods to enhance the representativeness of pre-existing PRO data.

METHODS AND ANALYSIS

Project overview

The approach consists of a multilevel framework derived from the Consolidated Framework for Implementation Research (CFIR) and a mixed-methods strategy. Figure 1 displays the project overview. In Aim 1, we will assess variations in nonresponse of Global-10 across multilevel factors to identify key areas of concern and organize our findings. In Aim 2, we will use qualitative interviews to understand the causes of nonresponse across the key areas identified from Aim 1, and to formulate strategies that can expand the reach of PROMs collection to underrepresented cancer patients, improve their PROMs completions, and enhance overall PRO data representativeness. In Aim 3, we will incorporate implementation science knowledge and findings from the first two aims into missing-data methods to manage nonresponse of the pre-existing Global-10 data and to evaluate their performance in preserving representativeness. In the final stages of Aim 3, we will compare the results yielded from different missing-data methods. This comparison will not only validate the robustness of our findings but also highlight the most effective modifications to missing-data methods to protect representativeness in PRO data with nonresponse.

Conceptual framework

To ensure thorough investigations into nonresponse and to facilitate the development of actionable mitigation strategies, this project draws from the CFIR, which has been used

to guide the systematic evaluation of determinants in the design and implementation of PROMs collection in clinical care.[23] The CFIR encompasses five major domains: Intervention Characteristics, Outer Setting (e.g., patient needs, external policies), Inner Setting (e.g., institute characteristics, implementation climate, and accessible information and technology), Characteristics of the Individuals Involved, and Implementation Process.[23-25] Our project focuses on the Inner Setting and Characteristics of the Individuals Involved (i.e., patients and providers) domains. We perceive the Inner Setting to include factors at the clinic level, such as facility characteristics and implementation climate, which are associated with leadership engagement, available resources, and accessible knowledge essential for PROMs collection in diverse populations and problem-solving.[20, 21] Providers' clinical workload and annual PROMs collection affect their willingness and ability to collect PROMs, address nonresponse, and reach minority groups.[19, 21] Patients' demographic characteristics, socioeconomic status, and health status influence their motivation to complete PROMs.[7-11] The multilevel framework will guide the design of quantitative analyses (Aims 1 and 3) to uncover the landscape of nonresponse and aid in the development of qualitative interview guides (Aim 2) to solicit knowledge on improving representativeness in data collection across clinic-, provider-, and patient- levels.

Study setting

We will use Global-10 data collected as part of routine care in MGB Radiation Oncology clinics. MGB is an integrated health system comprised of two academic medical centers as well as eight community hospitals and a large network of community-based physician office practices. In 2012, MGB initiated a standardized PROMs collection program for

routine clinical specialty care, offering participating physician practices and clinics the necessary technical infrastructure, personnel training, continuous education, and operational resources for successful implementation.[20, 26, 27] To date, the MGB PROMs Program accrues more than 6 million PROMs per year across more than 475 clinics from more than 80 medical, behavioral health, and surgical specialties, representing the largest repository of multispecialty PRO data in the US.

The MGB Radiation Oncology practices uniformly implemented PROMs collection across all clinic sites and remain active today. Because radiation therapy is a fundamental component of cancer care across nearly all cancer types for curative or palliative purposes, Radiation Oncology serves as a prime specialty from which to conduct our analyses to yield generalizable results applicable across the cancer care continuum. Furthermore, MGB Radiation Oncology clinics are in different settings (e.g., academic vs. community) and geographical locations and serve a diverse patient population, allowing for better capture of variations in sex, race/ethnicity, and socioeconomic status.

Data sources

Multiple data sources will be merged to conduct this study (Table 1).[28-30] Our primary data source is MGB Enterprise Data Warehouse (EDW), a system-wide data resource that contains harmonized medical, billing, claims and financial data, including PROMs data.

Aim 1: Characterize the nonresponse of the Global-10 across clinic-, provider-, and patient- levels

Study design and data analysis: Preliminary data show Global-10 completions from a total of 34,516 patients with 68,933 submissions representing 70% of the individuals who were assigned the Global-10 in the MGB Radiation Oncology clinics since the start of data collection in January 2015, with the lowest rate during the COVID-19 pandemic. Given that all patients are assigned the Global-10 as part of their initial visit to Radiation Oncology clinics, we will conduct a cross-sectional study focusing on the characterization of Global-10 nonresponse. Additionally, due to the probable differences in nonresponse mechanisms between children and adults, this proposal will focus only on adult patients (those aged 18 years or older). In the MGB Radiation Oncology clinics, patients must complete all assigned items (i.e., 10 items on Global-10) to finalize their submissions and obtain the summary scores (i.e., global physical and mental health).[31] Therefore, we will classify the completion to the assigned Global-10 as *response* and *nonresponse*. *"Response"* is defined as patients who completed all 10 items on Global-10. *"Nonresponse"* includes patients who missed at least one of the 10 items on Global-10. Within each clinic, we will calculate the overall frequencies and percentages for respondents and nonrespondents, respectively. Furthermore, we will describe the distributions of respondents and nonrespondents by factors at patient- and provider-levels for the overall sample and by each clinic, with a specific focus on underrepresented populations such as racial/ethnic minorities, older age, less-educated individuals, non-English speakers, etc. (Table 1).

We will identify the predictors of nonresponse. Our primary hypothesis is that there are significant relationships between nonresponse and patients' demographic characteristics (e.g., being a racial/ethnic minority, being of an older age, being a non-

English speaker, and having a low income), providers' data collection proficiency, and the history of the PROMs program in the clinics.[7-11, 18-21] Using bivariate analyses, we will assess the differences in distributions among respondents and nonrespondents across multilevel factors. Factors with p-values less than 0.20 will enter the multivariable model. For factors outside this threshold, we will refer to existing literature to determine their appropriateness for inclusion in multivariable analyses. We will use multinomial logistic regression and stepwise selection to identify significant predictors of nonresponse, adjusting for the random effects of clinics and providers.

Summary: By analyzing Global-10 data from the MGB Radiation Oncology clinics, we will characterize the heterogeneity in nonresponse of routinely collected PRO data across clinic-, provider-, and patient- level factors. This will not only facilitate our understanding of critical areas of concern but also guide our research in developing strategies to improve representativeness for both PROMs collection and PRO data analysis.

Aim 2: Identify multilevel causes of nonresponse and potential strategies to improve representativeness in PROMs collection

Study design and semi-structured interview guides: We will conduct 2 separate focus groups with clinical professionals (i.e., clinic leaders and providers) and approximately 25 1:1 in-depth interviews with cancer patients in Radiation Oncology clinics. Clinic leaders and providers will be purposively recruited. Eligible clinic leaders include chief-level executives, administrative leaders, PROMs directors, and clinician leaders.[18] Provider participants must have been actively involved in PROMs collection in the past year. Regarding patients, we will recruit adults aged 18 years or older who are receiving

care. We will employ quota sampling to ensure the inclusion of sex, race, ethnicity, and other minority groups. Patients will be recruited with the help of radiation oncology providers or through electronic communication. We will exclude patients with documented cognitive impairment or those unable to provide informed consent.

Building on the findings from Aim 1 and in accordance with our multilevel framework (Figure 2 and Table 1), we will develop semi-structured interview guides tailored for clinical professionals (i.e., clinic leadership and providers) and patients. For clinical professionals, we will explore (1) their perceived issues and causes of nonresponse and (2) potential strategies to enhance representativeness in data collection. For patients, we will solicit their insights regarding (1) PROMs collection overall, (2) the main challenges they face when deciding whether to complete PROMs, and (3) potential solutions from their perspectives (e.g., technology, rationale, etc.). Both interview guides will be pilot tested with 3 clinical professionals and 3 patients before their use.

Data collection and analysis: For clinical professionals, we will collect demographic characteristics, such as age, sex, job titles, years of experience in their respective fields, and history of PROMs collection. We will conduct focus groups separately to foster open discussion and gather a rich variety of perspectives. We plan to recruit 7 clinic leaders and 10 providers, specifically from clinics exhibiting the lowest and highest rates of nonresponse. We believe that 2 focus group interviews, with at least 5 clinical professionals in each, will achieve information saturation.[32]

For cancer patients, we will collect demographic characteristics and medical information (e.g., cancer stage, treatment type, and comorbidities) through the MGB EHR and pre-interview surveys as needed. The research team will conduct 1:1 in-depth

interviews with cancer patients to understand their experiences and insights. We estimate that each interview will last 45-60 minutes and approximately 25 patient interviews will be sufficient to reach thematic saturation.[33] A $50 gift card will be provided to each patient for remuneration.

Quantitative data will be summarized descriptively. All interviews will be professionally transcribed. The research team will analyze qualitative data using the content analysis approach, independently and in conference to facilitate rigor. Discrepancies in coding between team members will be discussed and arbitrated by a third party as necessary to reach consensus. Deductive coding will be used to map the themes to the components of our multilevel framework (Figure 2 and Table 1), and strategies addressing the causes of nonresponse across clinic-, provider-, and patient-levels. Inductive coding will be used for new themes. We will use NVivo software for data analysis and management and follow consolidated criteria for reporting qualitative research to draft results.

Summary: The qualitative study in Aim 2 will deepen our understanding of the issues and causes of nonresponse from both clinical professionals' and patients' perspectives to uncover mitigation strategies. Importantly, these strategies can effectively address the issue of "missing not at random (MNAR)." [34] The MNAR mechanism is the most difficult to address as it assumes that nonresponse is related to both observed (e.g., patients' characteristics) and unobserved factors.[34] Unlike other types of missing-data mechanisms which will be evaluated in Aim 3, nonresponse operated under MNAR cannot be fixed with *post hoc* statistical maneuvers, thus uncovering its potential causes during data collection will provide valuable information.

Aim 3: Develop effective modifications to missing-data methods to enhance the representativeness of pre-existing PRO data.

Aside from MNAR, the most probable mechanism for nonresponse of PRO data collected in routine cancer care is "missing at random (MAR)," given the established relationships between nonresponse and the demographic and clinical characteristics recorded in patients' medical records. MAR assumes that nonresponse is related to observed variables.[34] Advanced missing-data methods, such as Hot-deck imputation, multiple imputation (MI), and inverse probability weighting (IPW), are recommended for addressing MAR-based nonresponse.[34-37] However, these methods can sometimes result in extreme values or unbalanced weights, making it challenging to fully establish representative data for analysis.[38-41] We will seek to improve upon these approaches by incorporating multilevel factors based on our multilevel framework. A notable feature of Hot-deck imputation and MI is their ability to incorporate auxiliary variables – those related to outcomes or nonresponse but not part of the main analyses – to enhance their performance, making them well-suited to modification based on multilevel factors.[35-37, 42] IPW adjusts for nonresponse bias using complete cases without imputation.[40] Another mechanism for nonresponse is "missing completely at random (MCAR)", which assumes that nonresponse is unrelated to any variables.[34] MCAR is an unrealistic assumption in routinely collected PRO data as we know nonresponse bias exists. Therefore, in Aim 3, we will explore the solutions to MAR that incorporate the multilevel factors inherently influencing PROMs data collection.

Study design and data analysis: We will integrate determinants of nonresponse, derived from (1) our multilevel framework and (2) findings from the first two aims, into the

missing data analysis. The goal is to modify missing-data methods to improve their performance in preserving the representativeness of routinely collected PRO data. We will employ six missing-data methods to address the nonresponse of pre-existing Global-10 data (Table 2). Under the MCAR assumption, listwise deletion will be used as a standard approach for comparison, while Hot-deck imputation, MI, and IPW will be used for MAR. Specifically, when applying Hot-deck imputation, MI, and IPW, multilevel factors of nonresponse will be integrated into the analyses. This integration enables us to investigate whether the performance of these methods in achieving representativeness can be enhanced. Notably, although Hot-deck imputation, MI, and IPW are primarily recommended for nonresponse under the MAR assumption, they also effectively address nonresponse under the MCAR assumption and thus we will examine both assumptions in this proposal for completeness.[34, 35]

Performance evaluation: We aim to rigorously assess the performance of various missing-data methods to enhance the representativeness of Global-10 data, in both scenarios where information from successful PROMs collection is available and where it is absent. Our assessment will comprise a comprehensive comparative analysis focusing on (1) demographic characteristics, (2) summary scores, and (3) predictive validity between the complete cases and the overall sample after adjustment for each missing data technique.[31, 43-45] *For demographic characteristics*, we will compare the distributions of sex, age, race, ethnicity, language, education, employment status, and financial insurance type. Our goal is to determine whether the sample post-adjustment reflects the demographic distributions observed in the overall population who have been assigned the Global-10.[43, 45] *For physical and mental health summary scores*, we will

describe and compare their distributions (e.g., mean, standard deviation, minimum, and maximum) between complete cases and the post-adjustment sample. Favorable missing-data methods should produce summary scores with fewer outliers, smaller standard deviations, and lower mean values, especially since we account for the nonresponse in minority groups and cancer patients with advanced diseases and poor health status.[44, 46, 47] *Regarding the predictive validity*, we will use logistic regression to evaluate the ability of physical and mental health summary scores to predict healthcare utilization (e.g., urgent care visits, hospitalizations, etc.) or death.[44] Our hypothesis is that after accounting for the nonresponse, the adjusted summary scores will have stronger correlations with healthcare utilization or death than the scores from the complete cases.

Summary: By developing and examining modifications to statistical methods for handling missing data, Aim 3 can identify effective strategies to address nonresponse and increase representativeness in the analysis of pre-existing, routinely collected PRO data. Given the large volume of such data and significant heterogeneity in its quality, the findings from Aim 3 can guide the selection of appropriate statistical approaches and key determinants of nonresponse to improve representativeness to the extent possible when utilizing pre-existing PRO data for quality improvement and patient-centered cancer care.

Patient and public involvement

None.

ETHICS AND DISSEMINATION

This study has been approved by the Dana-Farber/Harvard Cancer Center (DF/HCC) IRB (24-225). The research team will take all necessary steps possible to protect participants from the few minimal risks potentially associated with the study. All patient identifiers will be removed prior to the analysis. Throughout all project activities, the study team members will adhere to all MGB policies, standards, and procedures, as well as any Data Use Agreements related to specific data sources. We will continue to protect confidentiality and prevent inappropriate access, use or disclosure of data.

In the qualitative studies, potential participants will be informed about the project, and the research staff will confirm their eligibility, provide additional study details, and answer any questions they may have. If a potential participant is willing to enroll, the study staff will obtain their written informed consent. Focus group interviews with clinical professionals will be conducted via a secure video-conferencing platform. In-depth interviews with patients will be conducted in a private room or conducted remotely using a secure video-conferencing platform or telephone, according to participant preference. All audio/video recordings, transcripts, surveys, and demographic forms for qualitative studies will be stored on secure, encrypted servers on password-protected computers, accessible only by the study research staff. The qualitative data will be collected using password-protected digital recorders. During transcription, all identifying information that could be used to link the data with the participant will be de-identified. Audio files will be destroyed once transcribed, and no personal identifiers will be linked to the transcripts. Study participants will not be identified in any reports, presentations, or publications resulting from this study. All quantitative and qualitative data will be stored on encrypted

study computers, and all analyses will be conducted at Brigham and Women's Hospital, where the study database will be hosted.

Study findings will be disseminated through peer-reviewed publications and presentations at national and international conferences.

This is a two-year study funded by the National Cancer Institute of the National Institutes of Health. The study team is currently preparing for data extraction and curation from the MGB EDW and other sources. We plan to dedicate 6 months to Aim 1, 9 months to Aim 2, and 6 months to Aim 3. The final 3 months of the project will focus on manuscript development. The anticipated date of completion is July 2026.

DISCUSSION

Our project is innovative in at least four ways. First, we will dissect nonresponse using a multilevel framework which has been widely applied in dissemination and implementation science but not yet commonly applied to nonresponse research. Second, the wealth of data available to us through MGB Radiation Oncology clinics, encompassing clinic-, provider-, and patient-level factors related to nonresponse, is novel in itself. Third, with no established guidelines for reporting and analyzing routinely collected PRO data with nonresponse, our project pioneers the characterization of PROMs completion by varied degrees of nonresponse across clinic-, provider-, and patient- level factors. This approach can disentangle the intricate landscape of nonresponse in cancer clinics and facilitate the assessment of relevant causes. Such insights have the potential to significantly impact future nonresponse mitigation during PROMs collection as well as robustly address its statistical management in the analysis of pre-existing, routinely collected PRO data.

Lastly, our project introduces methodological innovation by integrating implementation knowledge from PROMs collection experiences into missing-data methods. This integration aims to scrutinize the effectiveness of these methods in preserving the representativeness of routinely collected PRO data despite nonresponse, setting a precedent in methodological innovation.

There are several potential obstacles and limitations that warrant discussion. First, recruiting clinical professionals for qualitative interviews may pose a challenge due to their demanding schedules. To address this, we will liberally conduct focus group interviews via secure teleconferencing platforms outside of normal business hours. Second, recruiting underrepresented cancer patients may also be challenging, with some minority groups potentially reluctant to participate. If this occurs, we will increase the incentives. Third, there might be a lack of direct data sources for some aggregated level factors in our multilevel framework. In such cases, we will collect information through MGB administrative or human resources data or direct contact with clinical professionals. Fourth, our currently developed multilevel framework may not cover all potential factors. We will continue to add additional variables based on available databases and current evidence as the project ensues. Finally, as this is a cross-sectional study, causal relationships cannot be determined.

The completion of this project will elucidate the characteristics of nonresponse and its intricate associations with multilevel factors of successful, large-scale PROMs collection in diverse patient populations. Insights from this endeavor will guide the evolution and development of PROMs collection programs to expand their reach to underrepresented cancer patients and improve data representativeness. This, in turn,

enables the utility of PRO data for quality improvement and high-quality, equitable patient-centered cancer care.

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FIGURE LEGENDS

Figure 1. Project overview
PROMs: Patient-reported outcome measures

Figure 2. Multilevel framework of PROMs nonresponse
PROMs: Patient-reported outcome measures.

Contributors: CZ is the guarantor. CZ and JBL are the principal investigators of this project and led the study design. CZ, JBL, and MOE contributed to the conception and design of the study. CZ led the writing of this protocol manuscript. JBL, MOE, ALP and NEM contributed significantly to the editing of this manuscript. All authors contributed to the editing and final approval of the protocol.

Funding: CZ, JBL, and MOE are supported by the National Cancer Institute of the National Institutes of Health under Award Number R03CA292987. The funders had no role in the conceptualization, analysis or presentation of findings of this study.

Competing interests: Outside of the submitted work, ALP is co-developer of the Q-Portfolio measures and receives royalties when used for commercial purposes. ALP, CZ, and MOE are supported in part by the National Cancer Institute for unrelated work. All other authors have nothing to disclose.

Table 1. Proposed multilevel factors for the domains of inner setting and individual characteristics

DOMAINS	LEVELS	VARIABLES	DATA SOURCES
Inner setting	Clinic	• Administrative mode of PROMs (e.g., paper, tablet) • Average outpatient volume per week • Average years of training in providers • Average years in practice in providers • Average PROMs collection per week • Clinical level (community- or academic-) • Early adoption (PROMs program launched from March 2014 to December 2016) • History of PROMs program • Institute characteristics (e.g., total employees)	EDW, MGB administrative data, direct contact
Individual characteristics	Provider	• Average number of clinical patients per week • Average PROMs collection per week • Providers' characteristics (e.g., sex) • Years of training • Years in practice	EDW, MGB administrative data, Harvard catalyst, CMS, NPPES, direct contact
	Patient	• Age • Cancer diagnosis • Cancer stage at PROM submission • Comorbidity • Education • Employment status • Ethnicity • Financial insurance • Language • Race • Sex	EDW

PROMs: Patient-reported outcome measures; EDW: Enterprise data warehouse; MGB: Mass General Brigham; CMS: Center for Medicare & Medicaid Services; NPPES: National Plan & Provider Enumeration System.

Table 2. Missing-data mechanisms and proposed methods

MISSING-DATA METHODS	MCAR	MAR
Listwise deletion	√	□
Single imputation		
Hot-deck imputation	√	√
Hot-deck imputation with auxiliary variables	√	√
Multiple imputation (MI)	√	√
MI with auxiliary variables	√	√
Inverse probability weighting	√	√

MCAR: Missing completely at random; MAR: Missing at random.

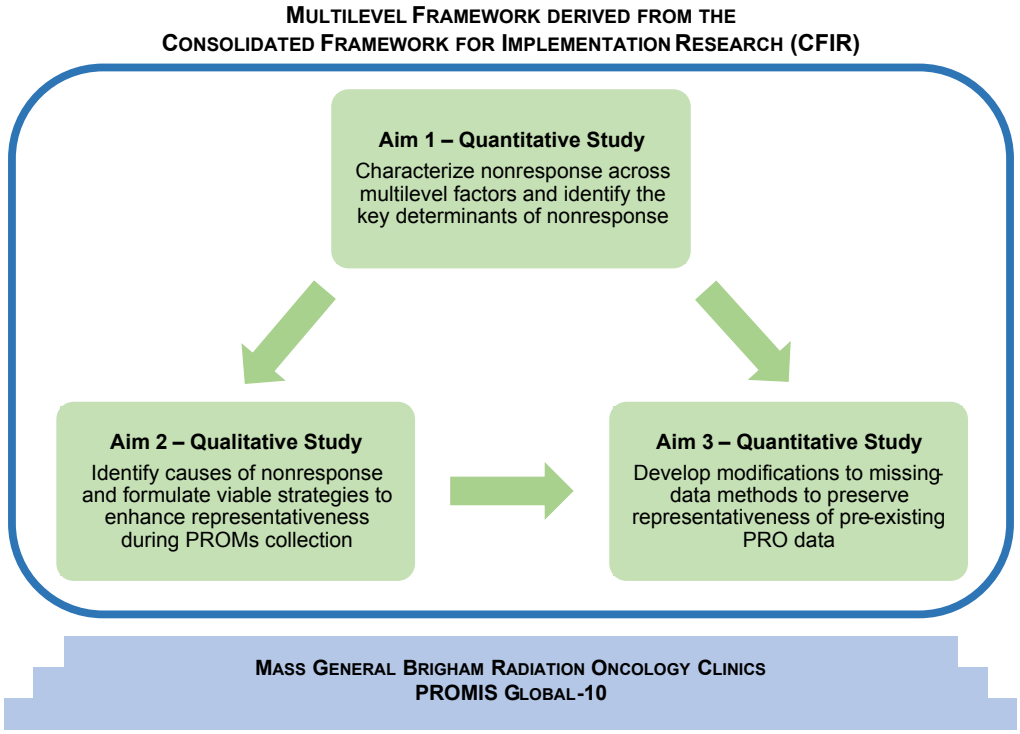

Figure 1. Project Overview

Notes: PROMs: Patient-reported outcome measures

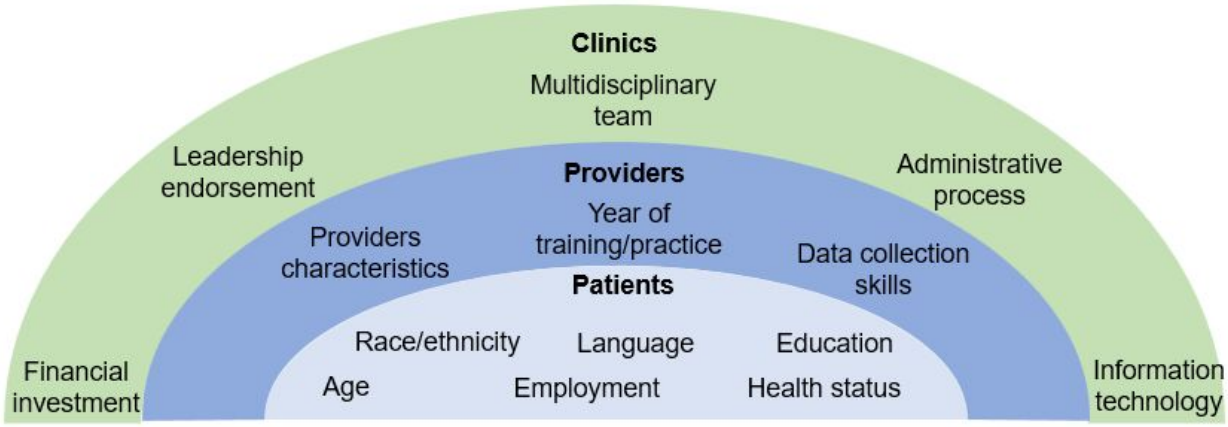

Figure 2. Multilevel Framework of PROMs Nonresponse

Notes: PROMs: Patient-reported outcome measures