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Proposal

Individualized Clinical Practice Guidelines for Pressure Injury Management: Development of an Integrated Multi-Modal Biomedical Information Resource

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Abstract

Background: Pressure ulcers (PU) and deep tissue injuries (DTI), collectively known as pressure injuries are serious complications causing staggering costs and human suffering with over 200 reported risk factors from many domains. Primary pressure injury prevention seeks to prevent the first incidence, while secondary PU/DTI prevention aims to decrease chronic recurrence. Clinical practice guidelines (CPG) combine evidence-based practice and expert opinion to aid clinicians in the goal of achieving best practices for primary and secondary prevention. The correction of all risk factors can be both overwhelming and impractical to implement in clinical practice. There is a need to develop practical clinical tools to prioritize the multiple recommendations of CPG, but there is limited guidance on how to prioritize based on individual cases. Bioinformatics platforms enable data management to support clinical decision support and user-interface development for complex clinical challenges such as pressure injury prevention care planning.

Objective: The central hypothesis of the study is that the individual's risk factor profile can provide the basis for adaptive, personalized care planning for PU prevention based on CPG prioritization. The study objective is to develop the Spinal Cord Injury Pressure Ulcer and Deep Tissue Injury (SCIPUD+) Resource to support personalized care planning for primary and secondary PU/DTI prevention.

Methods: The study is employing a retrospective electronic health record (EHR) chart review of over 75 factors known to be relevant for pressure injury risk in individuals with a spinal cord injury (SCI) and routinely recorded in the EHR. We also perform tissue health assessments of a selected sub-group. A systems approach is being used to develop and validate the SCIPUD+ Resource incorporating the many risk factor domains associated with PU/DTI primary and secondary prevention, ranging from the individual's environment to local tissue health. Our multiscale approach will leverage the strength of bioinformatics applied to an established national EHR system. A comprehensive model is being used to relate the primary outcome of interest (PU/DTI development) with over 75 PU/DTI risk factors using a retrospective chart review of 5000 individuals selected from the study cohort of more than 36,000 persons with SCI. A Spinal Cord Injury Pressure Ulcer and Deep Tissue Injury Ontology (SCIPUDO) is being developed to enable robust text-mining for data extraction from free-form notes.

Results: The results from this study are pending.

Conclusions: PU/DTI remains a highly significant source of morbidity for individuals with SCI. Personalized interactive care plans may decrease both initial PU formation and readmission rates for high-risk individuals. The project is using established EHR data to build a comprehensive, structured model of environmental, social and clinical pressure injury risk factors. The

comprehensive SCIPUD+ health care tool will be used to relate the primary outcome of interest (pressure injury development) with covariates including environmental, social, clinical, personal and tissue health profiles as well as possible interactions among some of these covariates. The study will result in a validated tool for personalized implementation of CPG recommendations and has great potential to change the standard of care for PrI clinical practice by enabling clinicians to provide personalized application of CPG priorities tailored to the needs of each at-risk individual with SCI.

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KEYWORDS

bioinformatics; electronic health record; pressure injury

Introduction

This project studies the development, validation, and timing of promising interventions to address consequences of spinal cord injury (SCI), specifically the primary and secondary prevention of pressure ulcers and deep tissue injury (PU/DTI), collectively known as pressure injuries (PrI). These chronic wounds are a major negative consequence of SCI. The Spinal Cord Injury Pressure Ulcer and Deep Tissue Injury (SCIPUD+) health care tool enables personalized PrI care planning, supporting identification and validation of best practices in SCI care for musculoskeletal health, and rehabilitation interventions.

More than 200 risk factors for PrI development have been reported for individuals with SCI [1], spanning multiple domains [2]. The Center for Medicare and Medicaid Services has determined that severe (ie, stage 3 and 4), hospital acquired PrI are entirely preventable “never events” and have discontinued reimbursement [3]. The clinical reality is that many people living with SCI continue to develop significant PrI, both in the community and hospital. Patients in acute care hospitals have 33% PrI incidence rates, with prevalence rates up to 69% [4,5]. On admission to skilled nursing facilities, PrI prevalence ranges between 10% and 26% [6,7]. Veterans with chronic SCI have incidence rates as high as 62% to 80% [8,9], and over their lifetime 34% will require at least three PrI related hospitalizations for treatment [10]. PrIs may lead to other serious medical complications, such as osteomyelitis, sepsis, and even death. In addition to the personal distress and negative impact on the quality of life (QoL) for the individual, PrI place a major cost burden on health care systems. PrI prevention is approximately 2.5 times more economical than treatment [11], with direct treatment costs for one stage 4 PrI exceeding US $100,000 over 6 years ago [12-15].

Primary PrI prevention is the first line of defense [16]. Clinical practice guidelines (CPGs) developed to aid clinicians in this goal combine a balance of evidence-based practice and expert opinion. There are multiple CPGs for PrI prevention [17-21], each with similar recommendations regarding risk assessment, prevention, PrI assessment, measurement, treatment and documentation. However, they also contain significant differences. The primary challenge with all CPGs is that there are many factors to consider. For example, the CPG from the Consortium for Spinal Cord Medicine, released in September 2014, contains a summary of over 25 recommendations to be followed by care providers [21]. Moreover, there is limited guidance on how to prioritize the recommendations for individual cases. It is overwhelming and even unrealistic to expect every recommendation to be implemented concurrently [2]. The relative importance of risk factors has not yet been investigated, limiting care planning, and prioritization of interventions. Unfortunately, as Thomason et al [22] found, although SCI physicians and nurses generally agree with the written CPG recommendations, they do not believe that these recommendations were fully implemented in their respective clinical settings. Furthermore, a European Pressure Ulcer Advisory Panel survey of PrI prevalence in 5000 hospitalized patients throughout Europe indicated that clinical expertise and standard treatment guidelines are not sufficient [23]. The International Pressure Ulcer Prevalence Study, conducted from 2006 to 2009, demonstrated an increase in PrI prevalence in the US. While overall PrI prevalence decreased modestly, the prevalence of suspected deep tissue injury increased during the same period [24]. The continued high incidence of chronic PrI, including recurrent wounds, underscores the need to develop new approaches to primary and secondary prevention.

The future of scientific research and evidence-based personalized practice will increasingly require multidisciplinary teams as the problems become more complex and the investigative tools more sophisticated. The Wound Healing Research Unit at Cardiff University, Wales initiated a multidisciplinary wound management team over 20 years ago [25]. This approach can optimize effective translation and validation of best practices for standard clinical practice. In 2013, the Veterans Health Administration (VHA) launched a 5-year strategic plan with the goal of moving the health care system for Veterans towards Personalized, Proactive, Patient-driven Care, delivered across the life continuum from prevention through tertiary care and end of life [26]. To achieve this goal for successful PrI management the patient-centered multidisciplinary team typically includes physicians, nurses, physical therapists, occupational therapists, dieticians, psychologists, and biomedical engineers [27,28].

Current PrI screening tools include a variety of risk assessment scales [9,29,30]. It is essential that they be validated as reliable for use within specific patient populations [31]. While sensitivity and specificity vary widely between scales, the Braden scale has the best balance for general population use (57.1%/67.5%) [32]. However, a review of the seven most widely used scales revealed that validation for use in the SCI population was limited [31], and there was a lack of reliability or responsiveness evidence for these individuals. A comparative effectiveness review of PrI risk assessment by the Agency for Health Care

Research and Quality found no difference between clinical judgment and the use of scales [33]. Tescher et al [34] commented that all at-risk patients are not created equal and concluded that the Braden scale does not assist the clinician in developing individualized prevention plans. As noted by Pancorbo-Hidalog et al and others [32,35,36], there is no data to suggest that the use of risk assessment scales prevents PrI. Thus, it appears that the evidence regarding the effectiveness of risk-assessment tools for preventing PrI is insufficient.

Primary prevention of PrI incidence and secondary prevention of PrI recurrence depend on reliably identifying the risk factors that contribute to its formation. A multidisciplinary expert panel found that while PrI development is influenced by multiple variables, and many risk factors have already been identified, several critical questions remain unanswered and require further research [2]. Most of the published research on PrI risk focuses on either nursing home residents or the population with acute SCI. However, the degree to which these risk factors apply to other populations has not been established. PrI environmental risk factors may vary between rural and urban populations due to ease of access to transportation, access to specialized clinical care, and air quality. For example, the Veterans Affairs SCI population includes a high proportion of individuals who receive life-long care in both urban and rural areas, and who may have different rates of primary PrI development [37,38].

The continued high incidence of PrI for many individuals at-risk in the hospital and community indicates that CPG, standardized pressure relief regimes, and risk assessment scales alone are insufficient. PrI management remains complex and multidimensional. Motivational interviewing helps individuals to adhere to personal care plans [39,40]. However, focusing primarily on motivation using a standardized approach for individuals with SCI is ineffective for secondary prevention [34]. This highlights the continued need for a personalized approach.

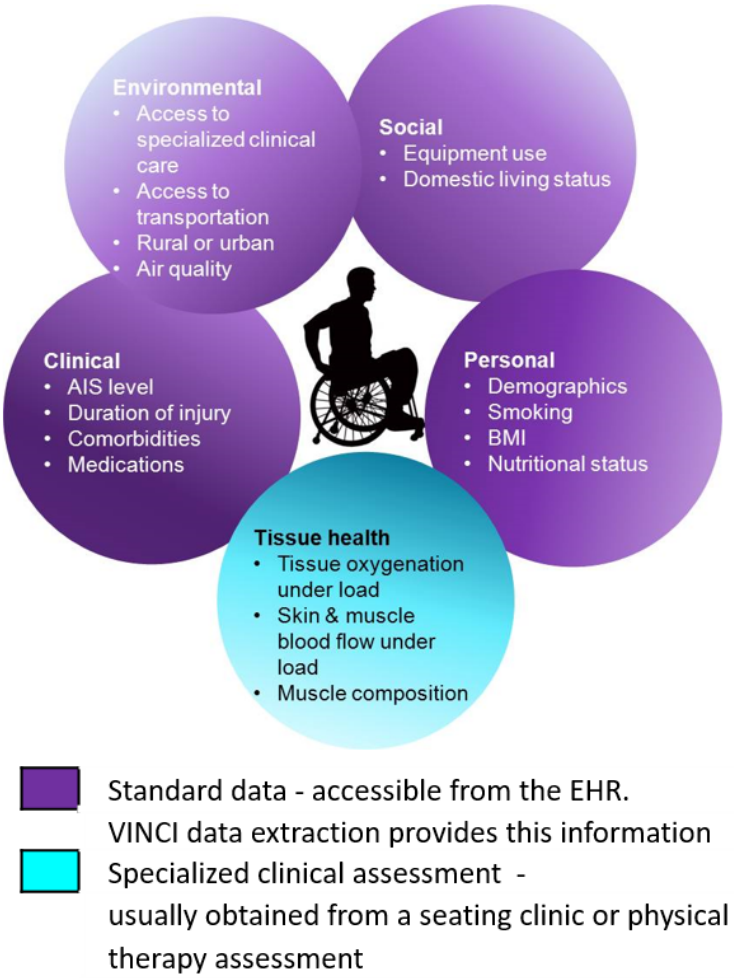
Individuals with SCI are at increased risk of PrI development. However, this devastating consequence of SCI appears to be unique for everyone. A regime of regular postural alteration and pressure relief is considered essential to minimize the risk of PrI development. Still, some individuals remain PrI free without regular pressure relief, while others perform regular pressure relief and repeatedly develop tissue breakdown. The transition from the inpatient hospital or living in a nursing home to the community following rehabilitation may impact environmental risk factors. Likewise, living alone or with a partner can impact social risk factors. CPG consider all these factors but do not provide relative prioritization.

The correction of all PrI risk factors for an individual with SCI can be both overwhelming and impractical to implement in clinical practice. The need to develop effective clinical tools to prioritize the multiple recommendations of CPG has been identified by experts in the field. In preparative work, our development and application of the preliminary SCIPUD+ Resource has shown that risk factors for primary prevention may not be the same as those for secondary prevention (ie, PrI recurrence) [41].

The application of biomedical informatics approaches enables systematic data extraction, storage, and analysis to provide clinical decision support and user-interfaces for addressing complex clinical challenges such as PrI prevention care planning. A systems approach is being used to develop and validate the SCIPUD+ Resource, a multivariate structural model that includes all core National Institute of Neurological Disorders and Stroke Common Data Elements (NINDS CDE) [42] and contributions from the many risk factor domains associated with PrI (Figure 1). These range from the individual's environment to local tissue health. The goal of the SCIPUD+ Resource is to provide a personalized health care tool to address a major consequence of SCI, specifically PrI prevention care planning. Personalized interactive programs can enhance best practices in SCI care by decreasing both initial PrI formation and readmission rates due to PrI recurrence for high-risk individuals, particularly Veterans with SCI.

The objective of this study is to develop a structural model of environmental, social, and clinical factors to provide weighted systemic insight into PrI risk in people with SCI to support personalized care plans for primary and secondary PrI prevention. The SCIPUD+ Resource will be developed using data sets extracted from the Veterans Affairs Informatics and Computing Infrastructure (VINCI) database [43] together with a cross-sectional study of tissue health profiles. This will be validated using an observational cohort study. The central hypothesis of this study is that the individual's risk factor profile provides the basis for adaptive, personalized care planning for PrI prevention based on CPG prioritization.

Figure 1. Multiple risk factor domains contribute to pressure ulcer (PU/DTI) risk. AIS: American Spinal Injury Association Impairment Scale; BMI: body mass index; EHR: electronic health record; VINCI: Veterans Affairs Informatics and Computing Infrastructure Database.



Methods

Study Design

This study employed a retrospective electronic health record (EHR) chart review of over 75 factors known to be relevant for PrI risk in individuals with SCI and routinely recorded in the EHR. We also perform tissue health assessments for a selected sub-group. Regulatory approval for the study was obtained from the local institutional review board. By applying a data-centric approach, we can leverage the power of the data resource provided by VINCI and the detailed personal characteristic database of tissue health to provide the weighted, adaptive, personalized SCIPUD+ Resource for primary and secondary PrI prevention.

The integrated SCIPUD+ Resource is being assembled from 2 databases: (1) one using data extracted from the VINCI EHR by informatics and text mining, and (2) another using tissue health data. PrI risk factor data collected at multiple retrospective time points include modifiable and nonmodifiable factors identified in cross-sectional and observational studies. Multiscale data extraction includes numerical, categorical and text data mining. A Spinal Cord Injury Pressure Ulcer and Deep Tissue Injury Ontology (SCIPUDO), is being developed to ensure robust and extensive information extraction from the free text clinical note. We will also carry out a cross-sectional study of tissue health profiles in a representative cohort of 60 individuals with SCI.

The Multi-Modality, Multi-Resource Information Integration Environment for Multi-Center Physiological and Clinical Research Studies (Physio-MIMI) cloud-based multi-modal data storage and access platform [44] creates a common Web-based user interface for data queries. It also enables the development of compatible analytical tools and easier sharing of complex data from multiple domains to support collaborative clinical and translational research using diverse data types. Another tool, Ontology-driven Web-based Research Data Capture (OnWARD) provides robust flexibility of input data storage in a relational database for detailed analysis. It can be quickly deployed and customized for any clinical study. OnWARD has eased the data entry burden in multiple clinical trials [45].

Structural modeling of factors from multiple domains and their co-impact on developing PrI will be used to provide weighted systemic insight into initial and recurrent PrI risk in people with SCI. A comprehensive model will be used to relate the primary outcome of interest (ie, PrI development) with covariates including environmental, social, clinical, personal, and tissue

health profiles and possible interactions among some of these covariates.

Cohort Extraction

The SCIPUD+ Resource is being developed using a detailed chart review of VINCI data employing International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for paraplegia and tetraplegia with a secondary filter using an SCI-specific stop code. The search timeframe is the preconversion date (September 2010 to September 2015) because the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes do not currently provide accurate delineation of SCI factors. The initial query returned approximately 36,000 different individuals and 120,000 encounters during the search timeframe across the VHA nationally. It was clarified that some individuals coded for SCI have a primary diagnosis of multiple sclerosis (MS) or amyotrophic lateral sclerosis (ALS). Therefore, we revised the code to develop a secondary filter to exclude individuals with MS and ALS since risk factors vary considerably in these neurodegenerative diseases compared to SCI. This secondary query revealed a study cohort of over 20,000 individuals with SCI, equivalent to about 8% of the total United States population. Within this cohort, a detailed review found that it includes more than 109,000 encounters. Furthermore, we have learned that each encounter encompasses an episode of care and may include different appointments stemming from the same visit, or an extended period of hospitalization. Thus, we have estimated the cohort includes about 500,000 different events and over 40 million data points.

Our research strategy builds on our existing methodologies to create the SCIPUD+ Resource to enable personalized care planning for PrI prevention based on the individual's holistic characteristics [41]. Analysis of multiple PrI risk factors requires a robust and scalable informatics approach to cope with challenges in volume and complexity. Clinical and demographic data is collected using systems with a variety of sampling rates and formats. Even when checklists and coding are required, data may be missing or only found in the free form note. During preliminary work, we found that ICD-9-CM codes markedly under-reported the number of PrI treated. In a population of 399 eligible patients, only 93 (23.3%) were coded for PrI. We have developed a pathway for construction of disease-specific ontologies for data extraction using Natural Language Processing (NLP) for complex, specialized clinical notes. We will create the dedicated domain ontology SCIPUDO by reusing terminology from existing systems ranging from anatomy (Systematized Nomenclature of Medicine-Clinical Trials), disease classification (ICD-9-CMand ICD-10-CM), medication (website RxNorm for clinical trial drug standardized nomenclature), and NINDS CDE. Due to Physio-MIMI's highly adaptable system architecture with domain ontology as a plug-and-play component, the proposed SCIPUD+ Resource can be developed by reusing much of the existing open-source tools that we have already developed. Figure 2 shows 2 hypothetical examples. In the first scenario, the clinical profile and tissue health response are the most critical domains. Potentially modifiable factors in these domains include spasticity and applied loads. Thus, the SCIPUD+ care plan would prioritize spasticity management and equipment provided. In the second scenario, the critical domains are personal and clinical factors. In addition to the potentially modifiable factors in the clinical domain, potentially modifiable factors in the personal domain include smoking and body mass index.

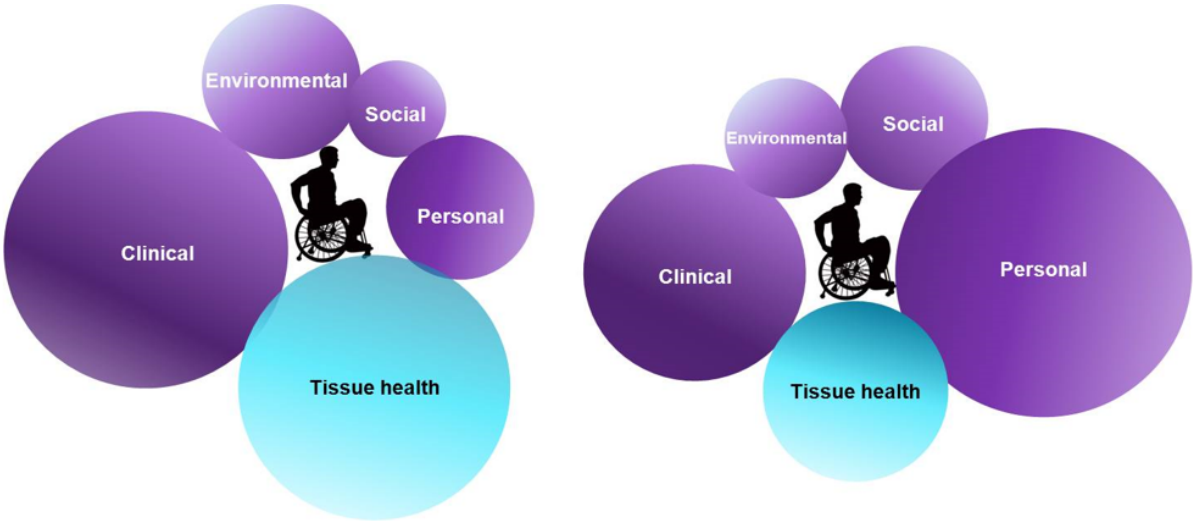
Sample Size Calculation

Based on our prior data, we defined the expected PrI incidence as 30% and a clinically significant difference as reducing the incidence by 50%. The basic PrI status extracted from the EHR is PrI or not PrI, leading to a dichotomous outcome. However, the severity of PrI differs. We will use text mining to further classify wound status as severe PrI (stage 3 or 4), minor PrI (stage 1 or 2), deep tissue injury, absent or unclassified, leading to a polytomous outcome. A first-line analysis model for dichotomous outcome uses logistic regression, while the first-line analysis model for a polytomous outcome uses multinomial logistic regression. Considering all variables and their possible interactions would lead to approximately 3082 covariates to be studied in each model. In practice, it is reasonable to expect that only a small portion of these covariates, possibly as few as 25 would be enough to predict PrI outcomes. Only clinically meaningful interactions need to be considered at the start of our modeling. To achieve a reasonably rich SCIPUD+ database that allows for a balanced cohort selection of the personal, environmental, social, and clinical factors and for an extensive study of the impact of these factors, we can and will oversample. Therefore, data will be extracted from a retrospective chart review of 5000 individuals selected from the study cohort of over 36,000 individuals with SCI using a stratified sampling scheme. We will retain 500 representative cases for further validation and testing. This sampling will provide more than 1418 (ie, 5000 minus 3082 minus 500) degrees of freedom, which is more than enough to determine the top 25 predictors. It will also validate and test these predictors with at least 80% power under a standard significance level of 0.05, assuming an average difference of PrI incidence of at least 0.15, and a moderately balanced number of cases [46-48]. The validation and testing of these top 25 predictors will be based on standard tests and bootstrap procedures.

Data Extraction and Processing

Raw data is extracted from VINCI using a stratified ICD-9-CM code search, de-identified and stored as a comma-separated values (CSV) file. Data formats include categorical, numerical and free-form text in clinical notes. Data to be collected includes factors identified as being possibly related to PrI development or healing either in cross-sectional or other observational studies. Annual evaluations for the complete study cohort will be included in the SCIPUD+ database, to determine changes over time. Any patient admission will also be reviewed, together with weekly in-patient and discharge encounters. We are particularly interested in the possible differences in PrI risk based on the level and extent of spinal injury and motor and sensory impairment. Thus, we will examine quadriplegia motor-complete (QMC), quadriplegia motor-incomplete (QMI), paraplegia motor-complete (PMC), and paraplegia motor-incomplete (PMI).

Figure 2. SCIPUD+ pressure ulcers/deep tissue injuries care plan model. Domain size indicates the relative importance for that individual.



(a) Clinical and Tissue Health domains predominate. (b) Personal and Clinical domains predominate.

We are developing SCIPUDO as the knowledge resource for processing specialized terms related to SCI, PrI, and deep tissue injuries. Parsing and analyzing clinical narratives present a unique set of challenges that distinguish it from the broader biomedical NLP approaches. There has been extensive work in creating clinical NLP systems focused on information extraction from free text in specific disease domains, such as cancer [49] and tuberculosis [50]. However, there is no community gold standard for SCI or PrI named entities to date. Thus, we will build our gold standard using manual annotations created by clinical team members who will review a random sample of records from over 20,000 clinical notes for this cohort extracted from VINCI. One to 3 clinicians will review each record. The SCIPUDO will enable: (1) term disambiguation (ie, between commonly used synonyms and acronyms of a term such as *quadriplegia and tetraplegia*), (2) term normalization (ie, syntactic variations of a term, such as singular or plural and acronyms will be normalized using classes and customized rules such as *pressure ulcer*, *PU*, or *PrU*), and (3) subsumption reasoning using class hierarchy to allow terms to be classified according to their broader semantic type.

Validated extracted data will then be collated using our established standard data collection forms and uploaded to the Physio-MIMI based integrated PrI risk assessment SCIPUD+ Resource. The Physio-MIMI backbone will provide extensible, scalable, and high-performance data management for storing and accessing large volumes of data rapidly. Reliable data storage through automated data replication and data integrity verification will ensure consistent data availability and effective disaster recovery with off-site data backup. Data quality assurance and metadata version control will be managed using a combination of GitHub, JSON, and the open source NSR data management environment [51].

Creation of the SCIPUD+ Environmental, Social and Clinical Domain Database

Input data for the SCIPUD+ database will be provided by synthesizing available EHR clinical data from VINCI, using a protocol based on our preliminary work. VINCI provides EHR data storage for all health care encounters within the VHA and is updated daily. A preliminary query on June 10, 2014, found that between 2009-2014 there were 16,076 individuals seen by the VHA with an ICD-9-CM code of 344.00 (ie, quadriplegia) and 24,052 individuals with an ICD-9-CM code of 344.1 (ie, paraplegia). Of these, 6420 (16.00%) in both groups were also coded for a PrI (ICD-9-CM code 707.00). Within the local area, there were 1021 encounters with individuals with quadriplegia and 1443 with paraplegia. The reported rate of PrI incidence was 14.00%. Extraction of clinical details will entail text mining of the free text clinical notes. SCIPUDO will enable robust text mining for data extraction from free form notes in addition to using ICD-9-CM codes to retrieve data of interest. A visual query interface will be adapted from OnWARD to allow all clinicians to directly query the SCIPUD+ Resource via a set of readily usable visual widgets that will be populated with the SCIPUDO classes to allow clinicians to construct queries, specific to the patient flexibly. All patient data will be stored in a firewall protected secure environment with role-based access control and audit trail logging.

Development and Validation of the SCIPUD+ Environmental, Social, and Clinical Structural Model

We will develop the SCIPUD+ user interface which will provide a single point of Web-based access to well-annotated and de-identified data generated from multiple domains. Modifiable and nonmodifiable factors will be considered (Figure 1). To develop the SCIPUD+ environmental, social and clinical PrI risk structural model we will consider PrI status as the response variable. We will employ general logistic and multinomial logistic models with linear mixed effects (transformed if necessary) and interaction terms to fit the data. Tree-based

models such as classification and regression tree (CART) and Random Forest will also be used to examine the relationship of the factors to the PrI status. Model and variable selection will be implemented to define the SCIPUD+ environmental, social, and clinical model. Final models will be validated using cross-validation. Both models, especially the tree-based models are useful to rank-order factors to identify specific critical variables for an individual, with a focus on modifiable factors (Figure 2).

Development of the Integrated SCIPUD+ Model

General logistic and multinomial logistic models with linear (mixed) effects and their possible interaction terms will then be fit to the data or their natural groups, and the significance of PrI development will be assessed. Natural groupings will be obtained using a cluster analysis of 5000 medical records and 60 detailed tissue health profiles to examine the association of these natural grouping with PrI frequency. The representativeness of the tissue health group will be compared with the larger sample drawn from the larger cohort extracted from VINCI EHR. The integrated model will be developed in the same way as the SCIPUD+ environmental, social and clinical structural model. Using statistical software R and Splus, tree-based models such as CART and Random Forest, will also be used to examine the relationship of all factors with PrI status. Model and variable selection based on both logistic and tree-based models will be implemented to define the integrated SCIPUD+ model. Final models will be validated using 10-fold cross-validation and some hold out cases using predictive measures. Both models, especially the tree-based models are useful to rank-order factors for identification of specific critical variables for an individual. We shall pay particular attention to modifiable factors. The comprehensive model proposed will allow us to borrow the degrees of freedom from all data points to develop the fully integrated SCIPUD+ Resource. We will determine structural models based on both data sources using standard statistical models, and directly using large-p small-n modern techniques for all factors. Special interest models, such as those focused on modifiable factors, will also be developed. The choice of essential features will depend on the optimization criteria used by a model fitting or learning algorithm. For example, the Random Forest provides 2 criteria for ranking the important features, also known as the variable of importance. One is based on the contribution to Model Accuracy and the other to Gini impurity by each included variable [52-54]. We will use the domain knowledge to guide our final choice of the model for different medical purposes if the final models differ significantly based on various criteria. We may also use XGboost as needed to derive and validate the best predictive model [55]. We expect that at most 25 top-ranked factors will be enough for modeling PrI risk as either a dichotomous or polytomous outcome. This will allow development of the SCIPUD+ care planning algorithm.

Results

As a preliminary high-level review, we ran a query using the Elixhauser Comorbidity index, which is a tool applied to analysis outcomes of interest to hospital administrators, such as predicting hospital resource use [56,57]. The 30 variables included are all dichotomous. This means that they are either present or absent, which makes categorization much more straightforward than a continuous variable such as the level of injury or even living status. The first outcome is that only 6.00% of the cohort of 40,128 Veterans with SCI have no comorbidities. We also know that many individuals in the cohort have more than one comorbidity. Based on the 5 most commonly coded comorbidities, it was determined that paralysis, the most common at 15.97%, was remarkably low for a cohort of Veterans with SCI. This finding provides an indicator that valuable clinical information is not coded and must be extracted from the clinical notes. The second most common comorbidity is depression. This has also been found in our relational analysis to occur concurrently with many other risk factors. Although we cannot determine which is the cause and which is the effect at this point, we can see it is a major psychological risk factor which will impact many aspects of personalized PrI prevention planning.

To determine the incidence of comorbidities of interest in our cohort, we have identified 226 ICD-9-CM codes of interest. We ran a Structured Query Language (SQL) query across all tables and created a summary table of all comorbidity ICD-9-CM codes. This table contains 1,681,050 records for 32,398 individuals (this total number of individuals varies from the overall cohort total because not all individuals have a recorded comorbidity). The current data represent raw counts which have not been corrected for repeated reports, which may be either a chronic condition such as diabetes or repeated occurrences such as PrIs (Table 1). These extracted data were imported into the query interface adapted from the Physio-MIMI and OnWARD, which enables interactive CDE query and cohort identifications.

Table 1. Elixhauser Comorbidity Index Query based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for the study cohort (N=32,398).

Parameter	n (%)
Five most commonly coded comorbidities	
Paralysis	6408 (5.97)
Depression	5324 (13.27)
Hypertension	4551 (11.34)
Heart disease	3702 (9.23)
Substance abuse	3494 (8.71)
Five least commonly coded comorbidities	
Obesity	1452 (3.62)
Neuro disorders	1125 (2.80)
Anemia	757 (1.89)
Weight loss	753 (1.89)
Gastric disease	230 (0.57)

Discussion

The project is using established EHR data to build a comprehensive, structured model of environmental, social and clinical PrI risk factors. A concurrent cross-sectional study will develop a structured model of tissue health PrI risk factors. Data from multiple domains will be integrated to provide personalized PrI care planning based on an individual's risk factor characteristics. The comprehensive SCIPUD+ health care tool will be used to relate the primary outcome of interest (ie, PrI development) with covariates that include environmental, social, clinical, personal and tissue health profiles as well as possible interactions among these covariates. The SCIPUD+ Resource will provide an extremely valuable PrI prevention care planning resource for nurses and other clinical care providers.

The study will result in a validated tool for personalized implementation of CPG recommendations. Maintenance of tissue health provides a foundation for all active duty military and Veterans with SCI to maximize their quality of active life. Recognizing that every person with SCI is an individual; the SCIPUD+ Resource will contribute to Personalized, Proactive, and Patient-Driven care for all. PrI risk characteristics will be used for the development of personalized CPG priority-based care plans for primary and secondary PrI prevention. The use of SCIPUD+ care planning will impact individual health and QoL. Recognizing that health care budgets are limited, the SCIPUD+ Resource will also support optimization of resource capital allocation.

The SCIPUD+ Resource has great potential to change the standard of care for PrI clinical practice by enabling clinicians to provide a personalized application of CPG priorities tailored to the needs of everyone with SCI. The use of our tool will allow clinicians to develop effective personalized care plans for primary and secondary PrI prevention for patients in their care. In the longer term, this research has excellent potential to directly impact standard of care by targeting interventions that will most effectively decrease PrI development for everyone. The population will benefit from a lower PrI incidence, more effective use of resources, and reduced health care costs.

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Conflicts of Interest

None declared.

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Abbreviations

AIS: American Spinal Injury Association Impairment Scale
ALS: amyotrophic lateral sclerosis
CART: classification and regression tree
CDE: common data elements
CPG: clinical practice guideline
DTI: deep tissue injury
EHR: electronic health record
ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification
MS: multiple sclerosis
NINDS CDE: National Institute of Neurological Disorders and Stroke Common Data Elements
NLP: natural language processing
OnWARD: Ontology-driven Web-based Research Data Capture
Physio-MIMI: Multi-Modality, Multi-Resource Information Integration Environment for Multi-center Physiological and Clinical Research Studies
PrI: pressure injuries
PU: pressure ulcer
QoL: quality of life
SCI: spinal cord injury
SCIPUD+: Spinal Cord Injury Pressure Ulcer and Deep Tissue Injury
SCIPUDO: Spinal Cord Injury Pressure Ulcer and Deep Tissue Injury Ontology
VINCI: Veterans Affairs Informatics and Computing Infrastructure Database
VHA: Veterans Health Administration

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Protocol

Development of a Path to Home Mobile App for the Geriatric Rehabilitation Program at Bruyère Continuing Care: Protocol for User-Centered Design and Feasibility Testing Studies

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Abstract

Background: As the population ages, the need for appropriate geriatric rehabilitation services will also increase. Pressures faced by hospitals to reduce length of stay and reduce costs have driven the need for more complex care being delivered in the home or community setting. As a result, a multifaceted approach that can provide geriatric rehabilitation patients with safe and effective person- and family-centered care during transitions from hospital to home is required. We hypothesize that a technology-supported person- and family-centered care transition could empower geriatric rehabilitation patients, engage them in shared decision making, and ultimately help them to safely manage their personalized needs during care transitions from hospital to home.

Objective: The purpose of this study is to design and test the feasibility of a novel Path to Home mobile app to manage the personalized needs of geriatric rehabilitation patients during their transitions from hospital to home.

Methods: This study will consist of (1) codesigning a patient- and provider-tailored mobile app, and (2) feasibility pilot testing of the mobile app to manage the needs of geriatric rehabilitation patients when leaving the hospital. In phase 1, we will follow a user-centered design process integrated with a modern agile software development methodology to iteratively codesign the personalized care transition Path to Home mobile app. In phase 2, we will conduct a single-arm feasibility pilot test with geriatric rehabilitation patients using the personalized care transition Path to Home mobile app to manage their needs during the transition from hospital to home.

Results: The project was funded in May 2018, and enrollment and data analysis are underway. First results are expected to be submitted for publication in 2019.

Conclusions: Our findings will help validate the use of this technology for geriatric rehabilitation patients discharged from the hospital to home. Future research will more rigorously evaluate the health and economic benefits to inform wide-scale adoption of the technology.

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KEYWORDS

patient discharge; care transition; user-centered design; geriatric rehabilitation; mHealth; transitional care; rehabilitation; health services for the aged; telemedicine

Introduction

Background

As the population ages, the need for appropriate geriatric rehabilitation services will also increase [1]. In 2011, older adults (aged 65 years and older) represented 14.4% of the Canadian population, which is expected to continue rising [2]. At the same time, hospitals face constant pressures to discharge patients earlier, which has driven the need for more complex care being delivered in the home [3]. Engaging patients and their informal caregivers in their care is crucial for optimal outcomes during the transitions from hospital to home. This includes patients' understanding of their specific health conditions, their ability to follow discharge instructions, and their knowledge of what signs and symptoms to watch for to seek medical care [4]. Patients admitted to geriatric rehabilitation often have a diagnosis of cognitive impairment and mild dementia resulting in short-term memory loss. Most of this patient population depend on their informal caregivers to provide support to them during the transition from hospital to home.

Challenges associated with care transitions are complex [5]. Gaps in the quality of care during care transitions include patients (1) leaving the hospital not being equipped to manage their care at home, (2) receiving conflicting information about managing their health condition, (3) leaving the hospital and then being unable to communicate with their health care provider who has their comprehensive health care plan, and (4) not being engaged or involved in decisions related to their care [6-10]. This puts older adults at greater risk of medical complications, including medication errors and lack of appropriate follow-up care [11-15]. In a recent study, older adults communicated the importance of active involvement and meaningful engagement in managing their personalized health needs while transitioning from the hospital to home [16].

The development of new technologies for personalized care could empower patients in managing their health care needs while navigating our complex health care system [17]. Monitoring patients remotely can improve treatment, prevent unnecessary readmissions to the hospital, and engage patients in managing their health conditions [18,19]. The use of mobile health (mHealth) apps has grown significantly, specifically in supporting the management of individual chronic diseases [20]. mHealth apps have been designed and implemented in diabetes [21,22], cardiovascular disease [23], and chronic obstructive pulmonary disease [24] to better engage patients in managing their own health condition. Key features of the care transition processes that lend themselves to an mHealth app solution include personalized discharge and transition plans, information regarding signs and symptoms related to a patient's medical condition, coordination of care, medication management, exercise planning, medical equipment needs, dietary requirements, lifestyle changes, appointment tracking, home and community care needs, fall prevention strategies, community resources, remote support, and interactive communication with the health care team.

Objective

No studies, to our knowledge, have looked at specifically using technology to facilitate the hospital-to-home transition processes to support patients in meeting their personalized needs and in providing them with better integration of care between health care sectors. We hypothesize that a technology-supported person- and family-centered care transition could empower geriatric rehabilitation patients, engage them in shared decision making, and ultimately help them to better manage their personalized needs during care transitions from hospital to home. The purpose of this study is to design and test the feasibility and acceptability of a novel Path to Home mobile app designed to manage the personalized needs of geriatric rehabilitation patients during their transitions from hospital to home.

Methods

Overview

This study will consist of (1) codesigning a patient- and provider-tailored mobile app, and (2) feasibility pilot testing of the mobile app to manage the needs of geriatric rehabilitation patients when leaving the hospital. In phase 1, we will follow a user-centered design process integrated with a modern agile software development methodology to iteratively codesign the personalized care transition Path to Home mobile app. In phase 2, we will conduct a single-arm feasibility pilot test with geriatric rehabilitation patients using the personalized care transition Path to Home mobile app to manage their needs during the transition from hospital to home.

Path to Home Passport

Bruyère Continuing Care, which offers care to the frail elderly, people with chronic and terminal illness, and persons with disabilities in Ottawa, ON, Canada, has developed a paper-based Path to Home workbook, codesigned by patients and health care providers. Its purpose is to be a central information repository that simplifies partnering health care providers with patients and their informal caregivers in reviewing and ensuring they understand their discharge instructions. This is extremely important to ensuring that prescribed medications are taken correctly, that exercises and lifestyle recommendations are followed, that appointments are kept, and that there is an understanding of the signs and symptoms that necessitate a visit to their primary care team [25]. When discharge instructions are not adhered to, the patient has a much higher probability of being readmitted to hospital [25]. Increasingly, patients and informal caregivers have online access tools (eg, phone, tablet, or laptop computer) with them when the patient is admitted and have asked for their discharge information to be more readily

available for review. Although the use of technology by older adults is limited, there have been proven benefits in informal caregivers being able to access discharge instructions to be shared with primary care providers [26]. Other mHealth apps have incorporated the ability to prompt patients by providing reminders and helpful tips and information [27].

Phase 1: Mobile App Design

Using the evidence-based content developed for the paper-based Path to Home workbook, we will collaborate with NexJ Health Inc (Toronto, ON, Canada), a provider of cloud-based population health management solutions, to design and configure a personalized care transition Path to Home mobile app (a minimum viable product for a mobile phone, tablet, or computer). NexJ Health's Connected Wellness platform is a well-developed technology solution that is designed to support multichannel communications between patients, informal caregivers, and health care providers. This app has been previously used in 17 research trials and 8 deployment evaluations to support patients in electronically tracking health behaviors and self-monitoring health data [28]. The prototype Path to Home mobile app will (1) allow patients to track progress on their discharge and care transition plans, (2) empower patients in making decisions about their own health and needs, and (3) improve information exchange between providers while patients are transitioning from the hospital to home.

Study Design and Methodology

We will follow a user-centered design process, integrated with a modern agile software development methodology [29-32]. User-centered design is an approach that involves end users in designing apps and has been shown to increase the usability of apps [31,32]. The approach will be iterative and will consist of 3 cycles in which we will engage patients, informal caregivers, health care providers, and management to design a series of prototypes of a patient-and provider-tailored mobile app (cycles 1-3), adjusting them according to end user feedback [32]. We will seek to obtain approval from the Bruyère Research Ethics Board and the University of Ottawa Ethics Board.

Setting and Participants

The study will take place at Bruyère Continuing Care, Ottawa, ON, Canada. Patients will be eligible to participate based on the following inclusion criteria: (1) 65 years of age or older, (2) English speaking, and (3) discharged to home or a community facility within the last 90 days. Patients with aphasia, receiving palliative care, unable to use technology, and not able to effectively communicate in English will be excluded. Informal caregivers aged 18 years or older who speak English and any health care provider who is part of the geriatric rehabilitation program will be eligible to participate.

Procedures and Data Collection

A unit staff member or unit manager will approach the potential participants. Once a participant has indicated interest in participating, a trained research assistant will meet with them in person to provide more information, to obtain consent, and to arrange a time for an interview. We will also recruit primary care providers through the local academic primary health care teams in the Champlain Local Health Integration Network, Ottawa, ON, Canada.

Cycle 1: Modeling the Care Transition Process

In the modeling phase, we will conduct a process mapping exercise and a needs assessment through semistructured interviews, using a semistructured interview guide, with intended users, including patients (2-3 participants), informal caregivers (2-3 participants), and health care providers (physicians, nurses, physiotherapists, occupational therapists, pharmacists, and social workers) from geriatric rehabilitation and from primary care (4-6 participants), to identify the specific user requirements, workflow, goals, metrics, and data sources that will inform the design of the app.

Cycle 2: Implementation of the Path to Home Mobile App

In the implementation cycle, the software development team will configure the Path to Home mobile app prototype (including forms, reports, notifications, and reporting database) and map the implementation of the clinical concepts and the inputs obtained from the intended users in the modeling phase.

Cycle 3: Evaluation of the Path to Home Mobile App Support for the Care Transition Process

In the evaluation cycle, we will conduct audio-recorded think-aloud sessions [33] with the intended users to evaluate the usability of the personalized care transition Path to Home mobile app while they are using it in real time. Participants will be encouraged to think aloud and provide feedback on the proposed workflow and their experience with the prototype. We will conduct usability testing to recognize the potential barriers to adoption. We will use the analysis of the think-aloud sessions and the usability testing to improve the prototype in the next iteration. Health care providers, patients, and informal caregivers will engage in further think-aloud sessions and usability testing as required. Modifications to the software will be based on user feedback in order to integrate patients' and providers' needs and preferences.

Data Analysis

Interviews and think-aloud sessions will be recorded and transcribed verbatim. For the interview transcripts, we will conduct a qualitative content analysis [34] to provide a comprehensive and accurate descriptive summary of the participants' perspectives. Two researchers will conduct the analysis independently and will meet to develop a code book. Discrepancies will be reviewed and resolved by a third researcher. The codes and themes from the interview transcripts will then be used to develop user personas [35,36]. Personas are a useful way to define user requirements, as they go beyond describing the characteristics of the users by capturing the mental processes used (including user expectations, prior experiences, and behaviors). We will conduct member checking with participants to better ensure the validity of the personas. These user personas will inform the user requirements and will be discussed with the research team until consensus is reached on how to integrate them into the Path to Home mobile app. For the think-aloud transcripts, 2 researchers will conduct the qualitative content analysis [34] and the discrepancies will be

reviewed by a third researcher. We will use data management software [37] to support this qualitative data analysis.

Phase 2: Single-Arm Feasibility Pilot Test

Following the app design and development, we will conduct a single-arm feasibility pilot test of the Path to Home mobile app. The specific objectives are to (1) determine whether it is feasible to provide a mobile app to geriatric patients with hip fractures and their informal caregivers, (2) determine whether a mobile app is acceptable to this population, (3) refine the methods for a larger study.

Setting and Participants

The pilot will take place in the geriatric rehabilitation program at Bruyère Continuing Care. This program uses an interdisciplinary approach to optimize independent function in geriatric patients. We will invite patients (n=30) who are being discharged from the geriatric rehabilitation program using a convenience sample. The sample size is not based on a sample size calculation, because the primary outcome of this study is not dependent on effect sizes. For feasibility studies, a sample size of approximately 24 to 50 has been previously recommended [38-40]. The inclusion criteria are patients and informal caregivers who (1) will need access to a mobile or computer device, and (2) must be followed by one of the local academic primary health care teams in the Champlain Local Health Integration Network.

Procedures and Data Collection

Early in the admission process, the unit manager will approach individual patients to seek their interest in participating in the study. The research assistant will then provide further information and obtain consent to participate. Following consent, the research assistant will ask each participant to complete a sociodemographic questionnaire that will ask participants about their age, sex, ethnicity, education level, relationship status, and living situation, as well as assessing their Technology Readiness Index score [41,42]. The Technology Readiness Index is a 16-item assessment tool that has been verified for validity, reliability, and usefulness in a specified population subgroup like the one proposed in this study [42].

After receiving training on how to use the Path to Home mobile app, patients and informal caregivers, as well as their health care providers, will obtain access to the app. We will ask the patients and their informal caregivers to complete information about their needs and preferences (eg, goals of care) and review discharge and transition information. At 30 days postdischarge, we will invite all the patients and informal caregivers to complete an electronic survey. We will send an email reminder notification at 1 and 2 weeks after the 30 days. The survey will be based on the previously developed paper-based version of the Path to Home workbook evaluation questionnaire and will be adapted to include statements about how much they agree with statements such as the following: (1) participants found the information in the app easy to understand, (2) participants found the information in the app helpful, (3) participants found the app easy to navigate, (4) participants found the information helped them (or their informal caregiver) to understand what they needed to do to prepare for discharge, (5) participants found the information helped them (or their informal caregiver) identify skills they needed to have a successful discharge, (6) participants found the organization of the app to make sense, (7) participants found the drawings and pictures helpful to understand the content, and (8) participants would recommend this app to other patients. The survey will also provide the opportunity for the participants to comment about what they liked best about the app and what they felt could be improved.

We will also conduct a follow-up phone call interview with patients (5-10 participants) and informal caregivers (5-10 participants). The interview guide will include questions about (1) participants' experiences with learning about and using the technology, (2) participants' overall evaluation and experience with the app, (3) participants' use of the app in their regular activities, and (4) whether they visited their primary care team within the recommended 2 weeks after discharge.

We will also interview health care providers (ie, geriatric rehabilitation, primary care; 5-10 participants) 30 days after the implementation to ask for their perspectives on the discharge processes and for their perspectives on the value of the Path to Home mobile app to empower patients and facilitate communication and sharing of information with the health care team. The interview guide will include questions about (1) participants' experiences of learning about and using the technology, (2) changes to the health care provider workflow required to effectively use the technology, (3) organizational changes required to support the technology, (4) health system barriers to and facilitators of effective implementation and evaluation, (5) participants' overall evaluation of and experience with the app, and (6) participants' use of the app in their daily work.

Data Analysis

We will use descriptive statistics to summarize the survey results using an Excel spreadsheet. The qualitative data portion of the survey will be analyzed using qualitative content analysis [34]. Interviews will be transcribed verbatim. The transcripts will be analyzed independently by 2 researchers using thematic analysis [43], identifying key themes demonstrating important contextual influences and practices related to the implementation and evaluation of the Path to Home mobile app. Discrepancies will be reviewed and resolved by a third researcher.

Privacy and Security

Privacy of users' data will be respected and enforced. Patients will need to provide explicit access for an informal caregiver or heath care provider to view their personal health information. Health care providers will be permitted to access a patient's health information only by (1) inviting the patient to access the app and having the patient explicitly accept the invitation, or by (2) accepting a patient's invitation to access their personal health information. We will consult the Privacy Officer at Bruyère Continuing Care to ensure that our app is compliant with our provincial privacy legislation (ie, the Ontario Personal Health Information Protection Act [44]). We will also follow standard procedures to deal with privacy breaches if they occur. We also ask users to consent to an agreement about the way their data may be used before they can use the app.

Results

The project was funded in May 2018, and enrollment and data analysis are underway. We expect to submit our first results for publication in 2019.

Discussion

Future Research

This proposed research will directly integrate input and feedback from all relevant stakeholders (health care providers, patients, and informal caregivers) in the design and development of a personalized care transition Path to Home mobile app for managing the needs of geriatric rehabilitation patients and facilitating shared decision making. We will use the findings to inform a larger-scale study to develop an understanding of the specific mechanisms by which the Path to Home mobile app is effective for patients and health care providers. We will test the implementation and evaluate the technology-based intervention for effectiveness in a larger randomized study.

This technology-supported care transition management approach has the potential to empower patients, enhance communication with health care providers, and provide better care and better access to relevant resources to improve management of older adults' personalized needs when discharged from hospital to home. The development of this new technology can potentially help to facilitate the care transition from hospital to home by integrating the app with electronic health records or other standard electronic health applications.

Conclusion

Our findings will help validate the use of this technology for geriatric rehabilitation patients discharged from the hospital to home. This research has the potential to optimize information delivery between health care providers and patients, to provide better access to specific care needs, to prevent unnecessary visits to the emergency department and reduce hospital readmissions, to improve the continuity of care, and to improve patient outcomes and experiences. Future research will more rigorously evaluate the health and economic benefits to inform wide-scale adoption of the technology.

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Authors' Contributions

CB was a major contributor in writing the manuscript. All coauthors were involved in the design of the project and critically appraised and edited the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review report from the Centre for Aging and Brain Health Innovation.

[PDF File (Adobe PDF File), 88KB - resprot_v7i9e11031_app1.pdf]

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Abbreviations

mHealth: mobile health

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Protocol

Validating a Machine Learning Algorithm to Predict 30-Day Re-Admissions in Patients With Heart Failure: Protocol for a Prospective Cohort Study

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Abstract

Background: Big data solutions, particularly machine learning predictive algorithms, have demonstrated the ability to unlock value from data in real time in many settings outside of health care. Rapid growth in electronic medical record adoption and the shift from a volume-based to a value-based reimbursement structure in the US health care system has spurred investments in machine learning solutions. Machine learning methods can be used to build flexible, customized, and automated predictive models to optimize resource allocation and improve the efficiency and quality of health care. However, these models are prone to the problems of overfitting, confounding, and decay in predictive performance over time. It is, therefore, necessary to evaluate machine learning–based predictive models in an independent dataset before they can be adopted in the clinical practice. In this paper, we describe the protocol for independent, prospective validation of a machine learning–based model trained to predict the risk of 30-day re-admission in patients with heart failure.

Objective: This study aims to prospectively validate a machine learning–based predictive model for inpatient admissions in patients with heart failure by comparing its predictions of risk for 30-day re-admissions against outcomes observed prospectively in an independent patient cohort.

Methods: All adult patients with heart failure who are discharged alive from an inpatient admission will be prospectively monitored for 30-day re-admissions through reports generated by the electronic medical record system. Of these, patients who are part of the training dataset will be excluded to avoid information leakage to the algorithm. An expected sample size of 1228 index admissions will be required to observe a minimum of 100 30-day re-admission events. Deidentified structured and unstructured data will be fed to the algorithm, and its prediction will be recorded. The overall model performance will be assessed using the concordance statistic. Furthermore, multiple discrimination thresholds for screening high-risk patients will be evaluated according to the sensitivity, specificity, predictive values, and estimated cost savings to our health care system.

Results: The project received funding in April 2017 and data collection began in June 2017. Enrollment was completed in July 2017. Data analysis is currently underway, and the first results are expected to be submitted for publication in October 2018.

Conclusions: To the best of our knowledge, this is one of the first studies to prospectively evaluate a predictive machine learning algorithm in a real-world setting. Findings from this study will help to measure the robustness of predictions made by machine learning algorithms and set a realistic benchmark for expectations of gains that can be made through its application to health care.

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KEYWORDS

electronic medical records; heart failure; machine learning; predictive algorithms; readmissions

Introduction

Big data solutions, particularly machine learning predictive algorithms, have demonstrated the ability to unlock value from large, complex data in real time in aviation, astronomy, transportation, education, marketing, news, finance, publishing, and even entertainment. The health care industry, on the other hand, is often widely regarded as a late adopter of big data solutions. In the United States, at least one of the reasons that contributed to this delay is the relatively low adoption of electronic medical records (EMRs) among hospitals. In 2008, the number of hospitals that had a basic EMR system was 9%; by 2015, this number grew to 96% [1]. The rapid growth in the EMR adoption, coupled with the shift in the US health care system from a volume-based to a value-based reimbursement structure has spurred investments into artificial intelligence (AI)–based solutions for health care problems [2].

The hospital re-admission rate is one of the metrics used to measure the quality of care provided by a hospital [3,4]. In the financial year 2017, the Centers for Medicare and Medicaid Services withheld more than US $500 million in payments to 2597 hospitals in the United States under its re-admissions reduction program [5]. Naturally, hospitals have begun implementing various interventions to reduce re-admission rates [6]. To optimize the use of expensive care transition interventions, one of the strategies adopted by hospitals has been to focus on patients predicted to be at a higher risk of re-admission [7]. The stratification of inpatients based on the risk of re-admission can offer care providers valuable insight to modify interventions, such as discharge planning and the opportunity to influence outcomes by proactively managing high-risk patients.

Hospital re-admission risk prediction models have been traditionally developed using hypothesis-driven statistical methods since the 1980s; and as of 2015 at least 94 unique models have been described in the published literature [8,9]. Although these risk prediction models are helpful decision-making tools, their utility is limited by considerations of generalizability, adaptability, and absolute predictive performance. First, most of these models have been developed using high-quality data from selected patient cohorts and therefore can have inconsistent external validity in other settings and patient populations, in the setting of missing data and over time [10]. Second, these models require health care personnel to calculate the risk score for every patient, thereby creating barriers to their adoption. Finally, these models often cannot be adapted to incorporate information that might be of predictive value in different patient populations, resulting in the suboptimal predictive performance. In contrast, machine learning analytical methods can be used to build flexible, customized, and automated predictive models using the information available in EMRs [11]. The promise of extracting predictive insights in real time from complex and voluminous EMR data has fueled a lot of excitement around the application of machine learning–based predictive methods in health care, where even a marginal increase in the performance could translate to meaningful gains in efficiency and quality.

Predictive models developed from EMR data using machine learning methods have their own share of generalizability challenges. First, models that are developed using a large number of predictors relative to the number of outcome events are prone to overfitting. A well-known example of this is Google Flu Trends, which predicted twice the actual number of influenza-related doctor visits in 2013 [12]. Second, models developed using EMR data are subject to bias resulting from patient self-selection, confounding by indication and inconsistent availability of outcome data [13]. Finally, the practice of medicine itself evolves, thereby impacting the accuracy of predictions over time. A study determined that the relevance of clinical data used to predict future inpatient orders “decayed” with an effective half-life of about 4 months [14]. Given these limitations, it is necessary to validate the predictive performance of machine learning–based models in an independent dataset before it can be adopted in the clinical practice.

A machine learning–based model to predict 30-day re-admissions in patients with heart failure was developed at Partners HealthCare System (PHS; Boston, MA, USA) in collaboration with Hitachi, Ltd (Tokyo, Japan). Details about the development of the prediction model are described in a separate paper [15]. Briefly, the model was trained using deidentified longitudinal medical record data of 11,510 patients with heart failure who were discharged alive after an inpatient admission in the financial years 2014-2015 from the PHS. There were 27,334 inpatient admissions and 6369 30-day re-admissions during this period. The final model included 3512 variables comprising demographics, encounter, diagnosis, procedure, medication, and laboratory information as well as selected extracts from ambulatory visit notes and discharge summaries. Deep unified networks—a new mesh-like network structure of deep learning with vertical and horizontal connections of neurons to avoid overfitting—was used to develop the risk prediction model. Ten-fold cross-validation was used to validate the model internally. The model showed moderate discriminative ability with a concordance statistic of 0.71. This paper describes the protocol for independent, prospective validation of this machine learning–based model trained to predict the risk of 30-day re-admission in patients with heart failure. Hence, this study aims to prospectively validate a machine learning–based predictive model for inpatient admissions in patients with heart failure by comparing its predictions of risk for 30-day re-admissions against outcomes observed prospectively in an independent patient cohort.

Methods

We have followed the guidelines suggested by Luo et al for reporting this protocol [16].

Study Design

The validation of the predictive model will be conducted as a prospective cohort study. The study has been approved by the Partners Human Research Committee, the Institutional Review Board for PHS.

Setting

The study will be conducted in 5 major hospitals that are a part of the PHS, a major health care provider in Massachusetts, USA.

Definition of Key Variables

Index Admission

Every inpatient admission for a patient diagnosed with heart failure that meets the eligibility criteria as outlined in Textbox 1 will be regarded as an index admission.

30-Day Re-Admission

Any inpatient admission that occurs within 30 calendar days from the date of discharge from an index admission, due to any cause, will be regarded as a 30-day re-admission. Every 30-day re-admission encounter is also regarded as a new index admission if it satisfies the eligibility criteria outlined in Textbox 1.

Prediction Goal

The model was trained to prognosticate the probabilities of 30-day re-admissions for every live discharge following hospital admission, based on the information available in the EMR up to the time of discharge.

Textbox 1. Eligibility criteria for patients and index admissions.

A. **Specific to the patient**

1. Age 18 years or older
2. Was not part of the dataset used to develop the algorithm
3. Diagnosed with heart failure, with any of the following heart failure International Classification of Diseases codes assigned as a principal diagnosis code:

- *International Classification of Diseases, Ninth Revision, Clinical Modification*
  - 402.01 Malignant hypertensive heart disease with heart failure
  - 402.11 Benign hypertensive heart disease with heart failure
  - 402.91 Unspecified hypertensive heart disease with heart failure
  - 404.01 Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
  - 404.03 Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end-stage renal disease
  - 404.11 Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
  - 404.13 Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end-stage renal disease
  - 404.91 Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
  - 428 All heart failure: left; systolic, diastolic, combined; acute, chronic, acute on chronic; unspecified
- *International Classification of Diseases, Tenth Revision, Clinical Modification*
  - 150 All heart failure: left; systolic, diastolic, combined; acute, chronic, acute on chronic; unspecified

B. **Specific to the index admission**

1. The patient was discharged alive
2. The patient was not discharged against medical advice

Patient associated with this admission does not transfer out of the Partners HealthCare System within 30 days of discharge.

Study Procedures

Identification of Eligible Index Admissions and 30-Day Re-Admissions

Customized reports will be generated daily from the EMR to alert the study staff about any heart failure patient discharged from an inpatient admission. Study staff will verify that all eligibility criteria are met, and flag index admissions associated with patients that were part of the development dataset for exclusion. The rationale of this criterion is to prevent "validation leakage," that is, to prevent the model from making an accurate prediction based on prior knowledge about a high-risk patient acquired from the training dataset [17]. For a 30-day period following the first encounter, the EMR system will automatically notify the study staff every time any one of these patients has a subsequent encounter within the PHS. Based on these alerts, an inpatient admission due to any cause will be recorded as a 30-day re-admission.

Data Extraction, Processing, and Storage

Information pertaining to every eligible index admission will be extracted from two centralized data warehouses that gather clinical information from various PHS hospitals. The files will be extracted in batches every 15 days and renamed if necessary to match the naming format of files originally used to train the algorithm. All files will be stored in a HIPPA (Health Insurance Portability and Accountability Act of 1996)–compliant manner at the study site.

Obtaining Predictions From the Model

The algorithm will be housed in a server dedicated for this project at the study site. After the initial set-up is complete, the algorithm will use all files pertaining to an eligible index admission as input and process them automatically to generate variables needed for the predictive process to run. It will then provide the output in the form of a text file with a probability value assigned for every index admission.

Statistical Analysis

Sample Size Calculation

Collins et al recommend a minimum of 100 events for externally validating a prognostic model [17]. The 30-day re-admission rate for heart failure index admissions in the PHS in financial years 2015-16 was 20.4%. Therefore, a minimum of 100/20.4%=491 index admissions will be required to conduct a validation study. We assume that up to 25% of re-admissions may occur outside PHS. Of these, we assume that about 50% of the admissions will be from patients who were part of the dataset used for the development of the algorithm and therefore will have to be excluded. Therefore, a total sample size of 1228 index admissions may have to accrue before we observe 100 eligible events (ie, 30-day re-admissions).

Evaluation of Model Performance

Evaluation of Discrimination Thresholds

The output provided by the model is a probability score for 30-day re-admission for each index admission. Multiple probability scores will be evaluated to determine the threshold that is the most optimal binary classifier of index admissions at-risk or not-at-risk for 30-day re-admissions. The following metrics will be used to evaluate thresholds:

1. Sensitivity: True positives/(true positives + false negatives)
2. Specificity: True negatives/(true negatives + false positives)
3. Positive predictive value (PPV): True positives/(true positives + false positives)
4. Negative predictive value (NPV): True negatives/(true negatives + false negatives)
5. Accuracy: Number of correct assessments (true positives + true negatives)/number of assessments

Evaluation of Overall Performance of the Model

The overall performance of the model was evaluated by:

1. Concordance statistic (C-index): This is equal to the area under the receiver operating characteristic curve, which is a plot of the true positive rate (sensitivity) against the false positive rate (1-specificity) at various discrimination threshold settings.
2. Model calibration: This refers to the agreement between the predictions made by the model and the observed outcomes. We will use contingency tables and survival plots to assess the relationship between predicted risk and observed 30-day re-admission rates.
3. Brier score: $1/N\ \Sigma(f_t-o_t)^2$, where N is the number of index cases, f_t is the forecast probability, and o_t is the outcome (1 if it happened, 0 if it did not). The Brier score measures the accuracy of a forecast [18]. The best possible score is 0.

Results

The project was funded in April 2017 and data collection began in June 2017. Enrollment was completed in July 2017. Data analysis is currently underway, and the first results are expected to be submitted for publication in October 2018.

Discussion

Principal Findings

Our study will prospectively evaluate the performance of a machine learning model that predicts the risk of 30-day re-admissions for patients with heart failure in a real-world hospital system. Risk prediction models are designed to aid clinical decision making, and in the context of heart failure, their implementation can potentially result in substantial reductions in rehospitalizations and cost savings [19]. Risk prediction models are not new to medicine, and there is no dearth of models developed using traditional statistical techniques [8,20]. However, the clinical adoption of risk prediction models remains quite low [21,22]. Some of the barriers reported by physicians for not using risk prediction models are lack of time, lack of trust in its validity, and uncertainty about generalizability to the specific patient population observed by an individual physician [21,22]. Machine learning models are well-placed to overcome these barriers. Automation is a fundamental feature of machine learning–based prediction models, thereby eliminating the need for input from the provider to calculate risk scores for every patient. Moreover,

machine learning models can be "fine-tuned" for different patient populations and even individual hospital systems, such that the prediction results are most generalizable to that population. Building a one size fits all prediction model that is generalizable to every hospital system is neither a desirable goal for a metric such as 30-day re-admissions, which reflects the quality of care at a particular hospital, nor an efficient utilization of the ability of machine learning analytical techniques to extract fine-grained information from thousands of variables, the "richness" of which may vary from one institution to another.

In this study, we will include any re-admission as an index admission in the analysis, as long as it meets the inclusion criteria for index admissions; this is similar to the method used for training the predictive model [15], and aligns with the definition used by the Centers for Medicare and Medicaid Services for 30-day all-cause re-admission rates [23]. This choice was made keeping in mind the intended real-world use of the model where it will be applied to every inpatient admission. The consequent relative increase in the prevalence of the outcome (ie, 30-day re-admissions) can be expected to result in higher sensitivity and PPV and lower specificity and NPV compared with a definition that does not allow re-admissions to be considered as index admission. We expect the impact on PPV and NPV to be substantially higher than that on the sensitivity and specificity because the former are prevalence-dependent metrics. We do not expect any change in the area under the receiver operating characteristic curve, calibration, and Brier score.

Rigorous evaluation of the validity of machine learning models is an important step to address barriers to the clinical adoption of these models; this information is valuable not only to better inform physicians but also to help hospital administrators in estimating the cost-effectiveness of investing into a machine learning–based prediction system. The 30-day re-admission rates vary across hospitals based on the sociodemographic profile of patients, access to care, and the case-mix of patients, among other factors [24]. Thus, predictive models that are generalizable across health care systems might result in the suboptimal utilization of information that might be of predictive value within a given hospital system. To ensure that predictive models "fine-tuned" to specific health care systems are dependable, prospective validation studies conducted periodically in independent patient samples should become the norm in the evaluation of machine learning–based prediction algorithms. The results from such studies will help detect the true performance of the model and estimate the frequency at which the algorithm needs to be fine-tuned.

Limitations and Strengths

This study has certain limitations. The use of this prediction model in the real world is, by design, intended to effect a change in the behavior of providers. As the prediction results from our model will not be available to physicians, this prospective validation cannot estimate any changes in the model's performance under such circumstances. In addition, we cannot detect re-admissions that may occur outside of PHS; this may result in an underestimation of the model performance. However, the model was trained using the same constraint. Thus, we do not expect attenuation in the model performance because of this constraint, compared with its performance after training.

This study also has several important strengths. To the best of our knowledge, this is the first study to prospectively evaluate a machine learning predictive model in a real-world hospital setting, and we hope that the detailed procedures described here will enable the design of similar studies to evaluate the performance of other machine learning predictive models. Second, in addition to the C-statistic, we also evaluate the sensitivity, specificity, PPV, and NPV of the machine learning predictive model. These metrics take the prevalence of the outcome into account, unlike the C-statistic that is independent of prevalence [25], and therefore have greater clinical relevance. Past studies have showed that PPV and C-statistic have minimal correlation for risk prediction models [26]. Finally, we evaluate the performance of the model 2 years after it was built and exclude patients who were part of the training dataset. These steps are essential to eliminate validation leakage and help to estimate the stability of the model over time.

Conclusions

The application of machine learning–based algorithms to diagnose diseases, prognosticate outcomes, and personalize treatments is increasing. Rigorous evaluation of their performance is critical for the widespread adoption. Findings from this study may better inform decisions related to the application of machine learning solutions in health care.

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Authors' Contributions

SK and SA designed the study protocol and prepared this manuscript. SG, JF, KJ, and JK provided feedback on the study protocol and the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
EMR: electronic medical record
HIPPA: Health Insurance Portability and Accountability Act
NPV: negative predictive value
PHS: Partners HealthCare System
PPV: positive predictive value

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Protocol

An e-Prehabilitation System of Care for Teenagers and Young Adults Diagnosed With Cancer: Protocol for a Qualitative Co-Design Study

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Abstract

Background: A diagnosis of cancer in young adulthood can pose many different and unique challenges for individuals. The provision of adequate and appropriate information as well as care and support for teenagers and young adults at the time of diagnosis is central to their health care experience going forward. Moreover, appropriate and accessible information provision is critical to ensure that young individuals with cancer feel equipped and empowered to make decisions about, and be involved in, their treatment and recovery throughout their experience; this is a concept known as prehabilitation. As digital interventions and resources that support teenagers and young adults with cancer are an increasingly desirable part of health care provision, this study will focus on the development of an age- and population-appropriate electronic prehabilitation (e-Prehabilitation) system of care.

Objective: We will conduct an exploratory, co-design research project that will inform the development of an e-Prehabilitation system of care to support teenagers and young adults diagnosed with cancer. A collaborative approach to data collection and prototype design will ensure that a patient-centered approach is embedded throughout.

Methods: A qualitative, co-design study utilizing surveys, interviews, and focus group discussions is being conducted with teenagers and young adults, health care professionals, and technologists.

Results: This research study is in progress; recruitment and data collection activities have commenced and findings are expected in early 2019.

Conclusions: The findings of this study will have important implications for informing the future development and evaluation of an e-Prehabilitation system of care to support teenagers and young adults diagnosed with cancer.

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KEYWORDS

digital health; human factors; co-design; prehabilitation; teenagers and young adults; cancer; mobile phone

Introduction

Background

Although cancer is relatively rare in teenagers and young adults (TYA; individuals aged 15-24 years) [1], the incidence rates in the United Kingdom have increased by around one-fifth over the last decade [1]. In the United Kingdom, from 2009 to 2011, 2234 new cases of cancer were diagnosed among TYA. The diagnostic profiles of cancers in TYA differ from those in adults, with lymphomas being the most common group of cancers

diagnosed in individuals aged 15-24 years [1]. Collectively, lymphomas, carcinomas, and germ cell tumors account for more than half of the total number of diagnoses of cancer in the 15-24-year-old population [1].

A diagnosis of cancer poses a range of physical, financial, and psychosocial challenges for young adults and their families [2-4], including disruption of education or career [5], family life [6], self-esteem or identity [7], peer and sexual relationships, and body image [8-10]. There is also a need to manage the side effects of treatment, both short and long term, and the possible impacts on future fertility [11-13]. These various challenges are often compounded by the developmental stages and changes that accompany young adulthood [14]. Thus, a diagnosis of cancer in young adulthood can pose many different and unique challenges for these individuals. As a consequence, there is a significant body of research that recognizes the importance of providing adequate and appropriate information as well as care and support to teenagers, young adults, and their families at the time of diagnosis [15-17]. Such information provision is critical in ensuring that young individuals feel equipped and empowered to make decisions about, and be involved in, their treatment and recovery, thereby enhancing a sense of mastery and control or self-efficacy [18].

There is an increasing interest in, and growing momentum regarding, the concept of "positive psychology" in the context of cancer [19]. Positive psychology includes building and strengthening the resilience of patients and their families following a diagnosis of cancer, adoption of coping strategies, and utilization of strengths based on assessments and interventions [20]. A key component of the positive psychology process is the proactive anticipation of challenges, which are likely to be encountered following a diagnosis of cancer and associated treatments to ensure that young individuals and their families can be equipped with information and effective coping strategies prior to the commencement of treatment, rather than during or after treatment, wherein a deficit or reactive model may have to be implemented [21].

The delivery of health-related interventions during the period between a patient's diagnosis and treatment commencement is known as prehabilitation [22]. Typically delivered during the intervening period between a patient receiving a diagnosis and his or her treatment initiation, strategies tend to be implemented to maximize an individual's fitness and adaptation, ultimately to have a positive impact on survival and associated patient-reported outcomes and coping [23-30]. The application of prehabilitation strategies is becoming more evident within health care, with a growing evidence base regarding their benefits for patients undergoing surgery [29,31], such as coronary artery bypass [32].

However, in the context of cancer care, prehabilitation is a relatively new and emerging concept. Against this backdrop, following a review of noncancer prehabilitation literature, cancer prehabilitation has recently been defined as follows:

> *...a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment, includes physical and psychological assessments that establish a baseline functional level, identifies impairments, and provides targeted interventions that improve a patient's health to reduce the incidence and the severity of current and future impairments, and provides targeted interventions that improve a patient's health to reduce the incidence and the severity of current and future impairments [22].*

In a review on cancer prehabilitation [22], it was concluded that opportunities exist for prehabilitation interventions to help support individuals with cancer. Such interventions may improve physical and psychological health outcomes, increase the number of potential treatment outcomes, and reduce direct and indirect health costs attributed to cancer. However, the paucity of prehabilitation research, developed interventions, and associated packages of care within this context indicates that there is an actual need to identify the best interventions for various groups of individuals affected by cancer [22]. Developing tailored prehabilitation interventions and associated packages of care for particular patient groups is critical to ensure that they are responsive to and meet the particular needs of these patient groups. Ultimately, doing so may help increase the rates of compliance with treatments, consequently having a positive impact on treatment survival outcomes [22]. Despite the potential benefits of an established prehabilitation program, there is a notable paucity of information that focuses on TYA with cancer within this context.

New interventions should be designed and developed in collaboration with the target population to help ensure their success. Evidence-based co-design in which an individual's experience is explored and collated to help develop service improvements [33] is one recognized way of ensuring a person-centered approach for care. In addition, young individuals are now digital natives [34]; thus, digital resources to support TYA with cancer are increasingly desirable. In a recent service evaluation survey on TYA with cancer at a clinical site in one area of the United Kingdom, TYA were responsive to the potential provision and development of digital resources that will support them during their cancer experiences [34]. In another service development initiative in the United Kingdom, a digital pathway, which is known as the Integrated Assessment Mapping (IAM) portal, was recently developed by the University Hospitals Bristol National Health Service (NHS) Foundation Trust and the TYA South West Cancer service. The project aimed to provide emotional and clinical support to TYA cancer patients using a holistic, age-appropriate digital platform [35]. Via a cocreation approach, 3 interconnected services were developed following engagement sessions with the TYAs. The 3 services included a TYA website, the IAM website and mobile app, and the SWIMMS patient database. Collectively, these 3 services provide support to patients based on their self-identified needs; additionally, the clinical care team and service providers are able to better identify the support needs of TYA with cancer based on the information provided by the patients themselves [35]. The IAM project highlights that it is possible to co-design, develop, and integrate an eHealth platform to provide support to TYA diagnosed with cancer.

Thus, collaborative engagement; prioritization of TYA's experiences and needs; and the development of a suitable,

effective, and appropriate digital health solution are the central tenants of this study. As the current evidence base for prehabilitation care is limited, particularly for TYA with cancer, this is the right time to develop an evidence-based and experientially informed system of care for this patient population.

Study Objectives

This exploratory research project will inform the development of an electronic prehabilitation (e-Prehabilitation) system of care to support TYA diagnosed with cancer. To achieve this, there are four overarching research objectives: (1) understand the needs of TYA with cancer at the time of diagnosis; (2) understand the potential role of eHealth solutions to assist in the prehabilitation care offered to TYA with cancer by health care professionals (HCPs); (3) identify appropriate technologies and technological platforms to support the delivery of an e-Prehabilitation system of care, and (4) generate the content of a prototype e-Prehabilitation system of care for use by HCPs and TYA diagnosed with cancer.

Methods

Study Design

This study draws on two main conceptual frameworks to ensure that the intervention is developed appropriately. First, the study draws on the Medical Research Council (MRC) Framework for the development, evaluation, and implementation of complex interventions to improve health [36]. Drawing on Stage I of the MRC Framework, activities in this study will focus on engaging with TYA and professionals working in health care or technologists working with digital health solutions and innovations in industry or the NHS and developing the theory to inform the development of the intervention. Theoretically, this study will draw on the Behavior Change Wheel as this provides a framework for understanding behavior as an enabler for behavior change interventions [37].

Ethics Approval

The ethical aspects of this study were approved by the Yorkshire and the Humber–Bradford Leeds research ethics committee, and it was endorsed by the lead author's University ethics committee (Research Ethics Committee Reference:17/YH/0352). The study has also received Research & Development approval from the relevant NHS Board in the United Kingdom.

Eligibility Criteria

The eligibility criteria for participation in the study are provided in Table 1. Although teenage and young adulthood is defined as the period between 15-24 years of age, 16-26 years is the age range for referrals for TYA to access services at the partnering clinical site. TYA and HCPs who fit the inclusion criteria and provide informed consent will be eligible to participate in the study.

Table 1. Eligibility criteria of the study participants.

Participant group	Inclusion criteria	Exclusion criteria
Teenagers and young adults (TYA)	• Young individuals aged 16-26 years • TYA who were diagnosed with cancer up to 3 years, but no less than 4 weeks prior to participation in the study. TYA may be undergoing acute anticancer treatments and therapies and maintenance treatments, or may be considered to have completed all treatments during the study period and up to 3 years postdiagnosis • Receiving or received services from the National Health Service in Scotland or partner cancer principal treatment center • Able to participate in data collection activities • Able to provide informed consent • Able to communicate sufficiently well in English	• Teenagers younger than 16 years • Young adults older than 26 years • TYA without a cancer diagnosis • TYA newly diagnosed with cancer (within the last 4 weeks) • TYA who received a diagnosis of cancer more than 3 years ago • Unable to provide informed consent • Unable to communicate sufficiently well in English
Health care professionals	• Members of the TYA cancer team or multidisciplinary team involved in the provision of care or services to TYA with cancer • Have experience of working with TYA who have or have had a diagnosis of cancer • Able to provide informed consent • Able to communicate sufficiently well in English	• Unable to provide informed consent • Unable to communicate sufficiently well in English
Technologists or digital health professionals	• Professionals with experience of working within the digital health space within the National Health Service or industry or academia • Able to provide informed consent • Able to communicate sufficiently well in English	• Unable to provide informed consent • Unable to communicate sufficiently well in English

Recruitment

Teenagers and Young Adults

Direct Recruitment

Patient databases will be screened for TYA who meet our inclusion criteria by members of the TYA cancer team at the recruiting site (Figure 1). A staff member will first approach potential participants in person or via email to introduce the possibility of participating in the study and to provide the study information material. Potential participants will be asked to complete or provide permission for the proxy completion of a consent-to-be-contacted form (Figure 1) to indicate their agreement for passing on their contact details to the research team. Only then will the research team contact TYA to further discuss participation in the study. If possible, we will capture top-level details of ineligibility for invitations to participate from the databases in partnership with the TYA cancer team.

Self-Referral

We will adopt a variety of self-referral strategies to provide TYA with opportunities to participate in the study. We will circulate study invitations in the form of recruitment advertisements or posters or postcards and display these at the recruiting principal treatment center and various other environment-appropriate locations throughout Scotland. Social media will be utilized to further increase the opportunities to recruit TYA; where appropriate, we will also post digital versions of the recruitment advertisements. Study-specific Twitter, Facebook, and email accounts have been created. We will also circulate information to other relevant support organizations working directly with TYA with cancer. If necessary, paid advertisements on social media and in the local press will be used to aid recruitment.

Potential TYA participants will be directed to a web-based screening questionnaire to establish their eligibility for study participation. The web-based screening questionnaire will also gather information regarding eligibility criteria that were not met. Thus, the research team can track reasons for non-participation at the screening stage.

Health Care Professionals

Researchers will directly invite HCPs such as consultant oncologists, psychologists, allied health professionals, social workers, specialist nurses, ward nurses, and youth support professionals to participate in the study. This will help ensure appropriate multidisciplinary participation in the study.

Technologists or Digital Health Professionals

Key individuals with a responsibility for digital health within the NHS, industry, and academia will be directly approached by members of the research team to participate in the study.

Participant Information and Informed Consent

TYA and professionals will receive information about the study before consenting to participate in any data collection activities (Figure 1). TYA participants will receive a written information sheet in age-appropriate language and a link to a video and audio information sheet created specifically for this project. The video clip will be made available via the project website. Professionals will receive a written participant information sheet distributed via email or hard copies. Potential participants (TYA and professionals) will have at least 24 hours to familiarize themselves with the study information and to decide whether or not they wish to participate. TYA and professionals will have the opportunity to ask questions prior to signing the consent form or recording verbal consent. In instances where it is not possible to obtain a written consent from the participants (eg, when conducting telephone interviews), verbal consent will be obtained instead at the start of the audio recording.

Incentives

The indirect benefits of taking part in this study for TYA and professionals are sharing experiences and contributing to the development of the design of a new digital health intervention. TYA will receive a study-specific certificate of participation from the research team, which may benefit their portfolio for further education and/or job applications. TYA will be reimbursed for their travel expenses for attending any data collection activities away from their home, and refreshments will be provided during any group data collection activities.

Data Collection

Throughout the data collection activities, we will utilize TYA's position of being an expert on the general knowledge of experiences of young TYA at the time of cancer diagnosis, based on their own experiences. By doing so, we will empower TYA to participate as expert representatives of others as well. There are 4 distinct streams of data collection in this study, as outlined in Figure 2.

Stream 1: Focus Group Discussions or Individual Interviews With Teenagers and Young Adults

We will conduct focus group discussions or individual interviews with TYA with a history of cancer diagnosis to develop an understanding of the issues they faced after the diagnosis. The focus group discussions will be conducted if at least three participants are available for discussion. If we are able to conduct focus group discussions, we aim to recruit up to 20 TYA who meet the inclusion criteria to participate in the first stage of data collection. We will conduct up to four separate focus group discussions with 3-7 participants each. However, if engagement levels for focus group discussions are low and we are unable to meet the minimum number of required participants (n=3) to conduct the discussions, we will conduct a series of 1-1 interviews instead of or alongside focus group discussions for the first stage of data collection. In this case, we will recruit up to 10 TYA who meet the inclusion criteria. Individual interviews will last up to 60 minutes and focus on the topics outlined above.

Stream 2: Interviews or Web-Based Survey with Health Care and Digital Health Professionals

Stream 2 will run concurrently with stream 1. In stream 2, the professionals will be invited to participate in one-off individual interviews to explore their preferences for the content and delivery of the e-Prehabilitation system of care, including the technology platform to be used and their requirements for the prehabilitation care resources and materials that should be

included in the intervention. Interviews will last approximately 30 minutes and will be conducted face-to-face or via telephone based on participants' preference and audio recorded. To enhance opportunities for participation, we will also provide the professionals with the opportunity to complete a short web-based survey. The link to the web-based survey will be distributed via email.

Stream 3: Design Workshops

Drawing on data gathered in streams 1 and 2, the research team will explore with TYA the technology platform to be used as well as the type, nature, and focus of the content of the material contained in the system and their requirements for this system. Design workshops will emphasize the need for technology that is not just designed for illness and medical activities. This requirement has been expressed by teenagers with a chronic medical diagnosis previously [38]. Participatory design activities for participants during stream 3 are shown in Table 2.

Stream 4: Consensus Activities

The data generated from streams 1-3, in combination with the findings from the literature, will be considered collectively to develop a low-fidelity prototype. In stream 4, we will endeavor to seek feedback from participants on this low-fidelity prototype. To do this, we will provide physical (as in face-to-face group or individual discussions) and/or electronic (as in a web-based discussion forum or survey) environments for participants (TYA and professionals) to access and comment on the low-fidelity prototype. If the interest from participants warrants a further face-to-face meeting, a session will be arranged to present the prototype to TYA and professionals together. However, if we find it difficult to bring people together physically, we will distribute an electronic version of the prototype (eg, via PDF files of wireframes of the suggested content) via email or secure transfer and ask for comments and feedback. Participation in stream 4 will be optional for both TYA and professional participants.

Figure 1. Flowchart of the recruitment. TYA: teenagers and young adults.

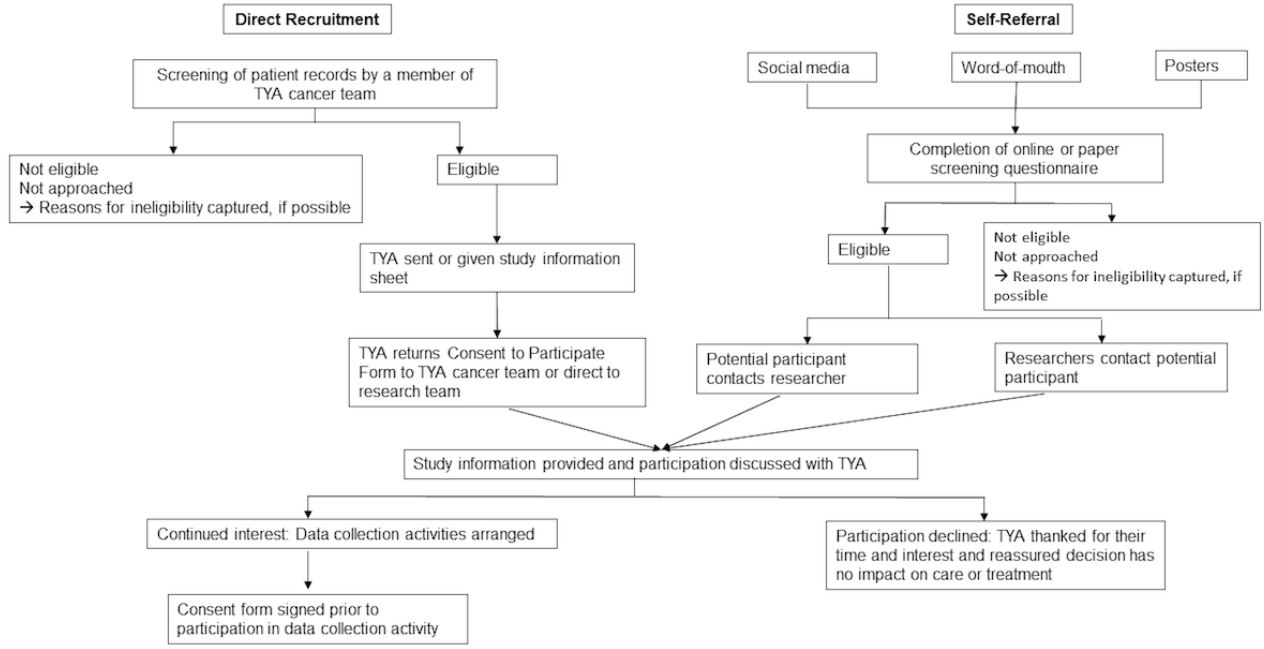

Figure 2. Flowchart of the different stages of data collection activities and outputs. TYA: teenagers and young adults; HCP: health care professionals.

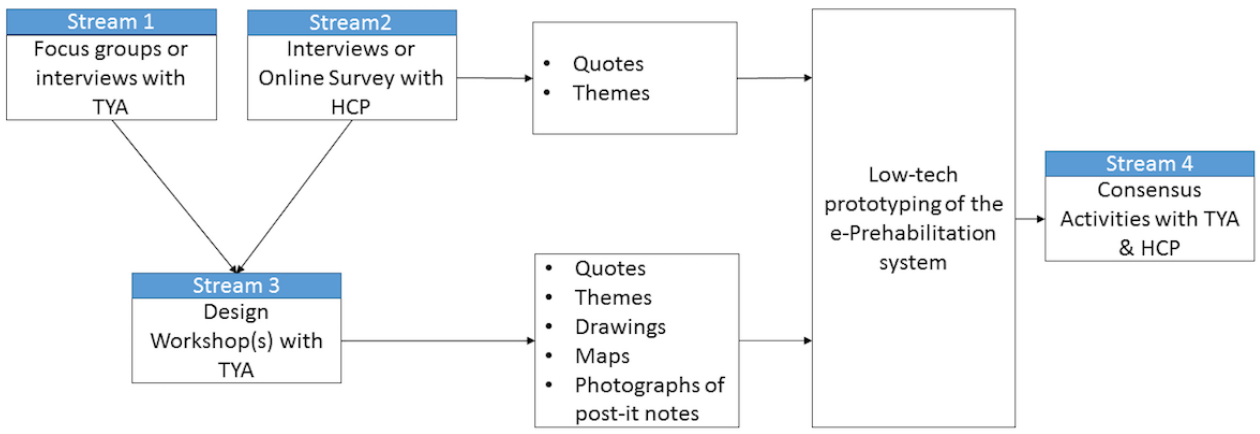

Table 2. Participatory design activities for stream 3.

Topics	Purpose	Tool kit of the methods (will be selected or adapted as appropriate)	Data output
Content—Nature and focus	To gather some ideas about the type of information displayed and collected	1. Researchers present a "Tree of ideas" made up of tag-clouds of themes generated from the focus group discussions or interview responses from streams 1 and 2. 2. Participants rate ideas as "keep," "lose," or "change" using color-coded post-it notes. 3. Verbal discussions and/or blank paper sheet for items labeled as "change," participants suggest how the item should be changed for being rated as "keep." 4. Participants rank ideas labeled as "keep" by priority using sequential numbers.	Voice recording, text (annotations), photographs of post-it notes
Content—Visual designs	To capture some ideas about how the information might look	1. Researchers provide A4 paper sheets with blank smartphone mock-ups. 2. Warm-up activity on paper prototyping. 3. Researchers provide examples of existing electronic cancer information tools via iPad (eg, Integrated Assessment Mapping website, websites and materials from cancer charities, video game: Re-Mission). 4. Participants formulate ideas or write descriptions of how the information could be visually presented on a smartphone app or website.	Drawings, text (annotations), voice recordings
Functions and features	To get a view of what the technology looks like and some of its properties	1. Researchers provide A4 paper sheets with blank smartphone mock-ups. 2. Participants formulate functions and features or write descriptions (what functions or features and how they work).	Drawings, text (annotations), voice recording
Contextual enquiry of technology use	To capture ideas and preferences on the type of digital health technology and how and when it would be used	1. Research team provides 3 printed maps of a fictional town with images of typical locations and buildings where teenagers and young adults might find themselves. Each map will represent a point in time of the cancer journey (Diagnosis, Treatment, and Survivorship). Color-coded stickers, pens, and post-it notes will also be provided. 2. Participants will indicate on the map which type of information they would access or seek and where they would use a digital health intervention to do so.	Maps, text (annotations), photographs of post-it notes, voice recordings

Demographic and Clinical Questionnaire

We will ask participants to complete a questionnaire to obtain the demographic and clinical (TYA only) characteristics of the participants on the day of the focus group discussions or interviews or web-based survey prior to participating in data collection activities. All data entries will remain anonymous.

Data Analysis

Focus Group Discussions, Interviews, and Web-Based Survey

Focus group discussions or interviews with TYA with cancer and professionals will be audio recorded and transcribed verbatim. Transcripts will be merged with field notes and outputs of brainstorming activities. During the analysis, two researchers will draw upon the research objectives and identify and develop themed categories to guide the data analysis. We will use NVivo (version 12; QSR International; Australia), a qualitative data analysis software package, to support these activities.

Thematic analysis is a useful approach for answering questions about the salient issues for a particular group of respondents or for identifying typical responses [39]. For reliability and validity purposes, two researchers will code a subsample of transcripts and field notes separately and then cross-check them together.

Design Workshops

Design activities will be audio recorded to capture the discussions and reflections about design processes and products. It is less likely that audio recordings from design workshops will be transcribed due to the expected levels of background noise. However, the research team will listen to them as an aide-memoire. We will take photographs of design sheets and maps that include post-it notes and stickers to avoid losing the sticky pads when being transported for analysis. With participants' permission, we will take photographs of group work interactions during streams 3 and 4.

As summarized in Table 2, the data output of the design workshop will comprise a number of different data types (texts, maps, and drawings). Two researchers will independently code the design ideas based on a predefined and piloted coding template using all available data sources. The coding of design ideas will be cross-checked between the researchers, and disagreement will be resolved by a third researcher. Independently, the two researchers will select the "single best" design idea from each group or individual work that will be considered for prototyping the e-Prehabilitation system.

Data Management

Participant Confidentiality

Personal data recorded on all documents will be considered as confidential, and participants will be allocated a unique study number by the research team for reporting purposes. Participants' personal details will not be recorded on any interview transcripts or surveys; only their designated unique study number will be included in these documents. Any identifiable information captured during the interviews will be anonymized during the transcription process. The participant identification key, which links the unique study number with the participants' name, will be stored in a separate location to participants' personal data.

Data Storage and Disposal

During the Study

All data will be stored in locked filing cabinets at the lead author's institution. Personal data will be stored in a separate filing cabinet from anonymized hard copies of the data. Focus group discussions or interviews will be digitally audio recorded on a password-protected recording device. All transcripts will be anonymized and stored in the secure, shared network of the lead author's institution on password-protected computers. Only authorized members of the research team will have access to the network drive and locked filing cabinets.

After the End of the Study

Personal data will be stored for 6-12 months after the study has ended to allow the dissemination of research findings to study participants. Anonymous research data will be stored for 10 years after this study has ended. After 10 years, the data will undergo a review process conducted by the University's Research Data Management and Sharing Team that will decide whether the data will remain in long-term storage or deleted.

Results

The recruitment and data collection for this study commenced in February 2018, and results will be submitted for peer review upon completion of data collection and analysis. The project is expected to end in early 2019.

Discussion

The current protocol describes a collaborative co-design study designed to focus on the development of an e-Prehabilitation system of care for TYA with cancer as well as its future use within the current service delivery models. The study design is appropriate for the development of an intervention, utilizing multiple perspectives and data collection methods. The findings from this study will have important implications for informing the future development of an e-Prehabilitation system of care to support TYA diagnosed with cancer.

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Conflicts of Interest

None declared.

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Abbreviations

e-Prehabilitation: electronic prehabilitation
HCP: health care professional
IAM: Integrated Assessment Mapping
NHS: National Health Service
MRC: Medical Research Council
TYA: teenagers and young adults

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Proposal

Blockchain Technology for Detecting Falsified and Substandard Drugs in Distribution: Pharmaceutical Supply Chain Intervention

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Abstract

Background: Drug counterfeiting is a global problem with significant risks to consumers and the general public. In the Philippines, 30% of inspected drug stores in 2003 were found with substandard/spurious/falsely-labeled/falsified/counterfeit drugs. The economic burden on the population drug expenditures and on governments is high. The Philippine Food and Drug Administration (FDA) encourages the public to check the certificates of product registration and report any instances of counterfeiting. The National Police of Philippines responds to such reports through a special task force. However, no literature on its impact on the distribution of such drugs were found. Blockchain technology is a cryptographic ledger that is allegedly immutable through repeated sequential hashing and fault-tolerant through a consensus algorithm. This project will develop and test a pharmacosurveillance blockchain system that will support information sharing along the official drug distribution network.

Objective: This study aims to develop a pharmacosurveillance blockchain system and test its functions in a simulated network.

Methods: We are developing a Distributed Application (DApp) that will run on smart contracts, employing Swarm as the Distributed File System (DFS). Two instances will be developed: one for Ethereum and another for Hyperledger Fabric. The proof-of-work (PoW) consensus algorithm of Ethereum will be modified into a delegated proof-of-stake (DPoS) or practical Byzantine fault tolerance (PBFT) consensus algorithm as it is scalable and fits the drug supply chain environment. The system will adopt the GS1 pedigree standard and will satisfy the data points in the data standardization guidelines from the US FDA. Simulations will use the following 5 nodes: for FDA, manufacturer, wholesaler, retailer, and the consumer portal.

Results: Development is underway. The design of the system will place FDA in a supervisory data verification role, with each pedigree type–specific *data source* serving a primary data verification role. The supply chain process will be initiated by the manufacturer, with recursive verification for every transaction. It will allow consumers to scan a code printed on the receipt of their purchases to review the drug distribution history.

Conclusions: Development and testing will be conducted in a simulated network, and thus, results may differ from actual practice. The project being proposed is disruptive; once tested, the team intends to engage the Philippine FDA to discuss implementation plans and formulate policies to facilitate adoption and sustainability.

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KEYWORDS

supply and distribution; information systems; counterfeit drugs; blockchain

Introduction

A recent report from the World Health Organization classified drug counterfeiting as a global problem. In low- to middle-income countries, an estimated 1 in 10 drugs in market circulation is falsified or substandard [1]. The consequences of this phenomenon pose significant risks to individuals and the public. They are most prevalent in areas where surveillance and regulation need improvement or are deficient and where medicines are in high demand but remain mostly unaffordable [2,3]. They are also rampant during disease outbreaks and epidemics when shortages of essential drugs tend to occur and when counterfeiting is most likely to rise.

Substandard drugs are dangerous. Falsified and substandard drugs, which could contain inactive ingredients, active ingredients but in the wrong dosage, or potential contaminants, could be lethal [4]. The lay press [5-8], replete with many personal anecdotes, as well as medical journals [9-12] have reported on the dangers of fake drugs. The use of antimicrobials of low quality may result in treatment failures and may increase antibiotic resistance in individuals and the community, resulting in higher mortality rates and the spread of highly resistant pathogens worldwide. Contaminants and impurities may induce allergic reactions and adverse drug reactions. Counterfeit drugs waste individual incomes and lead to increases in government economic burden. Furthermore, these may decrease the overall public confidence in the efficacy of authentic medicines [13,14].

The Philippine Food and Drug Administration (FDA), just like its US counterpart, has the mandate to ensure the safety, quality, and efficacy of food, medicines, and medical devices. The agency has repeatedly warned the public of fake pharmaceutical products peddled by counterfeiters that are circulating in the market. This warning comes with an advice to the general public to ensure that retailers where they obtain their drugs are certified by the FDA and that pharmacies display the Certificate of Product Registration, which the agency issues. In addition, the agency has a joint task force with the *Destroying Products Unfit for Human Consumption* (D-PUNCH) unit of the Philippine National Police [15]. The approach of D-PUNCH relies on the consumer reports of suspicious products or transactions to initiate action. In 2003, the agency reported that 30% of inspected drugstores were selling substandard/spurious/falsely-labeled/falsified/counterfeit (SSFFC) drugs [16].

Drugs move across a distribution chain that involves several participants. These typically include, but are not limited to, a manufacturer, a wholesaler, and a retailer. A regulatory body, such as the FDA, may test the quality of a batch of drug product before or while it is distributed down the supply chain. These participants enter into direct contract-based relationships with each other: for instance, a retailer may enter a contract with a certain wholesaler to purchase stocks of a certain drug product regularly and another contract with another wholesaler to purchase stocks of a different drug product regularly.

Blockchain is an electronic cryptographic ledger that follows a decentralized network model—instead of storing all information in one database such as in conventional cloud-based applications, the information is distributed and synchronized across all nodes in the network. A consensus algorithm is deployed within the network to mitigate the issue of transaction duplication (or *double spending*) by allowing nodes to verify *true* information. Once verified, information is then added to the hash value of a previous *block*, and the new sequence (ie, previous hash + newly verified information) is hashed to form a new *block* using a cryptographic (ie, one-way) hash function. A cryptographic hash value is a string of nonreadable letters and numbers of consistent length that represent information that was subjected to a hash algorithm. Each hash value is unique to the information from which it was derived. These characteristics, in addition to the network forcing continuous synchrony across all nodes, make blockchain immutable and tamper resistant. Although cryptographic hashing is one-way, the decrypted information can be rehashed and compared with the stored hash value in the ledger. Furthermore, the network can persist amidst node failure. The threshold for the number of nonfunctional nodes before network failure is a function of the number of nodes connected to the network. The more the nodes in the network, the less likely it is to fail [17].

A review of current and emerging technologies to mitigate the incidence of fake drugs cited blockchain as an emerging technology, with the potential for tracking and tracing drug products and reagents, counterfeit detection through information verification of supply chain participants, and as an avenue for the integration of anticounterfeit devices into the internet-of-things and interoperability between unrelated databases in the supply chain [18]. It also has the potential for governance by enabling traceability, record ownership, incentivization through automation of smart contracts, and promotion of policy through multisectoral disruption [19].

In our review of literature, we found no previous studies or reports on the effectiveness or impact of consumer-driven Certificate of Product Registration checking and initiation of D-PUNCH investigations on mitigating the counterfeiting issue.

The applications of blockchain technology in clinical practice and health care research are currently of great interest and are being explored for the potential for increased security of health information amidst the increasing frequency of cyberattacks. Other domains outside health care are also exploring its potential in providing a trusted environment in which participants can provide and avail various services.

This study will test the feasibility of applying the technology and its principles in a pharmaceutical surveillance system and its resistance to tampering.

Methods

Pharmacosurveillance Blockchain System

System Design and Development

The system prototype will be a distributed application (DApp) with a back-end distributed file system (DFS) supporting a private blockchain network [20]. It will use smart contracts.

An instance will be developed on the Ethereum blockchain platform, which is open-source and currently one of the largest public blockchain networks, boasting an active community and

a sizeable public repository of DApps. The platform currently uses a proof-of-work (PoW) consensus algorithm called Ethash; however, developers are planning to change it in the near future to a proof-of-stake (PoS) algorithm for scalability. Ideally, a delegated proof-of-stake (DPoS) or a practical Byzantine fault tolerance (PBFT) consensus algorithm fits the pharmaceutical supply chain environment, so modification may be necessary. Furthermore, Ethereum does not come with data encryption as default, which will incur additional development.

A second instance will be developed on the hyperledger fabric blockchain platform [21]. Unlike Ethereum, the platform is designed for private consortium networks. It is open-source, modularized, and uses data encryption and a DpoS or PBFT consensus algorithm by default.

Swarm, a DFS included as a native base layer service in Ethereum, is a good candidate for inclusion because of its default integration with the platform. The DFS component will store the DApp, smart contracts, and the blockchain. Swarm will be integrated into the system.

The system prototype will be designed with 5 starting nodes, one for each participant in the traditional drug distribution model: the manufacturer, the wholesaler, the retailer, and the FDA, as well as an additional node that will house a consumer portal website through which consumers can scan codes that come with the receipt of their purchases to view the drug distribution history. Smart contracts will be used to define contract-based relationships between participants, and the interfaces will reflect supply chains in which the logged account is involved. While data will be distributed across the DFS, accounts will only be able to visualize and decrypt files intended for them—in other words, subchains will exist within the network as shown in Figure 1.

Despite the orientation of the internode connections within the network, the movement of a drug product along the distribution network will be distributed across all nodes. The DApp would have the capacity to detect anomalies, unauthorized data insertions, and missing drug products by comparing DFS content with ledger records. Each step will be tagged with a timestamp for auditing.

The DApp front end will be stored in all nodes. Its interface will include a section that will display transactions performed along the distribution chains as well as detect anomalies and information discrepancies in a dashboard. It will trace the drug product as it moves along the chain and generate a timeline for each supply chain. Notifications will be displayed for shipments and anomalies detected in the chain. It will also allow the FDA account to define authorized manufacturers and dealers and store the definitions in a smart contract or encrypted file.

Figure 1. Two distinct distribution subchains within the blockchain network, highlighted blue and orange. The diagram on the left shows a distribution chain for a drug product, with blue lines representing distribution contracts. The diagram on the right shows a second distribution chain for another drug product within the same network, with orange lines representing distribution contracts. Client applications installed on nodes monitor transactions and track product movement. FDA: Food and Drug Administration; MAN: manufacturer; WS: wholesaler; RET: retailer.

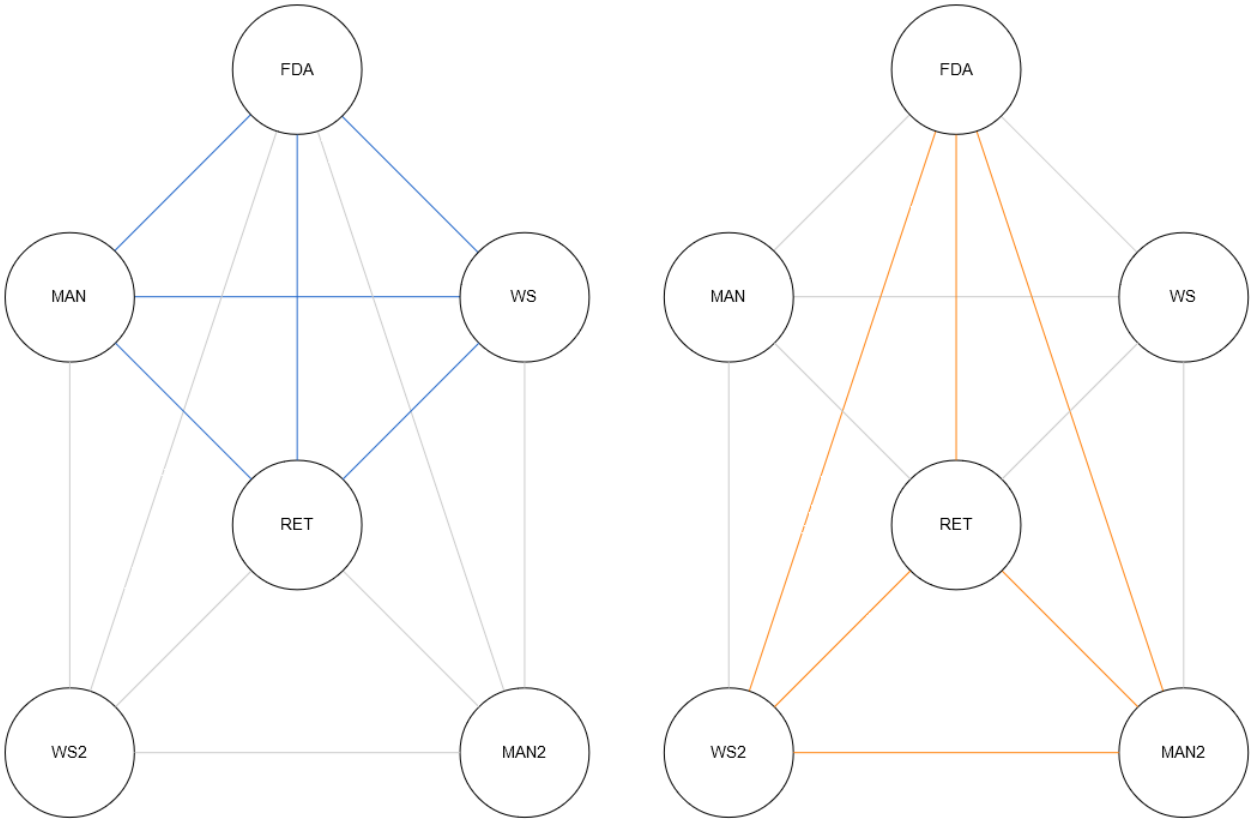
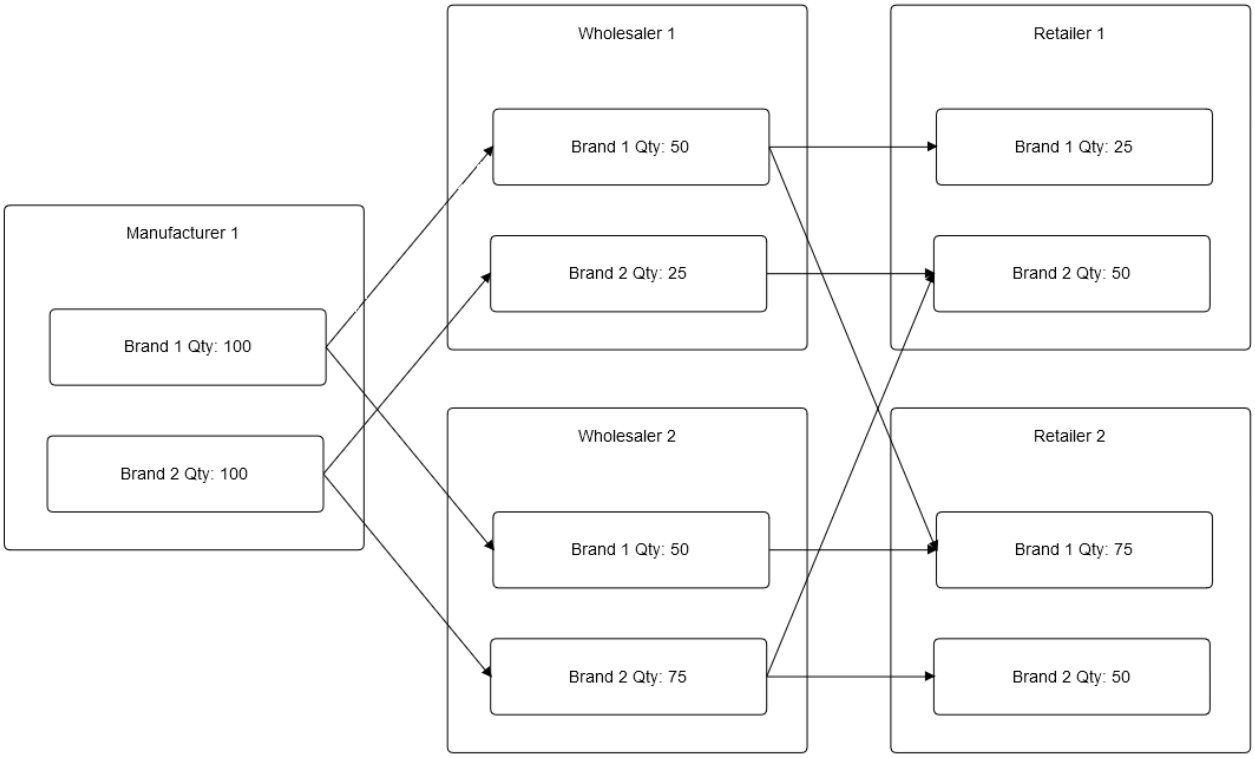


Figure 2. Possible branching and merging patterns in the drug distribution chain.



The system will adopt the GS1 pedigree standard [22] recommended in the Drug Supply Chain Security Act. The DApp will allow the drug supply chain participants to create product manufacture pedigrees, shipping pedigrees, and receipt pedigrees (where and when applicable), with each pedigree electronically signed and appended to the overall pedigree by each *author* (participant) down the supply chain. The content of each pedigree will satisfy, at minimum, the Standardization of Data and Documentation Practices for Product Tracing Guidance for Industry document published by the FDA [23]. The global identifier number (GTIN) will be used for identifiers.

Food and Drug Administration Account

The FDA account will have access to functions that allow the user to add information to reference smart contracts that define authentic drug products, supply chain participants, and contract relationships. Information uploaded by this account to the network will be considered authentic and will be used as the reference against which documents in the DFS will be checked. All sections and functions of the client application will be accessible to this account. Furthermore, this account verifies all transactions—all other accounts will automatically publish a session key encrypted with the FDA public key when they attempt to upload a file into the DFS.

Manufacturer Account

Information uploaded by this account to the network will have credentials and certificates linked and will initiate supply chains, which the system will subsequently track using the pedigree files in the DFS. Upon verification of identity and registered distribution contracts linked to the specific brand of drug product, the system will determine whether the merchandise moves along a registered chain and will verify consistency of information through each node.

Wholesaler and Retailer Accounts

Information uploaded by these accounts to the network will have credentials and certificates linked and will be validated by the system against the registries.

Distribution chains may branch out or merge at certain nodes, and the system should detect such patterns when it visualizes them into timelines. For improved auditing, the system will also track the amount or stock number of each brand of drug product that moves across each node, using the various pedigrees submitted by the supply chain participants.

Branching and merging patterns in Figure 2 will be visualized into 6 separate timelines, namely the following:

1. Brand 1: Manufacturer 1 (100), Wholesaler 1 (50), and Retailer 1 (25)
2. Brand 1: Manufacturer 1 (100), Wholesaler 1 (50), and Retailer 2 (25)
3. Brand 1: Manufacturer 1 (100), Wholesaler 2 (50), and Retailer 2 (50)
4. Brand 2: Manufacturer 1 (100), Wholesaler 1 (25), and Retailer 1 (25)
5. Brand 2: Manufacturer 1 (100), Wholesaler 2 (75), and Retailer 1 (25)
6. Brand 2: Manufacturer 1 (100), Wholesaler 2 (75), and Retailer 2 (50)

The system interface will include a mechanism by which drug products can be repackaged and shipped. Packages will be represented by receipt and shipping *pedigree envelopes* and will contain the GTINs of all drug products included in the package.

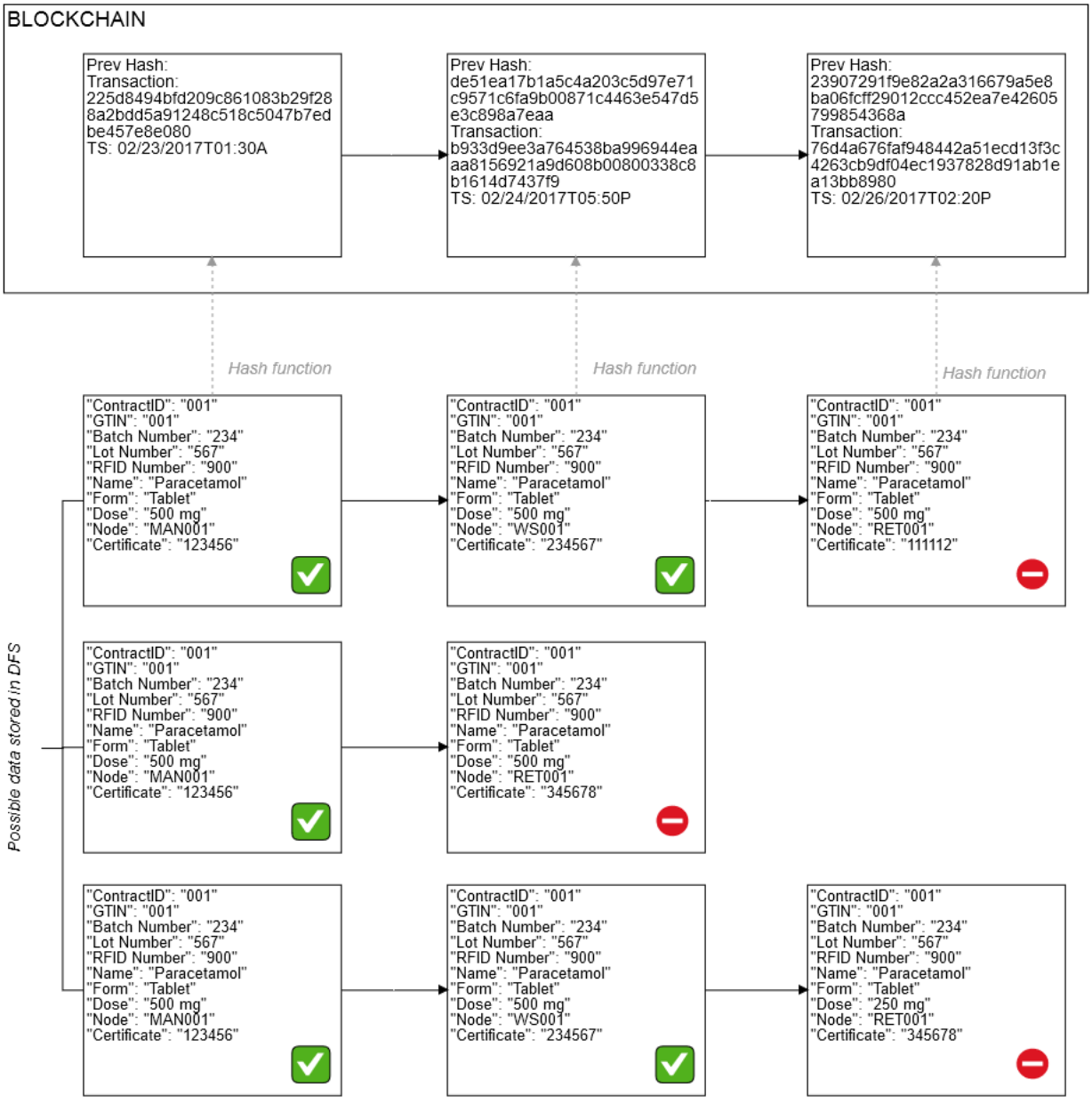
Figure 3 shows an example of data in the DFS and blockchain ledger records. When a manufacturer ships a batch of a drug product, a shipping pedigree is submitted into the network and the record is verified and counterchecked against the blockchain ledger by the DApp account of the recipient by using the Keccak-256 cryptographic hash function (used in Ethereum). It will send a notification to the network if the hash values do not match. In Figure 3, those marked with anomalous content have hash values different from those recorded in the blockchain ledger. The examples of anomalous information notifiable events are when certificates linked to the node identification do not match with those on record (hinting fraud), information supposedly recorded by a node is missing from the block (hinting at node failure or a skipped participant), and when the hash value of specific drug product information does not match its counterpart on record (hinting a typographical error or tampering of the drug product). All scenarios would need action from the FDA (or the regulating agency).

Database

The system database will be a DFS with 4 main parts:

1. The blockchain ledger.
2. The smart contracts repository, where real-world contracts, participants, and drug products will be defined.
3. The document repository, where the pedigrees will be stored.
4. The drug distribution history that contains a listing of the participants who possessed the drug at some point during the distribution, as well as information on shipments.

Figure 3. Example of anomalies that can be detected. Top row, information added by a node contains the wrong certificate. Middle row, information is missing from the block. Bottom row, drug product information is different from previous records or does not match the record in the distribution contract registry.



Radio-Frequency Identification Tags

Radio-frequency identification (RFID) tags will be used as an additional data point linked to a particular drug product. Each node will have an RFID scanner. RFIDs will be incorporated to drug product packages at the manufacturer level and will be added as a data point in pedigrees down the supply chain. Data mismatches will trigger notifications.

Drug Product Pathway

The following describes the proposed pathway for a drug product along the drug supply chain and how the proposed system will integrate into the workflow:

First, the process is initiated when a manufacturer creates a drug product and assigns a GTIN to each physical unit of drug product. A manufacturing pedigree is created for each physical unit of drug product and entered into the system. This document is then encrypted with a generated session key, which is then encrypted with the private key as well as the public key of the FDA account and stored in the DFS. The document is linked to its hash value in the DFS. The hash value is submitted to the network for verification. The FDA account is pinged by a premade smart contract and verifies each manufacturing pedigree by checking the credentials of the manufacturer.

Second, the manufacturer then groups the drug products into a shipment package and assigns an RFID. A shipping pedigree is created for each shipment package and entered into the system. Hash values of manufacturing pedigrees of drug products included in the shipment package are listed in the shipping pedigree. The session keys used previously are encrypted with the recipient public key and stored in the shipping pedigree. The shipping pedigree is then encrypted with a generated session key, which is then encrypted with the private key as well as the public keys of the FDA account and the recipient account. The shipping pedigree is identified by its hash value in the DFS. The hash value is submitted to the network for verification. The FDA and recipient accounts are pinged by premade smart contracts and verify each shipping pedigree by checking the credentials of the manufacturer and that the manufacturing pedigrees referenced in the shipping pedigree exist in the DFS and have been previously verified.

Third, the distributor receives the physical shipment package from the manufacturer and scans the RFID. The system then verifies that the RFID matches a shipping pedigree received in the DApp inbox and opens the pedigree. The recipient verifies that the manufacturing pedigrees referenced in the shipping pedigree exist and the GTINs match those of the physical drug products. The recipient then creates a receiving pedigree with the hash values of the manufacturing pedigrees of drug products actually received. This document is then encrypted with a generated session key that is then encrypted with the private key as well as the FDA's public key. The document is linked to its hash value in the DFS. The hash value is submitted to the network for verification. The FDA account verifies the pedigree like above.

Finally, a recursive process of shipment, verification, receipt, and verification occurs until the point of sale. The consumer receives a code along with the drug products purchased. The consumer then scans the code with a mobile phone camera, and is directed to a consumer portal where the distribution history of the drugs in the receipt is displayed.

Anomaly Detection

The system will be designed to detect 5 types of anomalies anywhere along the chain:

1. Missing nodes in the distribution chain.
2. Distribution chains that have not completed after a certain threshold.
3. Invalid node certificates.
4. Unregistered products entering the distribution chain.
5. Primary data point (ie, drug-related data, eg, dose) discrepancies.
6. Timestamp anomalies.

System Testing

After the development of the prototype, testing will be performed in a simulated network environment, evaluating 2 main parameters:

1. Benchmarks on various data corpus sizes (as a function of the number of transactions).
2. Capacity of the system to reliably detect the anomalies described above.

Analyses will be performed on the feasibility of the system for large-scale implementation based on these 2 main parameters. Assumptions and recommendations will be discussed in their respective sections.

Results

Interfaces

The system will have a DApp with a front end that provides a user interface. The DApp will have permissioned access to documents and records despite the said files existing in all nodes.

Log-In

The application will be locked behind a log-in interface with two-factor authentication as shown in Figure 4. It will ask for user credentials (username and password), as well as a verification code sent through an authenticator application. All credentials, including those for the authenticator application, will be issued by the FDA through the user management module integrated into the system. There may be several users for each supply chain participant account, and while each participant account is issued one pair of keys, the pedigrees submitted to the network will contain information on the currently logged-in user.

Figure 4. Log-in interface with two-factor authentication.

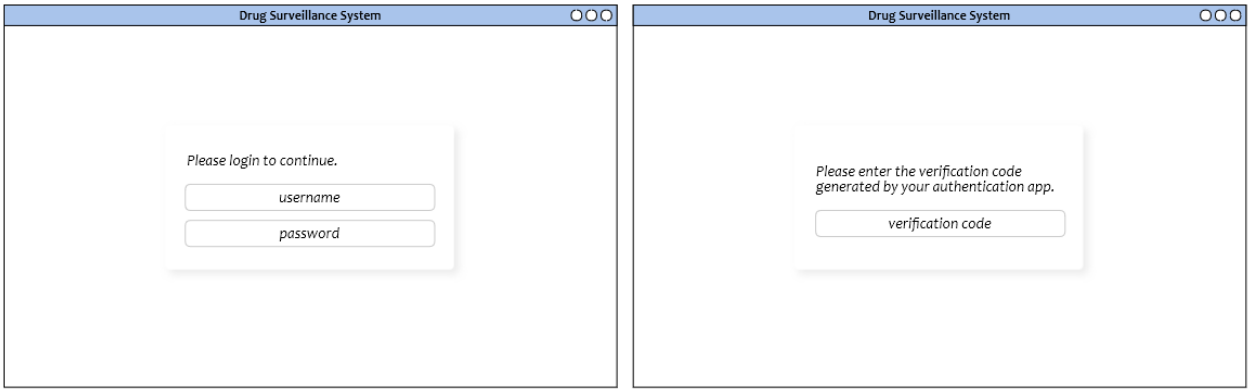
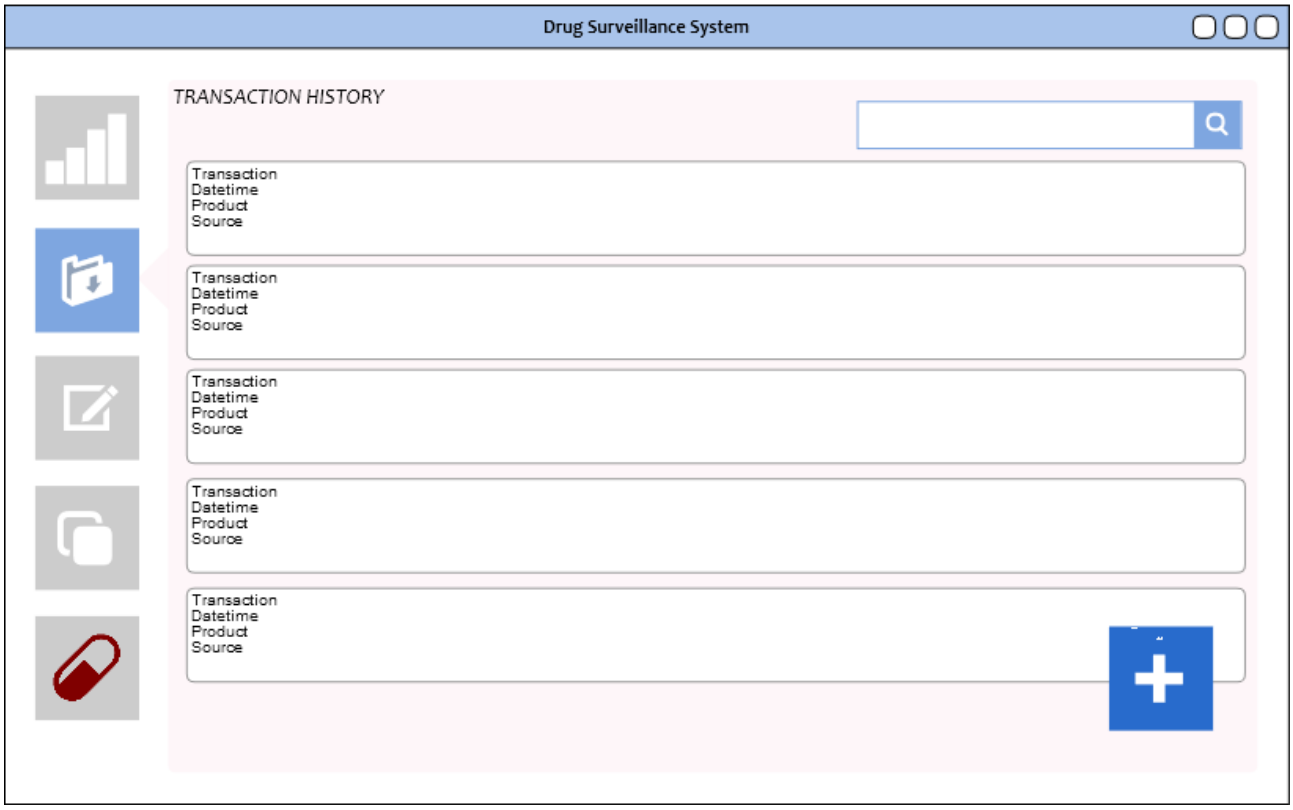


Figure 5. Transaction history, listing transactions made by the participant using the node.



Transaction History

The transaction history shown in Figure 5 is a simple data visualization widget that will be accessible to all accounts. Although the design involves the distribution of pedigree files across all nodes connected to the network, each file will have defined permissioned *recipients*, encrypted with session keys that would be, in turn, encrypted with keys of intended recipients. The (+) button at the lower right portion of the screen allows the participant to create a pedigree, append it to the overall document, and submit it to the network for verification.

Timeline Dashboard

The timeline dashboard generates graphs that illustrate the progress of a drug product along the supply chain. Anomalies in the information recorded by nodes will be marked with a red badge as shown in Figure 6. These badges can be clicked to show the latest submitted information from that particular node. The DApp will automatically verify pedigree documents in the DFS with the records in the blockchain ledger, the manufacturing pedigree, and the defined supply chain smart contracts. Should a malicious party insert a fraudulent document into the repository, bypassing an intended recipient, the system will be able to detect the anomaly.

Contract Registry

Figure 7 shows the screen after the *Contract* button (pen and paper) on the left panel is clicked and a new contract form is opened. Hovering over the contract icons to the right will display a small window with the details for that contract.

Figure 6. The timeline dashboard to visualize transactions along a distribution chain to highlight manufacturer shipment time to consumer purchase at a retailer. Diamond markers signifying transactions. A red diamond denotes a possible problem based on the information distributed on the network.

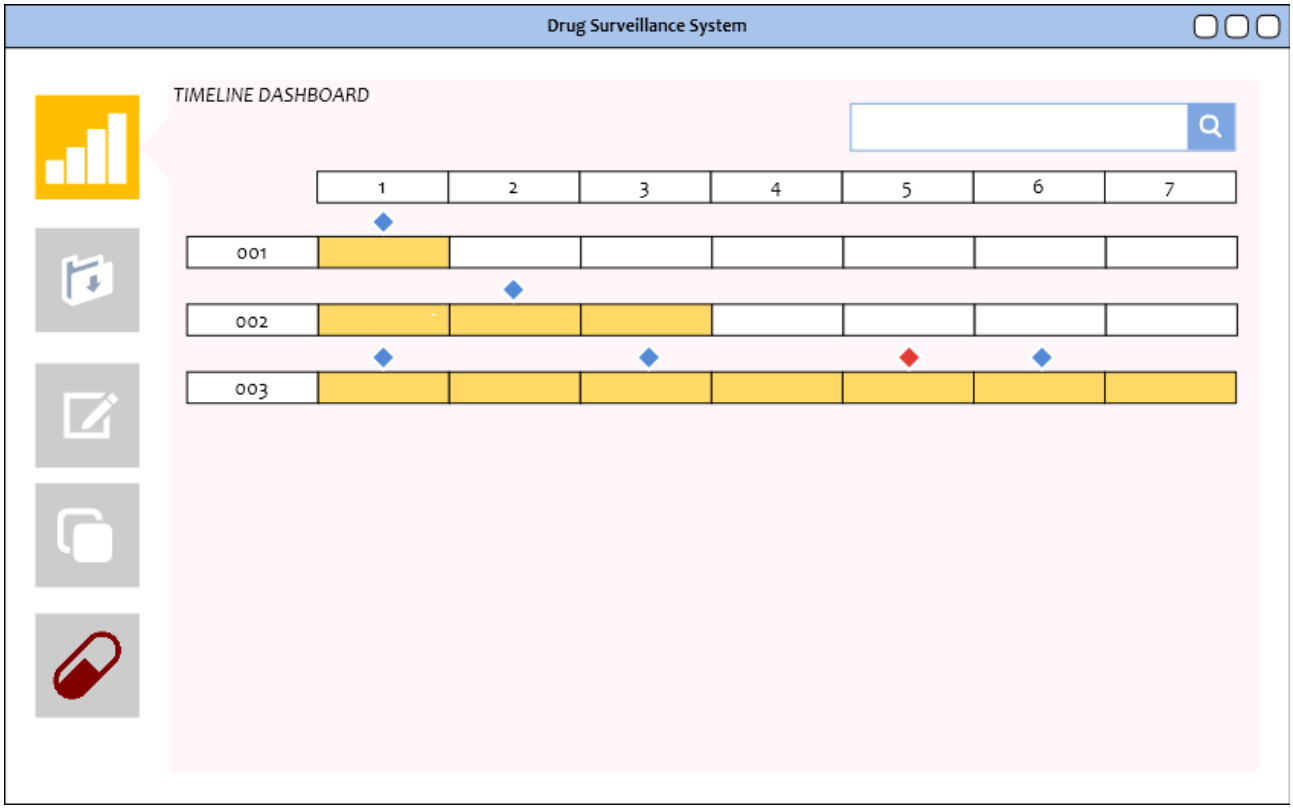


Figure 7. Contract registry interface only installed on the Food and Drug Administration (FDA) node and accessible to the FDA account.

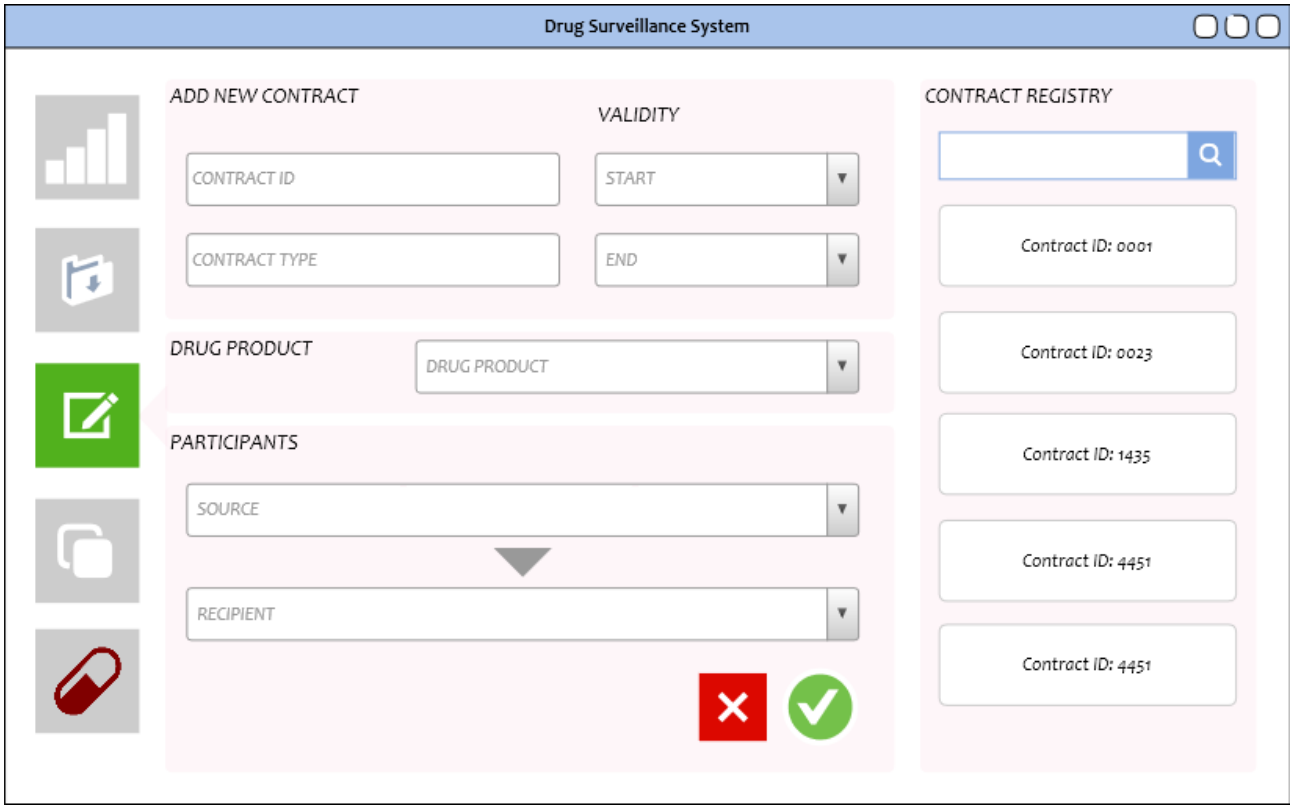
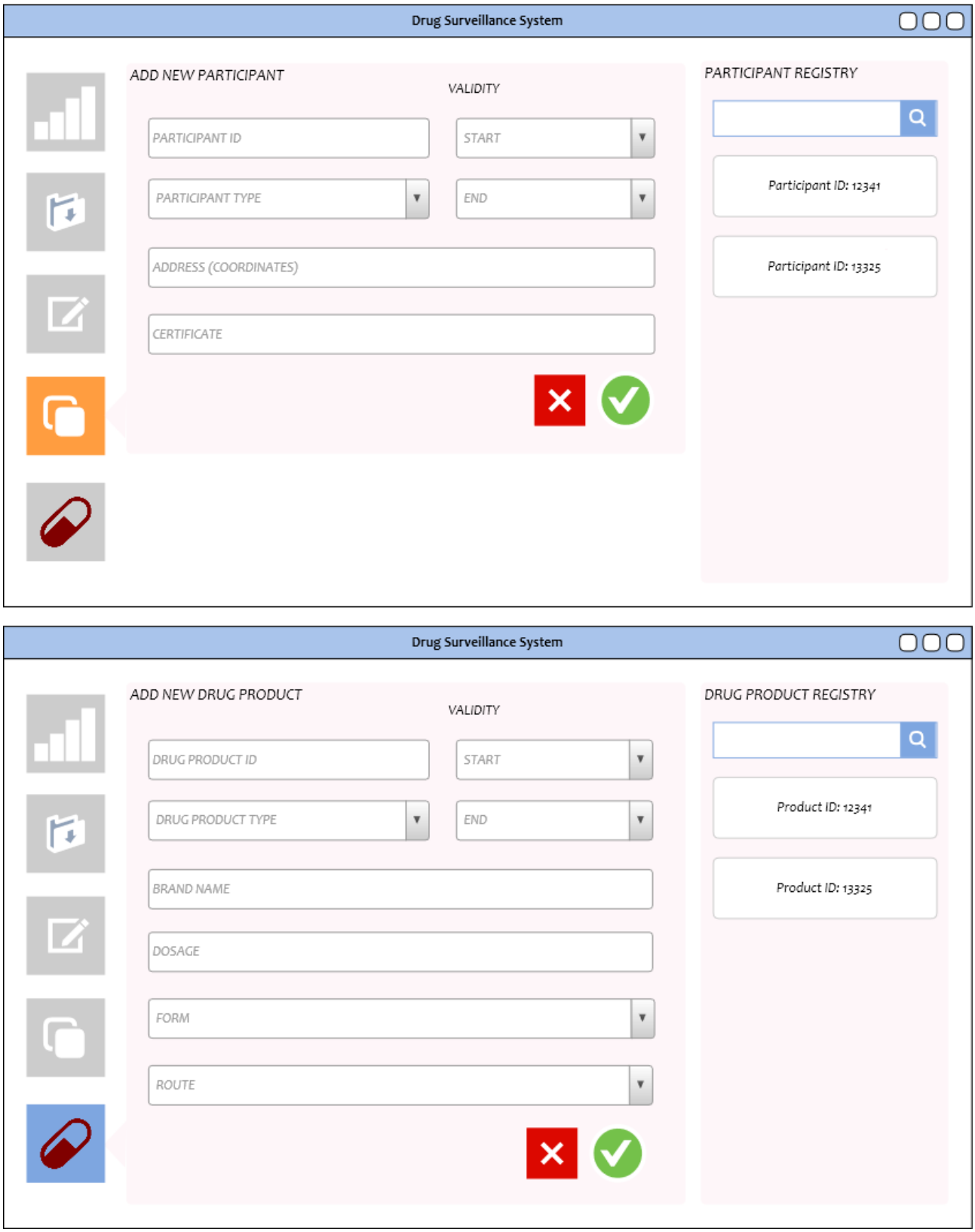


Figure 8. Participant and drug product registries. The corresponding forms for adding participants and drug products into the network are shown. These interfaces will only be accessible by the Food and Drug Administration.



The smart contract repository will contain the canonical definitions through which the system can detect information anomalies and broken supply chain sequence of events. The interface will refer to the set of definitions in the repository as *registries*. Only the FDA account can add and edit contracts. In the blockchain, once a contract is committed, the record of its creation cannot be modified, tampered with, or deleted.

A contract will minimally contain the name of the drug product, a source and recipient (both should be FDA-certified and registered to the system before the creation of the contract), and

other metadata such as unique identifiers, certificates, and start and end dates.

By design, there will be one contract assigned to each drug product transaction between 2 supply chain participants. At any point in time, a participant may have several contracts with other participants. The definitions will be instrumental in verifying transactions in the supply chain by allowing 2 layers of verification: first, the sender should be legitimate and certified by the FDA, and second, the hash values of the data in the DFS and the blockchain ledger must match, and the product information in the DFS must match those in the definitions.

Participant Registry and Drug Product Registry

The participant and drug registries serve to feed the input fields of the contract registry, containing the necessary data to distinguish between participants as well as between drug products (Figure 8). As with the contract registry interface, these will only be accessible by the FDA account. An option would be to allow other accounts to view the registries for reference; however, adding and editing privileges will be given only to the regulating agency.

Discussion

Technology Adoption

The pharmacosurveillance blockchain system being proposed is a highly disruptive intervention, particularly in the context of drug supply chains in a low-resource country such as the Philippines. It is projected to affect not just the pharmaceutical industry but the entire distribution chain and the consumer. Adoption and sustainability can only be achieved with consumer awareness and empowerment, as well as sound policy backing and good governance. The assessment of adoption potential at the feature level using the unified theory of acceptance and use of technology (UTAUT) and its extensions [24] for each affected sector may be performed once the technology has been developed and tested. In UTAUT, system performance, effort expected, social influences, and prevailing conditions will determine whether the introduction of new technology or device will be successful. In a developing country such as the Philippines, the last 3 components are likely to be the least predictable in determining the success of this disruptive technology.

As a portion of distributed SSFFCs travel outside the official drug supply chains, the system cannot detect them until they have reached the consumer. This is where consumer awareness and empowerment will play a significant role in the implementation: first, consumers should be aware that their purchases should come with a receipt that has a distribution history code that they can scan to verify the authenticity of the drug, and second, they should be empowered to report discrepancies to the FDA. In turn, the FDA has to have the capacity to accommodate, process, and respond to reports from the system and consumers.

In terms of policy, we recognize two important potential issues to resolve for successful adoption: first, local and national laws will have to recognize blockchain ledger records as a *source of truth*, admissible as evidence in the court of law. Second, policy will have to incentivize investments in infrastructure and human resources on the part of the participants in the drug supply chains. The FDA or another government agency will take on a capacity-building role, training key personnel from participants in the drug supply chain, not only on the use of the system but also the principles and best practices that facilitate the mitigation of the distribution of SSFFCs.

A DpoS or PBFT consensus algorithm is ideal for the project for several reasons: first, it eliminates the need for third-party *miners*, who would compete for computing power under PoW and currency under PoS, in a setting where resources are low and in an industry where participants have equal stake in the success of their own supply chains. Second, it is economical in terms of power consumption. Third, it is better designed for private consortium networks, of which the proposed system is an example. The FDA will be central to the verification process, typically paired with another participant with the authority to verify contract-specific information, for instance, a wholesaler must verify that the drugs in a recently received package and the shipping and manufacturing pedigrees match.

Assumptions and Limitations

Aside from assumptions on resources and infrastructure, the design of the prototype makes several additional assumptions that may affect implementation: first, that there is a regulatory agency such as FDA that exists and is monitoring the drug marketspace. Second, that the regulatory agency has the practice of certifying manufacturers, wholesalers, retailers, drug products, and reagents and has the practice or capacity to keep records of the certifications. Finally, that the participants in the drug supply chains implement, or have the capacity to implement, standards on the metadata surrounding the drug products with which they conduct business. Another major assumption is that the participants in the pharmaceutical distribution chain— manufacturers, distributors, retailers, and finally consumers are willing to participate in this disruption in the usual conduct of commerce. The consumer in the end will be willing to verify the authenticity of drug products and report anomalies that may be found. This will require awareness, training, and the desire to create an environment of authentic medication in the supply chain. In the event that these conditions are not met, a strategy to consider is to approach and engage the proper authorities: for instance, a government agency that regulates the drug product and reagent marketspace in the region, or certain policy makers and leaders with a pharmaceutical or public health focus that can formulate and push legislation to facilitate changing the environment favorably. In addition, a strategy to consider is to use the findings from the UTAUT analysis.

The study design has the following limitations:

1. The proposed system will only be able to detect drug movements that follow official distribution chains known to the regulatory agency. It cannot track falsified drugs that are distributed through routes outside of official distribution chains.
2. The proposed system will be developed and tested in a controlled simulated network; therefore, results obtained

from this study may not be reflective of actual performance when deployed in a real-world setting.

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Conflicts of Interest

None declared.

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Abbreviations

DApp: distributed application
DFS: distributed file system
DPoS: delegated proof-of-stake
D-PUNCH: Destroying Products Unfit for Human Consumption
FDA: Food and Drug Administration
GTIN: global identifier number
PBFT: practical Byzantine fault tolerance
PoS: proof-of-stake
PoW: proof-of-work
RFID: radio-frequency identification
SSFFC: substandard/falsely-labeled/falsified/counterfeit
UTAUT: unified theory of acceptance and use of technology

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Protocol

Use and Effects of Patient Access to Medical Records in General Practice Through a Personal Health Record in the Netherlands: Protocol for a Mixed-Methods Study

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Abstract

Background: In the Dutch health care system, general practitioners hold a central position. They store information from all health care providers who are involved with their patients in their electronic health records. Web-based access to the summary record in general practice through a personal health record (PHR) may increase patients' insight into their medical conditions and help them to be involved in their care.

Objective: We describe the protocol that we will use to investigate the utilization of patients' digital access to the summary of their medical records in general practice through a PHR and its effects on the involvement of patients in their care.

Methods: We will conduct a multilevel mixed-methods study in which the PHR and Web-based access to the summary record will be offered for 6 months to a random sample of 500 polypharmacy patients, 500 parents of children aged <4 years, and 500 adults who do not belong to the former two groups. At the patient level, a controlled before-after study will be conducted using surveys, and concurrently, qualitative data will be collected from focus group discussions, think-aloud observations, and semistructured interviews. At the general practice staff (GP staff) level, focus group discussions will be conducted at baseline and Q-methodology inquiries at the end of the study period. The primary outcomes at the patient level are barriers and facilitators for using the PHR and summary records and changes in taking an active role in decision making and care management and medication adherence. Outcomes at the GP staff level are attitudes before and opinions after the implementation of the intervention. Patient characteristics and changes in outcomes related to patient involvement during the study period will be compared between the users and nonusers of the intervention using chi-square tests and t tests. A thematic content analysis of the qualitative data will be performed, and the results will be used to interpret quantitative findings.

Results: Enrollment was completed in May 2017 and the possibility to view GP records through the PHR was implemented in December 2017. Data analysis is currently underway and the first results are expected to be submitted for publication in autumn 2019.

Conclusions: We expect that the findings of this study will be useful to health care providers and health care organizations that consider introducing the use of PHR and Web-based access to records and to those who have recently started using these.

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KEYWORDS

health records; patient access to records; patient participation; personal; decision making; shared; medication adherence; patient-centered care; self-management

Introduction

Background

Over the past decades, patient involvement in decision making and delivery of health care has become increasingly important to patients, health care providers (HCPs), and policy makers. Patient involvement is pursued because of autonomy principles, as an essential element of patient-centered care and as a means to improve the quality and efficiency of care [1-4].

Personal health records (PHRs) are tools that have been developed to facilitate patient involvement in decision making, disease management, and care coordination [5]. PHRs are electronic health records that are, in varying degrees, controlled by patients [6]. Standalone PHRs are completely managed by patients [6]. Patients may use them as their personal Web-based archive for storing documents about their health; for tracking and monitoring health data; and for sharing information with HCPs, family, or caregivers. Some standalone PHRs are interoperable with a particular HCP information system, and they may be used to access medical records that are maintained by HCPs [6]. In contrast, tethered PHRs, also called patient portals, are extensions of HCP electronic medical records where most data are maintained by HCPs. Patients can use tethered PHRs to view personal health information in their records; however, usually, they cannot enter data [6]. Through a tethered PHR or interoperable standalone PHR, patients can usually view a limited set of data, often including the problem list, medication list, allergies, test results, and, less frequently, consultation notes [7,8].

Although PHRs that allow patients access to personal health information are promising tools, evidence of their effects on patient-centered care, efficiency of care, and health outcomes is inconsistent [7,9,10]. In addition, adoption rates among patients vary greatly. A recent systematic review has reported that the adoption rates of patient access to summary records range from 9% to 69% in primary care in real-life experiments in the United States [11,12]. In Europe, the adoption rates of patient access to summary records through national systems in the United Kingdom and France have been low at 0.5% and 1.5%, respectively [13,14]. However, in Sweden, 38% of the population had adopted access to the medical records in primary and specialist care in 2017 [15].

In the Netherlands, electronic health records are widely used in general practice and specialist care. A national electronic health record system is not available. However, there is a vast variation in health information systems that are used, and most of these systems do not interoperate with each other. General practitioners (GPs) have a central role in the fragmented Dutch health care system, and they receive information from all HCPs who are involved with each of their patients and store this information in patients' general practice records (GP records).

In 2016, a law was passed obliging HCPs to provide their patients digital access to their medical records by 2020. Accordingly, Web-based access to medical records is increasingly being offered to patients, mainly through patient portals. In 2017, 30% of medical specialists offered Web-based access to the list of diagnoses and test results, and almost 25% of GPs allowed their patients Web-based access to their medication list. However, only few GPs offered access to other parts of medical records: 12% to the list of diagnoses, 11% to test results, and 3% to consultation notes [16]. The adoption of these services by patients is still low. In 2017, less than 10% of patients with a chronic disease actually accessed parts of their medical records, which may be partially explained by their lack of awareness about these services [16]. Standalone PHRs are rarely used in the Netherlands; in 2016, only 1% of the population used these records [17].

MijnZorgnet is a Web-based, noncommercial, standalone PHR that provides patients a secure environment to store and share health data. In the past, the PHR has been made interoperable with the electronic health records used in fertility care to study the effects of Web-based access to medical records. Patients reported that they found the PHR useful; however, this study did not demonstrate an effect on empowerment related to use of the PHR [18,19]. In addition, the PHR has been used and evaluated in maternity care. This study demonstrated an adoption rate of 4%, which was explained by the low perceived usefulness of the PHR by healthy women with uncomplicated pregnancies. The authors suggested that the PHR might be more useful if it would be embedded in standard care [20,21]. Searching for new ways to facilitate patient involvement and foster patient-centered care, MijnZorgnet has recently been made interoperable with the infrastructure of the Dutch National Connection Point, which is used for the exchange of summary records between GPs and out-of-hour GP services and of medication lists between GPs and pharmacies. The connection between MijnZorgnet and the National Connection Point provides an opportunity to offer patients Web-based access to the summary of their medical records in general practice and to explore whether patients are interested in using this service and if and how they may benefit from this. In this paper, we have described the protocol that we will use for our study to explore the adoption and effects of patient access to the summary of their GP records through the MijnZorgnet PHR.

Objectives

The aim of our study is to explore the use, experiences, and effects of patient access to the summary of GP records through the MijnZorgnet PHR. We intend to explore the barriers and facilitators for the adoption of PHR and Web-based access to GP records and investigate whether patients consider the information in the summary of their GP records useful. Furthermore, we aim to investigate whether access to GP records through PHR fosters patient involvement in their care and aim

to explore the perceptions of GP staff regarding patients' Web-based access to their records and patients managing their own PHRs.

Methods

Conceptual Framework

The conceptual framework of our study is summarized in Figure 1. We distinguished two components of the intervention: the standalone PHR and access to the summary of the GP record. We expect that access to the summary record may increase patients' knowledge and understanding of their conditions and treatments [7,22,23]. In addition, we assume that the standalone PHR may help patients monitor their health and that the messaging function of the PHR will provide them with another means to communicate with their GPs. We expect that GPs' and practice nurses' insight into their patients' symptoms, social context, and treatment plans advised by other HCPs will increase when they are invited by patients to view information stored in their PHRs.

Drawing on the Unified Theory of Acceptance and Use of Technology, we assumed that perceived performance (usefulness) of the PHR and access to GP records, perceived efforts needed to use the PHR and access GP records (usability), and social influence are the determining factors for the uptake and continuous use of the two components of the intervention [24]. Based on studies about patient portals, we added perceived health, presence of a chronic disease, eHealth habits, and concerns about privacy as the determining factors [25-27]. Moreover, we considered perceived support from the GP for using the intervention as a social influence. Following Snyder's model on patient involvement, we assumed that an increased insight into patients' medical situation and improved communication may enhance patient involvement and improve the doctor-patient relationship, which may subsequently affect satisfaction with care and utilization of health services and eventually health outcomes, although we expect that the latter will need more time to change than the 6-month period of our study [1]. In addition, we expect that patients who are more involved in their care may find both components of the intervention useful; thus, they are more likely to use this intervention. We assumed that sociodemographic factors, such as age, gender, education level, ethnicity and health status, health literacy and ideas about the roles of patients and GPs, and attitudes toward patient involvement are the moderators for uptake and effects [28-31].

Study Design

We have designed a multilevel mixed-methods study in which the qualitative strand at the patient level is embedded in the quantitative before-after study at the patient level [32]. Alongside the study strands at the patient level, there will be a qualitative strand at the general practice staff (GP staff) level. All participants of the study will be offered the intervention, and data will be collected at baseline and after 6 months from patients who adopt the intervention and use it at least once during the study period to view the summary of their GP record (users) and from those who do not (nonusers). We will collect quantitative and qualitative data concurrently and use qualitative data from the earlier phases for data collection instruments that we will apply in the later phases of the study. In addition, qualitative and quantitative data will be integrated for the analysis and interpretation of the results using qualitative results to complement and explain the quantitative results. We will utilize the guidelines provided by the Good Reporting of A Mixed Methods Study [33] and Consolidated Criteria for Reporting Qualitative Research [34]. The study design is summarized in Figure 2. The flowchart of the study is presented in Figure 3.

Figure 1. Conceptual framework. GP: general practitioner; GP staff/record: general practice staff/record; PHR: personal health record.

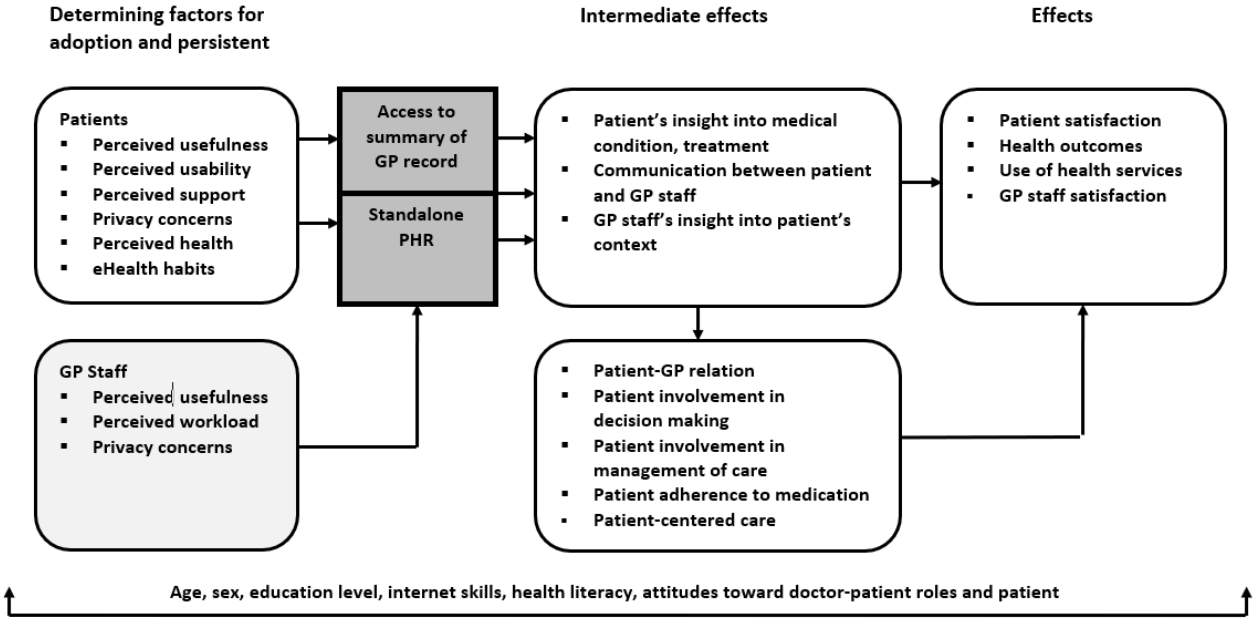


Figure 2. Study design. GP staff: general practice staff.

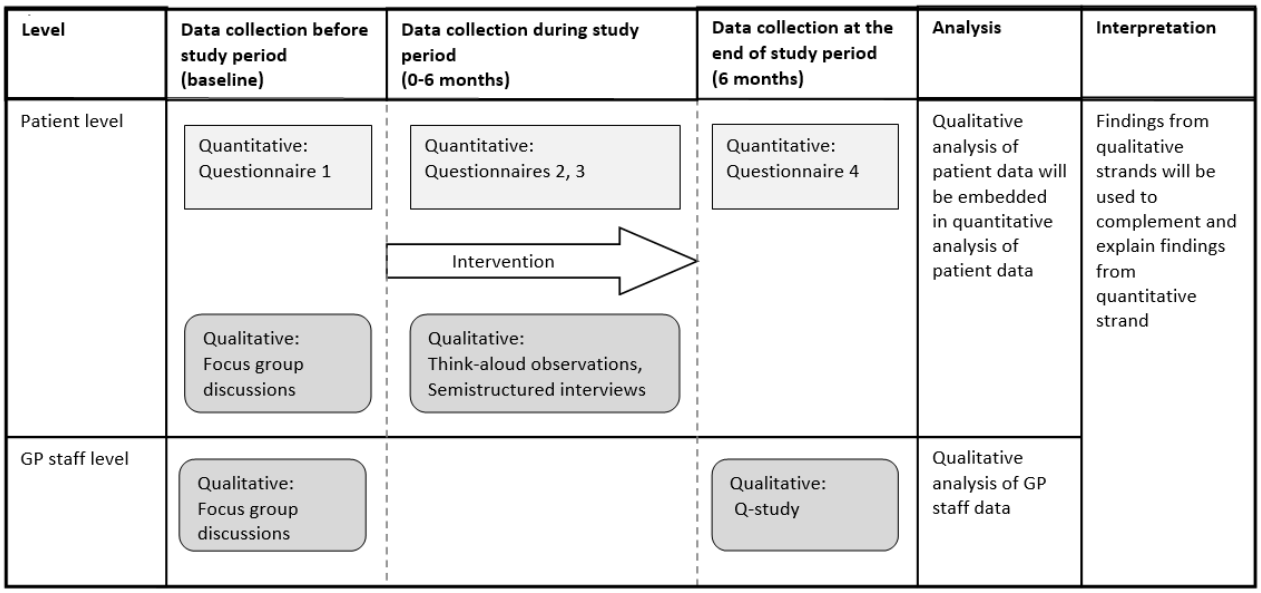
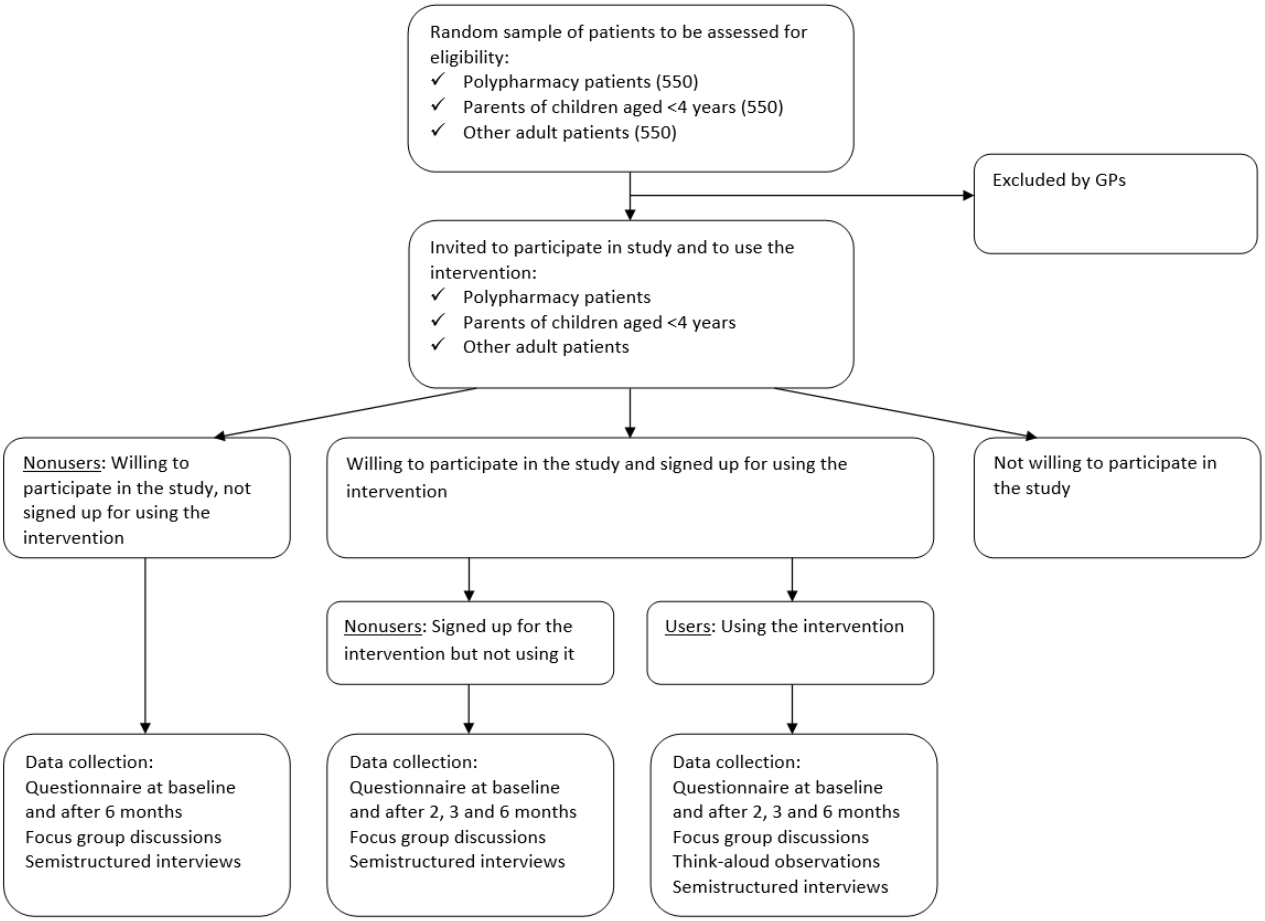


Figure 3. Flowchart of the study. GP: general practitioner.



Intervention: MijnZorgnet Patient Health Record With Web-Based Access to the Summary of General Practice Records

MijnZorgnet is a standalone PHR where patients can store personal health information. Patients may share information with HCPs or others by inviting them to their care team at MijnZorgnet and allowing them to view their PHR. Patients can also exchange messages with the members of their care team through MijnZorgnet. To log in to the MijnZorgnet PHR, patients use their digital identity code (DigiD) with short

message service verification. DigiD is the identity code that is used for government websites in the Netherlands.

The participants of this study will be able to view the summary of their GP records. This so-called "professional summary" is an automatically created set of data that was originally established to provide relevant information to HCPs working for out-of-hour GP services. The summary contains the list of medications that have been prescribed in general practice; the list of health problems, allergies, and contraindications; recent test results; and notes about the last 5 consultations with the GP, practice nurse, or practice assistant. This summary, including complete consultation notes and not including correspondence, is slightly different from the set of information that is recommended in the recently published guidelines by the Dutch College of General Practitioners and the Dutch Federation of Patient Organisations [35]. We chose to use the professional summary because this dataset is already automatically generated. In addition, drawing on the Open Notes study, we expect that access to complete consultation notes may be valuable to patients [8,36].

Patients will be able to see the summary of their record in "real time." The information is displayed with easy-to-understand names for the different parts of the records, which have been suggested by a panel of potential users who will not participate in the study. Medical terms in the problem list and the medication list are linked to websites with evidence-based information [37,38]. Participants may copy and paste information from their GP record to their PHR and share such information with other HCPs or their family or caregivers. They will not be able to add information to their GP records; neither will they be able to access medical records from hospitals through the PHR.

The PHR and Web-based access to the summary of the GP records will be introduced to patients in a brochure that they will receive together with the invitation to participate in the study, signed by their GPs. When they log in to the PHR for the first time, they will be guided through an instruction on how to use the PHR. In addition, the participants can contact the MijnZorgnet help desk about questions regarding the PHR and how to access their summary record. The GP staff can be approached for questions about the content of the summary record.

Setting, Study Population, and Sample Size

The study will be conducted in 3 group practices of GPs in the southeast of the Netherlands, where 18 GPs provide primary care to approximately 22,000 patients. This setting is a pragmatic choice based on the health information system that is used in these practices and the willingness of the GPs to provide Web-based access to their records and to participate in this study. Assuming that uptake, use, and effects will differ among different groups of patients, we will recruit a random sample from three groups of patients: (1) adult patients using five or more different types of medication (polypharmacy patients), (2) parents of children aged <4 years, and (3) other adult patients (those who do not belong to the first two groups). Both polypharmacy patients and parents of young children are frequent users of GP services, with an expected number of 5 and 2 contacts, respectively, with the GP during the 6-month study period [39]. They are likely to differ in terms of health status, age, internet use, and computer skills. Patients aged >75 years and those with severe cognitive or psychiatric problems will be excluded; furthermore, patients for whom access to the records may be harmful to themselves or others according to the GPs will be excluded.

Because of the lack of available figures, a proper power analysis to determine the sample size is not feasible. However, we expect that a sample of 50 users and 100 nonusers of the PHR in each group will be suitable for our aims. We assume that the uptake of the intervention will be approximately 10%, based on experiences in these practices along with the adoption rates of other eHealth interventions and based on the adoption rates of these services in the Netherlands [16]. With an expected participation rate of 25%-50% for research using questionnaires in general practice in the Netherlands [40,41] and an assumed uptake of the intervention of approximately 10% and taking into account that GPs may exclude some patients, we will use a random sample of 550 patients for each group for the quantitative study: 550 polypharmacy patients, 550 parents of children aged <4 years, and 550 other patients.

The participants of the qualitative study strand among patients will be obtained from the sample of participants of the quantitative study strand who indicate in the first questionnaire to be willing to participate in the qualitative study. To obtain a sample of patients who vary in age, gender, and education level, we will use purposive sampling. The sample size of the qualitative study strand among patients will be determined using the saturation principle. For the focus group study, we expect to achieve saturation across groups by conducting 3 focus group discussions (one for polypharmacy patients, one for parents of young children, and one for the other patients), with each group including 5-8 participants. In addition, we strive to achieve saturation within groups by inviting patients who differ in age, gender, and education level. If we feel that saturation has not been reached, we will consider conducting more focus group discussions. We will continue with think-aloud observations and semistructured interviews until we detect no new information in 3 consecutive observations or interviews.

For the study strand at GP staff level, we aim to include not only GPs but also practice nurses and practice assistants as participants to obtain a complete understanding of the use and effects of the PHR and to gain access to the summary of the GP records. Practice nurses and practice assistants also enter information in the GP records, and they may also be approached by patients with questions regarding the content of the records. Because their roles differ from those of the GP, their attitudes, experiences, and opinions concerning the PHR and access to the records may also differ, and therefore, their inclusion in the study may be useful. Sampling for the focus group study among GP staff will be performed purposively. To achieve saturation within focus groups, we will include at least two GPs, a practice nurse, a practice assistant, and a GP in training in each group. To achieve saturation across groups, we will conduct a focus group discussion with the GP staff in each of the 3 practices. All GPs, practice nurses, practice assistants, and GPs in training will participate in the Q-study at the end of the study period.

Recruitment Procedure and Informed Consent

Eligible patients will be invited to participate in the study to create a profile on MijnZorgnet and to sign up for Web-based access to the summary of their GP records. They will receive an invitation letter signed by their GP along with the study brochure and a consent form. In the invitation letter, a code will be included that patients can use to open the first digital questionnaire. The first page of this questionnaire is a consent form. If patients indicate on this page that they do not consent to participate, they will not be able to complete the questionnaire. In the first questionnaire, patients will be asked whether they are willing to participate in the qualitative study strands. We will send a reminder after 3 and 6 weeks to all patients who have not used the code in the invitation letter.

All patients who attend a focus group session or who are interviewed or observed during the think-aloud sessions will be asked to sign a consent form at the beginning of the session. Similarly, the GP staff will be asked to sign consent forms.

To sign up for Web-based access to the summary of their GP records, patients will need to go to the GP practice to hand-in the consent form for Web-based access to their records and for identification. Subsequently, they will receive an email with a link to the PHR and a link to activate the connection between the PHR and the summary of the GP record.

Outcomes of Interest

The primary outcomes of interest are the predictors for adoption of the PHR, which are defined as using the PHR at least once to access the summary of the GP record, including patient characteristics and perceived barriers and facilitators. Other primary outcomes are those related to patient involvement: playing an active in role decision making, disease management, and medication adherence. We included medication adherence because this is related to the knowledge about the condition and treatment and shared decision making and may be facilitated by having an overview of the medication list [42,43].

The secondary outcomes are patient-reported changes in use of GP services (number and type of contacts), patients' confidence in their communication with the GP, knowledge about the disease, satisfaction with GP care, and patient-reported perception of changes in the doctor-patient relationship. Patient-reported benefits and drawbacks and the opinions of the GP staff about patients using the PHR and access to the summary of the GP record are also secondary outcomes. We do not expect health outcomes to improve during the 6-month study period; therefore, we will not assess these.

Data Collection

At the patient level, we will collect quantitative and qualitative data; at the GP staff level, we will only collect qualitative data. Data collection at the patient level is summarized in Table 1.

Collection of Data at the Patient Level

Questionnaires

Participants will fill out Web-based questionnaires at baseline and after 2, 3, and 6 months (Q1, 2, 3, and 4, respectively). Q1 is the baseline questionnaire, and it includes self-generated items to assess the moderating factors that we included in the conceptual framework and a validated scale to assess health literacy, the Dutch version of the Set of Brief Screening Questions (SBSQ-D). The SBSQ-D contains 3 statements that are scored on a 5-point Likert scale ranging from 0 to 4. An average score of ≤2 indicates inadequate health literacy. In the Dutch setting, construct validity and internal consistency of the SBSQ-D have been found to be adequate, and the latter has a Cronbach alpha coefficient value of 0.69 [44,45]. To assess the determining factors of perceived usefulness and benefits, security and privacy concerns, and eHealth habits, Q1 includes some self-generated questions, which are formulated as statements to which the extent of agreement may be scored on a 5-point Likert scale. An item from the Dutch Consumer Quality index for general practice is included to assess the determining factor perceived health [46]. Furthermore, Q1 contains validated scales that measure the baseline levels of the (intermediate) effects. We will use the Partners in Health scale (PIH) to assess the effects on patients' perceived knowledge about their conditions and treatment (2 items), playing an active role in their treatment (4 items), and recognition and management of symptoms (2 items) [47]. This scale has been developed in Australia to assess patients' self-management skills. It has been used in the Netherlands among ambulatory patients with chronic diseases. Moreover, it demonstrated adequate internal consistency, Cronbach alpha 0.69 for active role, 0.89 for knowledge, and 0.66 for the recognition and management of symptoms [47,48]. Responsiveness has been demonstrated in ambulatory patients with chronic asthma in the United Kingdom and ambulatory patients with osteoarthritis in Australia [49,50]. Items are rated on a 9-point scale and averaged for each domain, with higher scores referring to, for example, a more active role. To the best of our knowledge, the PIH has not been used among the parents of young children. We adjusted the phrasing of the items for the parents and piloted the rephrased items among them. The Medication Adherence Report Scale (MARS-5) [51] is used to assess self-reported attitudes and behavior regarding medication adherence [51]. The scale contains 4 items about intentional adherence and one item about nonintentional nonadherence. The frequencies of nonadherent behavior are rated on a 5-point Likert scale (1: very often to 5: never), and the scores are summed up for either all 5 items or for the items of intentional and nonintentional nonadherence separately. The scale has been used in various studies in the Netherlands and has shown good internal consistency (Cronbach alpha approximately 0.80) [52-54]. Construct validity has been found to be inconsistent compared with objective measures for medication adherence, which may be related to anonymous or nonanonymous use of the scale [53-55]. Because we are interested in intentions to adhere rather than actual medication usage, we decided that we could use the scale in our study. The MARS-5 has been used in the Netherlands to identify changes in adherence, comparing the sum of scores over time [56].

An item from the Dutch Quality of Care Index for general practice on satisfaction with care in general practice [46] has been included to assess patient satisfaction with care. We have also included the Perceived Efficacy in Patient-Doctor Interactions scale (PEPPI-5) to measure patients' confidence in

their communication with their GPs. The 5 items of this instrument are rated on a 5-point Likert scale (1: not confident at all to 5: completely confident). The scores are summed and averaged [57,58]. Validation in a population of ambulatory patients with osteoarthritis in the Netherlands has demonstrated a high internal consistency (Cronbach alpha 0.92), fair test retest reliability, and high construct validity [57]. The PEPPI-5 has been used in the Netherlands to assess changes in the perceived confidence of patients in their interactions with HCPs over time [59,60]. We slightly changed the wording of 1 item because we expected the original phrasing to be confusing. The PEPPI-5 has not been validated among parents of young children.

In addition, Q1 contains 2 self-generated items assessing patients' use of GP services, asking them about the number and type of contact with the GP or practice nurse within the last 3 months. Q1 has been piloted, which has resulted in the rephrasing of the self-generated question on privacy and security concerns as well as the self-generated question on perceived usefulness.

Table 1. Data collection at the patient level.

Data to be collected	Quantitative data collection methods (point of time)	Qualitative data collection methods (point of time)
Moderating factors for uptake, use, and effects		
Age, sex, education level, internet use, and skills	Q1[a] (baseline)	—
Health literacy	Q1 (baseline): SBSQ-D[b]	—
Attitude toward patient-doctor roles and patient involvement	Q1 (baseline)	Focus group discussions (baseline); interviews (2-6 months)
Determining factors for uptake		
Expected usefulness; expected usability; concerns about privacy; perceived support from the general practitioner (GP)	Q1 (baseline)	Focus group discussions (baseline)
Perceived health; presence of a chronic disease	Q1 (baseline)	—
Use (reach, dosage, and fidelity)		
Personal health record (PHR) used to store data; PHR used to share data	Q2, Q3, and Q4[a] (2, 3, and 6 months, respectively)	Interviews (2-6 months)
Summary of general practice records (GP records) accessed	Log data: number of hit days during the study period (6 months); Q2, Q3, and Q4 (2, 3, and 6 months, respectively)	Interviews (2-6 months)
Experiences with PHR and access to the summary of GP records		
Experienced barriers and facilitators; experienced usability; experienced usefulness, benefits, and drawbacks	Q2, Q3, and Q4 (2, 3, and 6 months, respectively)	Think-aloud observations (1-3 months); interviews (2-6 months)
Primary outcomes: changes in the following		
Active role in decision making	Q1, Q4: PIH[c] (baseline, 6 months)	Interviews (2-6 months)
Active role in care delivery	Q1, Q4: PIH (baseline, 6 months)	Interviews (2-6 months)
Medication adherence	Q1, Q4: MARS-5[d] (baseline, 6 months)	Interviews (2-6 months)
Secondary outcomes: changes in the following		
Knowledge about the disease and treatment	Q1, Q4: PIH (baseline, 6 months)	Interviews (2-6 months)
Confidence in communication with the GP	Q1, Q4: PEPPI-5[e] (baseline, 6 months)	Interviews (2-6 months)
Satisfaction with GP care	Q1, Q4 (baseline, 6 months)	Interviews (2-6 months)
Patient-GP relationship	Q4 (6 months)	Interviews (2-6 months)
Use of GP services	Q1, Q4 (baseline, 6 months)	Interviews (2-6 months)

[a]Q1, Q2, Q3, and Q4: questionnaires 1, 2, 3, and 4, respectively.

[b]SBSQ-D: Dutch version of the Set of Brief Screening Questions.

[c]PIH: Partner in Health scale.

[d]MARS-5: Medication Adherence Report Scale.

[e]PEPPI-5: Perceived Efficacy in Patient-Doctor Interactions scale.

Q2 and Q3 are brief, containing 6 self-generated questions to check whether participants are able to navigate through the PHR, medication list, problem list, and consultation notes and are able to comment on the completeness and usefulness of the information. These questions are formulated as statements to which participants can express their agreement on a 5-point Likert scale. In addition, 2 open questions will be added asking how patients feel about using the PHR and about accessing the summary of their GP records.

Q4 is similar to Q1; it includes the same validated scales to assess for intermediate effects, allowing us to assess differences over time. It also contains self-generated items on the usability of the system and on usefulness of the PHR and information on the summary of the GP record and use of GP services, which are formulated as statements with a 5-point Likert scale to express patients' agreement or disagreement.

Log Data and Page Views

Log data on the number of days during the 6-month study period when the patients log in to the system (hit days in 6 months) and view their medication list, problem list, test results, and consultation notes will be collected to assess the actual utilization of the PHR to access the summary of GP records.

Routine Patient Data From General Practices

To describe our sample of study participants in relation to the population that the sample was obtained from, we will collect routine data (age, sex, prevalence of chronic disease, and frequency and number of contacts with the GP or practice nurse) from GP practices for the groups of patients from which we have obtained our samples.

Focus Group Discussions

Before the implementation of the intervention, we will conduct a focus group discussion with each of the 3 patient groups who participate in the study, for example, one with polypharmacy patients, one with parents of young children, and one with other adult patients. The sessions will start with a brief explanation about PHRs in general and MijnZorgnet specifically using a short movie. Subsequently, we will show the PHR and the pages that the patients will be able to view in their medical records in general practice. We will provide enough time for answering questions about the PHR and access to medical records and the National Connection Point. We will use a predefined topic list based on our conceptual framework to guide the discussion, including expectations about the usefulness of keeping a PHR and viewing the professional summary of the GP records and ideas about patient involvement in care and concerns about privacy and security. Two investigators will moderate the sessions, which will be audiotaped.

Think-Aloud Observation and Introspection

We will use the think-aloud method to assess the usability and usefulness of the MijnZorgnet PHR and avoid reporting bias [61-64]. We will ask patients to verbalize their thoughts while they perform predefined tasks, such as checking their medication list in their GP records. We will complement the think-aloud method with introspection [63], asking participants to explain why they performed tasks the way they did. To assess the extent to which information in the GP record is clear, understandable, desirable, and valuable to them, we will ask participants to comment on the information that they view in their GP records [65]. The think-aloud sessions will be conducted with patients who access their GP records for the first time through the PHR, and those who have logged in before. We will explain the method to them at the start of the session. Think-aloud observations and interviews will be audiotaped.

Semistructured Interviews

We will conduct semistructured interviews to explore patients' experiences, opinions, and concerns regarding the PHR and access to the summary of the GP records. A topic list has been established based on our conceptual framework, including barriers and facilitators for using the PHR and access to the summary GP record, usability and usefulness of the PHR to store and share information, experienced usefulness (understandability, credibility, and desirability) of the information in the GP records, experienced benefits and drawbacks related to the use of the PHR and accessing the summary GP record, experienced changes in relation with the GP, involvement in decision making and disease management, and patient-centeredness of care. The interviews will be conducted over a period of 5 months, which allows us to obtain information from more and less experienced patients. The interviews will be audiotaped.

Collection of Data at the General Practice Staff Level

Focus Group Discussions

We will conduct a focus group discussion with GPs, practice nurses, and practice assistants in each of the 3 centers for general practice before the implementation of the intervention. The topic list for these focus group discussions contains the perceptions of the GP staff about introducing a PHR and access to the summary of GP records regarding reporting habits, work load, relationship with patients, and ideas and concerns about confidentiality. The focus group discussions will be moderated by two researchers. The sessions will be audiotaped.

Ranking of Statements Using Q-Methodology

At the end of the study period, we will explore the opinions and concerns of the GP staff about the usefulness, benefits, and drawbacks of patient access to the professional summary of their record through the standalone PHR using Q-methodology [66-68]. Q-methodology is primarily a qualitative research method. However, it is a combination of quantitative and qualitative techniques used to identify shared opinions. Similar to other qualitative research methods, purposive sampling is used to obtain a sample of participants with variations in potentially relevant characteristics, for example, age or profession. Participants of a Q-study rank a set of statements on a response grid according to the extent they agree (+1 to +5), feel neutral (0), or disagree with each statement (−1 to −5). Using factor analysis (quantitative technique), the patterns of opinions among participants who share characteristics may be revealed [66,67]. We will formulate statements based on findings from the focus group discussions, think-aloud interviews, semistructured interviews, questionnaires, and literature.

Analysis

Analysis of Quantitative Data at the Patient Level

Descriptive statistics will be used to describe the characteristics of the users and nonusers for each group of participants. To assess whether nonusing and using responders are representative of polypharmacy patients, parents of young children, and other patients in the 3 practices, we will compare their characteristics with those of the population they were obtained from using two sample *t* tests for continuous variables and chi-square tests for categorical variables. We will perform multiple linear regression analyses to investigate the effects of age, sex, education level, perceived health, health literacy, and internet and eHealth use on the adoption of the PHR and access to the summary record, defined as having logged in at least once to the PHR and the summary record. We will use descriptive analyses for data derived from the questionnaires about perceived usefulness, experiences, opinions, and concerns and for log in data on the number of days (hit days) the users have accessed their GP records and viewed different parts of the records during the study period. For each group of patients, we will compare the means changes in in-person levels of playing an active role in decision making and in the management of condition and medication adherence over the 6-month study period between users and nonusers using two sample *t* tests. Similarly, we will analyze the secondary outcomes. We will use a P value <0.05 (two sided) as a criterion for statistical significance for all analyses. Because of the explorative character of our study, we will not correct for multiple testing using a more stringent P level. We will deal with the problem regarding multiple testing in the interpretation of results by primarily focusing on the primary outcomes and by integrating the qualitative findings with the results of quantitative comparisons. SPSS Statistics software (IBM Corp, Armonk, NY, United States) will be used for the analyses.

Analysis of Qualitative Data at the Patient Level

Focus group discussions, think-aloud observations, and semistructured interviews will be transcribed verbatim. Using the ATLAS.ti software (ATLAS.ti Scientific Software Development GmBH, Berlin, Germany), two researchers will code the data independently using open coding as well as coding within the predetermined topics: barriers and facilitators for uptake as well as concerns about privacy and security, usability, usefulness, benefits, and disadvantages. Within the topic usability, we will explore the accessibility of the system and ease to navigate through the PHR and the summary of the GP records. We define usefulness of access to the summary records as the understandability, credibility, and desirability of the information that was viewed. We consider usefulness of the PHR as the extent to which patients value the functionalities to store and share information through the PHR. We consider benefits as positive experiences resulting from the use of the PHR and accessing the summary record. The codes will be categorized into themes that will be defined by the research team in an iterative process. Using the framework approach for the analysis of qualitative data [69,70], we will search for patterns that we will use to complement and interpret our quantitative findings on fidelity, dose, reach, and effects.

Analysis of the Qualitative Data at the General Practice Staff Level

The focus group discussions with the GP staff will be transcribed verbatim and coded independently by two researchers. In an iterative process, the codes will be categorized and the themes and subthemes and potential patterns will be distinguished. We will analyze the Q-sorts using the PQMethod software (PQMethod, GNU GPL, Peter Schmolck, Munich, Germany). To identify the shared views among the groups who ranked the statements similarly, a by-person factor analysis of the Q-sorts will be performed. Of each of the resulting factors, a composite Q-sort will be produced, representing the ranked statements of a hypothetical person with a 100% factor loading on this factor. Two researchers will analyze the composite Q-sorts (factor arrays), comparing the statements that are ranked in the extremes of the grids and in the more neutral positions between the different factor arrays. Together, they will interpret identified shared views between certain groups of participants. The results of the focus group analysis and Q-methodology analysis will be used to complement findings at the patient level.

Ethical Approval

Ethical approval has been requested and granted under file number 2016-2942 by the research ethics committee of the Radboud University Nijmegen Medical Center based on the Dutch Code of Conduct for Health Research, the Dutch Code of Conduct for Responsible Use, the Dutch Personal Data Protection Act, and the Medical Treatment Agreement Act.

Results

Enrollment was completed in May 2017 and the possibility to view GP records through the PHR was implemented in December 2017. Data analysis is currently underway and the first results are expected to be submitted for publication in autumn 2019.

Discussion

Relevance

In this paper, we have described the protocol for studying patient access to GP records through a standalone PHR. To obtain a comprehensive understanding of the effects of this complex intervention, we designed a mixed-methods study of patients in general practice and GP staff, allowing us to assess the facilitators and barriers for the adoption of the intervention, actual use (reach, dose, and fidelity) of the intervention, and experiences and effects on patient involvement. To the best of our knowledge, this is the first study in the Netherlands to investigate patient Web-based access to summary records and use of a PHR in general practice. In addition, few studies on this topic have been carried out in Europe [71-74]. The uptake and effects of and experiences with Web-based access to medical records have been explored more extensively in the United States [26,36,75,76]. However, because the barriers and facilitators for the uptake and effects of Web-based access to medical records are likely to be determined using different factors, including social and cultural, the findings from studies

conducted in the United States may not be applicable to the European context.

Strengths and Limitations

Our protocol has some strengths and limitations. We consider the use of a clear conceptual framework as a strength of the study, even though drawing on two theories (the Unified Theory of Acceptance and Use of Technology and Snyder's model on patient involvement), it is a rather complex framework [1,25]. This framework has helped us include all variables that are likely to be relevant to our study, and it will also guide the interpretation of findings. The mixed-methods design enables us to assess the uptake and potential effects and obtain a deeper understanding of the use and nonuse of the intervention and the effects or absence of the effects [32]. Another strength is that we will conduct the study at two levels, patient level and GP staff level. GP staff is likely to influence the use and impact of the intervention among patients. Because the relationship between patients and GP staff may change due to the intervention, it is important to obtain information from both patients and GP staff. Another strong point of this study is the use of validated instruments to assess the effects of the intervention. However, these instruments have not been validated among parents of young children. Therefore, we will need to interpret the results based on the questionnaires on the effects on involvement-related outcomes in parents with great care. Multiple testing may be another limitation of our study. We will deal with this in the interpretation of our results by focusing on the primary outcomes and aligning qualitative findings with the results of the comparisons. We will conduct this study in the practices of GPs who are open to innovation and willing to provide their patients access to their records. We are aware that this setting is not representative of Dutch general practice. In addition, we are aware that our findings about adoption will need to be interpreted with caution because our participants, particularly those who take part in the focus group discussions, think-aloud observations, or semistructured interviews, will receive more information about the PHR and its use, than is likely to occur in a real-life setting. Furthermore, we realize that not including patients older than 75 years may also influence our findings. Obviously, we will take this into account during the interpretation of our results.

Implications for Clinical Practice or Further Research

We expect this proof-of-principle study to be useful for policy makers, patient organizations, and HCPs who want to increase patient-centered care and patient involvement through PHRs or portals that provide patients access to medical records. Further research will be necessary to assess the uptake, use, and effects of patients' access to different parts of their medical records using PHRs on their health outcomes in various European settings.

Conclusion

We described the protocol of a study that will be used to explore the uptake, use, and effects of patients' access to the summary of their GP records, through a standalone PHR, on their involvement and will be conducted among GP staff, polypharmacy patients, parents of young children, and other adult patients in the Netherlands. Taking into account the complexity of the intervention, we designed a mixed-methods study that will allow us to assess for the reach, dose, fidelity, and potential effects of using PHR on patient involvement in their care. The findings of this study will add to the existing knowledge about the implementation of PHRs and Web-based access to records in primary care and, therefore, are likely to be useful for HCPs, patient organizations, and policy makers.

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Authors' Contributions

All authors have been involved in the design of the protocol. MMTV drafted the manuscript. RBK, KvB, WJJA, and JAMK critically revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DigiD: Digital identification code
GP: general practitioner
GP records: general practice records
GP staff: general practice staff
HCP: health care provider
PEPPI-5: Perceived Efficacy in Patient-Doctor Interactions scale
PHR: personal health record
PIH: Partners in Health scale
MARS-5: Medication Adherence Report Scale
SBSQ-D: Dutch version of the Set of Brief Screening Questions

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Protocol

Effect of Peripheral Defocus on Axial Eye Growth and Modulation of Refractive Error in Hyperopes: Protocol for a Nonrandomized Clinical Trial

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Abstract

Background: Hyperopia occurs due to insufficient ocular growth and a failure to emmetropize in childhood. In anisohyperopia, it is unclear why one eye may remain hyperopic while the fellow eye grows toward an emmetropic state. Animal studies have shown that manipulating peripheral defocus through optical means while simultaneously providing correct axial focus can either discourage or encourage axial eye growth to effectively treat myopia or hyperopia, respectively. Myopia progression and axial eye growth can be significantly reduced in children and adolescents through the use of multifocal contact lenses. These contact lenses correct distance central myopia while simultaneously imposing relative peripheral myopic defocus. The effect of correcting distance central hyperopia while simultaneously imposing relative peripheral hyperopic defocus is yet to be elucidated in humans.

Objective: The objective of our study is to understand the natural progression of axial eye growth and refractive error in hyperopes and anisohyperopes and to establish whether axial eye growth and refractive error can be modified using multifocal contact lenses in hyperopes and anisohyperopes.

Methods: There are 3 elements to the program of research. First, the natural progression of axial eye growth and refractive error will be measured in spectacle-wearing hyperopic and anisohyperopic subjects aged between 5 and <20 years. In other words, the natural growth of the eye will be followed without any intervention. Second, as a paired-eye control study, anisohyperopes aged between 8 and <16 years will be fitted with a center-near multifocal design contact lens in their more hyperopic eye and a single-vision contact lens in the fellow eye if required. The progression of axial eye growth and refractive error will be measured and compared. Third, subjects aged between 8 and <16 years with similar levels of hyperopia in each eye will be fitted with center-near multifocal design contact lenses in each eye; the progression of axial eye growth and refractive error in these subjects will be measured and compared with those of subjects in the natural progression study.

Results: Recruitment commenced on 6 June 2016 and was completed on 8 April 2017. We estimate the data collection to be completed by April 2020.

Conclusions: This trial will establish whether axial eye growth can be accelerated in children with hyperopia by imposing relative peripheral hyperopic defocus using center-near multifocal contact lenses.

Trial Registration: ClinicalTrials.gov NCT02686879; https://clinicaltrials.gov/ct2/show/NCT02686879 (Archived by Webcite at http://www.webcitation.org/71o5p3fD2)

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KEYWORDS

hyperopia; axial eye growth; amblyopia; hyperopic defocus; anisohyperopia

Introduction

Background

Uncorrected hyperopia can cause blurring of distance vision and near vision and is a known risk factor for the development of strabismus and amblyopia [1]. There is a growing body of evidence that uncorrected hyperopia, in addition to visual consequences, may have a negative impact on educational attainment [2,3] and visuocognitive and visuomotor skills [4]. Hyperopia has received much less attention from research than myopia even though the impact of moderate to high levels of hyperopia, especially in one eye (anisohyperopia), can lead to amblyopia if not fully corrected at a young age [5]. Hyperopia occurs as a consequence of insufficient ocular growth and a failure to emmetropize in childhood, with the majority of hyperopic refractive errors resulting from an eye that is too short for its refractive power [6]. In anisohyperopia, it is unclear why one eye may remain hyperopic while the fellow eye grows toward an emmetropic state. Myopic eyes typically exhibit relative hyperopic blur in the periphery [7,8], which is thought to be a precursor of the development of myopia [9]. Studies on animals have suggested that manipulating peripheral defocus through optical means while simultaneously providing correct axial focus can either discourage or encourage axial eye growth to effectively treat myopia or hyperopia, respectively [10].

It has been established that myopia progression and axial eye growth can be significantly reduced in children and adolescents through the use of bifocal or dual-focus contact lenses [11-13]. These contact lenses are designed to correct distance central myopia while simultaneously imposing relative peripheral myopic defocus. This intervention relies on active accommodation, and the myopia control studies have shown that children accommodate normally with multifocal contact lenses [11]. In contrast to the myopic eye, the hyperopic eye tends to exhibit relative peripheral myopia [8].

This study explores the use of center-near multifocal design contact lenses to correct distance central hyperopia while simultaneously imposing relative peripheral hyperopic defocus. The aim is to determine, for the first time, whether axial eye growth can be accelerated in children with hyperopia and anisohyperopia to reduce the refractive error and improve visual outcome.

Study Objectives

The objectives of our study are to understand the natural progression of axial eye growth and refractive error in hyperopes and anisohyperopes, and to establish if axial eye growth and refractive error can be modified using center-near multifocal design contact lenses in hyperopes and anisohyperopes to improve visual outcome.

Methods

Study Design

There will be 3 elements to the proposed program of research:

1. *Natural progression*: Refractive error and axial eye growth will be followed over a 3-year period in hyperopic and anisohyperopic participants aged between 5 and <20 years to gain an understanding of the natural progression of these parameters in the specified cohort. This arm of the study does not involve an intervention.
2. *Hyperopic intervention*: For this part of the study, refractive error and axial eye growth will be followed in participants aged between 8 and <16 years over a 6-month period, after which the participants will wear bifocal soft contact lenses daily for 2 years. The intervention will then be withdrawn before the final data collection point 6 months later. The center-near design contact lenses will provide clear central vision at both distance and near, thus, exposing the retina to peripheral hyperopic defocus from the distance zone.
3. *Anisohyperopic intervention:* Anisometropes represent a unique example of ocular development, where the two eyes of an individual, with an identical genetic background and seemingly subject to identical environmental influences, can grow asymmetrically to produce significantly different refractive errors. Axial eye growth and refractive error will be followed in participants aged between 8 and <16 years over a 6-month period before being fitted with a center-near design bifocal soft contact lens in their more hyperopic eye, while the fellow eye will be fitted with a single-vision contact lens if required. The contact lenses will be worn daily for 2 years. The intervention will then be withdrawn before the final data collection point 6 months later. If and when the refractive error in the more hyperopic eye has reached a level similar to that in the less hyperopic eye (<0.25 diopter [D] interocular difference), both eyes will be fitted, if necessary, with bifocal center-near design contact lenses in line with the protocol for participants in the hyperopic intervention group.

For the study, healthy hyperopic children and adolescents will be recruited via the researchers' optometry practices and Aston University's Eye Clinic. A database search will be performed by the immediate research team to identify potential participants who meet the criteria for inclusion; these individuals will be contacted via post with information regarding the study and how to participate. A poster will also be displayed at both research venues as a means of recruiting other potential participants. Contact details will be stated on the poster to enable anyone interested in joining the study to contact the researcher for further details.

All participants, including parent(s) or guardian(s), expressing an interest in joining the study or wishing to recruit their child into the study will be provided detailed information regarding the study and will have the opportunity to ask questions before completing the consent form declaration.

Allocation to the contact lens-wearing and the natural progression arms of the study will not be randomized. Individuals who are willing and able to use contact lenses will be given the opportunity to be included in the contact lens arm of the study; those who do not want to wear, are unable to handle, or unsuitable for contact lenses will be given the opportunity to participate in the natural progression arm of the study.

After obtaining informed consent, all participants will undergo a number of visual assessments including a background questionnaire, axial length measures, subjective refraction, accommodative lag, amplitude of accommodation, stereopsis, vision and visual acuity, postcycloplegic objective refraction, postcycloplegic peripheral refraction at 30° temporally and nasally, and 20° superiorly and inferiorly, and pupil size.

For the natural progression study, the normal growth of the eyes will be followed at 7 visits over 3 years without any intervention. A topical cycloplegic (cyclopentolate hydrochloride 1%) will be used on visits 1, 2, 4, 6, and 7 (Table 1).

Participants in the intervention arms of the study will also have the normal growth and visual characteristics of the eyes followed at 7 visits over 3 years. In addition, they will have their suitability for contact lens wear determined at the second visit, 6 months after the first visit, which will require instructions on contact lens wear and follow-up appointments. In total, for participants in the intervention arms of the study, there will be 9 scheduled visits, with a cycloplegic used on visits 1, 2, 6, 8, and 9 (Table 2). There may be unscheduled visits if any problems arise as a result of contact lens wear. The participants, with parental support where necessary, will be instructed on how to insert, remove, and care for their contact lenses.

Table 1. Procedures for participants in the natural progression arm of the study.

Procedure	Visit 1 (month 1)	Visit 2 (month 6)	Visit 3 (month 12)	Visit 4 (month 18)	Visit 5 (month 24)	Visit 6 (month 30)	Visit 7 (month 36)
Informed consent	✓	✓	✓	✓	✓	✓	✓
Questionnaire	✓	✓	✓	✓	✓	✓	✓
Axial length	✓	✓	✓	✓	✓	✓	✓
Subjective refraction	✓	✓	✓	✓	✓	✓	✓
Accommodative lag	✓	✓	✓	✓	✓	✓	✓
Amplitude of accommodation	✓	✓	✓	✓	✓	✓	✓
Stereopsis	✓	✓	✓	✓	✓	✓	✓
Vision and visual acuity	✓	✓	✓	✓	✓	✓	✓
Postcycloplegic refraction	✓	✓		✓		✓	✓
Peripheral refraction	✓	✓		✓		✓	✓

Table 2. Procedures for participants in the intervention arms of the study.

Procedure	Visit 1 (month 1)	Visit 2 (month 6)	Visit 3 (month 7)	Visit 4 (month 8)	Visit 5 (month 12)	Visit 6 (month 18)	Visit 7 (month 24)	Visit 8 (month 30)	Visit 9 (month 36)
Informed consent	✓	✓			✓	✓	✓	✓	✓
Questionnaire	✓	✓			✓	✓	✓	✓	✓
Axial length	✓	✓			✓	✓	✓	✓	✓
Subjective refraction	✓	✓			✓	✓	✓	✓	✓
Accommodative lag	✓	✓			✓	✓	✓	✓	✓
Amplitude of accommodation	✓	✓			✓	✓	✓	✓	✓
Stereopsis	✓	✓			✓	✓	✓	✓	✓
Vision and visual acuity	✓	✓			✓	✓	✓	✓	✓
Postcycloplegic refraction	✓	✓				✓		✓	✓
Peripheral refraction	✓	✓				✓		✓	✓
Pupil size					✓				
Contact lens fitting		✓							
Contact lens aftercare			✓	✓	✓	✓	✓	✓	

For the anisohyperopes, the more hyperopic eye will be fitted with a commercially available soft multifocal contact lens and the less hyperopic eye will be fitted with a soft single-vision contact lens, if required. Participants with similar levels of hyperopia in each eye will be fitted with commercially available soft multifocal contact lenses in both eyes.

For anisohyperopic subjects, if the level of hyperopia in the more hyperopic eye reduces to a level which is similar to that of the less hyperopic eye, both eyes will be fitted with multifocal contact lenses if sufficient hyperopia remains, in line with the inclusion criteria for the second arm of the study.

For nonanisohyperopic subjects, the intervention will be stopped when the refractive error has reached a mean spherical error of +0.50 D. At the end of an intervention period of 24 months, contact lens wear will cease and the participants will be assessed for the final time after an interval of 6 months.

Inclusion Criteria

To be included in the study, the participants had to be aged between 5 and <20 years at the initial examination for the natural progression study and between 8 and <16 years at the initial examination for the intervention study. Furthermore, the parents must have read, understood, and signed the informed consent form, and the participants must have read, understood, and signed the assent form. The participants in the intervention groups had to agree to wear the prescribed contact lenses for a minimum of 10 hours per day, at least 6 days per week, for the 2-year duration of the intervention period and be in good general health with no contraindications to contact lens wear. Additionally, the following criteria had to be met: maximum manifest spherical refractive error of +6.00 D, maximum manifest cylindrical refractive error of −1.00 D, minimum anisometropia of >1.00 D in the anisohyperopic group (mean spherical error), maximum anisometropia of 1.00 D in the nonanisohyperopic group (mean spherical error), and minimum mean spherical refractive error of +2.00 D in the more hyperopic eye. Furthermore, participants had to be competent at handling contact lenses and understand the instructions provided to ensure safe wear.

Exclusion Criteria

The exclusion criteria were as follows: previous contact lens wear, participation in another clinical study, regular use of medication to treat ocular conditions, current use of systemic medication that may have an impact upon successful contact lens wear or vision, known ocular or systemic disease, findings identified during contact lens assessment that would preclude contact lens wear, and not being able to provide informed consent without the aid of an interpreter, as no funding was available for the provision of interpreter facilities.

Ethical Approval

The study was granted ethical approval by the National Health Service Research Ethics Committee on May 26, 2016, and by Aston University Research Ethics Committee on June 2, 2016. The trial is registered at ClinicalTrials.gov (NCT02686879).

Sample Size

Sample size has been calculated using G*Power (version 3.1.9; Franz Faul, Universität Kiel, Germany) for a significance level of alpha=.05 at 80% power while also allowing for attrition.

Statistical Analyses

All data will be analyzed using the commercially available software SPSS version 23 (IBM, NY, United States) using a repeated-measures mixed analysis of variance design with 1 between-subject factor and 1 within-subject factor. Principal outcomes measures are: change in axial eye growth and change in refractive error.

Results

Recruitment commenced on June 6, 2016, and was completed on April 8, 2017. We estimate the data collection to be completed by April 2020.

Discussion

The prevalence of myopia is increasing at an alarming rate in many parts of the world [14]. Given the association between myopia and increased risk of ocular comorbidity later in life due to excessive axial eye growth [15], the need to arrest myopia progression during childhood is clear.

There is now compelling evidence that axial eye growth and the subsequent myopia progression can be slowed through a range of interventions, including the use of multifocal contact lenses [11-13]. However, despite the lifelong burden and visual consequences of hyperopia commencing in early childhood, there is a paucity of evidence in relation to modulating axial eye growth in this cohort.

If it is possible to slow axial eye growth in myopes by manipulating the peripheral retinal image shell, encouraging axial eye growth in hyperopes using the same rationale is plausible, and this notion is supported by the literature on animal research [10]. Further, peripheral refraction measures differ as a result of retinal shape, with myopes typically exhibiting relative peripheral hyperopia and hyperopes tending to be relatively myopic in the periphery [8]. These characteristics support the proposal to impose relative peripheral hyperopic defocus aimed at stimulating axial eye growth in hyperopes. Indeed, the progression of axial myopia in children is associated with hyperopic relative peripheral defocus [16]. In addition to the primary outcome measures, changes in the relative peripheral refraction as a result of the intervention will be elucidated.

The clinical trial outlined here will determine, for the first time, whether axial eye growth and refractive error can be accelerated in hyperopic children using multifocal contact lenses. The outcome could have far-reaching implications for the visual prognosis of children with hyperopia.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report #1 from the College of Optometrists, London, UK (funder).

[PDF File (Adobe PDF File), 121KB - resprot_v7i9e173_app1.pdf]

Multimedia Appendix 2

Peer-reviewer report #2 from the College of Optometrists, London, UK (funder).

[PDF File (Adobe PDF File), 25KB - resprot_v7i9e173_app2.pdf]

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Abbreviations

D: diopter

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Protocol

Fertility Among Female Survivors of Childhood, Adolescent, and Young Adult Cancer: Protocol for Two Pan-European Studies (PanCareLIFE)

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Abstract

Background: Despite a significant number of studies on female fertility following childhood, adolescent, and young adult (CAYA) cancer, studies establishing precise (dose-related) estimates of treatment-related risks are still scarce. Previous studies have been underpowered, did not include detailed treatment information, or were based on self-report only without any hormonal assessments. More precise assessments of who is at risk for sub- or infertility are needed.

Objective: The objective of our study is to describe the design and methods of 2 studies on female fertility (a cohort study and a nested case-control study) among female survivors of CAYA cancer performed within the European PanCareLIFE project.

Methods: For the cohort study, which aims to evaluate the overall risk of fertility impairment, as well as the risk for specific subgroups of female CAYA cancer survivors, 13 institutions from 9 countries provide data on fertility impairment. Survivors are defined as being fertility impaired if they meet at least one of 8 different criteria based on self-reported and hormonal data. For the nested case-control study, which aims to identify specific treatment-related risk factors associated with fertility impairment in addition to possible dose-response relationships, cases (fertility impaired survivors) are selected from the cohort study and matched to controls (survivors without fertility impairment) on a 1:2 basis.

Results: Of the 10,964 survivors invited for the cohort study, data are available from 6619 survivors, either questionnaire-based only (n=4979), hormonal-based only (n=72), or both (n=1568). For the nested case-control study, a total of 450 cases and 882 controls are identified.

Conclusions: Results of both PanCareLIFE fertility studies will provide detailed insight into the risk of fertility impairment following CAYA cancer and diagnostic- or treatment-related factors associated with an increased risk. This will help clinicians to adequately counsel both girls and young women, who are about to start anticancer treatment, as well as adult female CAYA cancer survivors, concerning future parenthood and to timely refer them for fertility preservation. Ultimately, we aim to empower patients and survivors and improve their quality of life.

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KEYWORDS

fertility; late effects; childhood cancer; female; cohort study; case-control study

Introduction

Advances in diagnosis and treatment of childhood cancer have led to major improvements in 10-year survival rate, which now exceeds 80% [1]. As a consequence, the number of childhood cancer survivors has substantially increased and many of them have reached an age at which they consider parenthood. However, compromised reproductive function is an important and frequently encountered late effect of treatment in female cancer survivors with a high impact on quality of life [2-4]. Alkylating chemotherapy and radiotherapy involving the ovaries have been identified as the 2 main risk factors for fertility impairment, and postpubertal treatment seems to be more gonadotoxic than prepubertal treatment [5,6]. In addition, cranial radiotherapy may also impair fertility, and a possible role for nonalkylating agents must be considered [7].

Despite a significant number of studies on female fertility following childhood and adolescent cancer, studies establishing precise (dose-related) estimates of treatment-related risks are scarce. Previous studies have been underpowered [6,8,9], did not include detailed treatment information [10], or were based on self-report only without any clinical validation [11,12]. In addition, the different methods used to assess fertility (questionnaires, hormonal markers, and ultrasound measurements of the reproductive organs [13,14]), make it difficult to compare studies. More precise assessments of who is at risk, either for immediate and persistent infertility or a shorter-than-anticipated reproductive window, are essential to prevent involuntary childlessness, secondary infertility (ie, incomplete family planning), and increased use of artificial reproductive techniques [15]. Assessments should include both established and relatively new clinical markers, for example, evaluation of menstrual and pregnancy history or levels of follicle stimulating hormone (FSH) and anti-Müllerian hormone (AMH). Moreover, large childhood cancer survivor cohorts with detailed treatment and long-term follow-up data on fertility outcomes are needed to disentangle specific treatment-related fertility risks.

We, therefore, initiated the PanCareLIFE project. This pan-European project, originating from the PanCare network, is a European Union funded project (7th Framework Programme, Theme Health), coordinated by the University Medical Center Mainz (Germany), in which investigators from 10 countries provide data from over 15,000 CAYA cancer survivors [16]. The project is divided into 8 work packages (WP1-WP8), each with distinct activities, and addresses 3 research topics (ototoxicity, fertility, and quality of life). PanCareLIFE strives for survivors of childhood, adolescent, and young adult (CAYA) cancer to enjoy the same quality of life and opportunities as their peers who have not had cancer. The aim of this study is to describe the design, methods, and participating cohorts of 2 PanCareLIFE studies in WP3 (led by Amsterdam UMC, Vrije Universiteit, AUMC) on female fertility, a cohort study and a nested case-control study.

Methods

The PanCareLIFE Female Fertility Cohort Study

The aim of the female fertility cohort study is to evaluate the overall prevalence of fertility impairment among female CAYA cancer survivors who are at least 5 years past diagnosis and alive at the time of study assessment. Moreover, it aims to assess the prevalence of fertility impairment for specific subgroups of female CAYA cancer survivors based on cancer diagnosis, type of treatment (simple, yes or no, information on chemotherapy, radiotherapy, and surgery), age at treatment, and calendar period of treatment.

In total, 13 institutions from 9 countries (Germany, Czech Republic, Netherlands, Italy, Switzerland, France, United Kingdom, Norway, and Israel) collect cross-sectional data for the PanCareLIFE female fertility cohort study. These institutions, referred to as data providers, provide data from 16 different institutional cohorts in total. Two of these cohorts are registry-based cohorts (VIVE cohort and the Swiss Childhood Cancer Survivor Study cohort), whereas all other cohorts are hospital-based. Some of these data providers have previously collected their data as part of a local fertility study [3,8,17-21], whereas other data providers collect their data specifically during the PanCareLIFE project. All survivors included in the PanCareLIFE female fertility cohort study were treated between 1963 and 2014. However, each of the 16 cohorts encompasses a specific time period of treatment, as identified by the data providers. In addition, although most cohorts included all types of cancer diagnoses, some cohorts only included survivors who were diagnosed with a specific type of cancer (Table 1; see Multimedia Appendix 1 for an expanded version).

Study Population

The eligibility criteria for the female fertility cohort study as well as the different survivor groups identified based on eligibility and type of response are described in Figure 1. The base cohort includes all survivors meeting the inclusion criteria. Survivors who subsequently meet one of the exclusion criteria are deemed ineligible and are not invited for the study (excluded subjects). All remaining women have either been invited to participate in a local fertility study in the past or are specifically invited to participate in the PanCareLIFE female fertility study (invited subjects).

Those who do not respond to the invitation as well as those who actively refuse to participate are categorized as nonparticipants. Participants are defined as those who agree to participate by providing either questionnaire data only, hormonal data only, or both. All local ethical committees have approved the use of the collected data from their institute for the PanCareLIFE project.

Data Collection

For all women in the base cohort demographic, diagnostic and treatment-related data are collected from medical record files and registries. Basic demographic data include month and year of birth and of latest follow-up. Diagnostic data include type of diagnosis (based on the 3rd version of the International Classification of Childhood Cancer) [22] and month and year of diagnosis. Treatment-related data comprise surgery (yes or no), chemotherapy (yes or no), radiotherapy (yes or no), and bone marrow transplantation (yes or no) complemented with the starting month and year of each treatment. Diagnostic and treatment data are collected for all malignancies and possible relapses.

Data on fertility impairment are collected by questionnaire and hormonal assessments. A specific PanCareLIFE fertility questionnaire is developed for those data providers who collect questionnaire data on fertility issues during the PanCareLIFE project. This questionnaire evaluates sociodemographic and menstrual cycle characteristics, menopausal status, use of oral contraceptives and hormones, reproductive history, and smoking and alcohol behaviors. The questionnaire is translated from the original English into German, Czech, Italian, and Hebrew. All translated questionnaires are back-translated into English (by another translator) to check if the translation is performed properly.

Questionnaire data from questionnaires used by data providers for previous local fertility studies address fertility issues using different questions at different levels of detail and with different answer categories. Therefore, a specific task for WP3 investigators is to recode the relevant data from these questionnaires for compatibility with the variables used in the PanCareLIFE fertility questionnaire in close collaboration with the relevant data provider to make them as compatible as possible.

Hormonal measurements primarily involve the assessment of AMH levels. Study participants are asked to provide a blood sample during a clinic visit (which takes place either as part of standard follow-up care or is specifically scheduled for the study). Part of the sample is centrifuged and stored at −20°C. Subsequently, serum samples are transported in batches by courier to AUMC, where AMH levels are determined centrally in the endocrine laboratory. An ultrasensitive Elecsys AMH assay is used (Roche Diagnostics GmbH, Mannheim, Germany) with an intraassay coefficient of variation of 0.5%-1.8%, a limit of detection of 0.01 µg/L, and a limit of quantitation of 0.03 µg/L [23]. FSH levels are accepted if they have been measured within the previous 2 years or during standard patient care throughout the course of the PanCareLIFE project. FSH measurements are done locally and the results are sent to AUMC. Specifics about the timing of blood sampling, that is, during a natural menstrual cycle, during hormonal contraceptive therapy or hormone replacement therapy, during the pill-free interval, performed anytime (no cycle), during pregnancy, or unknown, are provided.

Data providers collect all data from their own survivor cohort, enter them into a local study database (under a unique PanCareLIFE-ID number), anonymize the data, check the quality of the data, and then send the data to the coordinating PanCareLIFE data center in Mainz. In this center, all subjects are assigned a new unique identification number. Subsequently, the data are compiled and sent to the WP3 investigators at AUMC, as seen in Multimedia Appendix 2.

Table 1. Characteristics of cohorts included in the cohort study and the nested case-control study.

Data provider or institute	Study cohort	Data	Women invited (n=10,964) of total base cohort[a] (N=14,379), n/N	Questionnaires provided (N=6547), n	Serum samples provided (N=1640), n	Time period of data collection
DCOG LATER (Amsterdam UMC, Erasmus Medical Center Rotterdam)[b], Netherlands	DCOG LATER cohort[c] [17]	PR[d]	1684/2190	1109	619	2004-2014
Netherlands Cancer Institute Amsterdam, Netherlands	Hodgkin Lymphoma cohort [19,21]	PR	275/450	203	0	1997-2016
Universitätsklinikum Bonn, Germany	VIVE cohort[c]	PR	4467/5909	2482	0	2014-2015
Westfaelische Wilhelms-Universitaet Muenster[b], Germany	Ewing 2008 Clinical Trials cohort	DU[e]	140/161	46	24	2015-2016
Charité - Universitätsmedizin Berlin, Germany	Berlin Hormone Analyses cohort[c] [3]	PR	344/402	83	69	2008-2009
Fakultni nemocnice Brno[b], Czech Republic	Cohort female 5-yr cancer survivors Brno[c]	DU	203/283	182	180	2015-2016
Fakultni nemocnice v Motol[b], Czech Republic	Cohort female 5-yr cancer survivors Motol[c]	DU	1063/1398	574	301	2014-2016
Istituto Giannina Gaslini[b], Italy	Gaslini female survivors cohort[c]	DU	814/1111	563	122	2015-2016
University of Bern, Switzerland	Swiss Childhood Cancer Survivor Study cohort 1[c] [18]	PR	977/1135	685	0	2007-2013
University of Bern, Switzerland	Swiss Childhood Cancer Survivor Study cohort 2[c] [18]	PR	228/335	113	0	2015-2016
Great Ormond Street Children's Hospital/University College London Hospital[c], United Kingdom	Hematopoietic stem cell transplantation cohort[c]	DU	93/95	50	44	2015-2016
Oslo University Hospital[b], Norway	Lymphoma survivor cohort [8]	PR	82/Unknown	51	46	2007-2009
Oslo University Hospital[b], Norway	Acute lymphoblastic leukaemia survivor cohort [21]	PR	103/175	82	65	2009-2010
University hospital Saint-Étienne[b], France	Rhone Alpe cohort 1[c]	PR	120/212	120	35	2005-2013
University hospital Saint-Étienne[b], France	Rhone Alpe cohort 2[c]	PR	220/284	102	62	2015-2016
Edmond and Lily Safra Children's Hospital, Sheba Medical Center[b], Israel	The Edmond and Lily Safra Children's Hospital Late Effects cohort[c]	DU	151/239	102	73	2015-2016

[a]Base cohort is the subjects fulfilling inclusion criteria of study.

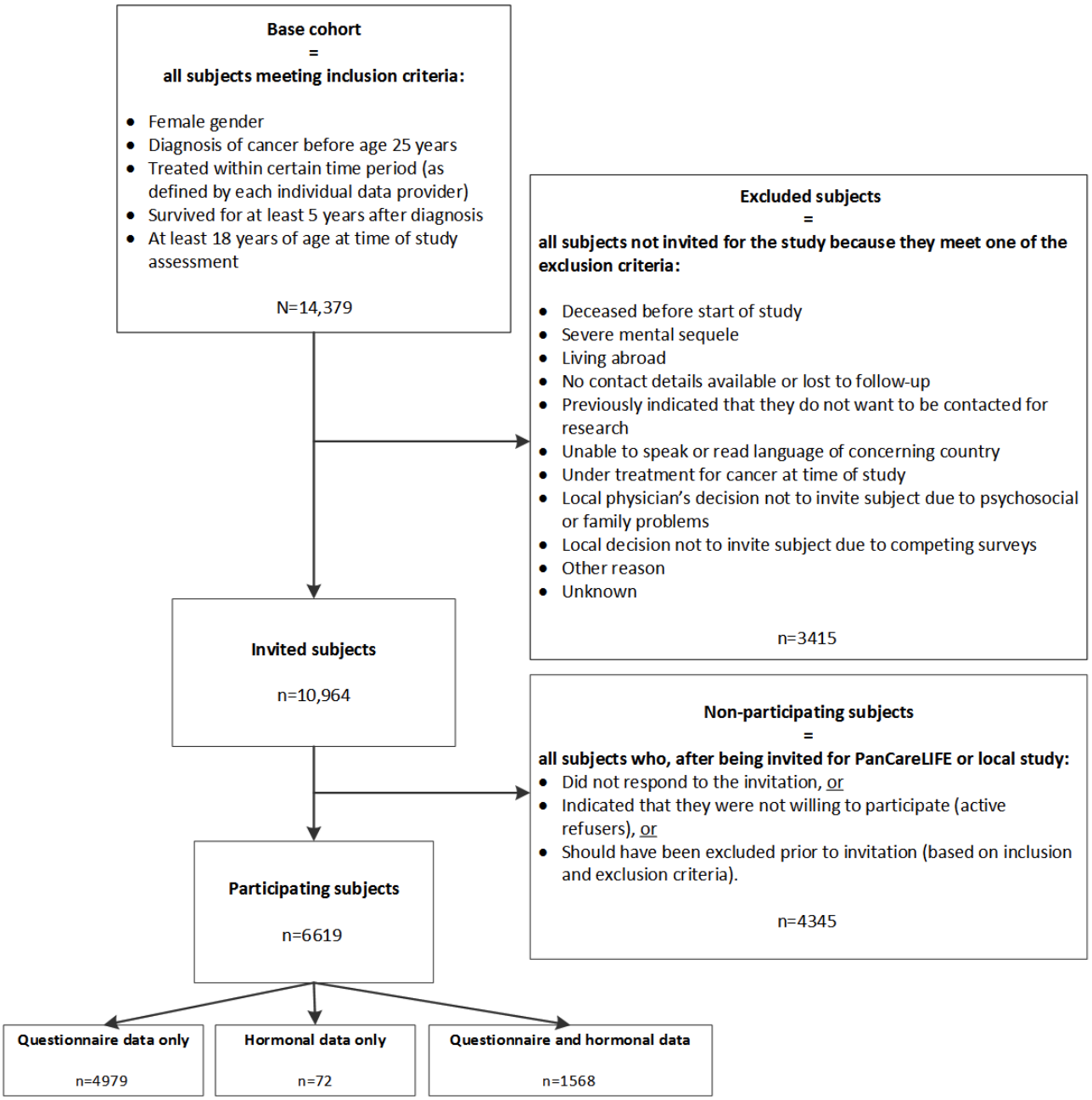
[b]Institutes participating in the nested case-control study.

[c]Various cancer diagnoses.

[d]PR: data collected prior to PanCareLIFE project.

[e]DU: data collected during PanCareLIFE project.

Figure 1. Flow chart of eligible, invited, and participating subjects of the 2 fertility studies within the PanCareLIFE project.



Definition of Primary Outcome

The primary outcome of the cohort study is *fertility impairment*. However, given the fact that the fertility data come from different sources, it is difficult to apply one standardized outcome definition of fertility impairment to all participating cohorts in the cohort study. Therefore, fertility impairment is defined according to 8 criteria based on self-reported and hormonal data (criteria 1, 2, and 6), hormonal data only (criterion 3), or on self-reported data only (criteria 4, 5, 7, and 8). These criteria were established by WP3 with a reproductive specialist (C.B. Lambalk). A survivor is classified as being fertility impaired if she meets at least one of the 8 criteria, as described in Textbox 1.

Low AMH is defined as an AMH level <0.5 µg/L [24]. For criteria 1 through 3, AMH is used to validate self-reported amenorrhea (criteria 1 and 2) or a high FSH level (criterion 3). When AMH levels are used for such validation purposes, levels obtained from serum samples drawn from a participant using any type of hormones are included. However, if only AMH levels are used to decide whether a survivor is fertility impaired or not, like in criterion 6, levels obtained from serum samples drawn during hormonal use are excluded. This is done because previous reports, although inconclusive, have shown that use of contraceptive hormones may significantly decrease AMH levels [25,26]. FSH levels are considered high when they are >30 U/L in a serum sample drawn during the midcycle peak (cycle day 12-16), >15 U/L in a sample drawn at any other moment during the menstrual cycle in case of amenorrhea, or if the survivor uses hormones at time of serum sampling [27]. When there is no information on the timing of the serum sampling, FSH levels are considered high if they are >30 U/L.

Textbox 1. Criteria used to define fertility impairment.

- Criterion 1: Primary amenorrhea (never had menses) in combination with a high follicle stimulating hormone (FSH) and/or a low anti-Müllerian hormone (AMH) level.
- Criterion 2: Secondary amenorrhea (no menses for >12 months before the age of 40) in combination with a high FSH and/or a low AMH level.
- Criterion 3: High FSH level in combination with a low AMH level, while being <40 years of age at time of study assessment.
- Criterion 4: Primary amenorrhea (without information on AMH or FSH level).
- Criterion 5: Secondary amenorrhea (without information on AMH or FSH level).
- Criterion 6: Low AMH level and <30 years of age at time of study assessment and not using exogenous reproductive hormones at time of blood sampling.
- Criterion 7: Use of artificial reproductive techniques (excluding those who reported male factor as the single cause of subfertility) and being <40 years of age at time of study assessment.
- Criterion 8: Tried to conceive for at least 12 consecutive months without success and being <40 years of age at time of study assessment.

Planned Data Analyses

The overall prevalence of fertility impairment will be defined as the number of participating survivors who are fertility impaired divided by the total number of participating survivors. The prevalence of fertility impairment will also be calculated for subgroups based on cancer diagnosis, type of treatment (chemotherapy, +/− surgery; radiotherapy, +/− surgery; both chemo- and radiotherapy, +/− surgery; and surgery only), age group at treatment, and calendar period at treatment. In addition, the prevalence of fertility impairment according to each of the different criteria will be calculated along with that of fertility impairment based on the criteria that evaluate ovarian function (criteria 1 to 6) and possible difficulties getting pregnant (criteria 7 and 8).

Multivariable logistic regression analysis will be used to investigate which diagnostic- or treatment-related risk factors influence the probability of being fertility impaired. All analyses will be adjusted for possible confounders, such as age at the time of study assessment, time since diagnosis, smoking status, BMI, and use of hormonal contraception. Furthermore, to detect possible selection bias, descriptive statistics will be used to describe any differences in age at time of study assessment, age at diagnosis, cancer diagnosis, time since diagnosis, and type of treatment between participants, nonparticipants, and excluded women, as seen in Figure 1. All statistical analyses will be performed by investigators of WP3 (AUMC) in close collaboration with the Biostatistical Support Group of both AUMC and University Medical Center Mainz.

The PanCareLIFE Female Fertility Nested Case-Control Study

The case-control study is nested within the cohort study, meaning that both cases and controls are selected from participants of the cohort study. However, only participants from institutions that are able to provide detailed treatment data are potential inclusions for the case-control study. This is the case for participants from 11 out of the 16 cohorts in the cohort study (Table 1).

The aims of the nested case-control study are to identify specific treatment-related factors associated with an increased risk of fertility impairment among CAYA cancer survivors and investigate possible dose-response relationships between cumulative dose of radiation from radiotherapy, cumulative dose of specific anticancer drugs, and the risk of fertility impairment.

Study Population

The minimal sample size to be included in the nested case-control study population is calculated *a priori*. From a previous study, it was expected that 19% of female childhood cancer survivors exposed to potentially gonadotoxic treatment (ie, the *exposed group*) have low AMH levels compared with 4% among survivors who did not receive such treatment [7]. Based on this information, it is decided to include at least 402 cases and 804 controls (1:2 match), thereby allowing subgroup analyses including up to 6 subgroups (n=67 cases per subgroup). This will enable the detection of an odds ratio of 5.63 with a power of 90% using Fishers' exact test within the subgroups.

Cases are defined as women who are fertility impaired, as assessed by the 8 criteria described in Textbox 1; controls are defined as survivors without fertility impairment (ie, all women who do not meet any of the 8 criteria). Controls were matched to cases on the following criteria: country of treatment, age at time of study assessment (±1 year), calendar year of treatment (±3 years), and age at first cancer diagnosis (±2 years).

Prior to identifying the cases it is estimated that using these 8 criteria, substantially more than the 402 required cases will be identified. Therefore, to include the 402 cases that are most likely to actually be fertility impaired, the decision was made to hierarchically structure these 8 criteria. Moreover, in making this hierarchy, we also considered the certainty by which each criterion can establish whether the remainder of the participants (ie, the *noncases*) are actually *not* fertility impaired (true controls). Criterion 1 is considered to reflect fertility impairment with the highest certainty and criterion 8 with the least, considering the ability of each criterion to also identify "true controls." First, women with self-reported (primary or

secondary) amenorrhea validated by a high FSH and/or a low AMH level are selected as cases, followed by women with an established high FSH level together with a low AMH level. Subsequently, women who reportedly have amenorrhea (primary or secondary) with no further information on AMH levels are selected, followed by those with an established low AMH level while being younger than 30 years and not using any hormones. Finally, women who indicate by self-report to have ever used some type of artificial reproductive technique and subsequently those who have ever tried to become pregnant for at least one year without success are selected as cases. Ultimately, for the nested case-control study, each case is identified as a case based on one criterion only. The process of case accrual ends after 402 cases are selected.

Data Collection

Additional data collected for all selected cases and controls include type, number of cycles, and cumulative doses of each chemotherapeutic agent. For radiotherapy data on site, fractionation schedules and cumulative doses are collected.

Planned Data Analyses

Multivariable regression models will be used to investigate which risk factors are most strongly associated with an increased risk of fertility impairment. For this purpose, the associations with individual chemotherapeutic agents and radiotherapy body sites and the risk of fertility impairment will be investigated along with the association with cumulative doses of these chemo- and radiotherapy body sites.

Results

The PanCareLIFE Female Fertility Cohort Study

The total base cohort consists of 14,379 female 5-year CAYA cancer survivors, 10,964 of whom are either invited for one of the local fertility studies in the past (n=8500) or for the PanCareLIFE female fertility study (n=2464) (Table 1). In total, data are available from 6619 survivors, either questionnaire-based only (n=4979), hormonal-based only (n=72), or both (n=1568), as seen in Figure 1. Of all questionnaires provided (n=6547), one-quarter (n=1517) consisted of the standardized PanCareLIFE fertility questionnaire. Serum AMH levels have been successfully determined in all 1640 women who provided a blood sample. FSH levels are available from 1242 women.

Table 2 shows the number of women from all participating cohorts who potentially meet each of the criteria for fertility impairment. For some data providers, fertility impairment cannot be assessed by all 8 criteria because not all necessary questionnaire or hormonal data are available for their study population since data were previously collected in local studies.

Table 2. Number of participants in the cohort study who could potentially meet the criteria of fertility impairment by participating cohort.

Name of study cohort	Criterion 1 (n=1455)	Criterion 2 (n=1566)	Criterion 3 (n=1207)	Criterion 4 (n=3133)	Criterion 5 (n=5861)	Criterion 6 (n=1640)	Criterion 7 (n=2759)	Criterion 8 (n=5050)
DCOG LATER cohort	615	615	614	1109	1109	619	1109	0
Hodgkin Lymphoma cohort	0	0	0	203	203	0	0	0
VIVE cohort	0	0	0	0	2482	0	0	2482
Ewing 2008 Clinical Trials cohort	22	22	2	46	46	24	46	46
Berlin Hormone Analyses cohort	69	69	69	83	83	69	0	0
Cohort female 5-y cancer survivors Brno	180	180	85	182	182	180	182	182
Cohort female 5-y cancer survivors Motole	236	236	198	574	574	301	574	574
Swiss Childhood Cancer Registry cohort 1	0	0	0	0	0	0	0	685
Swiss Childhood Cancer Registry cohort 2	0	0	0	0	113	0	0	113
Lymphoma survivor cohort	0	46	36	0	51	46	51	51
Acute lymphoblastic leukemia survivor cohort	0	65	10	0	82	65	82	82
Rhone Alpe cohort 1	35	35	9	120	120	35	0	120
Rhone Alpe cohort 2	62	62	0	101	101	62	0	0
Gaslini female survivors cohort	122	122	109	563	563	122	563	563
Hematopoietic stem cell transplantation cohort	42	42	40	50	50	44	50	50
The Edmond and Lily Safra Children's Hospital Late Effects cohort	72	72	35	102	102	73	102	102

Table 3. Number of cases and controls identified within study cohorts included in the nested case-control study.

Institute	Study cohort	Cases identified (n=450)	Number of controls matched	
			Controls identified within same cohort (n=801)	Controls identified within DCOG LATER cohort (n=81)
DCOG LATER	DCOG LATER cohort	120	238	N/A[a]
Westfaelische Wilhelms-Universitaet Muenster	Ewing 2008 Clinical Trials cohort	8	15	0
Fakultni Nemocinice Brno	Cohort malignant cancer survivors Brno	17	30	3
Fakultni Nemocnice v Motol	Cohort malignant cancer survivors Motol	128	232	19
Istituto Giannina Gaslini	Gasline female survivors cohort	91	179	2
Great Ormond Street Children's Hospital and University College London Hospital	Hematopoietic stem cell transplantation cohort	28	6	43
Oslo University Hospital	Lymphoma survivor cohort and Acute lymphoblastic leukemia survivor cohort	18	24	12
University hospital Saint-Étienne	Rhone Alpe cohort 1 and Rhone Alpe cohort 2	28	56	0
Edmond and Lily Safra Children's Hospital, Sheba Medical Center	The Edmond and Lily Safra Children's Hospital Late Effects cohort	12	21	2

[a]N/A: Not applicable.

Results show that within the total group of 6619 participants, criterion 1 could be evaluated among 21.98% (1455/6619) of the participants, criterion 2 among 23.66% (1566/6619), criterion 3 among 18.24% (1207/6619), criterion 4 among 47.33% (3133/6619), criterion 5 among 88.55% (5861/6619), criterion 6 among 24.78% (1640/6619), criterion 7 among 41.68% (2759/ 6619), and criterion 8 among 76.30% (5050/6619) of the participants. However, data providers who collect their data during the course of PanCareLIFE collect data for all 8 criteria. This results in a total group of 464 participants for whom all 8 criteria can successfully be evaluated.

All data are collected and entered into local electronic databases by data providers and sent to the coordinating data center in Mainz (WP1). These data are subsequently checked, merged, and cleaned by investigators from WP1 after which a final, aggregated dataset is sent to the investigators of WP3.

The PanCareLIFE Female Fertility Nested Case-Control Study

The selection of cases and controls has been successfully performed using the hierarchically-ordered criteria of fertility impairment. However, ultimately, it appears that this hierarchy can be discarded since, after the application of the 8th criterion, a total of 504 cases have been identified from the total eligible cohort. Of these, 13 cases are excluded, because no treatment data are available, and 41 because no appropriate matching controls can be found. Therefore, ultimately, 450 cases are included in the case-control study. If the cases identified by the last criterion (criterion 8) are not included in the nested case-cohort study, this will lead to fewer than the required 402 cases.

The 450 selected cases are matched to 882 controls. Some cohort cases cannot be matched to 2 controls owing to an insufficient number of controls in that cohort. However, because the Dutch Childhood Oncology Group - Long term Effects after Childhood Cancer cohort (see Table 1) includes more eligible controls than required, this cohort was used as a "back-up" control selection cohort [17]. In total, 9% (81/882) matched controls are selected from this cohort (Table 3). Overall, 2 matching controls are found for 432 cases, whereas for 18 cases, only one matching control could be identified. After the selection of cases and controls has been finalized, data providers are provided with a list of survivors in their cohort for whom they have to collect detailed treatment data.

Data analysis of both the PanCareLIFE cohort study and the case-control study is currently under way and the first results are expected to be submitted for publication in 2019.

Discussion

This paper describes the design and methods of 2 studies on female fertility within the PanCareLIFE project. Due to the large number of institutions collaborating within this project, these studies will encompass the largest group of CAYA cancer survivors among whom female fertility is investigated using both self-reported and hormonal data. Results will provide detailed insight into the prevalence of fertility impairment following CAYA cancer and the diagnostic- or treatment-related factors associated with an increased risk of fertility impairment.

This will help clinicians to adequately counsel both girls or young women who are about to start anticancer treatments as well as adult female CAYA cancer survivors about issues concerning their remaining reproductive life span and the possible need for fertility preservation interventions. Moreover, knowledge gained from the 2 studies can be incorporated into existing evidence-based clinical guidelines on female fertility for CAYA cancer patients and survivors [28,29].

The 2 fertility studies conducted within PanCareLIFE have several strengths. First, the international collaboration, as achieved in PanCareLIFE, has resulted in an unprecedented number of female CAYA cancer survivors for whom data on fertility impairment are available. Large study populations are essential to achieve statistically and clinically meaningful results. Moreover, the large sample size in the PanCareLIFE fertility studies will allow many subgroup analyses. For these analyses, survivors whose former treatment is presumed not to negatively affect fertility (as indicated by the literature available at time of data analyses) can serve as the reference group when calculating effect measures, such as relative risks or odds ratios. Second, within both PanCareLIFE fertility studies, a broad definition of fertility impairment has been employed using several criteria that have frequently been used in previous studies assessing fertility in female CAYA cancer survivors [11,12,30-33]. By doing so, a large set of data, as provided by the data providers, who collected their data prior to the PanCareLIFE project, could be incorporated into the PanCareLIFE fertility studies. Moreover, using a broad definition of fertility impairment will enable calculation of an overall prevalence of fertility impairment and the calculation of the specific criterion-specific prevalence of fertility impairment. Each criterion-specific prevalence can then be compared with those reported in previous studies among CAYA cancer survivors, which used the same definition (ie, criterion) for fertility impairment. Third, some criteria of fertility impairment employed within PanCareLIFE included self-reported outcomes that are validated by hormonal values. Attempts to endorse questionnaire-based fertility data by comparing them with objective hormonal markers is important because it is known that self-reported fertility data, especially on menstrual cycle regularities, have limited association with objective clinical markers [34].

For the cohort study, survivors are considered *fertility impaired* when they meet at least one of 8 criteria. For the nested case-control study, however, a hierarchy is applied to these criteria, meaning that a survivor is defined as a case based on the criterion that established fertility impairment with the presumed highest level of certainty, considering the ability of this criterion to also identify “true controls” (ie, survivors who are definitely *not* fertility impaired based on that criterion by the end of follow-up). The hierarchy applied to the 8 criteria is based on several considerations. Criteria 1 through 3 (primary or secondary amenorrhea combined with a high FSH and/or a low AMH and high FSH combined with a low AMH) are deemed strong indicators of fertility impairment because one marker of (in)fertility (amenorrhea and high FSH, respectively) is validated by another marker (ie, AMH). AMH is currently considered the marker of choice when it comes to measuring ovarian reserve because it seems to be the most stable marker, it is randomly measurable throughout the menstrual cycle and it seems to reflect reduced ovarian function early in the sequence of events leading to menopause [35,36]. Criteria 4 and 5 also include the outcome amenorrhea; however, in the cases of these criteria, it is not validated by FSH or AMH values, making them less certain criteria for fertility impairment because amenorrhea may also be caused by factors other than ovarian follicle depletion [37]. Women less than 30 years of age with an AMH level below <0.5 µg/L (criterion 6) are also considered to be fertility impaired [38]. However, because hormonal contraception use has shown to significantly decrease AMH levels [25], this criterion is evaluated among the nonhormone users only. The final 2 criteria include self-reported measures regarding pregnancy attempts (use of artificial reproductive techniques and unsuccessful pregnancy attempts for at least 12 months, respectively). Both criteria have proven to be good indicators of sub- or infertility [39,40]. They are, however, at the bottom of the hierarchy because they only apply to the subgroup of survivors who have already tried to become pregnant. Consequently, these criteria do not provide any information regarding fertility impairment in those who have not yet attempted to conceive at time of study assessment, as was true for a substantial portion (approximately two-thirds) of the included survivor population. By placing criteria 1 through 6 before 7 and 8, the number of women who are categorized as being fertility impaired based on the criteria that provide information on fertility impairment in the whole cohort, and not just in those who have attempted to become pregnant, is maximized. Moreover, it enables us to easily differentiate between fertility impairment rates of survivors based on all 8 criteria versus criteria 1 through 6 only.

The fertility studies within PanCareLIFE have some limitations. First, due to missing information, some of the data on fertility impairment collected in previous local studies cannot be successfully recoded to make them compatible with the data that are collected with the PanCareLIFE questionnaire. As a consequence, data from some cohorts cannot be considered when calculating the overall prevalence of fertility impairment. Second, our studies may be subject to selection bias because from about 60% of the total invited group of subjects’ outcome data from are available for the cohort study and even less for the nested case-control study. This could impact the generalizability of our study results. To estimate the risk of selection bias, participants will be compared with nonparticipants relative to age at time of study assessment and disease-related characteristics. Third, no information is available on the fertility outcomes of women treated for CAYA cancer who died before the study (after having survived for at least 5 years). Because many of these women might have been treated with relatively high (gonado)toxic treatment regimens, they would most probably have met at least one of the 8 criteria of fertility impairment, were they still living. As a consequence, the risk of fertility impairment calculated based on this study results might be an underestimation of the “true” risk. Furthermore, for some (sub)cohorts, not all self-reported or hormonal data needed to evaluate each of the 8 criteria are available, because these data were not collected during the local fertility study in the past. As a result, survivors within certain

cohorts can be evaluated by one or 2 criteria only. Hypothetically, these women could also have met one of the other criteria. However, because data for these other criteria are lacking, this group of women might be misclassified (ie, categorized as being *not fertility impaired*, whereas in reality, they are), also possibly leading to an underestimation of the overall prevalence of fertility impairment. For future studies, it is of high importance that researchers achieve consensus concerning the assessment of fertility impairment among female CAYA cancer survivors in late effects studies.

In summary, the 2 fertility studies conducted within PanCareLIFE will generate evidence-based knowledge concerning risk factors for impaired fertility among female CAYA cancer survivors as well as valuable information regarding differences in the prevalence of fertility impairment using different criteria to define this impairment. These results will enhance clinical practice because they will help health care practitioners provide adequate counseling concerning future parenthood to CAYA cancer survivors as well as new patients and refer these individuals to a reproductive specialist for fertility preservation in a timely manner. The ultimate objective is to empower patients and survivors and improve their quality of life.

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Authors' Contributions

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Expanded version of Table 1 (characteristics of cohorts included in the cohort study and the nested case-control study).

[PDF File (Adobe PDF File), 72KB - resprot_v7i9e10824_app1.pdf]

Multimedia Appendix 2

Flow of data collected for the two fertility studies within PanCareLIFE project.

[PNG File, 52KB - resprot_v7i9e10824_app2.png]

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Abbreviations

AMH: anti-Müllerian hormone
AUMC: Amsterdam UMC, Vrije Universiteit
CAYA: childhood, adolescent, and young adult
FSH: follicle stimulating hormone
WP: work package

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Corrigenda and Addenda

Metadata Correction: Conceptualization and Implementation of the Central Information Portal on Rare Diseases: Protocol for a Qualitative Study

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Related Article:

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The corresponding author of the paper “Conceptualization and Implementation of the Central Information Portal on Rare Diseases: Protocol for a Qualitative Study” (JMIR Res Protoc 2018;7(5):e112), made a mistake in the final stage of proofreading. The academic degrees of Leena Bruckner-Tuderman, Jörg Schmidtke, TOF Wagner, and Franziska Schauer were incorrectly listed as “PhD”. Instead, the degrees for all four of these authors should be “Dr med”, which represents an academic degree according to the German academic system.

The correction will appear in the online version of the paper on the JMIR website on September 6, 2018, together with the publication of this correction notice. Because this was made after submission to PubMed, Pubmed Central, and other full-text repositories, the corrected article also has been re-submitted to those repositories.

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Protocol

Monitoring Twitter Conversations for Targeted Recruitment in Cancer Trials in Los Angeles County: Protocol for a Mixed-Methods Pilot Study

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Abstract

Background: Insufficient recruitment of participants remains a critical roadblock to successful clinical research, particularly clinical trials. Social media provide new ways for connecting potential participants with research opportunities. Researchers suggest that the social network Twitter may serve as a rich avenue for exploring how patients communicate about their health issues and increasing enrollment in cancer clinical trials. However, there is a lack of evidence that Twitter offers practical utility and impact.

Objective: This pilot study aimed to examine the feasibility and impact of using Twitter monitoring data (ie, user activity and their conversations about cancer-related conditions and concerns expressed by Twitter users in Los Angeles County) as a tool for enhancing clinical trial recruitment at a comprehensive cancer center.

Methods: We will conduct a mixed-methods interrupted time series study design with a before-and-after social media recruitment intervention. On the basis of a preliminary analysis of eligible trials, we plan to onboard at least 84 clinical trials across 6 disease categories: breast cancer, colon cancer, kidney cancer, lymphoma, non-small cell lung cancer, and prostate cancer that are open to accrual at the University of Southern California (USC) Norris Comprehensive Cancer Center. We will monitor messages about these 6 cancer conditions posted by Twitter users in Los Angeles County. Recruitment for the trials will occur through the Twitter account (@USCTrials). Primary study outcomes—feasibility and acceptance of the social media intervention among targeted Twitter users and the study teams of the onboarded trials—will be assessed using qualitative interviews and the 4-point Likert scale and by calculating the proportion of targeted Twitter users who engaged with outreach messages. Second, impact of the social media intervention will be measured by calculating the proportion of enrollees in trials. The enrollment rate will be compared between the active intervention period and the prior 10 months as historical control for each disease trial group. This study has been funded by the National Center for Advancing Translational Science through a Clinical and Translational Science Award. Study approval was obtained from the clinical investigations committee at USC Norris and the institutional review board at USC.

Results: Recruitment on Twitter started in February 2018. Data collection will be completed in November 2018.

Conclusions: This pilot project will provide preliminary data and practical insight into the application of publicly available Twitter data to identify and recruit clinical trial participants across 6 cancer disease types. We will shed light on the acceptance of the social media intervention among Twitter users and study team members of the onboarded trials. If successful, the findings will inform a multisite randomized controlled trial to determine the efficacy of the social media intervention across different locations and populations.

Trial Registration: ClinicalTrials.gov NCT03408561; https://clinicaltrials.gov/ct2/show/NCT03408561 (Archived by WebCite at http://www.webcitation.org/72LihauzW)

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KEYWORDS

breast cancer; cancer; clinical research; clinical trial; colon cancer; kidney cancer; listening; lung cancer; lymphoma; monitoring; outreach; prostate cancer; recruitment; research participation; surveillance; Twitter; social media; social network

Introduction

Background and Rationale

Recruitment of study participants in clinical research, particularly clinical trials, remains a critical roadblock to successful clinical research [1-5]. A recent systematic review found that 76.1% (131/172) of randomized clinical trials (RCTs) discontinued due to poor recruitment [6]. Insufficient and slow participant recruitment delays scientific and medical progress that could benefit patients and increases the financial costs to institutions, industry, and taxpayers [7-9]. According to the National Center for Advancing Translational Sciences (NCATS), "evidence-based strategies to trial participant recruitment and patient engagement" are required to address this challenge [10,11].

With billions of users, social media provides new venues to better connect potential participants with research opportunities in a variety of disease and health contexts [12,13]. The term *social media* describes widely accessible Web-based and mobile technologies that allow users to view, create, and share information and to participate in social networking [14,15]. Users can create a public or semipublic profile and maintain a list of other users they follow or with whom they may share content [16,17]. Nearly 70% of US adults use some type of social media, which varies by factors such as age, gender, race, and ethnicity across a range of social media such as Facebook, YouTube, Pinterest, Instagram, Twitter, LinkedIn, and Snapchat [18-20]. Social media provides an unprecedented opportunity for delivering information to reach large segments of the population [11] as well as hard-to-reach subpopulations that deal "with sensitive, stigmatizing, or rare health conditions" [13,21-24].

Social Media Monitoring

The data that social media users generate by creating and interacting with Web-based information, also referred to as their *digital footprint* [25-28], provide a new data source for research. There has been an increase in using Twitter data for research, for example, to study public health and safety issues [29-33] and to monitor pharmaceutical products, potential drug interactions, and adverse events [34-38]. Social media monitoring (also referred to as *surveillance* or *listening*) describes the use of social media data (ie, user activity and their conversations) to gain insights into their interests, attitudes, and behaviors. In this study, we explore Twitter monitoring as a tool to examine cancer-related conditions and concerns expressed by Twitter users in Los Angeles County.

Using social media monitoring data for targeted clinical trial outreach is considered "active recruitment that occurs when research staff members approach and interact with specific individuals with the aim of enrolling them in research, usually on the basis of knowledge of characteristics that would make them suitable candidates for particular trials" [39]. To date, the clinical research community has focused little attention on the use of social media data in clinical research recruitment, for example, to identify potential study participants who have expressed specific health conditions and concerns and are most likely to participate in a clinical study [40,41]. Furthermore, sponsors have reported the lack of experienced vendors and internal teams as well as clinical research offices as main barriers to the adoption of social media monitoring and outreach strategies [42].

Twitter

Nearly 25% of US adults use the social media platform Twitter with billions of users across the world [18,19]. Twitter allows users to post short messages (tweets) that are limited to 280 characters [43]. Users can search for any public message and further engage with tweets, that is, they can *like*, reply, and *retweet* (share) them. Twitter is primarily a public social network. By default, basic Twitter account information such as the profile name, description, and location is public unless a user decides to opt out and make a private account [44,45].

Twitter and Cancer Communication

Due to the more public nature of Twitter, previous research suggested that Twitter provides a "rich and promising avenue for exploring how patients conceptualize and communicate about their specific health issues" [46]. The increasing use of Twitter among members of the cancer disease community is evidenced by the abundance of cancer-related hashtags used by Twitter users in their messages [46-51]. A hashtag is a user-generated word or phrase preceded by a hash or pound sign (#) and used to identify messages on a specific topic on Twitter. For example, among the most widely recognized hashtags used in Twitter messages for breast cancer are

#breastcancer, #bcancer, and #BCSM (breast cancer and social media) [52]. Researchers also emphasized Twitter as a "powerful and important tool in implementing and disseminating critical messages to the community in real-time" [53,54] and a "way to communicate with the public about cancer clinical trials and increase awareness and enrollment" [55]. A study on lung cancer, for example, found that Twitter messages focused on support, prevention, and clinical trials and were predominantly authored by individuals [55]. However, there is a lack of evidence that Twitter offers practical utility and impact.

Social Media and Clinical Trial Recruitment

More investigators are incorporating social media in their study recruitment strategy for human subjects' research in general and clinical trials with varying results [56-66]. In some cases, they also compared the social media recruitment outcomes to traditional methods [13]. However, the development of evidence-based social media recruitment methods based on the existing data poses challenges and requires more consistent and transparent frameworks for data collection, study design, quality assessment, debiasing techniques for social media data, and systematic reporting standards and clearly defined metrics [67-70]—most of which are currently lacking. In fact, many RCTs published in major journals do not provide adequate information about the patient recruitment process, including how they incorporated and measured social media [71]. As a result, it is difficult to gauge the effectiveness of social media–driven recruitment methods and their cost effectiveness across different disease types, target populations, and social media platforms.

Study Objective and Hypothesis

The objective of this pilot study is to examine the feasibility and impact of using targeted Twitter monitoring as a tool for enhancing and complementing clinical trial recruitment among Twitter users in Los Angeles County at a comprehensive cancer center. In collaboration with the USC Norris Comprehensive Cancer Center (USC Norris) at the University of Southern California (USC), where the study will be implemented, we will conduct a mixed-methods interrupted time series study design with a before-and-after social media recruitment intervention. We plan to onboard all clinical trials open for accrual, at least 84 based on a preliminary analysis of eligible trials for this study in 6 cancer disease categories: breast cancer, colon cancer, kidney cancer, lymphoma, non-small cell lung cancer, and prostate cancer (Multimedia Appendix 1, page 24). We will monitor messages about these cancer conditions posted by Twitter users in Los Angeles County. We hypothesize that Twitter monitoring data serve as a useful tool to enhance and complement clinical trial recruitment efforts, more specifically to identify and recruit participants for cancer trials, which may vary in success based on the cancer disease type, disease-related issues that impact trial eligibility, and other demographic factors.

The study has 2 primary outcomes. First, the feasibility and acceptance of the social media intervention among targeted Twitter users and the study teams of the onboarded trials, which will be assessed through qualitative interviews using a 4-point Likert scale and a number of quantitative measures to calculate the proportion of targeted Twitter users who engaged with outreach messages (measured through Twitter replies, mentions, *likes*, *retweets*, direct messages, following, and contact form use on the trial webpage). Second, the impact of the social media intervention will be measured by calculating the proportion of people who consented and enrolled in trials (ie, enrollment rate). The enrollment rate will be compared between the active intervention period and the prior 10 months as historical control for each disease trial group. To aid in the design of larger and more definitive studies, we also intend to estimate the effect size of the number of people enrolled associated with the use of targeted social media monitoring on Twitter as a tool for enhancing cancer trial recruitment. Finally, we aim to establish a method for implementing a social media–driven centralized clinical trial recruitment approach at a comprehensive cancer center, taking into account their internal workflows and processes. Textbox 1 lists the specific research questions we intend to answer with this study.

This protocol paper provides a detailed description of a social media monitoring and recruitment intervention on Twitter as well as clear metrics to assess its feasibility and impact. Such metrics include data on eligible Twitter users in Los Angeles County who have expressed specific health conditions and concerns; outreach messages to targeted Twitter users; their engagement with these messages either via Twitter or the trial webpage, completion of prescreening and screening procedures, and final consent and enrollment. It is our goal to contribute to the development of more transparent, evidence-based social media recruitment methods and measurement frameworks. Our findings will provide pilot data on the use of Twitter as a resource for identifying and recruiting clinical trial participants across 6 different cancer disease types and help to explore a new path for the application of publicly available Twitter data in support of centralized trial recruitment at a comprehensive cancer center.

Textbox 1. Research questions we intend to answer with this study.

1. How feasible is the application of social media monitoring to enhance recruitment in cancer trials among Twitter users in Los Angeles County?
   - What are the reasons for not enrolling eligible clinical trials?
   - How many trials and disease categories can be monitored for (on Twitter) at a time?
   - How does the proposed social media monitoring and recruitment intervention affect the workflow of the study team?
   - How much time and effort does it take to respond to the resulting inquiries from Twitter, to decide whether or not to follow up with a potential participant, and to bring the patient in for an evaluation?
   - How many targeted Twitter users engaged with the outreach message (measured through Twitter replies, mentions, likes, retweets, direct messages, following, and contact form use on the trial webpage)?
   - How does the social media intervention affect potential participants' satisfaction and their level of privacy concern?
   - How many targeted Twitter users were prescreened for eligibility?
   - How many targeted Twitter users were eligible based on prescreening?
   - How many targeted Twitter users were screened for eligibility?
   - How many targeted Twitter users were eligible based on screening?
   - How diverse are Twitter users that were targeted for outreach?
   - How diverse are Twitter users that were prescreened?
   - How diverse are Twitter users that were eligible based on prescreening?
   - How diverse are enrolled trial participants (measured by age, gender, and racial and ethnic background)?
2. How effective is the application of social media monitoring to enhance enrollment for clinical trials?
   - What is the enrollment rate (ie, number of people who consented and enrolled divided by the total number of people contacted) that results from social media monitoring on Twitter (recruitment rates will be compared between the active intervention period and the prior 10 months as historical control for each disease trial group)?

Methods

Ethical Approval and Protocol Amendments

Study approval was obtained from the clinical investigations committee (CIC) at USC Norris (Protocol 0S-17-7; Multimedia Appendix 2) and the institutional review board (IRB) at USC (Protocol HS-17-00811; Multimedia Appendix 3). This study is also registered at ClinicalTrials.gov (NCT03408561) [72]. Any amendments made to the study protocol will be reported to the IRB at USC and the Clinical Investigation Support Office (CISO) at USC Norris.

General Study Design and Study Setting

We will use a mixed-methods interrupted time series study design with a before-and-after social media intervention, also including qualitative interviews using a 4-point Likert scale, that will be implemented at USC Norris. Using both qualitative and quantitative analyses can enhance the validity of study findings [73,74]. The National Cancer Institute NCI has designated USC Norris as one of the nation's comprehensive cancer centers, a select group of institutions providing leadership in cancer treatment, research, prevention, and education. Data analysis and all other matters related to drafting of the manuscript will occur at the School of Medicine of USC.

Intervention

The social media monitoring and recruitment intervention to be tested in this study involves 2 steps: (1) monitoring disease-specific conversations by Twitter users in Los Angeles County with a focus on 6 cancer topics: breast cancer, colon cancer, kidney cancer, lymphoma, non-small cell lung cancer, and prostate cancer (Textbox 2), and (2) contacting eligible Twitter users (Textbox 3) via public reply with information about disease-specific cancer trials that are open to accrual at USC Norris.

To access public Twitter user data, we will use Symplur Signals [75], a health care social media analytics platform that maintains a database of curated disease- and health-related Twitter conversations and user data, updated daily and easily sortable by social media user type (eg, patient, physician, and health care organization), location and time zone, language, disease or health interests, and Twitter message content. We will review both retrospective and prospective data published by Twitter users in Los Angeles County between July 28, 2017 and November 30, 2018 to identify potential trial participants for each trial disease group. Two independent coders (including the study co-principal investigator, co-PI) will review the Twitter data to identify Twitter users eligible for targeted outreach.

Randomization

Several aspects of this study will be randomized to reduce selection bias. First, the order in which the cancer trial disease groups will be onboarded in this study will be shuffled randomly using a Fisher-Yates shuffle [76]. Second, the selection of the initial outreach messages will be randomized using a *true* random number generator [77]. Third, those Twitter users who are eligible and consent to enroll in one of the cancer trials will be randomized if required by the individual trial.

Textbox 2. Study eligibility criteria for clinical trials.

Inclusion criteria

- Focus on one of the 6 cancer disease types: breast cancer, colon cancer, kidney cancer, lymphoma, non-small cell lung cancer, or prostate cancer
- Be institutional review board–approved and open to accrual at the USC Norris Comprehensive Cancer Center
- Be a phase 1 trial in expansion, phase 2 or 3
- Be an interventional trial
- Recruit in English
- Recruit for at least 9 months at the point of enrollment
- Set a monthly accrual target ≥1 and annual accrual target ≥12

Exclusion criteria

- Phase 1 trials in dose escalation

Textbox 3. Study eligibility criteria used for Twitter user outreach.

Inclusion criteria

- Be located in Los Angeles County based on the self-reported description provided on user's Twitter profile (Multimedia Appendix 4)
- Mention in any of their Twitter messages at least one word or hashtag related to the 6 cancer disease types (Multimedia Appendix 5)
- Message is an original Twitter message or reply to another user's message
- Message indicates that Twitter user has been diagnosed with the cancer disease or that they know someone who has been diagnosed with the cancer disease

Exclusion criteria

- Cancer patients in remission (ie, signs and symptoms of that cancer have reduced)
- Cancer survivors (ie, there are no traces of cancer left)
- Persons younger than 18 years
- Persons who note that a relative or friend has died of the disease
- Retweets (ie, user shares message other Twitter users sent)

Eligibility

Characteristics of Eligible Clinical Trials

Clinical trials will be required to meet the eligibility criteria outlined in Textbox 2. The trial selection is independent of the stage of disease. The 6 cancer trial disease categories were selected based on 2 factors: the results of a preliminary Twitter data analysis in California to determine the most frequently mentioned cancer topics in the region, and the number of clinical trials at USC Norris that are open for accrual. Between January 1, 2016 and January 30, 2017, we found 36,502 Twitter users in California who had sent a total of 159,396 Twitter messages in English including at least one of the selected 6 cancer disease terms (unpublished data from Symplur Signals). Additionally, a preliminary analysis of clinical trials at USC Norris between January 1, 2017 and July 7, 2017 identified 84 clinical trials that were open for accrual and would be eligible for this study (Multimedia Appendix 1, page 24). We intend to onboard all eligible trials in the select 6 cancer disease areas that are open for accrual at the time of the onset of this study. Social media monitoring on Twitter will be used to identify potential cancer trial participants for all onboarded trials. We refer to this approach as "centralized trial recruitment" because we cluster trials into groups by disease and promote only 6 disease trial groups on Twitter rather than each individual trial. Including all cancer trials related to one disease type aligns with the Center's internal screening and triage process. The physicians and clinical research coordinators are divided into disease-specific teams and therefore will consider potential trial participants for all the relevant trials in that disease area. Finally, to reduce selection bias, we will onboard one disease trial group every 2 weeks in a randomized order. Once a clinical trial disease group is onboarded, the trials in that group stay on for the period of this study.

Characteristics of Eligible Twitter Users Selected for Targeted Outreach

Participant recruitment for the onboarded clinical trials will occur on the social network Twitter. The study will be limited to those Twitter users who meet the eligibility criteria outlined in Textbox 3. We will apply both Boolean and Regex location code categories (Multimedia Appendix 4) to determine user locations. Any Twitter user located in Los Angeles County who mentions one or more words related to the selected cancer disease topics (Multimedia Appendix 5) will be contacted via Twitter using the public reply feature. We will include all

potential trial participants in this study who express interest in trial participation via Twitter or through the contact form on the trial webpage (Figures 1 and 2) in response of the targeted outreach. They will be invited to an initial phone prescreening. See Figure 3 for details on study design and procedures.

Consent, Prescreening, and Screening Procedures

Prescreening of Twitter users to determine if they should be triaged to the USC Norris team will occur over the phone. See Multimedia Appendix 6 for the complete prescreening questionnaire. Verbal consent to participate in the social media study will be obtained before the initial prescreening. Persons who are eligible for triage to USC Norris must meet the eligibility criteria outlined in Textbox 4. After triage to the respective cancer disease contact at USC Norris, a physician and/or clinical research coordinator will contact the potential participant to obtain additional clinical information, describe available trials, and arrange an in-person evaluation to determine the eligibility for one of the individual trials, if appropriate. After the in-person visit, if the patient is considered to be a potential candidate, the physician will complete the informed consent process with the participant for the specific trial in question, and the formal screening and eligibility work-up will be completed. Twitter users who do not meet the eligibility criteria of any of the cancer trials open to accrual will be excluded from participation in this study, as well as persons who may be eligible (eg, disease, histology, stage, and prior treatment) but do not meet additional trial-specific requirements such as insurance or allergy to drug. These may vary by clinical trial. We will count these people as engaged but not enrolled and document the specific reasons.

Recruitment

Onboarding of Clinical Trials

Study teams of the onboarded cancer trials will not receive monetary or any other compensation for enrolling their clinical trials in this study. We will work closely with the CISO team at USC Norris to recruit all clinical trials in the select cancer disease areas that are open for accrual.

Figure 1. Example of a webpage (part 1) that includes information about the clinical trials on lung cancer that are open to accrual at the USC Norris Comprehensive Cancer Center (USC Norris). Squares and numbers show the following page elements: (1) the general description of the purpose of these types of cancer trials; (2) the study sites; (3) the target recruitment population; (4) a contact form that triggers an email to this study team; and (5) a list of the clinical trials at USC Norris including a URL link to the description on ClinicalTrials.gov for each trial.

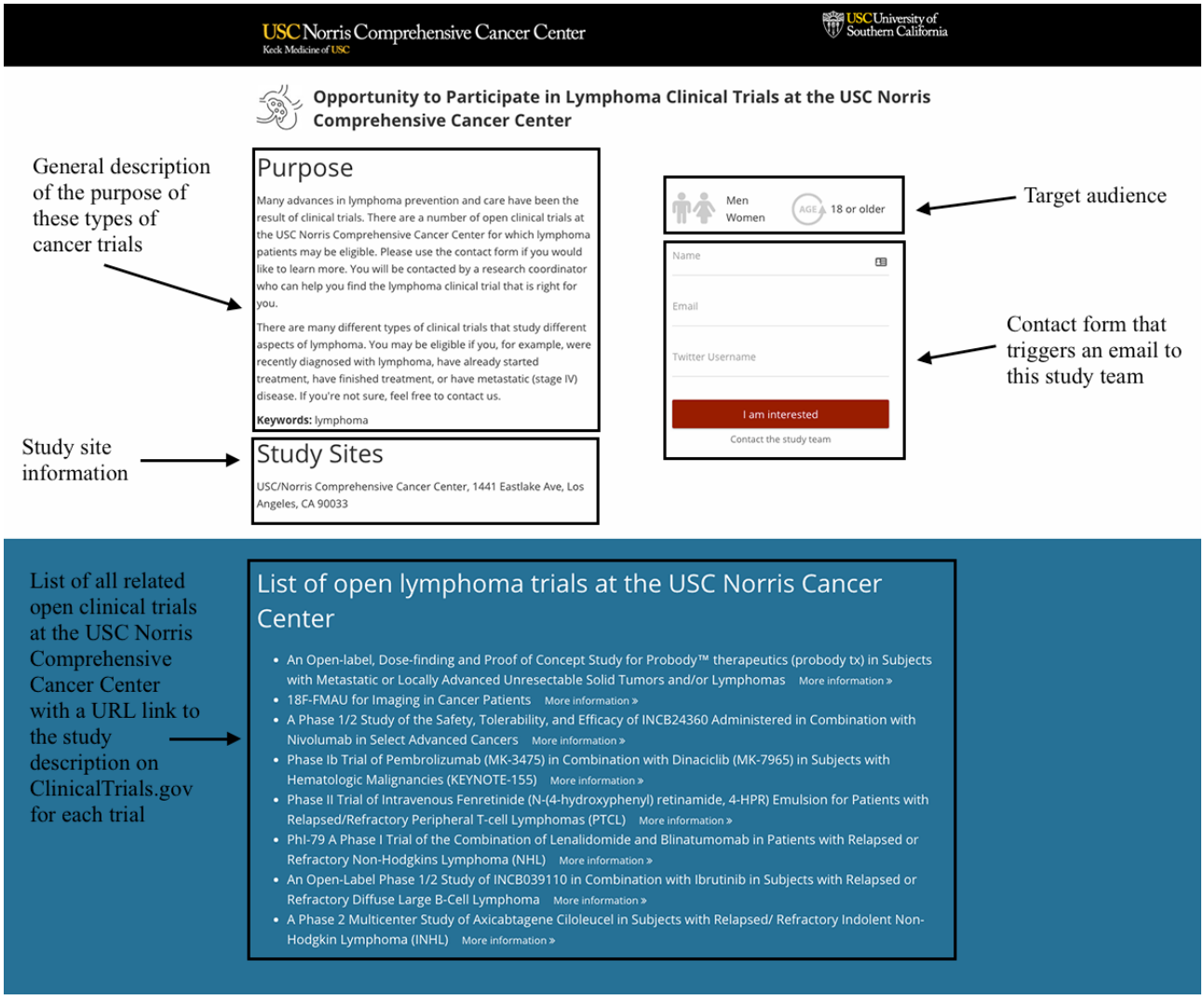
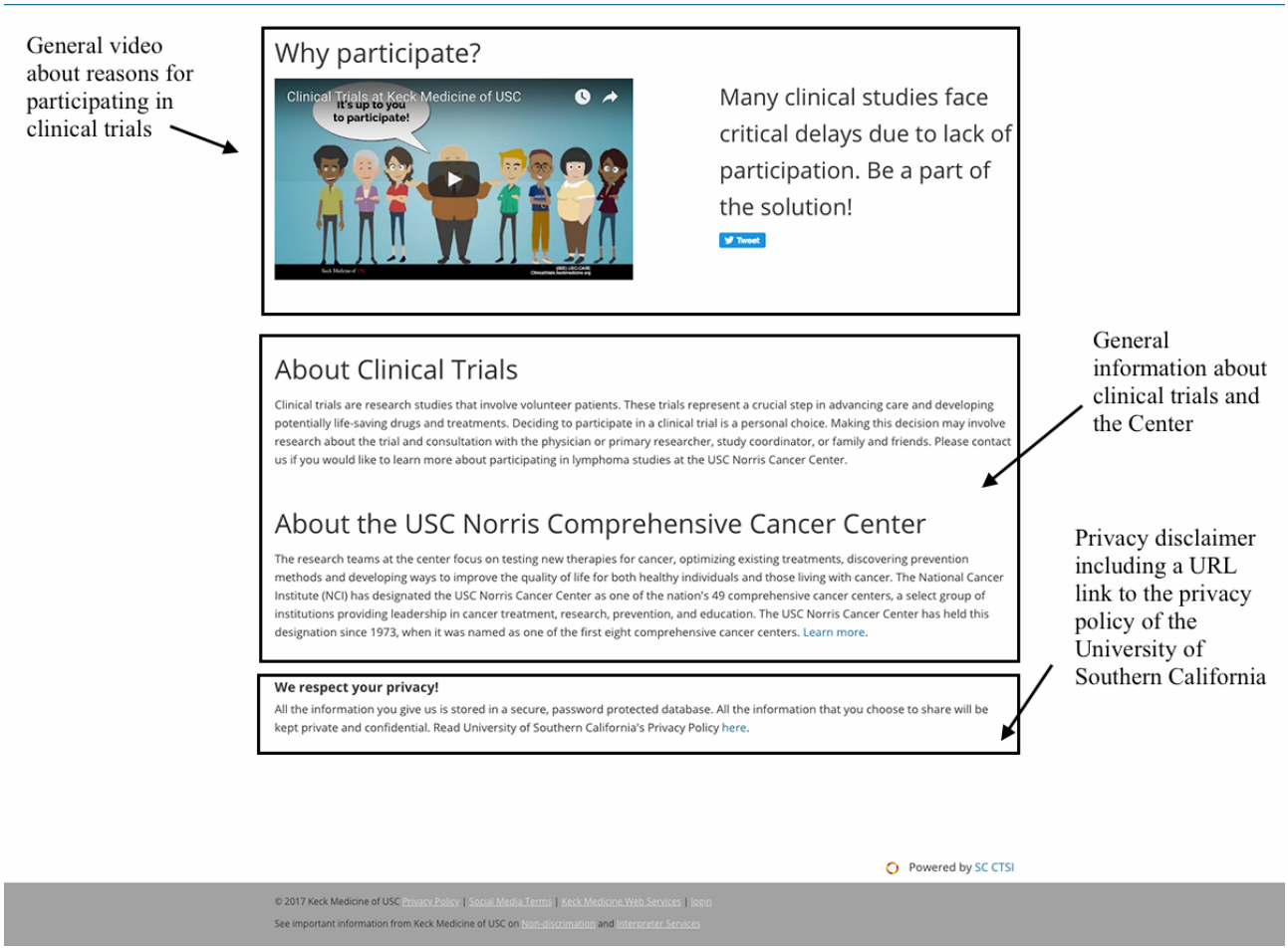


Figure 2. Example of a webpage (part 2) that includes information about the clinical trials on lung cancer that are open to accrual at the USC Norris Comprehensive Cancer Center (USC Norris). Squares highlight the following page elements: a general video about reasons for participating in clinical trials; general information about clinical trials and USC Norris; and a privacy disclaimer including a URL link to the privacy policy of the University of Southern California.



Recruitment of Twitter Users in Los Angeles County

Participants (ie, targeted Twitter users in Los Angeles County) will not receive monetary compensation for participating in the social media study but may receive compensation if they consent to participate in one of the clinical trials depending on the trial. Participants will be recruited using public replies to their Twitter messages that mention words related to the selected cancer disease types (Multimedia Appendix 5). We will use the @USCTrials Twitter account [78] for sending the targeted outreach messages. We will not use any advertised (paid) messages because Twitter does not permit paid advertisement of clinical trials [79].

The outreach (recruitment) messaging consist of three types of messages, which we refer to as the "outreach message package" (Textbox 5). An initial outreach message (Textbox 5), which is selected randomly (see Randomization section), is a personalized message to the person using their name (if available on Twitter) or Twitter handle (eg, @JaneDoe) referring to their previous mention of a specific cancer disease condition or concern and offering them more information (eg, "Dear Michael: We noticed your interest in #lungcancer and wanted to share the latest open clinical research opportunities @KeckMedUSC. You can find more information here: [URL] #ClinicalTrial"). The second message introduces the research project ensuring *investigator transparency* that "demands investigator truthfulness and honesty when interacting with research volunteers" and promoting "public trust in the research enterprise" (Textbox 5) as suggested by Gelinas et al [39]. The third message includes a disclaimer about the privacy risks of Twitter using the Privacy by Design framework, a globally recognized standard for privacy protection as suggested by Bender et al [24]. The disclaimer message points out security as a possible threat to privacy of social media users if the data are leaked (Textbox 5). Via the URL link in each message, Twitter users interested in the respective cancer clinical trials will be directed to a webpage (Figures 1 and 2) that includes information about *all* clinical trials in this disease category that are open to accrual at USC Norris. We call this approach *centralized trial recruitment*. Including all cancer trials related to one disease type in the same webpage aligns with the center's internal screening and triage process; the physicians and clinical research coordinators are divided into disease-specific teams and therefore will consider potential trial participants for all the relevant trials in that disease area.

Figure 3. Study flow diagram of study design and procedures. USC Norris: USC Norris Comprehensive Cancer Center.

Textbox 4. Study eligibility criteria for triage to the respective cancer disease contact at the USC Norris Comprehensive Cancer Center.

Inclusion criteria

- Have active cancer or recently underwent surgical resection for cancer
- Cancer is visible on scans (computed tomography, magnetic resonance imaging) unless recently resected
- Able to do activities of daily life independently (eg, eating, drinking, and bathing)

Exclusion criteria

- Have completed curative cancer therapy more than 12 months ago

Textbox 5. Outreach message package used to contact prospective clinical trial participants on Twitter.

Initial outreach messages (random selection for each outreach: the parameter "#disease" will be replaced with the respective cancer disease type [ie, breast cancer, colon cancer, kidney cancer, lymphoma, non-small cell lung cancer, and prostate cancer] and the parameter "URL" with a shortened link to the related trial disease group webpage):

- We noticed your interest in #disease and wanted to share the latest open clinical research opportunities @KeckMedUSC. You can find more information here: URL #ClinicalTrial
- We noticed your mention of #disease and wanted to reach out. Did you know about these open #disease studies @KeckMedUSC? You can find more information here: URL #ClinicalTrial
- We noticed your interest in #disease and wanted to share the latest open clinical research opportunities @KeckMedUSC. You can find more information here: URL #ClinicalTrial
- We noticed your interest in #disease and wanted to share that the following #disease clinical trials @KeckMedUSC are looking for participants. More information is available here: URL #ClinicalTrial
- We noticed your interest in #disease and thought you might be interested in open #disease clinical trials @KeckMedUSC that are looking for participants. More information is available here: URL #ClinicalTrial

Project-related message: We're reaching out to you as part of a research project trying to understand if Twitter can be used to better connect patients with clinical research opportunities.

Privacy and security disclaimer: The security of social media is not guaranteed. Contact us about the study. Don't post if concerned about privacy.

The trial disease group webpage (Figures 1 and 2) includes a general description of the purpose of these types of cancer trials, the target recruitment population, study site information, a contact form that triggers an email to this study team, a list of the clinical trials at USC Norris including a URL link to the description on ClinicalTrials.gov for each trial, a general video about reasons for participating in clinical trials, general information about clinical trials and USC Norris, and a privacy disclaimer including a URL link to the privacy policy of USC. Twitter users will also be able to contact the study team through Twitter using either the public reply or mention options or the direct message feature that allows them to send private messages to the @USCTrials Twitter account. As part of the outreach and recruitment approach, we (ie, @USCTrials Twitter account) will also *follow* each targeted Twitter user to whom the outreach message package was sent. This adds the respective person (Twitter account) to the network of @USCTrials and allows them to send us private, direct messages to the @USCTrials account, which some Twitter users may prefer. By default, Twitter only allows direct messages to be sent to followers to prevent misuse.

Recruitment of Clinical Trial Study Team Members

Study teams of the onboarded cancer trials will not receive monetary or any other compensation for participating in the study team interviews. We will work closely with the CISO team at USC Norris to invite and recruit (via email using USC's email system) study team members of the enrolled clinical trials to participate in an interview (ie, PIs, clinical research coordinators, and recruitment specialists).

Qualitative Interviews

Prescreening Interviews With Twitter Users

Brief survey interviews with targeted Twitter users (ie, potential study participants who contacted the study team in response to the social media outreach) will be conducted by the study team during prescreening over the phone. The goal of the prescreening questionnaire (Multimedia Appendix 6) is to collect demographic information about the Twitter users who expressed interest in trial participation, to better understand their perception of the social media intervention, in particular, their level of privacy concern, and to determine their eligibility regarding the triage to the USC Norris team for further screening.

Postqualitative Interviews With Clinical Trial Study Team Members

Postqualitative interviews with study team members of the onboarded clinical trials (PIs, clinical research coordinators, and recruitment specialists) will be undertaken to explore their views of and acceptance of the social media intervention. The interview guide will be based on the research questions to assess feasibility and acceptance (Textbox 1). The interview guide is under development and will be submitted to the USC IRB for review. As data are collected and the study team conducts the

initial analyses, elements of the guide may require revision, and any important issues that emerge will be added. Interviews will be audio-recorded and take approximately 1 hour.

Outcomes

The study has 2 primary outcomes. The first outcome will be feasibility and acceptance of the social media intervention among targeted Twitter users and the study teams of the onboarded trials. We will conduct qualitative interviews using a 4-point Likert scale to assess the feasibility and the level of acceptance. We will further use a number of quantitative measures to assess the feasibility by calculating the proportion of targeted Twitter users who engaged with outreach messages (measured through Twitter replies, mentions, *likes*, *retweets*, direct messages, following, and contact form use on the trial webpage). The second outcome will be the impact of the social media intervention, which we will measure by calculating the proportion of people who consented and enrolled in trials (ie, enrollment rate). The enrollment rate will be compared between the active intervention period and the prior 10 months as historical control for each disease trial group (see Textbox 6 for a list of primary outcomes and definitions to be included in this study).

Control Group

There is no prospective control group in this study. Recruitment rates that result from the social media intervention will be compared between the active intervention period and the prior 10 months as historical control for each disease trial group.

Sampling Quota

Due to the lack of previous studies that explored this type of social media monitoring intervention for clinical trial recruitment, we do not provide a sampling quota. That said, we looked at research studies that had recruited participants via Twitter to determine potential baseline data or estimates. However, as the scoping review by Topolovec-Vranic and Natarajan from 2016 demonstrates [13], there are multiple issues regarding the comparison of social media recruitment strategies and results used in different studies. The authors looked at 30 research studies that had used social media for recruitment and compared the results with at least one traditional recruitment method. The review shows the lack of reporting standards for social media recruitment. Among the issues, study teams report combined data for social media recruitment (eg, for Facebook and Twitter combined) so that it is impossible to know how many participants were recruited using one social media type. The definition of social media used by authors also varies across the literature. Some study teams combine websites such as Twitter and Facebook with other types of tools such as Craigslist and classify all of them as social media. This has an effect on the results and conclusions that can be drawn about their effectiveness and enrollment rates.

Textbox 6. Primary outcomes and definitions.

Outcome: Feasibility and Acceptance

- Reasons for not enrolling in eligible clinical trials
- Number of cancer disease types and studies that can be monitored on Twitter simultaneously by the study team
- Effect of social media intervention on workflow of study teams
- Time and effort required to respond to the resulting inquiries by targeted Twitter users (eg, decide whether or not to follow up with a potential participant, to bring the patient in for an evaluation)
- Diversity of Twitter users targeted for outreach (measured by age, gender, and racial and ethnic background)
- Number of targeted Twitter users who engaged with outreach message (measured through Twitter replies, mentions, likes, retweets, direct messages, following, and contact form use on the trial webpage)
- Effect of social media intervention on potential participants' satisfaction and their level of privacy concern
- Number of targeted Twitter users who were prescreened for eligibility
- Diversity of prescreened Twitter users (measured by age, gender, and racial and ethnic background)
- Number of targeted Twitter users who were eligible based on prescreening
- Diversity of Twitter users who were eligible based on prescreening (measured by age, gender, and racial and ethnic background)
- Number of targeted Twitter users who were screened for eligibility
- Number of targeted Twitter users who were eligible based on screening
- Diversity of Twitter users who were eligible based on screening (measured by age, gender, and racial and ethnic background)
- Diversity of enrolled participants (measured by age, gender, and racial and ethnic background)

Outcome: Impact

- Enrollment rate per month: number of people enrolled per month divided by number of people targeted on Twitter per trial disease group per month (recruitment rates that result from the social media intervention will be compared between the active intervention period and the prior 10 months as historical control for each disease trial group)

Finally, there are few research studies that report the use of Twitter for participant recruitment. However, these studies focused on other diseases or health conditions (eg, pregnancy, smoking cessation). We decided not to use the recruitment results reported by these studies as baseline data or estimates, as we believe that the disease or health condition of a study as well as the type of "ask" (eg, completion of a Web-based survey, participation in clinical trial) influences the engagement and enrollment rate among potential participants. Hence, we will use the preliminary data from this study to estimate the effect size of the number of people enrolled associated with the use of targeted social media monitoring on Twitter as a tool for enhancing recruitment to cancer trials.

Data Collection, Confidentiality, and Security

Feasibility and Impact Data

Study team members will be provided with tracking sheets to collect data on the potential participants and enrollees. For example, they will track information on who was contacted via Twitter, when a Twitter user was contacted, their Web-based engagement with the outreach message, if targeted Twitter users used the contact form on the clinical trial webpage to contact the study team, and the results of the prescreening phone call. The USC Norris team members will use tracking sheets to track information about the potential participants who were screened, their eligibility, and enrollment.

Study data will be collected using the system REDCap (Research Electronic Data Capture) at USC. REDCap is a secure Web-based application designed to support data capture for research studies [79], providing (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for importing data from external sources. Provision of data to the IRB, National Institutes of Health (NIH), and Food and Drug Administration is facilitated by this database system. Additionally, the prescreened participants that we triage to the USC Norris team for further screening will be documented in the USC Clinical Trials Management System (CTMS) to be able to track their enrollment in one or more clinical trials.

Interview Data

Verbatim transcription of audio-recorded interviews with the study team members of the enrolled clinical trials will be reviewed for completeness. Transcripts of interviews will be entered, managed, and coded using Atlas.ti (ATLAS.ti Scientific Software Development GmbH), a qualitative data management computer program.

Data Confidentiality and Security

The data we collect will only be viewed by the study team for this project. Identifiers such as name, Twitter username, age, and gender data are collected and stored in a secure, Health Insurance Portability and Accountability Act–compliant database REDCap at USC for no longer than 1 year and will be deleted after that time. Additionally, the prescreened participants that we triage to the USC Norris team for further screening will be documented in the secure USC CTMS, which is based on the Web-based software system OnCore and designed to streamline the process of managing clinical trials. We will not store the internet protocol addresses of respondents. Names of noneligible individuals will not be maintained. The data for analysis will be deidentified.

Data Analysis

Analysis of Qualitative Interview Data

To facilitate the qualitative data analysis of the interviews with the study team members of the onboarded clinical trials, we will develop an initial code list based on the interview guide. The code list will be modified throughout the coding process. Each coded transcript will be discussed line by line until the coding team (including the co-PI) comes to an agreement about code definitions and how they should be applied. Important themes will be summarized and used to understand acceptance with the social media–based intervention for cancer clinical trials. Count outcomes will be presented as median and interquartile range; nominal outcomes will be presented as N (%). We will explore participant and study team characteristics between the 2 cohorts to examine where differences might lie by including them as potential covariates in the models. Comparisons of the before- and after-time periods will be made using generalized estimating equations for appropriate outcome type (Poisson, means, and prevalence) accounting for the type of cancer.

Analysis of Quantitative Data

The impact of the social media intervention will be determined comparing monthly enrollment rates during the active intervention period (ie, number of people enrolled per month divided by number of people targeted on Twitter per trial disease group per month) versus the prior 10 months as historical control for each disease trial group (ie, breast cancer, colon cancer, kidney cancer, lymphoma, non-small cell lung cancer, and prostate cancer) using generalized estimating equations, accounting for intradisease random effects and trends. Analyses will be performed in SPSS v24 [40]. As this is a pilot study, *P* values are of limited use to determine group differences, so we will focus on observed effect sizes (Cohen *d*, relative risk). Additional quantitative data will be calculated using proportions of targeted Twitter users who engaged with outreach messages (measured through Twitter replies, mentions, *likes*, *retweets*, direct messages, following, and contact form use on the trial webpage). To aid in the design of larger and more definitive studies, we also intend to estimate the effect size of the number of people enrolled associated with the use of targeted social media monitoring on Twitter as a tool for enhancing cancer trial recruitment.

Risk Analysis

Anticipated Risk

This research project presents minimal-risk research. We will use public user data from the social network Twitter. Identifiable information such as human subjects' names and Twitter handles will not be included in the analysis dataset. Patient identifiers do not apply. We have implemented the following measures to

ensure data and information confidentiality and to minimize risk (see Data Confidentiality and Security section). We will further abide by USC IRB regulations and the USC Privacy of Personal Information policy. In general, all data will be entered into a computer and database that is password protected. The data will be stored using appropriate, secure computer software and encrypted computers. The IRB-approved study protocol details further information on procedures for monitoring and assessing study-related concerns (Multimedia Appendix 1, page 16).

Anticipated Challenges

We identified a number of scientific, ethical, and regulatory challenges to this study. Refer to the IRB-approved study protocol for further information on perceived ethical and regulatory issues and how we will manage these challenges and related risk (Multimedia Appendix 1, pages 17-18).

Dissemination of Study Findings

The study authors plan to publish the study findings in a peer-reviewed journal and at topic-related conferences (to be determined at a later date). All listed authors and/or contributors are compliant with guidelines outlined by the International Committee of Medical Journal Editors for author inclusion in a published work. Public access to the study protocol and other necessary aspects will be made available through our ClinicalTrials.gov identifier (NCT03408561). Furthermore, to support research transparency and reproducibility, we will share the deidentified research data after publication of the study results. We will share the deidentified data on Figshare, a repository where users can make all of their research outputs available in a citable, shareable, and discoverable manner. We will use a data-sharing agreement that provides for (1) a commitment to using the data only for research purposes and not to identify any individual participant and (2) a commitment to securing the data using appropriate computer software.

Results

This study has been funded by the NCATS through a Clinical and Translational Science Award (CTSA) award (Multimedia Appendix 7). Study approval was obtained from the CIC at USC Norris (Protocol 0S-17-7; Multimedia Appendix 2) and the IRB at USC (Protocol HS-17-00811; Multimedia Appendix 3). This study is also registered at ClinicalTrials.gov (NCT03408561). Study recruitment via Twitter started in February 2018. Data collection will be completed in November 2018.

Discussion

Limitations

We recognize that this pilot study will not have sufficient resources to recruit a truly representative sample. Thus, the generalizability of the study results is somewhat limited. Twitter messages from locations outside of Los Angeles County, as well as messages in other non-English languages such as Spanish, and therefore nonspeakers of English, will not be included. Moreover, the social media intervention favors those with internet access and could therefore introduce potential bias into the clinical trials. Regardless of the fact that social media users "have grown more representative of the broader population" [18], Twitter users tend to be younger (40% are aged 18-29 years), college graduates, and located in urban areas [18,19], compared with the "average" study participant. It is also worth mentioning that based on Pew Research data from 2018, the percentage of Twitter users among the black population (26%) is now higher than the percentage of white (24%) and Hispanic (20%) Twitter users [18]. Recruiting via Twitter has the potential to select for this segment of the population and could therefore introduce bias. Future research will need to determine the extension of the findings and conclusions to the population at large. However, we will keep a detailed account of the environment surrounding this research and include a rich description in our final report to ensure that the study findings and the described method for implementing a centralized social media intervention at a comprehensive cancer center are transferable to other academic settings. Additionally, much of the Twitter data we use will be prospective. However, we also include retrospective social media data (ie, relevant Twitter messages sent by users in Los Angeles County 6 months before study onset). The fact that these messages are older than the messages in the prospective dataset may affect the likelihood of a targeted Twitter user engaging with the outreach message. Furthermore, the possibility remains that factors such as disease awareness months and trending news will affect the attention to outreach messages. Finally, we must consider that successful social media engagement may not necessarily correlate with clinical trial enrollment due to variables that affect the clinical trial consent and enrollment process and are unrelated to social media monitoring and outreach.

Practical Significance

This pilot project will provide preliminary data and practical insight into the application of publicly available Twitter data to identify and recruit clinical trial participants at a comprehensive cancer center across 6 cancer disease types. If successful, the findings of this study will inform a multisite RCT to determine the efficacy of the social media intervention described here across different locations and populations. In addition, data from Twitter users and study team members of the onboarded clinical trials will be translated into a preliminary set of testable questions to further examine challenges around the use of social media monitoring in clinical trial recruitment in general and at comprehensive cancer centers.

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Conflicts of Interest

The private-sector partner Symplur will provide access to Twitter user data and advise us on the search strategy using a combination of keywords and hashtags. We have involved the USC Office of Compliance to manage the conflict of interest (COI) from our private-sector partner. USC complies with the Public Health Service (PHS) regulations on Responsibility of Applicants for Promoting Objectivity in Research for which PHS funding is sought (42 CFR Part 50, Subpart F). All disclosed conflicts will be reviewed by USC's COI Review Committee (CIRC) and either eliminated or managed before commencing research. Members of the Symplur team will not be involved in the data collection, analysis, and interpretation. The study PIs, coinvestigators, and expert consultants do not report any COI at this point in time. In addition, the project team will fully disclose any conflicts in presentations and publications.

Multimedia Appendix 1

Institutional review board–approved study protocol.

[PDF File (Adobe PDF File), 1MB - resprot_v7i9e177_app1.pdf]

Multimedia Appendix 2

Approval notice provided by the clinical investigations committee at the USC Norris Comprehensive Cancer Center.

[PDF File (Adobe PDF File), 1MB - resprot_v7i9e177_app2.pdf]

Multimedia Appendix 3

Approval notice provided by the institutional review board at the University of Southern California.

[PDF File (Adobe PDF File), 108KB - resprot_v7i9e177_app3.pdf]

Multimedia Appendix 4

Boolean and Regex location code categories for identifying Twitter users in LA County.

[PDF File (Adobe PDF File), 238KB - resprot_v7i9e177_app4.pdf]

Multimedia Appendix 5

Keywords and hashtags for monitoring Twitter user conversations in LA County and for identifying potential clinical trial participants.

[PDF File (Adobe PDF File), 240KB - resprot_v7i9e177_app5.pdf]

Multimedia Appendix 6

Consent and prescreening questionnaire for targeted Twitter users who contact the study team.

[PDF File (Adobe PDF File), 412KB - resprot_v7i9e177_app6.pdf]

Multimedia Appendix 7

National Institutes of Health summary statement of approved study. Relevant pages of peer-review report for center grant have been extracted from overall summary statement.

[PDF File (Adobe PDF File), 293KB - resprot_v7i9e177_app7.pdf]

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Abbreviations

CIC: clinical investigations committee
CISO: Clinical Investigation Support Office
COI: conflict of interest
CTMS: Clinical Trials Management System
IRB: institutional review board
NCATS: National Center for Advancing Translational Sciences
NIH: National Institutes of Health
PHS: Public Health Service
PI: principal investigator
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
USC: University of Southern California
USC Norris: USC Norris Comprehensive Cancer Center

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