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A longitudinal study of symptom burden in outpatients with advanced cancers based on Electronic Patient Reported Outcome (ePRO) platform: a single institution, prospective study protocol

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ABSTRACT

Introduction: A novel and brief electronic Patient Report Outcome (ePRO) Platform is needed in routine patient care in psycho-oncology clinic for implementing evidence-based symptom management in outpatients with advanced cancer. We describe the protocol for establishing the methodology and examining the dynamic changes of symptom burden by a single institution longitudinal study to provide critical parameters needed of implementing this ePRO platform for better symptom management.

Methods and analysis: The study focused on the advanced patients with lung cancer, stomach cancer, esophagus cancer, liver cancer, colorectal cancer or breast cancer. The study primary outcome focused on the study of symptom burden in advanced patients with fatigue, pain, insomnia, anxiety, depression, nausea and vomiting. The secondary outcomes included feasibility of using ePRO, symptom related QoL, reasons of no changes of symptom burden, defining frequency of PRO assessments and cut-points, items for screening, and management of comorbidity. The prospective study will monitor patient's symptom burden, physical and psychological health outcomes with the validated multi-symptom assessment tool MD Anderson Symptom Inventory (MDASI), and other PRO instruments (Insomnia Severity Index, Hospital Anxiety and Depression Scale, PHQ-9, and EQ5D5L). After initial outpatient visit for baseline assessment, ePRO system automatically pushes ePRO follow-up notification in weekly basis in 4 weeks (short message through mobile phone) to patients. The characteristics and changing trajectory of symptoms burden of outpatients with advanced cancer will be described. Parameters for using PROs, such as optimal time points for follow-up and cut-off point for alert will be determined. The feasibility of ePRO platform to track the changes of target symptoms in outpatients will be evaluated based on the completion rate, drop-

out rate, loss rate of follow-up and the reminder times of platform and research assistant.

Ethics and dissemination: The study protocol and related documents were approved by the Institutional Research Board (IRB) of Peking University Cancer Hospital on 14 May 2019 (2019YJZ34). The manuscript is based on the latest protocol of Version 4.0, 30 June 2019

RESULT: This study will provide a rational synthesis of current methods and evidences for using ePRO in psycho-oncology outpatient clinic.

CONCLUSION: The conclusion of this study will provide evidence to support the implementation of ePRO platform in routine patient care. **Trial Registration:** chictr.org.cn ChiCTR1900023560

Key words: advanced cancer, symptom management, outpatients, Electronic Patient Reported Outcome, a longitudinal study

There are several strengths and limitations of this study.

- The study is a prospective cohort study with a total of 7 follow-ups conducted within 4 weeks. It focuses on establishing a symptom management platform for outpatient ePRO and obtain the dynamic symptoms trajectory of patients outside the hospital
- Instead of a single tumor site, patients are recruited from six most common tumor sites: lung cancer, gastric cancer, esophageal cancer, liver cancer, colorectal cancer, breast cancer.
- PRO data are collected using an e-questionnaire based on WeChat, a major communication app in China.

- A group of questionnaires are used to measure the comprehensive well-being of patients, mainly including MDASI-C, ISI, HADS, PHQ-9, EQ5D5L.

- A relatively small sample size may be a limitation.

INTRODUCTION

According to the official report by the National Central Cancer Registry of China, cancer is the leading cause of death in China; there were 4.3 million newly diagnosed cancer cases and 2.8 million cancer deaths in 2015 in China. Lung cancer, gastric cancer, liver cancer, esophageal cancer and colorectal cancer ranked as the top five cancers in male, and breast cancer, lung cancer, gastric cancer, colorectal cancer and esophageal cancer rank as the top five cancers in female [1]. Cancer patients suffer from various symptoms due to the disease itself and treatment-related adverse reactions [2-4]. Studies have shown that one third of patients undergoing cancer treatments reported three or more moderate to severe symptoms [5]. The symptom burden of advanced cancer patients is even more serious.[4, 5] if the symptoms were not addressed properly in time, which will affect the quality of life and daily functions negatively and even shorten the survival period of patients.

In recent years, several studies have shown that good symptoms management based on patient-reported outcome (PRO) can benefit advanced cancer patients. For example, a single-centered study published in JAMA in 2017 showed that systematic symptom monitoring can significantly prolong the survival of patients by 5.2 months [6], which even achieved better results than most newly approved anti-cancer drugs in 2016. In 2019, a multi-centered study of Web-based follow-up of PRO symptoms demonstrated once again that this approach could bring survival benefits to patients. [7]

However, there are few studies on effective symptom management of the cancer patients in routine patient care in China. The clinical doctors and nurses need a help for how to quickly capture the patient's dynamic change on symptom burden in patient's routine clinic appointment under the busy

working flow, and the patients also need an approach for reporting symptoms actively. A lot of the symptom management were dealed with in the outpatient clinic, however, there is no existing monitoring system on patients' status when they are out of the hospital.

In order to resolve this problem, we established an ePRO platform to monitor the symptom changes when the patients left the clinic and go back home. The study is designed to monitor the changes of the symptom burden through PROs, and symptom control practice among outpatients who self-referred or referred by oncologists to clinic of department of psycho-oncology. With lack of longitudinal data of physical, psychological, social symptom burden for Chinese oncology patients, the proposed study aimed to include PROs of multiple symptom assessment tool, functioning measure and HRQoL measure. Since there are many differences between the Chinese culture and Western culture, the ePRO platform is also in different format. In Western countries, the electronic application is mainly through e-mail, but e-mail was not widely used in Chinese population especially in the elderly. We inserted the ePRO platform in the Wechat applet in mobile, for Wechat is the most popular social networking app in China.

The purpose of this study is to describe the changes of the symptoms of outpatients and the impact of the symptoms changes on the quality of life in patients, to determine the optimal times of follow-up, the appropriate cut-off point of the alert thresholds for intervention. We also aim to examine the experience， acceptance and compliance of patients with the ePRO platform, and to provide the evidence for the platform to be used in clinical practice.

METHODS AND ANALYSIS

Study design

This is a real-world, ongoing, longitudinal single-centered prospective study with a total of 7 follow-ups conducted within 4 weeks after the first visit of the symptom management clinic. The flow chart of this study is shown in Figure 1.

Setting

This study was initiated by Department of Psycho-oncology In Peking University Cancer Hospital and started on June 2019 and is estimated to be completed before 31 March 2020. The site is the symptom management outpatient clinic in Peking University Cancer Hospital.

Study population and eligibility criteria

Patients are either self-referred or been professionally referred by oncologists in the institution for managing difficult pain or psychological symptoms. Eligible patients are required to be 1) Over 18 years of age; 2) fluency in Chinese; 3) a confirmed diagnosis of advanced lung cancer, liver cancer, gastric cancer, esophageal cancer, colorectal cancer and breast cancer. Exclusion criteria included 1) a history of major severe mental disorders, unable to cooperate with the investigator; 2) poor physical condition, judged by the attending physician, not suitable for participating in the study; 3) being not able to use ePRO platform.

Study objectives

The primary objective is systemic monitoring changes of target symptoms （including fatigue, insomnia, anxiety, depression, nausea and vomiting） in patients with advanced cancer in the symptom management clinic of Peking University cancer hospital during a systematic follow-up within 4 weeks.

The second objectives are as follow:

(1) Evaluating the feasibility of tracking changes in target symptoms in outpatients through the ePRO follow-up system.

(2) Observing the improvement of quality of life in patients seeking symptom management in Department of Psycho-Oncology within 4 weeks after initial visiting.

(3) Finding out the reasons why the symptoms of outpatients cannot be improved within 4 weeks after the first visiting through a qualitative research.

(4) Determining the appropriate frequency of PRO symptom screening through the description and analysis of the changes in patients' symptoms during the 4-week follow-up after initial visiting.

(5) Determining the alert score of each PRO symptom through the analysis of the symptom changes during the follow-up 4 weeks after initial visiting.

(6) Exploring the most appropriate PRO items for the targeted symptoms of the screening.

(7) Analyzing the effects of co-morbidity and chronic diseases on symptom burden and symptom management of cancer patients.

Withdrawal criteria

Patients undergo a brief interview with a research assistant to identify the following exclusion criteria: (1) major communication difficulties; (2) inability to commit to the required 7 follow-up PRO (i.e., too ill to participate); (3) cognitive impairment;(4) those who do not follow the study protocol (deliberately providing incorrect PRO data) ;(5) those who ask to withdraw from the research or (6) other conditions that require withdrawal as assessed by the investigator

Outcomes

Primary Outcomes

The primary outcomes are the improvement on the intensity of the patients' target symptoms and the PRO impact of target symptoms on patient's life in 4 weeks after the initial visiting.

Secondary Outcomes

The second outcomes include as follow:

(1) Feasibility of tracking patients' symptoms with ePRO which contains two feasibility indexes:

1) At least 50% of patients completed self-report within 24 hours after being sent the follow-up message; more than 70% of patients completed self-report within 24 hours after being called; at least 70% of patients complete all self-reports within 4 weeks.

2) The percentage of patients who met the eligibility criteria agreed to participate in the study is 80%.

(2) Determining the changing trends of target symptoms intensity and their impact on quality of life over a 4-week period.

(3) Semi-structured interviews were conducted with patients whose symptom improvement score was less than 2 points after 4 weeks, and the causes of uncontrolled symptoms were analyzed.

(4) Determining the appropriate frequency of PRO screening for different symptoms with the method of looking for significant changes in PRO scores (such as using generalized mixed effect model).

(5) Determining the alert scores of PRO screening for different symptoms with clinical significance were determined by the criterion validity (such as EQ-5D) using the regression analysis model.

PRO instruments, Data collection, management and monitoring

Totally 9 data collection instruments were used in this study,

(1) MD Anderson Symptom Inventory, MDASI.

MDASI [8][9] is a widely used symptom inventory with 19 items (13 items for symptom severity, 6 items for life interference), 0=Nothing, 10=Most severity. Psychometric study has revealed that the Chinese version of MDASI has good reliability and validity, which has showed that MDASI is feasible to be used to measure the severity of multiple symptoms and their impact on function in Chinese cancer patients. Moreover, we have added 5 more items for specific cancer sites in our study to capture these special characteristics: “constipation” and “cough” for lung cancer; “dysphagia for gastrointestinal cancer”; “hot flashes and upper extremity edema for breast cancer”. A single “quality of life” item was used to anchor this study.

(2) Insomnia Severity Index, ISI

It is a validated scale for measuring insomnia severity in the last two weeks. There are total 7 items, 0-4 score for each item, with the sum score of 0-28. 0-7 score indicates no insomnia; 8-14 score indicates subclinical insomnia; 15-21 score indicates moderate insomnia, 22-28 score indicates severe insomnia. Simplified Chinese version of ISI has been validated by Lin et al [10].

(3) Hospital Anxiety and Depression Scale, HADS

HADS has 14 items with a score spectrum of 0-4 for each item, which is used to measure the anxiety and depression for the patients in the past week. It is more used for patients with somatic symptoms in the general hospitals with good reliability and validity and recommended to used for patients with advanced cancer or receiving palliative care [11].

(4) 9 Item Patient Health Questionnaire, PHQ-9

PHQ-9 is used to evaluate the depression of patients in the past two weeks. The score spectrum of symptoms severity is from 0=none at all to 3=almost every day, and the total score was from 0-27. Depression can be considered when the sum score is ⩾10. Simplified Chinese version of PHQ-9 has a good validation [12].

(5) EuroQol Five Dimensions questionnaire-5L version, EQ-5D-5L

EQ-5D-5L is a multidimensional measurement for health-related quality of life, which contains these five domain to describe patients' health: 1) mobility; 2) self-care; 3) usual activities; 4) pain/discomfort; 5) anxiety/depression, with a scale from 0=No difficulty to 4=extremely difficulty [13]][14]

(6) Distress Thermometer, DT

DT is recommended by NCCN in the distress management guideline and has been introduced to China from 2007. DT has only one item with a scale from 0=No distress to 10=extremely distress.

Problem list including 5 domains: practical problem, communication problem, emotion problem, physical problem, spirit and religion problem. It is recognized as the briefest tool for distress screening, especially in busy oncology clinical practice [15].

(7) General demographic and disease data. General demographic data includes age, sex, occupation, etc. The latter includes disease diagnosis, staging, treatment, medication, etc.

(8) ECOG score. This is a health tool that evaluates cancer patient functional status and clinically stratifies these patients` ability to tolerate therapies, which runs from 0 to 5, with 0 denoting perfect health and 5 death [16].

(9) Charlson Comorbidity Index. Comorbid conditions are best evaluated with use of the Charlson Comorbidity Index. Many studies have shown that the impact of comorbidities is significant on the survival outcomes and prognosis of cancer patients. Here are the conditions used in the comorbidity and the number of points they are awarded: score of 1 for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, and diabetes mellitus(in terms of diabetes mellitus, score of 1 for uncomplicated and 2 for end organ damage); score of 2 for moderate to severe chronic kidney disease, hemiplegia, leukemia, malignant lymphoma, solid tumor(2 in case of presence and 6 in case tumor is metastatic), liver disease(mild 1 point, moderate to severe 3 points) and AIDS [17].

PRO data are collected using an ePRO platform. ePROhub™ is dedicated on ePRO clinical research on patient's data collection, assessment and management launched by ePRO Vision (Beijing) Health Technology Co Ltd. in 2018. The platform consist of ePROcell™ and ePROhub™ two parts. Smartphone-based client, ePROcell™, is for patient's ePRO reporting and clinician's ePRO data management, intervention and project management. ePROhub™ platform, the EDC

(electronic data capture) complied, is the cloud based symptom, management platform to store and assess patient's data, support clinicians manage patient's data and intervention activities with AI (artificial intelligence) capability, output data to other database platform for further data processing. Figure 2 shown below gives total picture in Peking University Cancer Hospital project case.

ePROcell™ is fully integrated with internet-based WeChat, the most popular and the biggest social network application in China, to maximize WeChat's advantages of world-class user experience and massive population coverage into ePRO practice enable ePRO data collection- and management happening anywhere and anytime is possible. The pre-register patients can easy click the landscape-screen to answer relevant questionnaires and sending back to clinicians via cloud-based ePROhub™. The e-informed consent and e-signature is implemented before- and after reporting to secure ePRO data effectiveness and integrity. The pre-defined threshold of server symptom plus triage process support clinician efficiently communicate with patients via ePROcell™ when e-alert and e-reminder occurred.

According to the pre-defined schedule, ePROcell™ automatically send out reminder message to patients during the reporting-day, and confirmation message after patient submit. With PRO-calendar and PRO management from ePROcell™, clinicians could easily review- and manage project progress anytime to secure data quality, reporting progress and project quality. The ePROcell™ frequently visit patient's and clinical data stored in ePROhub™ and integrated backend database platform to support clinicians' regular patient's symptom following up and symptom management activities, which is the most efficient way to deliver effective symptom intervention and routine care with desired data-driven patient-centered care.

The cloud-based ePROhub™, located in hospital's datacenter, is the data management platform and has dedicated data communication channel with the backend database platform REDCap, the US free of Charge SQL database platform, via it's API (Application Program Interface) to synchronize pre-defined clinical data, like CRF (case report form) and scale, and patient's ePRO data. The output data could be converted to professional statistics program, like SAS or SPSS,

with standard data format for their final data analysis. All data are deidentified and stored in the REDCap platform. Data monitoring is carried out regularly by the IRB of Peking University Cancer Hospital.

Quality control

Investigators received standard operating procedure training before recruiting the patients.

Sample size calculation

We will use the group-based trajectory model (GBTM) to identify subgroups with distinct trajectories of symptom development during the 4 week of investigation. Previous studies showed that about 30% of patients with advanced lung cancer reported higher symptom burden than the others. (ref: Cleeland CS et al. Levels of symptom burden during chemotherapy for advanced lung cancer: differences between public hospitals and a tertiary cancer center. J Clin Oncol. 2011 Jul 20;29(21):2859-65.). To obtain a 95% confidence interval as 22%-38%, we will need 148 evaluable patients. Considering a 20% attrition, we will recruit 185 patients.

Data analysis

For inclusion in the final analysis, at least the baseline assessment and one successful follow-up is required. The last observation carried forward imputation method will be used to impute missing data. We will conduct a sensitive analysis to exam whether the symptom burden of the complete cases is significantly different from that of cases with missing.

Continuous data will be described as mean±SD while categorical data will be described as number and percentage. The changing trends of target symptoms intensity over time will be

presented by line charts. The improvement on the intensity of the patients' target symptoms and the PRO impact of target symptoms on patient's life in 4 weeks after the initial visiting will be analyzed by general linear mixed model, while the appropriate frequency of ePRO screening for different symptoms will be determined according to significant change point of ePRO score. The impact of target symptoms intensity on quality of life, the alert value of each symptom and, most appropriate PRO items for the targeted symptoms of the screening and the effects of co-morbidity and chronic diseases on symptom burden and symptom management will be analyzed by regression models. Differences are considered statistically significant if the two-tailed p values of <0.05. All quantitative data analysis will be performed using R 3.6.1 and Python 3.7.4, while the transcription of qualitative interview will be coded and analyzed using NVivo 11.0.

Patient and public involvement

Patients and the general public were not involved in the design, recruitment and implementation of the study. We have no plans of informing the study participants regarding the results of this study. However, the results will be disseminated to the applicants in the form of a published article as requested.

ETHICS AND DISSEMINATION

The protocol is registered and any amendments to the research protocol will be submitted for IRB approval. The results in this study will be first reported at relevant medical conferences and then will eventually be published in peer-reviewed journals.

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Contributors LT, YP, YH and QS contributed to the study design. LT, YP, YH, XH, ZL, CZ, XW, YZ, SH, YW, YZ, LS, BW, XL performed the study. YP, YH, XH, ZL, CZ, XW drafted the initial manuscript. LT and QS revised the draft. All authors have reviewed and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the (IRB) of Peking University Cancer Hospital on 14 May 2019 (2019YJZ34).

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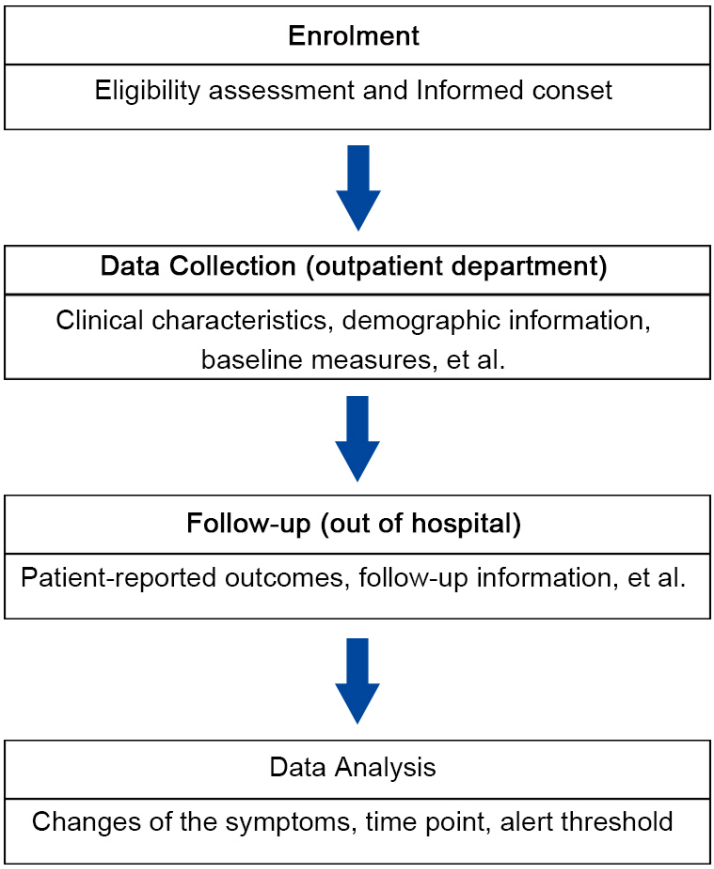

Figure 1 The flow chart of this study

90x99mm (300 x 300 DPI)

Figure 2 Peking University Cancer Hospital project case

160x59mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Check
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	✓
	2b	All items from the World Health Organization Trial Registration Data Set	✓
Protocol version	3	Date and version identifier	✓
Funding	4	Sources and types of financial, material, and other support	NA
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	✓
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	✓
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	✓
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	✓
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	✓

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	✓
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	✓
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	NA
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	✓
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	✓
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	✓
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	✓
Methods: Assignment of interventions (for controlled trials)			**NA**
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	✓
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	✓
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	✓
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	✓
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	✓
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	✓
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	✓

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	✓
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	✓
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	✓
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	✓
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	✓
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	✓
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	✓
	31b	Authorship eligibility guidelines and any intended use of professional writers	✓
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	✓

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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A longitudinal study of symptom burden in outpatients with advanced cancers based on Electronic Patient Reported Outcome (ePRO) platform: a single institution, prospective study protocol

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A longitudinal study of symptom burden in outpatients with advanced cancers based on Electronic Patient Reported Outcome (ePRO) platform: a single institution, prospective study protocol

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ABSTRACT

Introduction: A novel and brief electronic Patient Report Outcome (ePRO) Platform is needed for implementing evidence-based symptom management in outpatients with advanced cancer. We describe the protocol for establishing the methodology for measuring symptom burden, and for then to provide critical parameters needed to implement better symptom management on the ePRO platform.

Methods and analysis: The study focuses on the patients with advanced lung cancer, stomach cancer, esophagus cancer, liver cancer, colorectal cancer or breast cancer. The primary outcome is the changes of symptom burden, The study will prospectively monitor patient's symptom burden, physical and psychological outcomes with MD Anderson Symptom Inventory (MDASI), and other PRO instruments (ISI, HADS, PHQ-9, and EQ5D5L).The secondary outcomes include feasibility of using ePRO, symptom related QoL, reasons for no changes of symptom burden, defining frequency of PRO assessments and cut-points, items for screening, and management of comorbidity. After initial outpatient visit for baseline assessment, ePRO system automatically sends ePRO follow-up notification weekly for 4 weeks to patients. The characteristics and changing trajectory of symptoms burden of outpatients with advanced cancer will be described. Parameters for using PROs, such as optimal time points for follow-up and cut-off point for alert will be determined. The feasibility of ePRO platform to track the changes of target symptoms in outpatients will be evaluated.

Ethics and dissemination: The study protocol and related documents were approved by the Institutional Research Board (IRB) of Peking University Cancer Hospital on 14 May 2019

(2019YJZ34). The manuscript is based on the latest protocol of Version 4.0, 30 June 2019. The results of this study will be disseminated through academic workshops, peer-reviewed publications and conferences.

RESULT: The study will provide data to guide the development and implementation of ePRO for psycho oncology.

Trial Registration: chictr.org.cn ChiCTR1900023560

Key words: advanced cancer, symptom management, out-patients, Electronic Patient Reported Outcome, a longitudinal study

There are several strengths and limitations of this study.

- The study is a prospective cohort study with a total of 7 follow-ups conducted within 4 weeks. It focuses on establishing a symptom management platform for outpatient ePRO and obtain the dynamic symptoms trajectory of patients outside the hospital
- Instead of a single tumor site, the six most common tumor sites are represented: lung cancer, gastric cancer, esophageal cancer, liver cancer, colorectal cancer, breast cancer.
- PRO data are collected using an e-questionnaire based on WeChat, a major communication app in China.
- A group of questionnaires are used to measure the comprehensive well-being of patients, mainly including MDASI-C, ISI, HADS, PHQ-9 **and** EQ5D5L.

INTRODUCTION

According to the official report by the National Central Cancer Registry of China, cancer is the leading cause of death in China; there were 4.3 million newly diagnosed cancer cases and 2.8 million cancer deaths in 2015 in China. Lung cancer, gastric cancer, liver cancer, esophageal cancer and colorectal cancer rank as the top five cancers in men, and breast cancer, lung cancer, gastric cancer, colorectal cancer and esophageal cancer rank as the top five cancers in women [1]. Cancer patients suffer from various symptoms due to the disease itself and treatment-related adverse reactions [2-4]. Studies have shown that one third of patients undergoing cancer treatments reported three or more moderate to severe symptoms [5]. The symptom burden of advanced cancer patients is even more serious.[4, 5] if the symptoms were not addressed properly in time, which will affect the quality of life and daily functions negatively and even shorten the survival period of patients.

In recent years, several studies have shown that good symptom management based on patient-reported outcome (PRO) can benefit advanced cancer patients. For example, a single-centered study published in JAMA in 2017 showed that systematic symptom monitoring can significantly prolong the survival of patients by 5.2 months [6], which even achieved better results than most newly approved anti-cancer drugs in 2016. In 2019, a multi-centered study of Web-based follow-up of PRO symptoms demonstrated once again that this approach could bring survival benefits to patients. [7]

However, there are few studies on effective symptom management of the cancer patients in routine patient care in China. The clinical doctors and nurses need a help for how to quickly capture the patient's dynamic change on symptom burden in patient's routine clinic appointment

under the busy working flow, and the patients also need an approach for reporting symptoms actively. A lot of the symptom management are dealt with in the outpatient clinic, however, there is no monitoring system on patients' status when they are out of the hospital.

In order to resolve this problem, we have established an ePRO platform to monitor the symptom changes when the patients have left the clinic and gone back home. The platform is designed to monitor the changes of the symptom burden through PROs among outpatients. With lack of longitudinal data of physical, psychological, social symptom burden for Chinese oncology patients, the proposed study aimed to include PROs of multiple symptom assessment tool, functioning measure and HRQoL measure. Since there are many differences between the Chinese culture and Western culture, the ePRO platform is also in different format. In Western countries, some of the electronic applications are through e-mail, but e-mail **is** not widely used in Chinese population especially by the elderly. We inserted the ePRO platform in the Wechat applet in mobile, for Wechat is the most popular social networking app in China. It was reported the popularization rate of Wechat in China in 2018 was 87.3%, and according to our experiences, most of our patients, even the elderly can use Wechat.

The purpose of this study is to describe the changes of the target symptoms (pain, insomnia, fatigue, anxiety, depression, nausea and vomiting) of outpatients within 4 weeks after their first visit in the symptom management clinic and to test the feasibility to track patients' symptom changes through ePRO platform, to examine the impact of symptom changes on quality of life, to explore the causes of uncontrolled symptoms within four weeks; to determine the appropriate frequency, PRO items and alert score of PRO screening for different symptoms; to analyze the effects of co-morbidity and chronic diseases on symptom burden and symptom management of

cancer patients.

METHODS AND ANALYSIS

Study design

This is a real-world, ongoing, longitudinal single-center prospective study with a total of 7 follow-ups conducted within 4 weeks after the first visit of the symptom management clinic (on Day 1, Day 3, Day 7, Day 10, Day 14, Day 21 and Day 28). The flow chart of this study is shown in Figure 1(Figure 1: The flow chart of this study). After the last follow-up, a semi-structured interview will be conducted with patients whose symptom scores worsen or improved less than 2 points after 4 weeks.

Setting

This study was initiated by Department of Psycho-oncology In Peking University Cancer Hospital and started on June 2019 and is estimated to be completed before 31 March 2020. The site is the symptom management outpatient clinic in Peking University Cancer Hospital.

Study population and eligibility criteria and recruitment

Patients who visit the symptom management clinic for managing difficult pain or psychological symptoms. Most of the patients are recommended by their oncologist, some patients were recommended by other patients who had been treated in this clinic, while some patients saw advertisement of this clinic. Those patients include both patients undergoing active treatment for

cancer and patients only having palliative symptomatic management. Eligible patients are required to be 1) Over 18 years of age; 2) fluency in Chinese; 3) a confirmed diagnosis of advanced lung cancer, liver cancer, gastric cancer, esophageal cancer, colorectal cancer and breast cancer. Exclusion criteria include 1) a history of major severe mental disorders, unable to cooperate with the investigator; 2) poor physical condition, judged by the attending physician, not suitable for participating in the study; 3) being not able to use ePRO platform.

All the eligible patients who visit the symptom management clinic at the first time will be invited to participant in this study by the doctors in this clinic. If the patients are interested in this study, a research assistant will inform this study to patients in detail and get their written inform consent.

Study objectives

The primary objective is systemic monitoring changes of target symptoms (including pain, fatigue, insomnia, anxiety, depression, nausea and vomiting) in patients with advanced cancer in the symptom management clinic of Peking University cancer hospital during a systematic follow-up within 4 weeks.

The second objectives are as follow:

(1) Evaluating the feasibility of tracking changes in target symptoms in outpatients through the ePRO follow-up system.

(2) Observing the improvement of quality of life in patients seeking symptom management in Department of Psycho-Oncology within 4 weeks after initial visiting.

(3) Finding out the reasons why the symptoms of outpatients cannot be improved within 4 weeks

after the first visiting through a qualitative research.

(4) Determining the appropriate frequency of PRO symptom screening through the description and analysis of the changes in patients' symptoms during the 4-week follow-up after initial visiting.

(5) Exploring the most appropriate PRO items for the targeted symptoms of the screening.

(6) Determining the alert score of each PRO symptom through the analysis of the symptom changes during the follow-up 4 weeks after initial visiting.

(7) Analyzing the effects of co-morbidity and chronic diseases on symptom burden and symptom management of cancer patients.

Withdrawal criteria

Patients undergo a brief interview with a research assistant to identify the following exclusion criteria: (1) major communication difficulties; (2) inability to commit to the required 7 follow-up PRO (i.e., too ill to participate); (3) cognitive impairment;(4) those who do not follow the study protocol (deliberately providing incorrect PRO data) ;(5) those who ask to withdraw from the research or (6) other conditions that require withdrawal as assessed by the investigator

Outcomes

Primary Outcomes

The primary outcomes are the changes on the intensity of the patients' target symptoms (including pain, fatigue, insomnia, anxiety, depression, nausea and vomiting) in 4 weeks after the first

visiting.

Secondary Outcomes

The second outcomes include as follow:

(1) Feasibility of tracking patients' symptoms with ePRO which contains two feasibility indexes:

1) At least 50% of patients completed self-report within 24 hours after being sent the follow-up message; more than 70% of patients completed self-report within 24 hours after being called; at least 70% of patients complete all self-reports within 4 weeks.

2) The percentage of patients who met the eligibility criteria agreed to participate in the study is 80%.

(2) The impact of changing trends of target symptoms intensity on quality of life over a 4-week period.

(3) The causes of uncontrolled symptoms within 4 weeks.

(4) The appropriate frequency of PRO screening for different symptoms with the method of looking for significant changes in PRO scores (such as using generalized mixed effect model).

(5) The most appropriate PRO items for the targeted symptoms of the screening, with the optimal reliability and validity.

(6) The alert scores of PRO screening for different symptoms with clinical significance were determined by the criterion validity (such as EQ-5D) using the regression analysis model.

(7) The effects of co-morbidity and chronic diseases on symptom burden and symptom management of cancer patients.

Study instruments, Data collection, management and monitoring, qualitative interview

Totally 9 study instruments are used in this study, including 6 PRO instruments.

(1) PRO instruments

MD Anderson Symptom Inventory, MDASI.

MDASI [8][9] is a widely used symptom inventory with 19 items (13 items for symptom severity, 6 items for interference), 0=Nothing, 10=Most severity. Psychometric study has shown that the Chinese version of MDASI has good reliability and validity, so that the Chinese MDASI can be used to measure the severity of multiple symptoms and their impact on function in Chinese cancer patients. Moreover, we have added 5 more items for specific cancer sites in our study to capture special characteristics: constipation is added to all cancers, hot flash and upper limb lymphedema is specific for breast cancer, cough is specific for lung cancer and swallowing difficulty is specific for esophagus cancer. A single "quality of life" item was used to anchor this study.

Insomnia Severity Index, ISI

It is a validated scale for measuring insomnia severity in the last two weeks. There are total 7 items, 0-4 score for each item, with the sum score of 0-28. 0-7 score indicates no insomnia; 8-14 score indicates subclinical insomnia; 15-21 score indicates moderate insomnia, 22-28 score indicates severe insomnia. Simplified Chinese version of ISI has been validated by Lin et al [10].

Hospital Anxiety and Depression Scale, HADS

HADS has 14 items with a score spectrum of 0-4 for each item, which is used to measure the anxiety and depression for the patients in the past week. It is used for patients with somatic symptoms in the general hospitals with good reliability and validity and recommended for patients with advanced cancer or receiving palliative care [11].

9 Item Patient Health Questionnaire, PHQ-9

PHQ-9 is used to evaluate the depression of patients in the past two weeks. The score spectrum of symptoms severity is from 0=none at all to 3=almost every day, and the total score was from 0-27. Depression can be considered when the sum score is ⩾10. Simplified Chinese version of PHQ-9 has a good validation [12].

EuroQol Five Dimensions questionnaire-5L version, EQ-5D-5L

EQ-5D-5L is a multidimensional measurement for health-related quality of life, which contains these five domain to describe patients' health: 1) mobility; 2) self-care; 3) usual activities; 4) pain/discomfort; 5) anxiety/depression, with a scale from 0=No difficulty to 4=extremely difficulty [13]][14]

Distress Thermometer, DT

DT is recommended by NCCN in the distress management guideline and was introduced to China in 2007. DT has only one item with a scale from 0=No distress to 10=extreme distress. Problem list including 5 domains: practical problem, communication problem, emotion problem, physical problem, spirit and religion problem. It is recognized as the briefest tool for distress screening, especially in busy oncology clinical practice [15].

The target symptoms are measured by PRO instruments: pain and fatigue are measured by MDASI; depression is measured by HADS-D and PHQ-9; anxiety is measured by HADS-A; insomnia is measured by ISI and MDASI; nausea and vomiting is measured by MDASI.

(2) General demographic and disease data questionnaire.

General demographic data includes age, sex, occupation, etc. The latter includes disease diagnosis, staging, treatment, medication, etc.

(3) ECOG score.

This is a health tool that evaluates cancer patient functional status and clinically stratifies these patients` ability to tolerate therapies, which runs from 0 to 5, with 0 denoting perfect health and 5 death [16].

(4) Charlson Comorbidity Index.

Comorbid conditions are best evaluated with use of the Charlson Comorbidity Index. Many studies have shown that the impact of comorbidities is significant on the survival outcomes and prognosis of cancer patients. Here are the conditions used in the comorbidity and the number of points they are awarded: score of 1 for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, and diabetes mellitus(in terms of diabetes mellitus, score of 1 for uncomplicated and 2 for end organ damage); score of 2 for moderate to severe chronic kidney disease, hemiplegia, leukemia, malignant lymphoma, solid tumor(2 in case of presence and 6 in case tumor is metastatic), liver disease(mild 1 point, moderate to severe 3 points) and AIDS [17].

(5) Data collection

PRO data are collected using an ePRO platform. ePROhub™ is dedicated on ePRO clinical research on patient's data collection, assessment and management launched by ePRO Vision (Beijing) Health Technology Co Ltd. in 2018. The platform consist of ePROcell™ and ePROhub™ two parts. Smartphone-based client, ePROcell™, is for patient's ePRO reporting and clinician's ePRO data management, intervention and project management. ePROhub™ platform,

the EDC(electronic data capture) complied, is the cloud based symptom, management platform to store and assess patient's data, support clinicians manage patient's data and intervention activities with AI (artificial intelligence) capability, output data to other database platform for further data processing. The system could recognize the individual scores of MDASI items due to the cut-point that we set-up. For those scale that needed to be calculate for results, such as PHQ-9, were captured by WeChat first, save in RedCape and calculate later. Figure 2 (Figure 2: Peking University Cancer Hospital project case) shown below gives tot below gives total picture in Beijing Cancer Hospital project case.

ePROcell™ is fully integrated with internet-based WeChat, the most popular and the biggest social network application in China, to maximize WeChat's advantages of world-class user experience and massive population coverage into ePRO practice enable ePRO data collection and management happening anywhere and anytime is possible. The pre-register patients can easy click the landscape-screen to answer relevant questionnaires and sending back to clinicians via cloud-based ePROhub™. Figure 3 shows a screen shot to show how the platform looked to patients (Figure 3: The screen of platform looked to patients).The e-informed consent and e-signature is implemented before- and after reporting to secure ePRO data effectiveness and integrity. The pre-defined threshold of server symptom plus triage process support clinician efficiently communicate with patients via ePROcell™ when e-alert and e-reminder occurred.

According to the pre-defined schedule, ePROcell™ automatically send out reminder message to patients during the reporting-day, and confirmation message after patient submit. With PRO-calendar and PRO management from ePROcell™, clinicians could easily review and

manage project progress anytime to secure data quality, reporting progress and project quality. The ePROcell™ frequently visit patient's and clinical data stored in ePROhub™ and integrated backend database platform to support clinicians' regular patient's symptom following up and symptom management activities, which is the most efficient way to deliver effective symptom intervention and routine care with desired data-driven patient-centered care.

The cloud-based ePROhub™, located in hospital's datacenter, is the data management platform and has dedicated data communication channel with the backend database platform REDCap, the US free of Charge SQL database platform, via it's API (Application Program Interface) to synchronize pre-defined clinical data, like CRF (case report form) and scale, and patient's ePRO data. The ePRO platform could recognize the individual scores of MDASI items due to the cut-point that we set-up. For those scale that needed to be calculate for results, such as PHQ-9 are captured by WeChat first, saved in REDCap and calculated later. The output data could be converted to professional statistics program, like SAS or SPSS, with standard data format for their final data analysis. All data are deidentified and stored in the REDCap platform. Data monitoring is carried out regularly by the IRB of Peking University Cancer Hospital.

（6）Semi-structured interview

A face to face interview, will be conducted following an interview outline but if it is difficult for patients to come to the hospital, the interview could be done over the phone.

Quality control

Investigators received standard operating procedure training before recruiting the patients. A standardized operation process manual and an operation video has been made and distributed to all

the research assistant. The Group training was organized for one time while individual (one-to-one) training were carried out one-to-one. After the training, all research assistants required to pass a test of practical operation to getting start on their official work.

There will be a Question & Answer session to solve operation problems after around 10 cases enrolled. In addition, the practical problems that faced by research assistants will be shared in WeChat working group at any time.

Sample size calculation

We will use the group-based trajectory model (GBTM) to identify subgroups with distinct trajectories of symptom development during the 4 week of investigation. Previous studies showed that about 30% of patients with advanced lung cancer reported higher symptom burden than the others [18]. The 95% confidence interval according to different symptom prevalence are 40%, 32.11-47.89%; 30%, 22.62-37.38%; 20%, 13.56-26.44%. To obtain a 95% confidence interval as 22%-38%, we will need 148 evaluable patients. Considering a 20% attrition, we will recruit 185 patients.

Data analysis

For inclusion in the final analysis, at least the baseline assessment and one successful follow-up is required. The last observation carried forward imputation method will be used to impute missing data. We will conduct a sensitivity analysis to exam whether the symptom burden of the complete cases is significantly different from that of cases with missing data.

Continuous data will be described as mean±SD while categorical data will be described as number and percentage. The changing trends of target symptoms intensity over time will be presented by line charts. The improvement on the intensity of the patients' target symptoms and the PRO impact of target symptoms on patient's life in 4 weeks after the initial visiting will be analyzed by general linear mixed model, while the appropriate frequency of ePRO screening for different symptoms will be determined according to significant change point of ePRO score. The impact of target symptoms intensity on quality of life, the alert value of each symptom and, most appropriate PRO items for the targeted symptoms of the screening and the effects of co-morbidity and chronic diseases on symptom burden and symptom management will be analyzed by regression models. Differences are considered statistically significant if the two-tailed p values of <0.05.

The recoded qualitative materials will be transcribed into words and be analyzed using a thematic analysis to develop a frame work of topics on causes of uncontrolled symptoms. All quantitative data analysis will be performed using R 3.6.1 and Python 3.7.4, while the transcription of qualitative interview will be coded and analyzed using NVivo 11.0.

DISCUSSION

Advanced cancer patients suffered from severe symptom burden and ePRO platform could be a useful tool to monitor and to manage the patients' symptoms at home and it is urgent to incorporate ePRO into patients' electronic health record [19]. This is a feasibility study to

investigate the use of an electronic patient-reported outcome platform, and this data will provide guide to apply this novel platform in clinical practice of symptom management.

The patients who visit symptom management clinic at the first time usually suffered one or more kinds of severe symptoms and will be given drug-therapy or non-drug therapy or both to address their symptoms. Usually in the first few days after their first visit, the symptoms will change rapidly. So we arrange 7 follow-up on Day 1, Day 3, Day 7, Day 10, Day 14, Day 21 and Day 28 after the first visit.

The information security is very important. Information of completion progress would be shown on the physician sites. Each response on WeChat requires an authorized security token to be submitted, a secure network connection ensures that collected responses were only sent to the database established in Beijing Cancer Hospital. The ePRO and data transmission network were reviewed and approved by the information security engineer of Beijing Cancer Hospital.

So far this ePRO platform hasn't been investigated into patient records and the ePRO platform will send a notification to remind the patients who get worsen symptoms to visit the symptom management clinic as soon as possible. It is urgent to incorporate ePRO into patients' electronic health record. ePRO platform could be a useful tool to monitor and manage the patients' symptoms at home.

If the results of this study show this platform is feasible to use and is acceptable by the patients, our next goal is to implement ePRO into clinical practice by integrate it with patient's electronic health record. We hope this platform could be helpful for clinicians to capture their patients'

symptom change in-time and offer a more flexible symptom/ medication management when worsening symptoms were developed.

Although there are culture differences between Chinese and Western culture, the intervention that this study describes could be replicated in many countries allowing for the use of alternative mobile platforms, and the results would be widely applicable.

Patient and public involvement

Patients and the general public were not involved in the design, recruitment and implementation of the study. We have no plans of informing the study participants regarding the results of this study. However, the results will be disseminated to the applicants in the form of a published article as requested.

ETHICS AND DISSEMINATION

The protocol is registered and any amendments to the research protocol will be submitted for IRB approval. The results in this study will be first reported at relevant academic conferences, workshops and then will eventually be published in peer-reviewed journals.

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Contributors LT, YP, YH and QS contributed to the study design. LT, YP, YH, XH, ZL, CZ, YZ, SH, YW, YZ, LS, BW, XL performed the study. YP, YH, XH, ZL, CZ drafted the initial manuscript. LT and QS revised the draft. All authors have reviewed and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the (IRB) of Peking University Cancer Hospital on 14 May 2019 (2019YJZ34).

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Figure 1: The flow chart of this study

Figure 2: Peking University Cancer Hospital project case

Figure 3: The screen of platform looked to patients

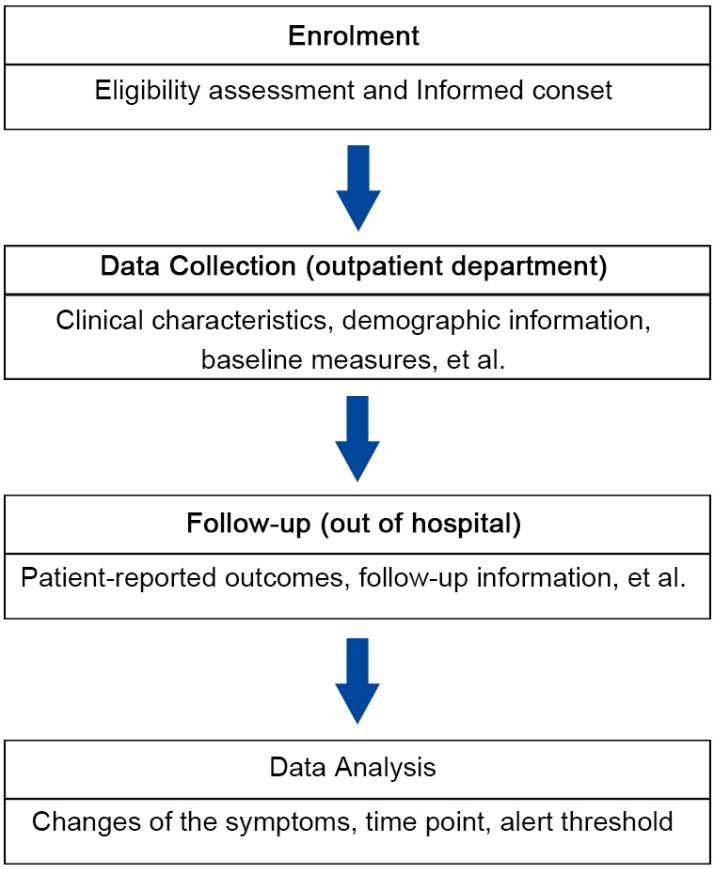
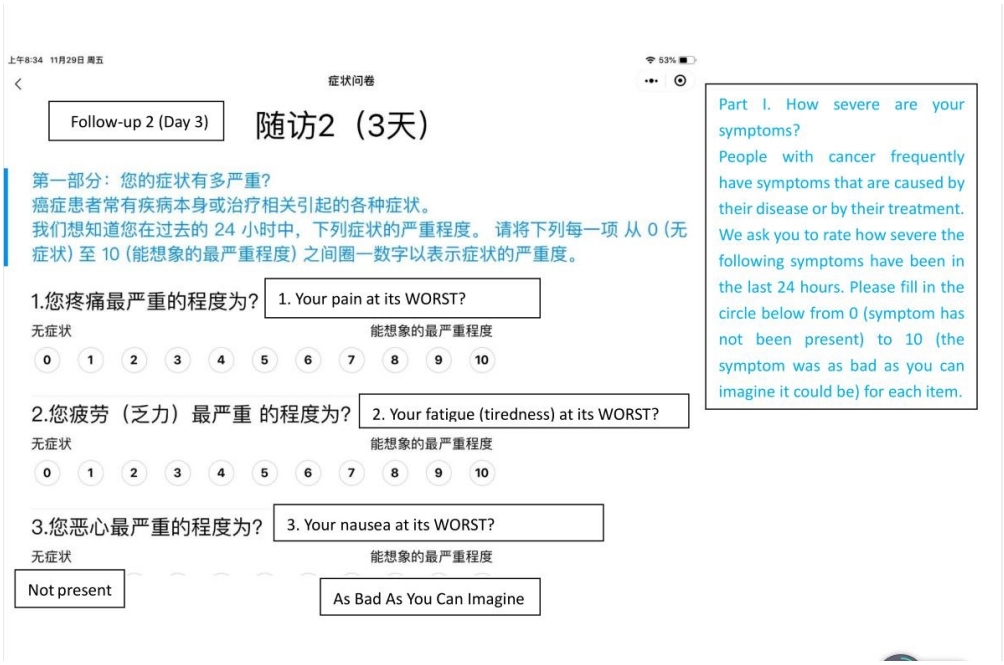


Figure 1 The flow chart of this study

90x99mm (300 x 300 DPI)

Figure 2 Peking University Cancer Hospital project case

160x59mm (300 x 300 DPI)



The screen of platform looked to patients

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A longitudinal study of symptom burden in outpatients with advanced cancers based on Electronic Patient Reported Outcome (ePRO) platform: a single institution, prospective study protocol

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A longitudinal study of symptom burden in outpatients with advanced cancersbased onElectronic Patient Reported Outcome (ePRO) platform: a single institution, prospective study protocol

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ABSTRACT

Introduction: An electronic Patient Report Outcome (ePRO) platform is needed for implementing evidence-based symptom management in outpatients with advanced cancer. We describe the overall protocol and the methodology for measuring symptom burden, to provide critical parameters needed to implement symptom management on the ePRO platform.

Methods and analysis: The study focuses on patients with advanced lung cancer, stomach cancer, esophagus cancer, liver cancer, colorectal cancer or breast cancer. The primary outcome is the change of symptom burden. MD Anderson Symptom Inventory (MDASI), and other PRO instruments (ISI, HADS, PHQ-9, and EQ5D5L) were used. The secondary outcomes include feasibility of using ePRO, symptom related QoL, reasons for no improvement of symptoms, defining frequency of PRO assessments and cut-points, items for screening, and management of comorbidity and satisfaction with ePRO platform in patients and health providers. After initial outpatient visit for baseline assessment, ePRO system will automatically send follow-up notification 7 times over 4 weeks to patients. The characteristics and changing trajectory of symptoms of patients will be described. Parameters for using PROs, such as optimal time points for follow-up and cut-off point for alert will be determined. The feasibility of ePRO platform to track the changes of target symptoms in outpatients will be evaluated.

Ethics and dissemination: The study protocol and related documents were approved by the Institutional Research Board (IRB) of Peking University Cancer Hospital on 14 May, 2019

(2019YJZ34). The results of this study will be disseminated through academic workshops, peer-reviewed publications and conferences.

Trial Registration: chictr.org.cn ChiCTR1900023560

Key words:advanced cancer, symptom management, out-patients, Electronic Patient Reported Outcome, a longitudinal study

There are several strengths and limitations of this study.

- The study is a prospective cohort study with a total of 7 follow-ups conducted within 4 weeks. It focuses on establishing a symptom management platform for outpatient ePRO and obtain the dynamic symptoms trajectory of patients outside the hospital
- Instead of a single tumor site, the six most common tumor sites are represented: lung cancer, gastric cancer, esophageal cancer, liver cancer, colorectal cancer, breast cancer.
- PRO data are collected using an e-questionnaire based on WeChat, a major communication app in China.
- A group of questionnaires are used to measure the comprehensive well-being of patients, mainly including MDASI-C, ISI, HADS, PHQ-9 and EQ5D5L.

INTRODUCTION

According to the official report by the National Central Cancer Registry of China, cancer is the leading cause of death in China; there were 4.3 million newly diagnosed cancer cases and 2.8 million cancer deaths in 2015 in China. Lung cancer, gastric cancer, liver cancer,

esophageal cancer and colorectal cancer rank as the top five cancers in men, and breast cancer, lung cancer, gastric cancer, colorectal cancer and esophageal cancer rank as the top five cancers in women[1]. Cancer patients suffer from various symptoms due to the disease itself and treatment-related adverse reactions [2-4]. Studies have shown that one third of patients undergoing cancer treatments reported three or more moderate to severe symptoms [5]. The symptom burden of advanced cancer patients is even more serious.[4, 5]If the symptoms are not addressed properly in time, the quality of life and daily functions will be affected negatively and even shorten the survival period of patients.

In recent years, several studies have shown that good symptom management based on patient-reported outcome (PRO) can benefit advanced cancer patients. For example, a single-centered study published in JAMA in 2017 showed that systematic symptom monitoring can significantly prolong the survival of patients by 5.2 months [6], which even achieved better results than most newly approved anti-cancer drugs in 2016. In 2019, a multi-centered study of Web-based follow-up of PRO symptoms demonstrated once again that this approach could bring survival benefits to patients.[7]

However, there are few studies on effective symptom management of the cancer patients in routine patient care in China. The clinical doctors and nurses need a help for how to quickly capture the patient's dynamic change on symptom burden in patient's routine clinic appointment under the busy work flow, and the patients also need an approach for reporting symptoms actively. A lot of the symptom management are dealt with in the outpatient clinic, however, there is no monitoring system on patients' status when they are out of the hospital.

In order to resolve this problem, we have established an ePRO platform to monitor the symptom changes when the patients have left the clinic and gone back home. The plat form is designed to monitor the changes of the symptom burden through PROs among outpatients. With lack of longitudinal data of physical, psychological, social symptom burden for Chinese oncology patients, the proposed study aimed to include PROs of multiple symptom assessment tool, functioning measure and HRQoL measure. Since there are many differences between the Chinese culture and Western culture, the ePRO platform is also in different format. In Western countries, some of the electronic applications are through e-mail, but e-mail **is** not widely used in Chinese population especially by the elderly. We inserted the ePRO platform in the Wechat applet in mobile, for Wechat is the most popular social networking app in China. According to the latest report, there are 1.15 billion monthly active user of WeChat, over 80% population in China [8]. And according to our experiences, most of our patients, even the elderly can use Wechat.

METHODS AND ANALYSIS

Study design

This is a real-world, ongoing, longitudinal single-center prospective study with a total of 7 follow-ups conducted within 4 weeks after the first visit of the symptom management clinic(on Day 1, Day 3, Day 7, Day 10, Day 14, Day 21 and Day 28). The flow chart of this study is shown in Figure 1 (Figure 1: The flow chart of this study). After the last follow-up, a

semi-structured interview will be conducted with patients whose symptom scores worsen or not improved after 4 weeks.

Setting

This study was initiated by Department of Psycho-oncology In Peking University Cancer Hospital and the study was started in June 1st, 2019 and was planned to be finished by December 31, 2020. However, the completion data may be delayed for a few months because of the COVID-19. The site is the symptom management outpatient clinic in Peking University Cancer Hospital.

Study population and eligibility criteria and recruitment

Patients who visit the symptom management clinic for managing difficult pain or psychological symptoms. Most of the patients are referred by their oncologist, some patients were referred by other patients who had been treated in this clinic, while some patients saw advertisements. Those patients include both patients undergoing active treatment for cancer and patients receiving palliative symptomatic management. Eligible patients are required to be 1) Over 18 years of age; 2) fluent in Chinese; 3) a confirmed diagnosis of advanced lung cancer, liver cancer, gastric cancer, esophageal cancer, colorectal cancer and breast cancer.;4) ability to give consent. Exclusion criteria include 1) a history of major severe mental disorders, unable to cooperate with the investigator; 2) poor physical or mental condition,

judged by the attending physician, not able to complete the whole study; 3) being not able to use ePRO platform.

All eligible patients who visit the symptom management clinic at the first time will be invited to participate in this study by the doctors in this clinic. If the patients are interested in this study, a research assistant will inform patients in detail and get their written informed consent.

Study objectives and outcomes

The primary objective is systemic monitoring changes of the intensity of target symptoms (including pain, fatigue, insomnia, anxiety, depression, nausea and vomiting) in patients with advanced cancer in the symptom management clinic of Peking University cancer hospital during a systematic follow-up within 4 weeks.

The second objectives are as follow:

(1) Evaluating the feasibility of tracking changes in target symptoms in outpatients through the ePRO follow-up system.

1) At least 50% of patients completed self-report within 24 hours after being sent the follow-up message; more than 70% of patients completed self-report within 24 hours after being called; at least 70% of patients complete all self-reports within 4 weeks.

2) The percentage of patients who met the eligibility criteria agreed to participate in the study is 80%.

(2) Observing the changes of quality of life in patients seeking symptom management in Department of Psycho-Oncology within 4 weeks after initial visiting.

(3) Finding out the reasons why the symptoms of outpatients cannot be improved within 4 weeks after the first visiting through a qualitative research.(interview)

(4) Determining the appropriate frequency of PRO symptom screening through the description and analysis of the changes in patients' symptoms during the 4-week follow-up after initial visiting.

(5) Exploring the most appropriate PRO items for the targeted symptoms of the screening.

(6) Determining the alert score of each PRO symptom through the analysis of the symptom changes during the follow-up 4 weeks after initial visiting.

(7) Analyzing the effects of co-morbidity and chronic diseases on symptom burden and symptom management of cancer patients.

(8) To explore the satisfaction with ePRO platform in patients and health provider by a focus group interview.

Withdrawal criteria

Patients undergo a brief interview with a research assistant to identify the following exclusion criteria: (1) major communication difficulties; (2) inability to commit to the required 7 follow-up PRO (i.e., too ill to participate); (3) cognitive impairment;(4) those who do not follow the study protocol (deliberately providing incorrect PRO data) ;(5) those who ask to withdraw from the research or (6) other conditions that require withdrawal as assessed by the investigator

Study instruments, Data collection, management and monitoring, qualitative interview

Totally 9 study instruments are used in this study, including 6 PRO instruments. The patients need to fill all the questionnaires only for three times at the baseline assessment, Day 14 and Day 28 follow-up. At other follow-ups, patients only need to fill MD Anderson Symptom Inventory with only 19 items.

(1) PRO instruments

MD Anderson Symptom Inventory, MDASI.

MDASI [9][10] is a widely used symptom inventory with 19 items (13 items for symptom severity, 6 items for interference), 0=Nothing, 10=Most severity. Psychometric study has shown that the Chinese version of MDASI has good reliability and validity, so that the Chinese MDASI can be used to measure the severity of multiple symptoms and their impact on function in Chinese cancer patients. Moreover, we have added 5 more items for specific cancer sites in our study to capture special characteristics: hot flash and upper limb lymphedema is specific for breast cancer; cough is specific for lung cancer and swallowing difficulty is specific for esophagus cancer; constipation is added to all cancers, because pain is one of the most common symptoms in advanced cancer patients in all types of cancer and the proportion of these patients using opioid is high. Constipation is one of the most common side effects using opioid, so we added constipation to all cancers. Additionally a single “quality of life” item was used to anchor this study.

Insomnia Severity Index, ISI

It is a validated scale for measuring insomnia severity in the last two weeks. There are total 7

items, 0-4 score for each item, with the sum score of 0-28.0-7 score indicates no insomnia; 8-14 score indicates subclinical insomnia; 15-21 score indicates moderate insomnia, 22-28 score indicates severe insomnia. Simplified Chinese version of ISI has been validated by Lin et al [11].

Hospital Anxiety and Depression Scale, HADS

HADS has 14 items with a score spectrum of 0-4 for each item, which is used to measure the anxiety and depression for the patients in the past week. It is used for patients with somatic symptoms in the general hospitals with good reliability and validity and recommended for patients with advanced cancer or receiving palliative care [12].

9 Item Patient Health Questionnaire, PHQ-9

PHQ-9 is used to evaluate the depression of patients in the past two weeks. The score spectrum of symptoms severity is from 0=none at all to 3=almost every day, and the total score was from 0-27. Depression can be considered when the sum score is ⩾10. Simplified Chinese version of PHQ-9 has a good validation [13].

EuroQol Five Dimensions questionnaire-5L version, EQ-5D-5L

EQ-5D-5L is a multidimensional measurement for health-related quality of life, which contains these five domain to describe patients' health: 1) mobility; 2) self-care; 3) usual activities; 4) pain/discomfort; 5) anxiety/depression, with a scale from 0=No difficulty to 4=extremely difficulty[14]][15]

Distress Thermometer, DT

DT is recommended by NCCN in the distress management guideline and was introduced to China in 2007. DT has only one item with a scale from 0=No distress to 10=extreme distress. Problem list including 5 domains: practical problem, communication problem, emotion

problem, physical problem, spirit and religion problem. It is recognized as the briefest tool for distress screening, especially in busy oncology clinical practice [16].

The target symptoms are measured by PRO instruments: pain and fatigue are measured by MDASI; depression is measured by HADS-D and PHQ-9; anxiety is measured by HADS-A; insomnia is measured by ISI and MDASI; nausea and vomiting is measured by MDASI.

(2) General demographic and disease data questionnaire.

General demographic data includes age, sex, occupation, etc. The latter includes disease diagnosis, staging, treatment, medication, etc.

(3)ECOG score.

This is a health tool that evaluates cancer patient functional status and clinically stratifies these patients` ability to tolerate therapies, which runs from 0 to 5, with 0 denoting perfect health and 5 death [17]. This measure is done by doctors.

(4) Charlson Comorbidity Index.

Comorbid conditions are best evaluated with use of the Charlson Comorbidity Index. Many studies have shown that the impact of comorbidities is significant on the survival outcomes and prognosis of cancer patients. Here are the conditions used in the comorbidity and the number of points they are awarded: score of 1 for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, and diabetes mellitus(in terms of diabetes mellitus, score of 1 for uncomplicated and 2 for end organ damage); score of 2 for moderate to severe chronic kidney disease, hemiplegia, leukemia, malignant lymphoma, solid tumor(2 in case of presence and 6 in case tumor is metastatic), liver disease(mild 1 point, moderate to severe 3 points) and AIDS[18]. It is determined by chart review.

(5) Data collection

PRO data are collected using an ePRO platform. ePROhub™ is dedicated on ePRO clinical research on patient's data collection, assessment and management launched by ePRO Vision (Beijing) Health Technology Co Ltd. in 2018. The platform consist of ePROcell™ and ePROhub™ two parts. Smartphone-based client, ePROcell™, is for patient's ePRO reporting and clinician's ePRO data management, intervention and project management. ePROhub™ platform, the EDC(electronic data capture) complied, is the cloud based symptom, management platform to store and assess patient's data, support clinicians manage patient's data and intervention activities with AI (artificial intelligence) capability, output data to other database platform for further data processing. The system could recognize the individual scores of MDASI items due to the cut-point that we set-up. For those scale that needed to be calculate for results, such as PHQ-9, were captured by WeChat first, save in RedCape and calculate later. Figure 2 (Figure 2: Peking University Cancer Hospital project case) shown below gives tot below gives total picture in Beijing Cancer Hospital project case.

ePROcell™ is fully integrated with internet-based WeChat, the most popular and the biggest social network application in China, to maximize WeChat's advantages of world-class user experience and massive population coverage into ePRO practice enable ePRO data collection and management happening anywhere and anytime is possible. The pre-register patients can easy click the landscape-screen to answer relevant questionnaires and sending back to clinicians via cloud-based ePROhub™. Figure 3 shows a screen shot to show how the platform looks to patients (Figure 3: The screen of platform looked to patients).The

e-informed consent and e-signature is implemented before- and after reporting to secure ePRO data effectiveness and integrity. The pre-defined threshold of server symptom plus triage process support clinician efficiently communicate with patients via ePROcell™ when e-alert and e-reminder occurred.

According to the pre-defined schedule, ePROcell™ automatically send out reminder message to patients during the reporting-day, and confirmation message after patient submit. With PRO-calendar and PRO management from ePROcell™, clinicians could easily review and manage project progress anytime to secure data quality, reporting progress and project quality. The ePROcell™ frequently visit patient's and clinical data stored in ePROhub™ and integrated backend database platform to support clinicians' regular patient's symptom following up and symptom management activities, which is the most efficient way to deliver effective symptom intervention and routine care with desired data-driven patient-centered care.

The cloud-based ePROhub™, located in hospital's datacenter, is the data management platform and has dedicated data communication channel with the backend database platform REDCap, the US free of Charge SQL database platform, via it's API (Application Program Interface) to synchronize pre-defined clinical data, like CRF (case report form) and scale, and patient's ePRO data. The ePRO platform can recognize the individual scores of MDASI items due to the cut-point that we set-up. For those scale that needed to be calculate for results, such as PHQ-9 are captured by WeChat first, saved in REDCap and calculated later. The output data could be converted to professional statistics program, like SAS or SPSS, with standard

data format for their final data analysis. All data are DE identified and stored in the REDCap platform. Protocol monitoring is carried out regularly by the IRB of Peking University Cancer Hospital.

（6）Semi-structured interview

To explore the reasons for why some symptoms could not be improved within 4 weeks after the first visiting. A semi-structured interview will be done in patients with any symptom severity item score of MDASI increased or decreased less than 2 points. The guide of interview was developed with stockholder among our mean problem: why some symptoms could not be improved within 4 weeks after the first visiting. Stockholders include physicians and nurses in symptom management clinic, patients and caregivers. A face to face interview, will be conducted following an interview outline but if it is difficult for patients to come to the hospital, the interview will be done over the phone.

The recoded qualitative materials will be transcribed into words and be analyzed using a thematic analysis to develop a frame work of topics on causes of uncontrolled symptoms. All quantitative data analysis will be performed using R 3.6.1 and Python 3.7.4, while the transcription of qualitative interview will be coded and analyzed using NVivo 11.0.

Quality control

Investigators received standard operating procedure training before recruiting the patients. A standardized operation process manual and an operation video has been made and distributed to all the research assistant. The Group training was organized for one time while individual

(one-to-one) training were carried out one-to-one. After the training, all research assistants required to pass a test of practical operation to getting start on their official work.

There will be a Question& Answer session to solve operation problems after around 10 cases enrolled. In addition, the practical problems that faced by research assistants will be shared in WeChat working group at any time.

Sample size calculation

We will use the group-based trajectory model (GBTM) to identify subgroups with distinct trajectories of symptom development during the 4 week of investigation. Previous studies showed that about 30% of patients with advanced lung cancer reported higher symptom burden than the others [19]. To obtain a 95% confidence interval for 30%, we will need 148 evaluable patients, which was according to different symptom prevalence for 40%, 32.11-47.89%; 30%, 22.62-37.38%; 20%, 13.56-26.44%. Considering a 20% attrition, we will recruit 185 patients.

Data analysis

For inclusion in the final analysis, at least the baseline assessment and one successful follow-up is required. The last observation carried forward imputation method will be used to impute missing data. We will conduct a sensitivity analysis to examine whether the symptom burden of the complete cases is significantly different from that of cases with missing data.

Continuous data will be described as mean±SD while categorical data will be described as number and percentage. The changing trends of target symptoms intensity over time will be presented by line charts. The improvement on the intensity of the patients' target symptoms and the PRO impact of target symptoms on patient's life in 4 weeks after the initial visiting will be analyzed by general linear mixed model, while the appropriate frequency of ePRO screening for different symptoms will be determined according to significant change point of ePRO score. The impact of target symptoms intensity on quality of life, the alert value of each symptom and, most appropriate PRO items for the targeted symptoms of the screening and the effects of co-morbidity and chronic diseases on symptom burden and symptom management will be analyzed by regression models. Differences are considered statistically significant if the two-tailed p values of <0.05.

Patient and public involvement

Patients and the general public were not involved in the design, recruitment and implementation of the study except development of the semi-interview guide. We have no plans of informing the study participants regarding the results of this study. However, the results will be disseminated to the applicants in the form of a published article as requested.

ETHICS AND DISSEMINATION

The protocol was approved by the IRB of Peking University Cancer Hospital on 14 May 2019 (2019YJZ34) and any amendments to the research protocol will be submitted for IRB

approval. The results in this study will be first reported at relevant academic conferences, workshops and then will eventually be published in peer-reviewed journals.

DISCUSSION

Advanced cancer patients suffered from severe symptom burden and ePRO platform could be a useful tool to monitor and to manage the patients' symptoms at home and it is urgent to incorporate ePRO into patients' electronic health record [20]. This is a feasibility study to investigate the use of an electronic patient-reported outcome platform, and this data will provide guide to apply this novel platform in clinical practice of symptom management.

The patients who visit symptom management clinic at the first time usually suffer from one or more severe symptoms and will be given drug-therapy or non-drug therapy or both to address their symptoms. Usually in the first few days after their first visit, the symptoms will change rapidly. So we arrange 7 follow-up on Day 1, Day 3, Day 7, Day 10, Day 14, Day 21 and Day 28 after the first visit.

The information privacy is very important. Information of completion progress would be shown on the physician sites. Each response on WeChat requires an authorized security token to be submitted, a secure network connection ensures that collected responses were only sent to the database established in Beijing Cancer Hospital. The ePRO and data transmission network were reviewed and approved by the information security engineer of Beijing Cancer Hospital.

So far this ePRO platform hasn't been investigated into patient records and the ePRO platform will send a notification to remind the patients with worsening symptoms to visit the symptom management clinic as soon as possible. It is urgent to incorporate ePRO into patients' electronic health record. ePRO platform could be a useful tool to monitor and manage the patients' symptoms at home.

If the results of this study show this platform is feasible to use and is accepted by the patients and staff, our next goal is to implement ePRO into clinical practice by integrate the ePRO with patient's electronic health record. We hope this platform could be helpful for clinicians to capture their patients' symptom change in-time and offer a more flexible symptom/ medication management when worsening symptoms develop.

Although there are culture differences between Chinese and Western culture, the intervention that this study describes could be replicated in many countries allowing for the use of alternative mobile platforms, and the results would be widely applicable.

Contributors LT, YP, YH and QS contributed to the study design. LT, YP, YH, XH, ZL, CZ, YZ, SH, YW, YZ, LS, BW, XLperformed the study. YP, YH, XH, ZL, CZdrafted the initial manuscript. LT and QS revised the draft. All authors havereviewed and approved the final manuscript.

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Figure 1: The flow chart of this study

Figure 2: Peking University Cancer Hospital project case

Figure 3: The screen of platform looked to patients

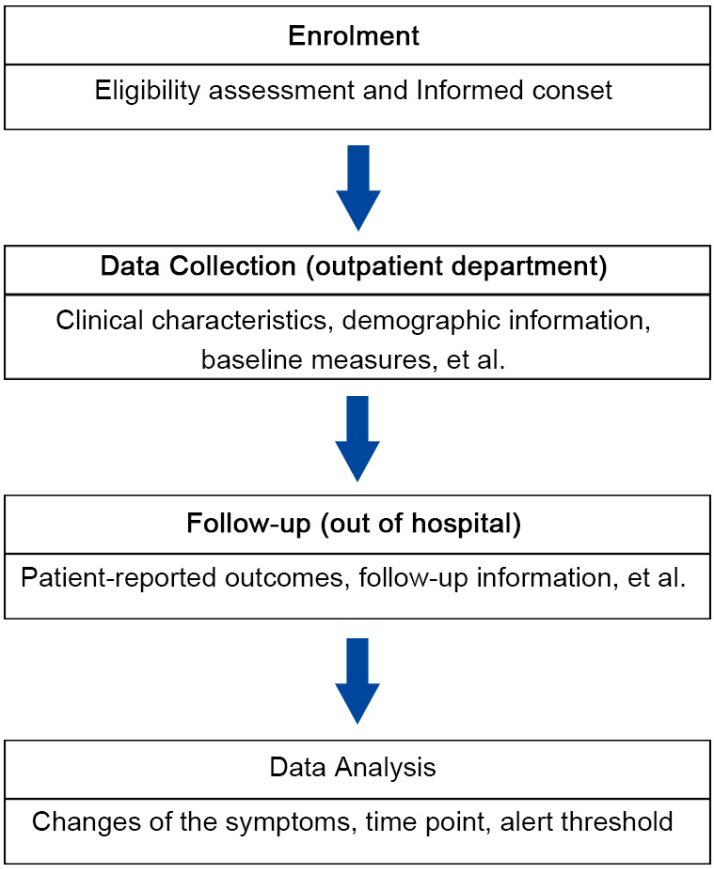
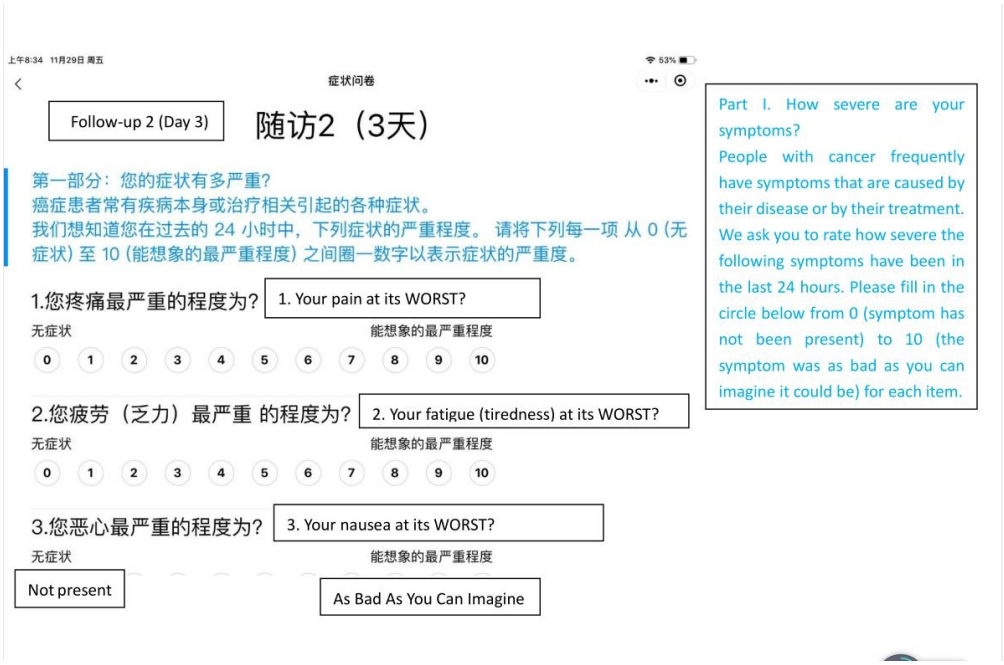


Figure 1 The flow chart of this study

90x99mm (300 x 300 DPI)

Figure 2 Peking University Cancer Hospital project case

160x59mm (300 x 300 DPI)



The screen of platform looked to patients

315x207mm (96 x 96 DPI)