1. STUDY TITLE

Using mHealth Technology to Evaluate Daily Symptom Burden Among Adult Survivors of Childhood Cancer: A Feasibility Study

2. WORKING GROUPS

Primary: Cancer Control and Intervention

3. INVESTIGATORS

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4. BACKGROUND

4.1 Symptom burden among childhood cancer survivors

Cancer therapies predispose childhood cancer survivors to different late effects, including physical and psychological sequelae, chronic health conditions, subsequent neoplasms, and premature death.[1-4] In addition to these late effects, a significant proportion of survivors also experience different symptoms, including pain, abnormal sensation, memory problems, somatization, pulmonary symptoms, and cardiac symptoms.[5] Over 75% of survivors reported experiencing multiple symptoms.[5] In a recent SJLIFE study, four distinct symptom clusters, representing subgroups of survivors having different patterns of physical, somatic, and psychological symptoms, were identified.[6] More severe symptom clusters were significantly associated with poorer quality of life, and physical and cognitive performance deficits.[6] Additionally, previous research has reported the association between experiencing a greater symptom burden and an increased risk of mortality.[7]

4.2 Traditional methods to assess symptom burden and limitations

Patient-generated health data (PGHD) are clinically relevant health information that can be captured directly from patients in the non-clinical/home setting.[8] PGHD (inclusive of symptom rating, physical activity reporting, and other health parameters) are traditionally assessed using survey instruments. Symptom assessments often use a large window of the time frame between assessments requiring participants to recall symptom experiences (i.e., 7 days using the PROMIS or 4 weeks using the SF-36), which might introduce recall bias. Additionally, symptom burden may fluctuate over time, especially among individuals who have a high disease burden; however, there is a paucity of research demonstrating the within- and between-person variability of

symptom experiences in cancer populations. Assessing the rhythm of symptom change by considering within-person variability may indicate a signal for a change of health conditions and suggest for further clinical assessment and interventions.

4.3 Novel methods to assess symptom burden and challenges ahead

Ecological momentary assessment (EMA) is the real-time reporting of symptoms and other patient-reported outcomes (PROs).[9] Due to its real-time nature, EMA is less subject to recall bias than retrospective surveys and recognizes the fluctuation in symptom severity.[10-12] With the increasing accessibility of mobile health (mHealth) technology, EMA can be quickly assessed through handheld devices such as tablets and smart phones.[13,14] Leveraging mHealth technology to assess daily symptoms and health outcomes among the mobile health population (e.g., adolescents and young adults) provides promising opportunities to improve risk prediction of impaired health status and to offer early real-time interventions.[9,15,16] Previous studies have identified barriers of using mHealth for collecting PROs or behavioral interventions, such as protecting personal health information, technology failure (i.e., Wi-Fi connection issues or application malfunction), and user effort (i.e., time consuming).[17-19] Barriers to mHealth implementation can lead to a poor compliance with research engagement.[17,20,21] Ways to address barriers to mHealth applications include taking precaution for data security, using a user-friendly, integrated mHealth platform for data collection, and applying artificial intelligence to minimize the effort of participants.

This present study was conducted in 2019 and aimed to assess the feasibility and compliance status of a mHealth platform used to collect daily symptom data and test the association of daily symptom fluctuation and future quality of life within a 3-month window among adult survivors of childhood cancer enrolled in both the CCSS and SJLIFE studies. To improve adherence to daily symptom reporting, we applied technology-based, clear communication methods with participants throughout the study. Furthermore, this study evaluated participant satisfaction and collected qualitative feedback about the mHealth platform used for daily symptom assessment and communication with healthcare providers. *This study was initially approved by St. Jude IRB and the preliminary findings for Aims 1 and 2 (see Section 5) were included in the pilot study section of an NCI R01 grant proposal (funded in 2021; MPIs: Huang/Yasui). We plan to refine the analysis for Aim 2 (see criteria listed in Section 6.4) and conduct new analysis for Aims 3 and 4 (see Section 5). We believe it is useful to publish all of the findings in a peer-review journal to highlight our successful strategy and clinical implications for future mHealth application in CCSS.*

5. SPECIFIC AIMS

Aim 1: To assess the response rate and adherence rate of a daily symptom assessment over a 3-month window through an mHealth platform.

Aim 2: To estimate the within- and between-person variability for the severity of 20 individual symptoms and domain scores of symptom burden.

Aim 3: To estimate the associations of daily symptom burden with future quality of life.

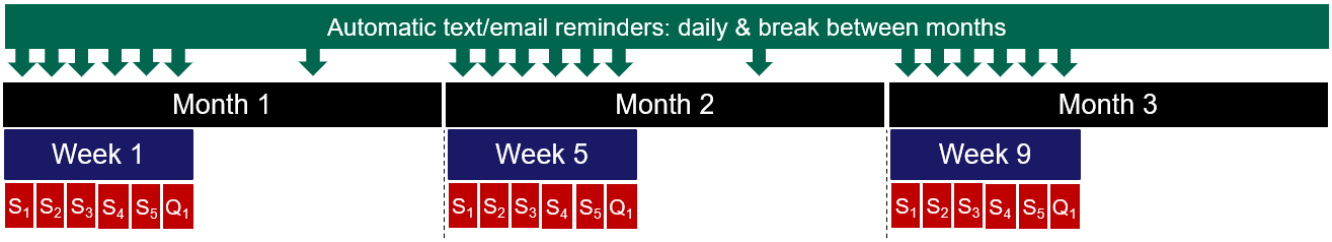
Aim 4: To assess the satisfaction and identify the barriers of using mHealth platform for the daily symptom assessment.

6. DATA SOURCES

6.1 Study Design

This prospective study was an internet-based, mobile platform-enabled study used to examine clinical meaningful symptoms (e.g., pain, fatigue, sleep disturbance, anxiety, etc.) and quality of life among adult survivors of childhood cancer who took part in both the CCSS and SJLIFE studies. Participants were asked to report their symptoms for 5 days per week on Weeks 1, 5, and 9 over a 3-month period (Figure 1). At the end of each week, participants were asked to complete a quality of life assessment. Automatic text and e-mail reminders for the daily symptom report (daily for 5 days) and weekly quality of life assessment (once per week) were sent during Weeks 1, 5, and 9 using DatStat Connect. The automatic communications included the links to the online surveys to be completed that day.

Figure 1. Study timeline



Note, S = symptom assessment; Q = quality of life assessment

6.2 Study sample

This study included adult survivors of childhood cancer who were dual enrollees of CCSS and SJLIFE studies. Specific inclusion criteria were: diagnosed with childhood cancer before 18 years of age, and at least 18 years of age at the time of enrollment. Data were collected from May 2019 to October 2019. Sixty survivors were invited to participate, 20 from each symptom burden groups (low, moderate, and high) based on the 2016 SJLIFE data freeze. The low, moderate, and high burden groups represent lower physical and mental summary scores (PCS and MCS) of the SF-36 by <0.5 SD, 0.5-0.99 SD and >1.0 SD as compared to the norm, respectively. Symptom burden was calculated based on 37 items/10 domains that are included in the SJLIFE survey. We were interested in examining whether the response rate and adherence rate were different between survivors who had different levels of symptom burden.

- Low symptom burden (0-1 symptom domains)
- Moderate symptom burden (2-5 symptom domains)
- High symptom burden (6-10 symptom domains)

6.3 Symptom variables

This study focused on twenty symptoms commonly experienced by childhood cancer survivors. The selection of these symptoms was based on the prevalence of individual symptoms[5,6] and an opinion survey of 15 faculty members of St Jude Comprehensive Cancer Center's Cancer Control and Survivorship Program who provide clinical care for childhood cancer patients and survivors. In the survey, if a study participant identified a symptom as present in the past 24 hours, then the participant was asked to indicate the severity of the symptom in the past 24 hours (mild, moderate, severe).

<u>20 individual symptoms:</u>

- Irritability
- Anxiety
- Depression
- Fatigue or feeling week
- Difficulty falling or staying sleep at night
- Sleepy during the day
- Poor memory
- Lack of concentration
- Shortness of breath
- Chest pain during physical exercise
- Numbness or tingling
- Problem with balance
- Headache
- Bodily pain
- Swelling
- Cramps
- Constipation
- Diarrhea
- Lack of appetite
- Poor coordination

6.4 Outcome variables

Response rate: Out of the 60 participants invited, 39 (65%) enrolled in this study.

Adherence rate: Weekly adherence was defined as completing at least 4 of the 6 (5 symptom surveys and 1 quality of life assessment) surveys distributed each week. Overall adherence was defined as completing at least 12 of the 18 surveys distributed throughout the entire study.

Symptom impact: To assess the impact of symptom burden on the participants' subsequent quality of life and functional status, participants were asked to complete 6 domains from the PROMIS 29 and the Neuro-QOL Cognitive Function-Short Form. Item responses were uploaded to the HealthMeasures Score Service to generate a T-score for each domain.

- PROMIS-29 contains 6 domains of functional status:
    - Anxiety
    - Depression
    - Fatigue
    - Sleep Disturbance
    - Pain Interference
    - Pain Intensity
- Neuro-QOL Cognitive Function contain 1 single domain.

6.5 Satisfaction and feedback

At the end of the 3-month study, participants were asked to complete an online 8-item satisfaction survey to provide feedback on their experience participating in the study. Participants were asked to report to what degree (5 categories: strongly agree, agree, neither agree nor disagree, disagree, strongly disagree) they agreed with the following statements:

- It is easy for me to complete brief daily symptom evaluations (e.g., a few days in a week) over the past 3 months.
- I would be willing to take part in symptom evaluations on a regular basis to help doctors understand more.
- I would be willing to take part in symptom evaluations 2-3 times per day to help doctors learn the symptom changes on a daily basis.
- I am interested in taking part in a clinical trial to help doctors use my symptom data for advancing treatment strategies.
- In the future studies, I would be interested in receiving a report after my symptom evaluations are done.

- I am interested in discussing problematic symptoms with my oncologists or primary care physicians.
- I am interested in learning skills for self-managing my problematic symptoms.
- I believe that effective symptom controls may improve my quality of life.

Additionally, participants were encouraged to provide any feedback regarding the barriers of using mHealth platform for daily symptom assessment through an open-ended box.

6.6 Covariates

Participants' sociodemographic and treatment information were obtained from the SJLIFE database. See Appendix Table 1 for more details about the classification of each variable.

Sociodemographic variables:

- Age at survey
- Time since diagnosis
- Sex
- Race/ethnicity
- Educational attainment

Clinical variables:

- Any chemotherapy
  - Anthracycline
  - Methothrexate
  - Plant Alkaloids
  - Cyclophosphamide
  - Bleomycin
  - Cytarabine
  - Steroid
- Any radiation
  - Brain radiation
  - Chest radiation
  - Pelvic radiation
- Invasive surgery

7. STATISTICAL METHODS

NOTE, preliminary analyses for Aims 1 and 2 were previously completed and included in an NCI R01 grant proposal (funded in 2021; MPIs: Huang/Yasui). We plan to refine the analysis for Aim 2 (see criteria listed in Section 6.4) and conduct new analysis for Aims 3 and 4. We will publish all findings in a peer-review journal.

Aim 1: To assess the response rate and adherence rate of a daily symptom assessment over a 3-month window through a mHealth platform.

- Descriptive analysis for binary outcomes of study enrollment and adherence were used to assess the response rate and adherence rate for each study time point and the overall study period.

Aim 2: To estimate the within- and between-person variability for the severity of 20 individual symptoms and domain scores of symptom burden.

- Logistic regression models with random effects were used to univariately assess the within-person and between-person variability of each individual symptom over the three months and linear models with random effects were used to assess the within-person and between-person variability of each domain of the symptom burden over the three months. The within-person variability is decomposed into within-week (day to day) variability and between-week (across the three weeks over the three months).

Aim 3: To estimate the associations of daily symptom burden with future quality of life.

- Linear models will be used to estimate the associations of symptom burden with quality of life with an adjustment of important covariates (social-demographic and treatment factors). We will use the propensity score method for continuous exposure variables for covariate adjustment, given the sample size limitation.

Aim 4: To assess the satisfaction and identify the barriers of using mHealth platform for the daily symptom assessment.

- Descriptive analysis will be used to assess the satisfaction with the daily symptom assessment and future use for survivorship care based on the 8-item satisfaction survey.
- Qualitative analysis will be used to categorize the barriers of using mHealth platform for daily symptom assessment based on qualitative feedback through an open-ended box.

8. REFERENCES

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Appendix: Tables

Table 1. Participant Characteristics

	N (%) or Mean (SD; range)
Age at survey (in years)	
Age at survey (%)	
18 – 29.9 years	
30 – 39.9 years	
≥ 40 years	
Time since diagnosis (in years)	
Time since diagnosis (%)	
10 – 19 years	
20 – 29 years	
≥ 30 years	
Sex (%)	
Male	
Female	
Race/ethnicity (%)	
White	
Non-white	
Cancer diagnosis (%)	
Acute lymphoblastic leukemia	
Other leukemia	
Hodgkin lymphoma	
Non-Hodgkin lymphoma	
Central nervous system (CNS) tumor	
Sarcomas	
Wilms tumor	
Neuroblastoma	
Retinoblastoma	
Other solid tumors	
Anthracycline by doses (%)	
0 mg/m2	
1 – 249.9 mg/m2	
>= 250 mg/m2	
Methothrexate (%)	
Plant Alkaloids (%)	
Cyclophosphamide by doses (%)	
0 mg/m2	
1 – 4000 mg/m2	
4001 – 7999.9 mg/m2	
>= 8000 mg/m2	
Bleomycin (%)	
Cytarabine (%)	
Platinum chemo (%)	
Steroid (%)	
Brain radiation by doses (%)	
< 18 Gy	
18 – 29.9 Gy	

30 – 39.9 Gy	
>= 40 Gy	
Chest radiation by doses (%)	
< 10 Gy	
>= 10 Gy	
Pelvic radiation (%)	
Invasive surgery (%)	
Pain prevalence (%)	

Table 2. Participant Enrollment, Adherence, and Response Rate

	N (%)
Invited	
Enrolled	
Responded ≥3 Symptoms Week 1	
Responded ≥3 Symptoms Week 5	
Responded ≥3 Symptoms Week 9	
Responded QOL Week 1	
Responded QOL Week 5	
Responded QOL Week 9	
Responded ≥4 reports (symptoms and QOL) Week 1	
Responded ≥4 reports (symptoms and QOL) Week 5	
Responded ≥4 reports (symptoms and QOL) Week 6	
Responded ≥12 reports (symptoms and QOL) over 3 months	

Table 3. Variability of daily symptoms

	Month 1		Month 2		Month 3	
Symptom	Between-Person	Within-Person	Between-Person	Within-Person	Between-Person	Within-Person
Irritability						
Anxiety						
Depression						
Fatigue or feeling weak						
Difficulty falling asleep or staying asleep at night						
Sleepy during the day						
Poor memory						
Lack of concentration						
Shortness of breath						
Chest pain during physical exercise						
Numbness or tingling						
Problem with balance						
Headache						
Bodily pain						

Swelling						
Cramps						
Constipation						
Diarrhea						
Lack of appetite						
Poor coordination						

Table 4. Multivariable association between symptom burden and quality of life

	Anxiety	Depression	Fatigue	Sleep Disturbance	Pain Interference	Pain Intensity	Cognition
Symptom Burden							
Low	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Moderate							
Severe							
Age at survey							
18 – 29.9 years	Ref	Ref	Ref	Ref	Ref	Ref	Ref
30 – 39.9 years							
≥ 40 years							
Time since diagnosis							
10 – 19 years	Ref	Ref	Ref	Ref	Ref	Ref	Ref
20 – 29 years							
≥ 30 years							
Sex (%)							
Male	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Female							
Race/ethnicity							
White							
Non-white	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Anthracycline							
Yes							
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Methothrexate							
Plant Alkaloids							
Cyclophosphamide							
Yes							
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Bleomycin							
Cytarabine							
Platinum chemo							
Steroid							
Brain radiation							

Yes							
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Chest radiation							
Yes							
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Pelvic radiation							
Invasive surgery (%)							

Table 5. Participant Satisfaction

	Strongly agree/Agree N(%)	Neutral N(%)	Strongly disagree/Disagree N(%)
It is easy for me to complete brief daily symptom evaluations (e.g., a few days in a week) over the past 3 months.			
I would be willing to take part in symptom evaluations on a regular basis to help doctors understand more.			
I would be willing to take part in symptom evaluations 2-3 times per day to help doctors learn the symptom changes on a daily basis.			
I am interested in taking part in a clinical trial to help doctors use my symptom data for advancing treatment strategies.			
In the future studies, I would be interested in receiving a report after my symptom evaluations are done.			
I am interested in discussing problematic symptoms with my oncologists or primary care physicians.			
I am interested in learning skills for self-managing my problematic symptoms.			
I believe that effective symptom controls may improve my quality of life.			