Does a Smartphone App Help Patients with Cancer Take Oral Chemotherapy as Planned?

Joseph A. Greer, PhD; Jamie Jacobs, PhD; and Molly Ream, BA

Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, Massachusetts

Original Project Title: Mobile Application for Improving Symptoms and Adherence to Oral Chemotherapy in Patients with Cancer

PCORI ID: IHS-1306-0316
HSRProj ID: 20143571
ClinicalTrials.gov ID: NCT02157519

https://doi.org/10.25302/4.2019.IHS.130603616
Table of Contents

ABSTRACT .................................................................................................................................................. 3
BACKGROUND ........................................................................................................................................ 5
PARTICIPATION OF PATIENTS AND OTHER STAKEHOLDERS IN THE DESIGN AND CONDUCT OF
RESEARCH AND DISSEMINATION OF FINDINGS .................................................................................. 9
  Phase 1 .................................................................................................................................................. 12
  Phase 2 .................................................................................................................................................. 22
METHODS ............................................................................................................................................. 23
  Phase 1 .................................................................................................................................................. 23
  Forming the study cohort ......................................................................................................................... 23
  Phase 2 .................................................................................................................................................. 26
  Study outcomes: primary outcome measures ....................................................................................... 28
  Study outcomes: secondary outcome measures ..................................................................................... 29
  Potential moderators: measures for exploratory analyses .................................................................... 30
  Aim 1: To implement a patient-centered mobile app to assess symptoms, side effects, and adherence to oral
  chemotherapy that is feasible for use with oncology patients ................................................................... 35
  Aim 2: To evaluate the efficacy of the mobile application
  in improving adherence and patient-reported clinical outcomes ............................................................ 35
  Aim 3: To evaluate the efficacy of the mobile application
  in improving quality of oncology care .................................................................................................... 35
  Exploratory Aim: To determine whether particular patient demographic and clinical characteristics
  moderate the effect of the study intervention .......................................................................................... 35
RESULT .................................................................................................................................................... 38
  Phase 1 .................................................................................................................................................. 38
  Phase 2 .................................................................................................................................................. 40
  Aim 1: To implement a patient-centered mobile app to assess symptoms, side effects, and adherence to oral
  chemotherapy that is feasible for use with oncology patients ................................................................... 44
  Aim 2: To evaluate the efficacy of the mobile application
  in improving adherence and patient-reported clinical outcomes ............................................................ 45
  Aim 3: To evaluate the efficacy of the mobile application
  in improving quality of oncology care .................................................................................................... 45
  Exploratory Aim: To determine whether particular patient
demographic and clinical characteristics moderate the effect of the study intervention.......................... 48
DISCUSSION .......................................................................................................................................... 68
  The study results in context ...................................................................................................................... 69
  Implementation of study results .............................................................................................................. 71
  Generalizability .................................................................................................................................... 73
  Subpopulation Considerations .............................................................................................................. 73
  Study limitations ................................................................................................................................. 74
  Future research ................................................................................................................................. 74
CONCLUSION ......................................................................................................................................... 75
REFERENCES .......................................................................................................................................... 77
B. ABSTRACT

Background: Patients prescribed oral chemotherapy receive less support for adherence and monitoring of symptoms from oncology clinicians than do patients prescribed traditional infusion chemotherapy, resulting in poor adherence, lower-quality care, and worse disease outcomes. No theory-based, efficacious interventions exist to promote adherence and symptom monitoring for patients prescribed oral chemotherapy.

Objectives: The primary aims of this study were to (1) develop a patient-centered, smartphone mobile application (app) to facilitate adherence to oral chemotherapy and symptom management for patients with cancer; and (2) test the effect of the app on improving adherence to oral chemotherapy, symptoms, quality of life (QOL), and quality of care in a randomized controlled trial (RCT).

Methods: A multidisciplinary research team worked with key stakeholders to develop the mobile app, soliciting feedback on app content, usability, and patient-centeredness from 4 groups: patients/families (n = 8); oncology clinicians (n = 8); cancer practice administrators (n = 8); and representatives from the health system, community, and society (n = 8), as well as patients (n = 10) and oncology clinicians (n = 8) from the Massachusetts General Hospital. Then, from February 18, 2015, to October 31, 2016, 181 patients with diverse malignancies prescribed oral chemotherapy enrolled in an RCT to receive the mobile app intervention or standard oncology care. The primary outcomes were adherence and self-reported symptoms and QOL. Adherence was measured by the Medication Event Monitoring System Cap (MEMSCap) and by self-report. The secondary outcomes were patient perceptions of quality of care and utilization (ie, hospitalizations and emergency department visits). Patients completed the self-report questionnaires at baseline prior to randomization and at 12 weeks.
Results: Feedback from stakeholders and patient participants greatly informed intervention development and showed that the app was perceived as useful and acceptable. The final app incorporated features including a treatment plan, reminder system, symptom reporting modules, and patient resources. Patient-reported data were transmitted to the oncology team via HIPAA-compliant email on a weekly basis. The mobile app intervention group and control group did not differ over time with respect to the primary outcomes of adherence, self-reported symptoms, and overall QOL, or in the secondary outcomes of quality of care and utilization. In examining specific domains of QOL, patients in the mobile app group had a smaller reduction in social well-being over time ($M_{\text{diff}} = 1.67; SE = 0.74; F_{1161} = 5.13; p = .025; 95\% \text{ CI}, –3.12 \text{ to } –0.21$). Subgroup analyses showed that patients with poor self-reported adherence and high anxiety at baseline who were randomized to the app had improved MEMSCaps adherence rates compared with the standard care group. Finally, older patients randomized to the app reported improved QOL compared with those receiving standard care.

Conclusions: Feedback from stakeholders and patient partners was instrumental in optimizing relevancy, feasibility, and acceptability of the study methods and app intervention. Across all patients, the mobile app was not efficacious in improving adherence or symptoms. However, patients at greater risk for nonadherence may benefit.

Limitations: Use of daily MEMSCap as the primary study outcome may have raised participant awareness of adherence across both study groups, perhaps diminishing intervention effects. Additionally, generalizability of study findings is limited due to the restricted diversity of this well-educated sample at an academic institution.
C. BACKGROUND

Cancer care delivery has shifted in the past decade, with a substantial increase in the prescription of oral cancer therapies as an alternative to traditional intravenous chemotherapy. In 2010, approximately 16% of patients receiving cancer treatment were prescribed oral agents, and this figure is expected to surpass 25% in coming years, given advances in the study of tumor genetics and the number of oral chemotherapy agents in current development. Patients overwhelmingly prefer oral administration to intravenous due to the enhanced convenience of home administration, the mitigation of problems related to intravenous access such as pain or discomfort, and an increased sense of control of the chemotherapy environment. In fact, patients prescribed oral chemotherapies report less interference in their daily activities, corresponding to better quality of life (QOL).

Patients and oncology clinicians have encountered unique challenges as cancer care becomes increasingly delivered in the outpatient and home setting. While patients prescribed traditional intravenous chemotherapy receive direct supervision in infusion centers, where they are monitored and treated for symptoms and side effects, individuals prescribed oral chemotherapy take their medications at home with limited oversight, monitoring, and support from their oncology clinicians. The toxicities of oral chemotherapy are equivalent to those of intravenous chemotherapy, including nausea, vomiting, fatigue, and diarrhea, yet the lack of regular contact with the oncology team is a barrier to proper use of this regimen. For example, symptoms such as difficulty swallowing, nausea, and vomiting may interfere with taking oral agents if not treated appropriately. Patients and their families often must assess and manage symptoms on their own and, in turn, may not adhere to the treatment regimen as intended.

Patient adherence is often defined as taking a medication as prescribed regarding daily amount, dosage, and frequency; it is vital to the efficacy of an oral chemotherapy regimen. Importantly, poor adherence to oral anticancer treatment is associated with poor survival rates and with disease progression. Despite the importance of adherence for optimal cancer outcomes, several systematic literature reviews have shown that adherence rates to
oral chemotherapy in patients with cancer vary widely, with adherence ranging from as high as 100% to as low as 16%. These estimates vary based on patient sample, medication type, follow-up period, assessment measure, and calculation of adherence. Various patient, provider, treatment-related, and health care system factors are associated with treatment adherence, including patient health beliefs regarding treatment efficacy, cognitive impairments, inadequate social support, psychological distress, poor communication with providers, adverse effects of treatment, and difficulty accessing care or costs of medications. More specifically, studies have shown that patients who are male, older, living alone, nonwhite, of low socioeconomic status, treated in community versus academically based centers, or depressed are more likely to be nonadherent. In addition, presence of severe side effects, greater complexity of cancer treatment (eg, variable dosing schedules), and greater length of time on treatment are associated with poor adherence to oral chemotherapy. Other potential barriers to oral chemotherapy adherence may include patient forgetfulness, misunderstanding of dosing instructions, and attitudes toward the effectiveness of the chemotherapy. In addition, patients with elevated distress are more likely to struggle with adherence. In our own longitudinal investigation of patients receiving chemotherapy for advanced non–small cell lung cancer, approximately 30% had heightened baseline anxiety symptoms, which significantly predicted the occurrence of chemotherapy dose delays and reductions. Given that 10% to 25% of patients receiving cancer treatment become clinically depressed, many patients on oral chemotherapy will experience psychological distress that could interfere with adherence.

There is a critical need to overcome the challenges associated with the fragmentation of care related to oral chemotherapy administration, with specific attention to medication adherence and symptom management. Recently updated standards from the American Society of Clinical Oncology (ASCO) and Oncology Nursing Society now include comprehensive guidelines for prescribing, documenting, and monitoring patient treatment with chemotherapy, including oral agents. These standards include recommendations for discussing and documenting a chemotherapy treatment plan based on the type of medication, dosage, anticipated duration of treatment, and goals of therapy. Furthermore, the ASCO
Quality Oncology Practice Initiative has been examining quality metrics for oral chemotherapy administration pertaining to documentation of treatment plan, patient consent and education, and ongoing monitoring of oral agents. Despite these guidelines, very few interventions to improve adherence and monitoring for patients prescribed oral chemotherapies have been tested. In a recently published systematic review, we identified only 12 adherence interventions for patients with cancer, with some resulting in mixed findings and most lacking methodological rigor, with nonrandomized designs and small sample sizes. Thus, theory-based interventions that are accessible to patients in order to promote adherence and symptom management are critically needed.

Mobile health (mHealth) technology provides an opportunity for support and monitoring in a minimally burdensome, maximally accessible approach. Evidence suggests that interventions delivered via mobile technologies can improve health behaviors in patients with cancer. In addition, mobile smartphones allow for ecological momentary assessments by facilitating repeated evaluation of participants’ symptoms and adherence behaviors in real time, which may enhance the provision of care for patients prescribed oral chemotherapies. Smartphone mobile applications (apps) may be an ideal platform to administer a supportive intervention that promotes adherence and symptom management for patients prescribed oral chemotherapy. Thus, with support from the Patient-centered Outcomes Research Institute, we conducted a 2-phase study to develop a patient-centered mobile app to assess symptoms, side effects, and adherence to oral chemotherapy that is feasible and efficacious for use with oncology patients.

In phase 1, we developed an acceptable and feasible patient-centered mobile app informed by qualitative feedback from key stakeholders, patients, and oncology clinicians. In phase 2, we conducted a randomized controlled trial (RCT) to demonstrate feasibility and evaluate the efficacy of the mobile app in improving adherence as well as patient-reported clinical outcomes. Aim 1 of phase 2 was to test feasibility based on rates of completion of symptom reports in the mobile app. We hypothesized that at least 75% of participants assigned to the mobile app intervention would complete symptom surveys for at least 9 of the 12 study weeks. With respect to evaluating the efficacy of the mobile app in improving primary
outcomes (aim 2), we hypothesized that patients prescribed oral chemotherapy for cancer who were randomly assigned to the mobile app intervention would report better medication adherence, fewer symptoms and side effects, and improved quality of life compared with the control group (ie, patients receiving standard care). The third aim of phase 2 was to evaluate the efficacy of the mobile application in improving quality of oncology care. We hypothesized that patients who were randomly assigned to use the mobile application would report greater satisfaction with medical care and have fewer emergency department visits and hospitalizations compared with the control group. Finally, we explored treatment heterogeneity by examining whether particular patient demographic and clinical characteristics (eg, cancer type, age, gender, baseline self-reported adherence) moderated the effect of the study intervention, thereby identifying any key subgroups of participants who may have responded differently to the mobile application.
D. PARTICIPATION OF PATIENTS AND OTHER STAKEHOLDERS IN THE DESIGN AND CONDUCT OF RESEARCH AND DISSEMINATION OF FINDINGS

In accordance with PCORI Methodology Standard PC-1, we engaged individuals representing the population of interest (ie, patients with cancer, their family members, clinicians, administrators, and policymakers) in formulating research questions; defining characteristics of the intervention, study design, and outcomes; monitoring study progress; and developing plans for dissemination and implementation. To include a representative, diverse, and comprehensive group of stakeholders,45 we identified 4 core stakeholder groups (Figure 1) by drawing from a population-based model for patient-centered care from the Medical College of Wisconsin.46 We selected stakeholders from across the United States (13 states), thus reaching outside our local academic medical community. We identified patients and family members from the Massachusetts General Hospital (MGH) Cancer Center Patient and Family Advisory Council. To be eligible, the stakeholder must have been able to represent the interests and perspectives of at least 1 of the 4 groups. Members of the investigative team (Drs. Greer, Temel, Pirl, Safren, Lennes, Jethwani, and Buzaglo) organized a list of stakeholders from these 4 cancer community groups. We contacted stakeholders to explain their involvement and study procedures. Thirty-two stakeholders assisted with the study, representing the following 4 key stakeholder groups: (1) oncology patients and family members (n = 8); (2) oncology clinicians (n = 8); (3) cancer practice setting administrators (n = 8); and (4) representatives of the health system, community, and society (n = 8). Stakeholders were involved in the study as research collaborators/consultants and were remunerated up to $1 000 for their time and effort. These stakeholders were involved in both phase 1 and phase 2 of the study. In addition to the stakeholder groups, we enrolled 10 MGH patients prescribed oral chemotherapy and 8 MGH oncology clinicians as participants during phase 1 of the study to review the mobile app wireframes (ie, screen blueprints) and provide feedback. These patients and clinicians were considered study participants, and they each signed IRB-approved, HIPAA-compliant consent forms prior to participation. Relevant characteristics of these participants are presented in Table 1. The specific involvement of the stakeholders, as well as the patient and clinician participants, in each study phase is detailed below.
Figure 1. Stakeholder Groups and Engagement

FOCUS GROUPS
- Patients/family
- Oncology clinicians
- Cancer practice settings
- Health system, community, and society

BIANNUAL UPDATES
- Complete analyses prepare dissemination
- Preliminary analyses
- Trial and data collection
- Mobile app development

FOCUS GROUPS
- Patients/family
- Oncology clinicians
- Cancer practice settings
- Health system, community, and society
Table 1. Phase 1: Characteristics of MGH Patients and Oncology Clinicians

<table>
<thead>
<tr>
<th>MGH Patient Characteristic (n = 10)</th>
<th>M (SD) or N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58.40 (8.02)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Men</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Hispanic or Latino/a</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>College</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>High school graduate/GED</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Single</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
</tr>
<tr>
<td>Non–small cell lung cancer</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1 (10%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MGH Oncology Clinician Characteristic (n = 8)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Men</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Clinician type</td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Nurse practitioner</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Area of expertise</td>
<td></td>
</tr>
<tr>
<td>Genitourinary oncology</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>Breast oncology</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Thoracic oncology</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1 (12.5%)</td>
</tr>
</tbody>
</table>
### Phase 1

First, we conducted a pretrial planning interview with the first 4 stakeholder groups to solicit feedback about the proposed study topic, design, and intervention to ensure relevancy, acceptability, and the potential for dissemination. The patient/family interview took place in person at the MGH Cancer Center, and the 3 other group interviews occurred as teleconference calls. Specifically, we addressed the following topics: (1) perceived importance of monitoring oral chemotherapy remotely; (2) barriers to communication between patients and the oncology team regarding management of side effects and medication adherence; (3) the potential role of the mobile app to address barriers to quality of cancer care; (4) the potential feasibility, acceptability, and usability of an mHealth intervention; and (5) system barriers and facilitators to implementation. We identified consistent themes about the planned intervention and study design from these interviews. Feedback from this stage was integral in informing the development of the mHealth intervention. For example, stakeholders recommended a symptom monitoring feature with interpretable graphics, emphasized the importance of distinguishing urgent versus nonurgent symptoms within the symptom reporting module, provided guidance on optimizing patient–physician communication while minimizing burden, and suggested methods for promoting participant engagement with incentivizing app features. We incorporated each of these recommendations into the final mobile app version. The interview guides for these focus groups are presented in Appendix A and a summary of feedback is presented in Table 2.
Table 2. Phase 1 and Phase 2 Feedback From 4 Stakeholder Focus Groups

<table>
<thead>
<tr>
<th>Patients/family members</th>
<th>Phase 1 (Pretrial Focus Groups) Mobile App Development and Design</th>
<th>Phase 2 (Posttrial Focus Groups) Ideas for Analyses, Future Iterations, and Dissemination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Weekly symptom checker:</td>
<td>• Other possible variables we should analyze in this or future iterations of this study:</td>
</tr>
<tr>
<td></td>
<td>• Consider using a graph as a display for symptom progress over time. Patients often have a good day followed by a series of bad days, so it can be hard to remember the good days—this will help patients visualize their progress and motivate them.</td>
<td>• Provider–provider communication (specifically coordination between the oncologist and the primary care physician)</td>
</tr>
<tr>
<td></td>
<td>• Identify the immediate symptoms and resolutions, and the long-term symptoms and resolutions.</td>
<td>• Mental health services and palliative/supportive medication (ie, antinausea drugs)</td>
</tr>
<tr>
<td></td>
<td>• Make patients aware of the symptom reporting process and what will be reported to the physician:</td>
<td>• Distance from patient’s residence to where patient is receiving care</td>
</tr>
<tr>
<td></td>
<td>• Give patients an option to rate a symptom as “bad” but manageable without needing a call from the physician.</td>
<td>• Distance from patient’s residence to residence of caregivers/support system</td>
</tr>
<tr>
<td></td>
<td>• Make sure that patients are not afraid to report symptoms.</td>
<td>• Proxy use by caregivers (“did/how often did your loved one help you use the app?”)</td>
</tr>
<tr>
<td></td>
<td>• Have patient bring her or his phone to clinic with app to show any changes/progress to the physician.</td>
<td>• Tech literacy or comfort with technology</td>
</tr>
<tr>
<td></td>
<td>• Educational resources:</td>
<td>• “Are you confident in your own efficacy of treatment?” “How confident are you with your own ability to adhere to your treatment plan?”</td>
</tr>
<tr>
<td></td>
<td>• Make sure that websites are user-friendly, patient-specific, and reputable.</td>
<td>• Perhaps look at subgroup of hematologic malignancies only.</td>
</tr>
<tr>
<td></td>
<td>• Some websites and online support groups include patients that are very sick, which can provoke a lot of anxiety for many patients who have fewer symptoms.</td>
<td>• Possible features for future iterations of the app:</td>
</tr>
<tr>
<td></td>
<td>• Patient–physician communication:</td>
<td>• Provide a line graph view over entire months/length of app use displaying symptom trends.</td>
</tr>
<tr>
<td></td>
<td>• Ensure that physicians using the application will act on symptom reports and feedback regarding patient’s adherence and symptom management.</td>
<td>• Option to give app access to loved ones/caregivers as well, so that they can see how patient symptoms/adherence has been, or help the patient use the app</td>
</tr>
<tr>
<td></td>
<td>• Patients would appreciate getting notification that the physician has viewed their message (eg, read receipt).</td>
<td>• Track all meds the patients is taking, huge investment to make something broadly applicable.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Weekly symptom reports to go directly into medical records rather than be sent via email</td>
</tr>
</tbody>
</table>
- Provide patients with an option to report high-severity symptoms, but mark as manageable, and not in need of a call from their doctor.
- Usability, feasibility, acceptability:
  - If patients are very sick, then they might not report symptoms accurately—some might report more modestly or not at all.
  - Find a way for the app to screen different symptoms (eg, loss of appetite, depression) and triage the information to a relevant clinician (nutritionist, social worker, psychiatrist, etc).
- Patients who are easily distracted or bored might not use the application frequently if it is not interactive enough.
- It is essential that doctors positively reinforce patients in clinic by bringing up their app-related symptom/adherence reports.
- Conduct a brief feasibility study with patients before the RCT and meet with them a few weeks in to see if they are using the app correctly or having any difficulties.

**Oncology clinicians**

- Personalized oral chemotherapy plan:
  - Consider using Adhere Tech bottles (which have a technology that counts pills).
  - Make sure the plan is editable.
  - Have a feature that allows patients to opt out/edit/utilize/personalize medication reminders.
  - Tailor personalized plan: ability to reduce frequency of reminders if patient is stable,

- Can examine any age differences? Were younger people more likely to use the app?
- Were there any reports or questionnaires on the clinician side?
- Were patients with more symptoms at baseline more likely to benefit from the app?
- Was the amount of time patients have been on oral therapy related to how well they are managing their symptoms, and how much an app may benefit them? The first 1 to 2 months tend to be the most challenging and include the most side effects.

- Organizations to communicate findings with:
  - Healthcare for All (umbrella organization for Patient and Family Advisory Councils): host webinars every 2 to 3 weeks; also may do newsletter
  - Facing Cancer Together
  - Facebook
  - ASCO
  - Drug Information Association
  - Partners-affiliated hospitals
AND ability to increase frequency of reminders if patient is more symptomatic.

- Educational resources:
  - Drive educational content based on common side effects of the patient’s specific drug/disease.
  - Collaborations with a pharmaceutical company could help with dissemination of information and sustainability.
  - Would be helpful to have a feature that organizes medical information (appointments/scan schedule).

- Patient–physician communication:
  - Be mindful of when messages/reports are delivered to physicians so that we are engaging them and not annoying them.
  - Make sure that patients do not view the app as the only way to communicate with their medical team.

- Usability, feasibility, acceptability:
  - Print on a smartphone is small and might be hard to read—check with Connected Health to see if having the app on an iPad is feasible.
  - Consider customizing app for specific regimens.
  - Create subgroups/cohorts that might benefit more than others (very beneficial for data collection and seeing effects based on disease/medication/age group).
  - Think of a way to make app appealing to patients (move away from an app that serves as an at-home reminder that patient has cancer): Utilize wellness as a driving force,

- How was the complexity of the medication regimen?
  Could examine how many other medications patients were taking.
- Did you look at whether patient had a caretaker or someone else who is looking out for him or her?
- Information should automatically upload into EPIC so that clinicians could easily see adherence and symptom reports right before meeting with a patient in clinic.
- Next steps: Wouldn’t want to get notified every time a pill is missed, but would want to be notified for things that are clinically relevant (eg, if patient missed taking medication for a whole week).
- Allow for customization for each clinician: What is the threshold each physician wants for different patients or groups of patients?
- There is a worry of extra burden for staff if they are getting too much information that can wait. Maybe extra step question for patient is do you want this to send immediately or would you like to log and bring it up at next appointment.
although wellness could be too broad so try to hone in on specifics.
- Consider the liability of symptom reporting, especially for symptoms like fever or neutropenia.

| Health care representatives | Personalized oral chemotherapy plan:  
|-----------------------------|------------------------------------------------------------------|
|                             | - This section is important and distinguishes itself from other general resources because it is customized and tailored to the specific patient.  
|                             | - Identify/compare patients to others in their same cohort (disease)—by motivation, support system.  
|                             | - Weekly symptom checker:  
|                             |   - It is important to strike a balance so it is user friendly, yet not burdensome.  
|                             |   - Provide anchors and operational definitions for symptom severity and frequency (e.g., constipation: definition, how often, how severe, when to contact doctor).  
|                             |   - One goal should be to empower patients to report symptoms through app and hopefully speak up more during their clinic visits.  
|                             | - Educational resources:  
|                             |   - Provide patients with education on lab results and how to access them (on the app, possibly) and interpret results.  
|                             | - Patient–physician communication:  
|                             |   - Foster communication between patient and health care team (not just physician - ie NP).  
|                             |   - Provide patients with resources on how to talk to their physician during clinic visits regarding symptoms.  

|                             | Is it possible that people who could engage with the app were already better off in terms of adherence?  
|                             | - If the patient uses the app, but the clinician does not read the symptom report email, that could affect the experience and satisfaction. Is there a way to look at this?  
|                             | - How might disease progression have affected results (very heterogeneous group with heme and solid malignancies and staging)?  
|                             | - Is it possible to examine any data on financial distress or cost of medications in relation to adherence?  
|                             | - Next steps: Get impressions of oncologists who were involved in the study (was the email format for symptom reports useful; what kind of patients would they want to have access to this app?).  
|                             | - Potential avenues for dissemination: Cancer Support Community Newsletter; Oncology Nursing Society; Medscape; Apple, Google, and social networking technological spheres; joint effort between number of oncology organizations to host a webinar.  

- Understand patient satisfaction on an ongoing basis and satisfaction with communication with care team.
- Capture patient–physician communication as an outcome.

- Usability, feasibility, acceptability:
  - Sustainability: Consider if patients in RCT will use app after the trial is over.
  - If they will discontinue app, make sure that transition is done in a way that will not create a void.
  - Design program so that it is rewarding for patients to use.
  - It might be helpful to collect baseline data on patient beliefs and expectations regarding oral chemotherapy meds, as well as coping styles.

- Education and training for the mobile app:
  - Research assistants, study staff
  - Training video as part of app

- Identification of patients/recruitment:
  - Query electronic health records THEN approach physician.

- Engage clinicians throughout app development and RCT so that they will be interested and compliant with patient–physician communication—it is crucial that physicians bring up reported symptoms at clinic visit or app could be a total flop.

- Feedback from patients
  - Access to medication and having enough meds throughout the study

<table>
<thead>
<tr>
<th>Practice administrators</th>
<th>Personalized oral chemotherapy plan:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Make sure to stratify by line of therapy if variation exists (ie, oral chemo as first line/first line of oral chemo, but not first line of treatment/second line of oral, or above).</td>
</tr>
</tbody>
</table>

|                          | Is there any way to capture cost? Prevent hospital admissions? |
|                          | Think of the app as a motivational tool. Some will like and benefit from more connectivity with their |
• Ability to track patient hits on oral chemo plan
• Info for patients on how to proceed when they miss a medication dose
• Feature that allows patients to log in when they have renewed their prescription
  • Weekly symptom checker:
    • If patient decides to report symptoms more than once a week, how will that be reported to the team?
    • Give patients an option with new/worsening symptoms to have someone call them when they report a symptom; don’t rely only on hard stops.
    • Method of tracking phone calls regarding symptoms and compare between arms
    • Once a week is not burdensome for physician, but every day would be.
    • Ability to triage new/worsening symptoms for communication purposes
• Educational resources:
  • Ability to track patient hits on educational resources
• Patient–physician communication:
  • Consider asking patients if they feel like their symptom reports are being heard and addressed by team.
  • Have a point person for patient emails aside from MD (ie, NPs).
  • Ability to see who is viewing the patient emails
  • Look at past info on how physicians act on new/worsening symptoms
• Usability, feasibility, acceptability:

providers, but others may not. Would like to think of other engagement features.
• It would be interesting to see whether patients who used the app for certain reasons (ie, symptom reporting versus medication reminders) were more likely to benefit.
• Could examine specific symptoms on the MDASI to see if app had any benefit?
• It is impor to capture utilization as an outcome to generate interest with payers.
• Potential for pharmacy involvement as a next step; the app might be more helpful for the pharmacy team than the oncology clinicians
• Dissemination of findings to pharmacy and nursing groups: Hematology/Oncology Pharmacy Association and American Society of Health Systems Pharmacists; Oncology Nursing Society; Sigma Theta Tau
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Comfort level with mobile app may be different for elderly population—good thing to assess in the beginning.</td>
</tr>
<tr>
<td></td>
<td>• Provide patients with contact info for app troubleshooting.</td>
</tr>
<tr>
<td></td>
<td>• Emphasize that patients can still call their doctor if they are having new/worsening symptoms so that we do not hinder their willingness to speak up.</td>
</tr>
</tbody>
</table>
Next, we met individually with the 10 MGH patient and 8 oncology clinician participants to review the app content using wireframes created by the research and design teams (see Figure 2). Using semistructured interview guides (see Appendix B), we solicited feedback in 3 domains: (1) components of the mobile app, (2) feasibility and usability of the app, and (3) weekly in-app symptom assessments. We directed integrated feedback from this stage regarding the aesthetics, frequency of push notifications, and incorporation of the patient’s treatment plan into the mobile app design (see Appendix C).

Finally, after developing the beta version of the app, we invited members of the initial patient and family stakeholder group (n = 8) to participate in user acceptance testing. Research and development staff observed stakeholders during their initial interactions with the mobile app and asked them to complete specific tasks (eg, “How do you think you would go about adding your oral chemotherapy medication into this app?”). Stakeholders were asked to share general and specific feedback about task intuitiveness. We further refined the app based on their responses. In summary, feedback from key stakeholder groups as well as patient and clinician participants in phase 1 had a significant impact regarding maximizing the patient experience, optimizing patient–clinician communication within the app, and refining study procedures for phase 2.
Figure 2. Wireframes (Screen Blueprints) for CORA Mobile App

- **eCare-AD**
  - My treatment plan
    - Manage my medication reminders
    - Monitor symptoms and side effects
    - Education library
    - Contact my doctor

- **My Treatment Plan**
  - Have any changes been made to your treatment plan since you last visited it on (date)?
    - Yes
    - No
    - I’m not sure
  - Treatment Goal: X
  - Medication Name: X
  - Dose: X amount per day
  - Schedule: X times daily
  - While taking (drug name), it’s important you look out for these symptoms...
    - Special Instructions:
      - Food and drug restrictions
      - What to do if miss a dose

- **Symptom Feedback**
  - Your scores show that you are experiencing worse fatigue (tiredness). Is this symptom acceptable to you at this time?
    - Yes
    - No
  - Thank you. This information will be given to your oncology provider. You may also want to discuss this problem during your next clinic visit as well as learn about how to cope with fatigue by selecting the Education Library tab.

- **Symptom Report**
  - You can view your symptom monitoring scores each week in the form of a chart. Select any of the symptoms below to see this chart.
    - Fatigue (tiredness)
    - Nausea
    - Lack of appetite
    - Constipation

← Choose another symptom
Phase 2

The 4 key stakeholder groups from phase 1 were also involved as research collaborators/consultants for phase 2 of the study, during which we tested the efficacy of the mobile app intervention in a randomized controlled trial. We maintained consistent communication with stakeholders throughout the RCT in the form of surveys, quarterly newsletters, a midstudy luncheon, and a final presentation and focus group. At the initiation of the RCT, we emailed stakeholders a survey to collect feedback regarding participant recruitment and retention, as well as clinician engagement. We then distributed a newsletter summarizing the recommendations we received and describing how we had incorporated stakeholder feedback into our study procedures (see Appendix D). We also sent biannual newsletters that described updates about overall study progress, including participant accrual, upcoming stakeholder engagement opportunities, recent press highlights, study-related presentations or publications, and any other relevant information. We held a midstudy luncheon at MGH (and via teleconference call) for all stakeholders, during which we discussed study progress and facilitated initial conversations about dissemination. Last, we conducted final focus groups with each of the initial 4 key stakeholder groups at the end of the study to present preliminary results and discuss plans for dissemination and implementation. The patient/family stakeholder group participated in person at a luncheon while the other 3 groups from across the country participated via teleconference. Feedback from this final engagement was instrumental in informing the next steps for this project. Table 2 displays a summary of feedback from these final stakeholder focus groups. For example, stakeholders recommended examining the role for social support in monitoring adherence and symptoms, suggested the option to integrate information directly into the electronic health record (EHR), provided ideas for implementation with involvement of pharmacy groups, and encouraged dissemination via society newsletters, organizational webinars, posts, and listservs.
E. METHODS

Phase 1

Study design. We used an mHealth intervention development framework47 to guide the creation of our smartphone-based, patient-centered intervention with maximum usability, acceptability, and feasibility. In phase 1, we (ie, the investigative team of oncologists, psychiatrists, and psychologists) developed the mobile app intervention through an iterative process with the Partners Center for Connected Health, patients, clinicians, and the 4 key stakeholder groups (n = 32) described previously. Stakeholder groups also provided feedback regarding the design and implementation of the RCT in phase 2 of the study. See the Stakeholder Engagement section for an in-depth description of the iterative, multistep process we undertook to ensure usability and feasibility of the mobile app intervention. Briefly, we first led focus groups with key stakeholders to solicit feedback regarding the study design, clinically relevant content, and functionality of the mobile app. We then worked with our technology partners to create screen blueprints (known in the software development industry as wireframes) of the proposed mobile app. Next, we presented the wireframes to MGH patients (n = 10) and clinicians (n = 8) to solicit feedback on the content, design, and patient centeredness of the intervention. After incorporating this feedback and refining the mobile app content, we invited patients and families from the original stakeholder group to participate in user acceptance testing with the beta version of the app to assess task intuitiveness and to share general feedback. We further modified the app based on feedback from each stage of this process in order to ensure optimal usability and feasibility for testing in the RCT. The Dana Farber/Harvard Cancer Center Institutional Review Board approved the study.

Forming the study cohort

Stakeholder groups. Drawing from a model of population-based patient-centered care, the investigative team identified stakeholders from various cancer community groups across a diverse range of expertise. Thirty-two stakeholders comprised 4 key stakeholder groups: patients and families (n = 8); oncology clinicians (n = 8); cancer practice administrators (n = 8);
and representatives of the health system, community, and society (n = 8). Stakeholders included pharmacists, health care leaders, lawyers, and patient advocates. These individuals were consultants on the study and not participants; therefore, no demographic or other personal information was collected from these individuals.

**MGH patients.** Patients were eligible to participate if they had a cancer diagnosis, had a current or past prescription for oral chemotherapy, and were the primary owner and user of a smart mobile phone with an iOS or Android operating system. Eligibility criteria also included age ≥ 18, ability to respond to survey questions in English, and a performance status ≤ 2 on the Eastern Cooperative Oncology Group (ECOG) measure. We implemented the age criterion to maximize the likelihood that patients were administering their own medications. We chose an ECOG performance status ≤ 2 to ensure that patients had sufficient functioning to participate in the study. We required patients to be receiving their care at MGH or a community affiliate (ie, Mass General/North Shore Cancer Center, Mass General West, or Mass General Cancer Center at Emerson-Bethke). We excluded patients with comorbid acute or psychiatric symptoms or neurological dysfunction that would interfere with consent and participation. Additionally, we excluded patients who were enrolled in oral chemotherapy clinical trials because the strict adherence monitoring of drug trials, could influence the proposed study outcomes. After screening the EHR to determine preliminary eligibility and obtaining permission from the patient’s treatment team, a trained Research Assistant (RA) either contacted the patients by phone or approached them in private clinic settings within MGH Cancer Center to explain the study and invite the patient to complete the eligibility screen.

**MGH oncology clinicians.** Oncology clinicians included board-certified oncologists or nurse practitioners who maintained at least 25% clinical practice at one of the study sites. Study staff directly approached and recruited 8 oncology clinicians to participate in qualitative interviews either in person or over the telephone.

**Study setting.** The patient and family member stakeholder focus groups, as well as the individual MGH patient and clinician interviews, took place in person on site at the MGH Cancer Center in order to optimize involvement and feedback. Interviews with the remaining 3
stakeholder groups took place via teleconference call to accommodate individuals who resided throughout the United States.

**Intervention.** We did not administer an intervention during phase 1.

**Follow-up.** Stakeholders continued to provide feedback into phase 2 regarding the mobile app content. During this period, we solicited feedback primarily in the form of email surveys (eg, see Appendix D), biannual newsletters, a midstudy luncheon, and final focus groups (see Table 2).

**Study outcomes.** The primary study outcome for phase 1 was to develop a patient-centered mobile app to assess symptoms, side effects, and adherence to oral chemotherapy that is feasible for use with oncology patients. The criteria for success was to ensure that the mobile app met standards for usability, acceptability of delivery, and patient-centeredness per expert evaluation and qualitative feedback from interviews with oncology patients, clinicians, and key stakeholders.

**Data collection and sources.** A trained clinical psychologist and psychology postdoctoral fellows administered all individual and group interviews. The semistructured interviews with the stakeholder groups, MGH patients, and MGH oncology clinicians were audio-recorded and stored on the secure, encrypted MGH server. See Appendices A and B for the interview guides used during phase 1 of the study.

**Analytic and statistical approaches.** Study staff reviewed all interviews so that the feedback obtained could inform modifications and refinements to the mobile app. Specifically, trained research assistants transcribed the feedback from the interviews to generate a complete list of comments, impressions, and recommendations from the MGH patient and clinician participants in phase 1 as well as from the 4 key stakeholder groups. After the completion of each focus group, we shared a summary of the focus group results with the stakeholders via email and again elicited any final feedback. The investigative team, including the study staff who conducted the interviews, then reviewed these reports for comprehensiveness and accuracy. Finally, in close collaboration with the technology experts at the Partners Center for Connected Health, the investigative team decided by consensus how to modify the app and optimize user engagement in consideration of all feedback generated from
the interviews. The investigative team also considered the impact of stakeholders’ recommendations on the scientific integrity and feasibility of the study.

**Conduct of the study.** During phase 1 of the study protocol, we submitted 1 amendment to the IRB. Specifically, on July 10, 2014, we submitted an amendment proposing to change the format of stakeholder focus groups to individual or group interviews in order to best accommodate the scheduling needs of our collaborators. This amendment was approved by the IRB on July 15, 2014.

**Phase 2**

**Study design.** We enrolled patients with diverse malignancies who were prescribed oral chemotherapy to participate in a nonblinded, randomized, parallel assignment efficacy trial of the mobile app intervention compared with standard oncology care (ClinicalTrials.gov Identifier: NCT02157519). Patients were receiving care at the MGH Cancer Center or a community affiliate. Independent of the research team, the study statistician developed a computer-generated randomization scheme stratified by cancer type (hematologic malignancy versus solid tumor) to ensure that relatively equal proportions of diagnoses were represented in each study group. The Dana-Farber/Harvard Cancer Center Office of Data Quality then randomly assigned participants 1:1 to either the mobile app intervention group or the standard oncology care control group. The first 5 patients who were randomized to the mobile app intervention participated in beta testing. After they completed the study, research staff conducted a semistructured 20-minute interview to gather their feedback on the app’s feasibility, usability, and aesthetics, allowing users to suggest revisions. The research team also interviewed 5 oncology clinicians whose patients were randomized to the mobile app regarding their conversations about the app with patients and helpfulness of the symptom reporting feature.

**Forming the study cohort.** Eligibility criteria for patients in the RCT during phase 2 of the study were nearly identical to those of MGH patients participating in phase 1 development (see Phase 1: Forming the Study Cohort: MGH Patients). However, for the RCT, patients were also required to have a current and active prescription for oral chemotherapy in order to enroll.
After screening the EHR to determine potential eligibility of patients, a study staff member obtained permission from the patient’s oncology team to approach the patients and explain the study. On receiving permission from the oncology clinicians, an RA contacted the patients by telephone or approached them in a private clinic room to assess interest and complete a brief screen to confirm eligibility. Our recruitment protocol addressed Methodology Standard PC-2 by systematically identifying all patients who were prescribed oral chemotherapy via the EHR. Unlike other methods of recruitment that we considered, such as patient self-referral or clinician referral, systematic searching of the EHR eliminated any selection bias in screening and enrolling of participants. Furthermore, once they were enrolled, we used the same standard operating procedures with all participants to ensure that there were no biases in retention. To address the representativeness of participants, we recruited patients at 3 community affiliate sites in addition to the main academic hospital site. This approach facilitated the enrollment of participants who choose not to receive care at a tertiary medical center for financial, geographical, or other reasons.

**Study setting.** We recruited patients from MGH Cancer Center or one of the community affiliates listed previously. Study visits took place in conjunction with scheduled outpatient oncology appointments.

**Interventions**

**Mobile app intervention.** Patients randomly assigned to receive the mobile app intervention met with the RA to download the mobile app (Chemotherapy Assistant, or CORA) to their personal smartphone. RAs oriented the patients on how to use the app, enter their treatment plan, and complete weekly symptom and adherence reports. They instructed participants to use the mobile app for approximately 12 weeks. The mobile application intervention consisted of several elements that we had developed and refined based on stakeholder and participant feedback in phase 1. The essential app components included the medication treatment plan and reminder features, a symptom and adherence reporting module that was transmitted weekly to the respective oncology clinician, and educational resources (see Appendix E). Push notifications reminded patients to take their medications and complete weekly symptom and adherence reports. Push notifications are pop-up messages
that appear on the mobile device to remind the user to engage with the app. No extra staffing was required, as patients who reported serious symptoms (eg, fever) were instructed within the app to call their oncology clinician or go to the nearest emergency department. Patients were informed during the consent process and app orientation process that their reporting would not be monitored in real time, so that there was no expectation of an immediate response. The research team encouraged oncology clinicians to follow up on the weekly symptom reports based on their clinical judgment, though no data were collected from clinicians about how such reports may have affected their clinical care. Patients were asked to store their oral chemotherapy medication in a Medication Event Monitoring System cap and bottle.

**Standard oncology care.** Patients randomly assigned to standard care did not receive the mobile app but rather received care as usual from their oncology clinicians. These participants were also asked to store their oral chemotherapy medication in the Medication Event Monitoring System Cap and bottle.

**Follow-up.** Patients completed the baseline self-report surveys prior to randomization. Subsequently, study staff contacted patients by telephone or during a routine clinic visit to have them complete an identical survey 12 (+/–3) weeks after the baseline assessment. Patients had the option to complete surveys on paper or via REDCap, an electronic HIPAA-compliant survey tool. On completion of the postassessment survey, RAs instructed participants on how to delete the mobile app from their smartphone.

We followed up with participants at 2 weeks postbaseline and at 6 weeks postbaseline to ensure that they completed study procedures per the protocol. Additionally, if a patient who was randomized to the mobile app group did not complete a weekly symptom report during the first active week of the study, a study staff member called to make sure the mobile app was working properly. Attrition was not significant in our study.

**Study outcomes: primary outcome measures**

**Adherence to oral chemotherapy medication.** We employed a multimethod assessment of adherence given that all sources of measurement (eg, self-report, pill counts, pharmacy refill data, and electronic monitoring) have different strengths and limitations with
potential for bias. The assessment therefore included remote electronic monitoring devices and self-report instruments as follows:

1. Medication Event Monitoring System (MEMS)® Cap. The MEMSCap records the date and time that the pill bottle is opened and medication is taken. These data were stored on the MEMSCap and collected by the study team postassessment. MEMSCaps are widely used in adherence monitoring and have been used in patients with cancer.50

2. Morisky Medication Adherence Questionnaire (MMAS-4). The MMAS-4 is a brief, self-report, validated measure to assess medication-taking behavior over the past week. Patients are asked to respond to each of 4 items with a “yes” or “no.” The 4-item scale has good sensitivity in identifying nonadherent individuals.51

3. Pill Diary. We provided patients with a weekly log to keep track of medication doses that they took without using the MEMSCap. Usage of the pill diary was optional, but all patients received one as a backup for documenting adherence.

Symptoms and side effects. To assess symptoms, patients completed the M.D. Anderson Symptom Inventory (MDASI), a 19-item instrument that assesses the most common physical and psychological symptoms related to cancer. The MDASI assesses the severity of symptoms at their worst in the past 24 hours on a 0-to-10 scale, with 0 being “not present” and 10 being “as bad as you can imagine.” Two subscales are computed to measure interference and severity of symptoms. The measure has been validated in patients with diverse malignancies, and test–retest and internal consistency reliability is confirmed.52 The MDASI demonstrated strong reliability in this sample (severity $\alpha = .93$; interference $\alpha = .94$).

Quality of life. We administered, the Functional Assessment of Cancer Treatment–General (FACT-G), a 27-item questionnaire that assesses physical, social/family, emotional, and functional well-being during the previous week, to assess QOL. The validated measure utilizes a 5-point scale from 0 (not at all) to 4 (very much). It has sound psychometric properties, is used widely in patients with cancer,53 and showed good reliability in this sample ($\alpha = .70$).

Study outcomes: secondary outcome measures

Treatment satisfaction. The Functional Assessment of Chronic Illness Treatment–Treatment Satisfaction–Patient Satisfaction (FACIT-TS-PS) is a 29-item questionnaire that
assesses patient satisfaction with doctor and staff communication, competence, and confidence, as well as trust in providers and overall satisfaction. Higher scores indicate greater satisfaction. The FACIT-TS-PS has high validity and reliability, and the instrument demonstrated strong reliability in this sample (α = .91). To reduce questionnaire burden on patients, we administered 5 subscales of the FACIT-TS-PS, which assess satisfaction with (1) clinician explanations, (2) interpersonal treatment, (3) comprehensiveness of care, (4) nurse communication, and (5) confidence and trust in the doctor and treatment staff.

**Urgent visits.** We administered the Resource Utilization Questionnaire, an adapted 3-item questionnaire, to inquire about the number of emergency department visits and hospital admissions in the past 3 months.

**Potential moderators: measures for exploratory analyses**

**Sociodemographics.** Participants reported their gender, race, ethnicity, religion, marital status, smoking history, income, and level of education on a baseline demographic questionnaire. Research staff collected data from the electronic health record on patients’ age, cancer diagnosis, ECOG performance status, therapy dosing schedule (continuous dosing versus interval dosing), type of oral therapy (targeted therapy versus oral chemotherapy), number of concomitant medications, and duration of oral therapy treatment.

**Mood.** The Hospital Anxiety and Depression Scale (HADS) was designed for medical patients and demonstrates adequate psychometric properties for use among individuals with cancer. Composed of 14 items, the instrument contains 2 subscales that measure anxiety and depression symptoms in the past week, with scores ranging from 0 (no distress) to 21 (maximum distress). A threshold of > 7 indicates clinically significant anxiety or depression, and a score of > 11 indicates definitive anxiety or depression. A trained study psychologist followed up with all patients who scored > 11 on the depression subscale. The HADS demonstrated strong reliability in this sample (α = .94).

**Social support.** The Multidimensional Scale of Perceived Social Support (MSPSS) is a 12-item questionnaire that assesses perceived social support on 1-to-7 scale, with 1 being “very strongly disagree” and 10 being “very strongly agree.” Three subscales, each comprising 4 items, are computed to assess perceived social support from family, friends, and significant
The MSPSS has adequate test–retest and internal reliability, and high factorial validity. The MSPSS demonstrated strong reliability in this sample ($\alpha = .96$).

**Health literacy.** The Rapid Estimate of Adult Literacy in Medicine is a 2- to 3-minute assessment of medically relevant vocabulary (66 total words) that has been shown to correlate well with other measures of various literacy skills.

**App usability.** The study team adapted the App Usability Questionnaire from the System Usability Scale (SUS), a validated, easily administered scale. We adapted the 10-item SUS to a simplified, 6-item Likert scale ranging in response from “strongly disagree” to “strongly agree.” Final scores can range from 0 to 30. Higher scores indicate higher perception of usability. Scores above 21 (ie, 70% of total score) can be considered to have good usability.

**Data collection and sources.** The study RA called all participants at the time of post-assessment and reminded them to complete the self-report questionnaire and return the electronic pill bottle, either at their next clinic visit or by mail. RAs checked questionnaires in real time for incomplete items and solicited clarification from participants. Of the 181 patients randomized in this trial, 12 did not complete post-assessment questionnaires. Of these patients, 7 withdrew from the study: 4 patients opted to discontinue because of study burden, 2 were unable to continue because their phone became incompatible with the mobile app, and 1 became too ill to continue in the study. An additional 4 patients died prior to completing post-assessment questionnaires, and 1 patient was lost to follow-up.

We were unable to retrieve MEMS data from 11 patients. Of these patients, 9 did not return their MEMS pill bottle to our study team, we were unable to download data from 1 participant’s bottle due to a technical issue, and 1 participant’s MEMScap was lost in the mail.

**Analytic and statistical approaches.** We used SPSS ([computer program] Version 22.0. Chicago, IL: SPSS) to conduct statistical analyses, first with all available baseline and follow-up data and then using Multiple Imputation to account for missing data. We described demographic and clinical characteristics with measures of central tendency or percentages (see Table 3).
Table 3. Phase 2: Sociodemographic, Clinical, and Psychosocial Characteristics in the Full Sample and by Study Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (Standard Deviation) or N (%)</th>
<th>Full Sample (n = 181)</th>
<th>Standard Care (n = 90)</th>
<th>Mobile App (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range = 21-88)</td>
<td></td>
<td>53.30 (12.91)</td>
<td>53.76 (12.08)</td>
<td>52.85 (13.74)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>97 (53.6%)</td>
<td>51 (56.7%)</td>
<td>46 (50.5%)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>84 (46.4%)</td>
<td>39 (43.3%)</td>
<td>45 (49.5%)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>159 (87.8%)</td>
<td>75 (83.3%)</td>
<td>84 (92.3%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>10 (5.5%)</td>
<td>4 (4.4%)</td>
<td>6 (6.6%)</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>5 (2.8%)</td>
<td>5 (5.6%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino/a</td>
<td>4 (2.2%)</td>
<td>4 (4.4%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Multiracial</td>
<td>2 (1.1%)</td>
<td>2 (2.2%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.6%)</td>
<td>0 (0.0%)</td>
<td>1 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino/a</td>
<td>5 (2.8%)</td>
<td>4 (4.4%)</td>
<td>1 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced degree</td>
<td>81 (44.8%)</td>
<td>35 (38.9%)</td>
<td>46 (50.5%)</td>
<td></td>
</tr>
<tr>
<td>Some college/technical school</td>
<td>44 (24.3%)</td>
<td>27 (30.0%)</td>
<td>17 (18.7%)</td>
<td></td>
</tr>
<tr>
<td>College graduate</td>
<td>42 (23.2%)</td>
<td>21 (23.3%)</td>
<td>21 (23.1%)</td>
<td></td>
</tr>
<tr>
<td>High school graduate/GED</td>
<td>14 (7.7%)</td>
<td>7 (7.8%)</td>
<td>7 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>Relationship status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/ living with someone as if married</td>
<td>136 (75.1%)</td>
<td>68 (75.6%)</td>
<td>68 (74.7%)</td>
<td></td>
</tr>
<tr>
<td>Single, never married</td>
<td>17 (9.4%)</td>
<td>7 (7.8%)</td>
<td>10 (11.0%)</td>
<td></td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>13 (7.2%)</td>
<td>8 (8.9%)</td>
<td>5 (5.5%)</td>
<td></td>
</tr>
<tr>
<td>Noncohabitating relationship</td>
<td>9 (5.0%)</td>
<td>6 (6.7%)</td>
<td>3 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Loss of long-term partner/widowed</td>
<td>5 (2.8%)</td>
<td>1 (1.1%)</td>
<td>4 (4.4%)</td>
<td></td>
</tr>
<tr>
<td>Declined to respond</td>
<td>1 (0.6%)</td>
<td>0 (0.0%)</td>
<td>1 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-time or part-time work or school</td>
<td>110 (60.8%)</td>
<td>56 (62.2%)</td>
<td>54 (59.3%)</td>
<td></td>
</tr>
<tr>
<td>Characteristic</td>
<td>Full Sample (n = 181)</td>
<td>Standard Care (n = 90)</td>
<td>Mobile App (n = 91)</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------------</td>
<td>------------------------</td>
<td>---------------------</td>
<td></td>
</tr>
<tr>
<td>Retired/unemployed/disability</td>
<td>69 (38.1%)</td>
<td>33 (36.7%)</td>
<td>36 (39.6%)</td>
<td></td>
</tr>
<tr>
<td>Other or missing</td>
<td>2 (1.1%)</td>
<td>1 (1.1%)</td>
<td>1 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Has children</td>
<td>140 (77.3%)</td>
<td>72 (80.0%)</td>
<td>68 (74.7%)</td>
<td></td>
</tr>
<tr>
<td>Religion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catholic</td>
<td>79 (43.6%)</td>
<td>45 (50.0%)</td>
<td>34 (37.4%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>37 (20.4%)</td>
<td>20 (22.2%)</td>
<td>17 (18.7%)</td>
<td></td>
</tr>
<tr>
<td>Protestant</td>
<td>24 (13.3%)</td>
<td>10 (11.1%)</td>
<td>14 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>26 (14.4%)</td>
<td>12 (13.3%)</td>
<td>14 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>Jewish</td>
<td>9 (5.0%)</td>
<td>1 (1.1%)</td>
<td>8 (8.8%)</td>
<td></td>
</tr>
<tr>
<td>Muslim</td>
<td>1 (0.6%)</td>
<td>0 (0.0%)</td>
<td>1 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Declined to respond</td>
<td>5 (2.8%)</td>
<td>2 (2.2%)</td>
<td>3 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; $25 000</td>
<td>16 (8.8%)</td>
<td>9 (10.0%)</td>
<td>7 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>$25 000-$50 000</td>
<td>19 (10.5%)</td>
<td>12 (13.3%)</td>
<td>7 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>$51 000-$100 000</td>
<td>40 (22.1%)</td>
<td>17 (18.9%)</td>
<td>23 (25.3%)</td>
<td></td>
</tr>
<tr>
<td>$101 000-$150 000</td>
<td>49 (27.1%)</td>
<td>24 (26.7%)</td>
<td>25 (27.5%)</td>
<td></td>
</tr>
<tr>
<td>&gt; $150 000</td>
<td>51 (28.2%)</td>
<td>25 (27.8%)</td>
<td>26 (28.6%)</td>
<td></td>
</tr>
<tr>
<td>Declined to respond</td>
<td>6 (3.3%)</td>
<td>3 (3.3%)</td>
<td>3 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>60 (33.1%)</td>
<td>30 (33.3%)</td>
<td>30 (33.0%)</td>
<td></td>
</tr>
<tr>
<td>Non–small cell lung cancer</td>
<td>33 (18.2%)</td>
<td>16 (17.8%)</td>
<td>17 (18.7%)</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>26 (14.4%)</td>
<td>15 (16.7%)</td>
<td>11 (12.1%)</td>
<td></td>
</tr>
<tr>
<td>High-grade glioma</td>
<td>21 (11.6%)</td>
<td>12 (13.3%)</td>
<td>9 (9.9%)</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>12 (6.6%)</td>
<td>4 (4.4%)</td>
<td>8 (8.8%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>8 (4.4%)</td>
<td>2 (2.2%)</td>
<td>6 (6.6%)</td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td>7 (3.9%)</td>
<td>3 (3.3%)</td>
<td>4 (4.4%)</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>7 (3.9%)</td>
<td>3 (3.3%)</td>
<td>4 (4.4%)</td>
<td></td>
</tr>
<tr>
<td>Low-grade glioma</td>
<td>5 (2.8%)</td>
<td>4 (4.4%)</td>
<td>1 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Characteristic</td>
<td>Full Sample (n = 181)</td>
<td>Standard Care (n = 90)</td>
<td>Mobile App (n = 91)</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------</td>
<td>-----------------------</td>
<td>------------------------</td>
<td>--------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Nongastrointestinal stromal tumor sarcoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage of disease (solid staged tumors only; n = 85)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (1.2%)</td>
<td>1 (2.6%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2 (2.3%)</td>
<td>2 (5.1%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>5 (5.9%)</td>
<td>1 (2.6%)</td>
<td>4 (8.7%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>4 (4.7%)</td>
<td>2 (5.1%)</td>
<td>2 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>73 (85.9%)</td>
<td>33 (84.6%)</td>
<td>40 (87.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Metastatic disease (solid tumors only; n = 121)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of oral therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>121 (66.9%)</td>
<td>56 (62.2%)</td>
<td>65 (71.4%)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>60 (33.1%)</td>
<td>34 (37.8%)</td>
<td>26 (28.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of oral therapy in months (range = 0-136)</strong></td>
<td>12.70 (20.87)</td>
<td>13.36 (22.12)</td>
<td>12.04 (19.67)</td>
<td></td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>89 (49.2%)</td>
<td>49 (54.4%)</td>
<td>40 (44.0%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>87 (48.1%)</td>
<td>40 (44.4%)</td>
<td>47 (51.6%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5 (2.8%)</td>
<td>1 (1.1%)</td>
<td>4 (4.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of prescribed medications (range = 0-19)</strong></td>
<td>5.82 (3.99)</td>
<td>5.98 (4.02)</td>
<td>5.67 (3.97)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
Aim 1: To implement a patient-centered mobile app to assess symptoms, side effects, and adherence to oral chemotherapy that is feasible for use with oncology patients. To assess feasibility of participants using the mobile app, we examined completion rates of symptom reports during the 12-week study period. The app was considered feasible if 75% of participants assigned to the intervention completed 75% of possible symptom reports or more than 9 total reports. We examined participants’ perception of app usability by interpreting the means and standard deviations on the app usability questionnaire. Scores above 70% were considered acceptable, those between 80% and 90% were considered good, and those above 90% were considered superior.

Aim 2: To evaluate the efficacy of the mobile application in improving adherence and patient-reported clinical outcomes. For tests of aim 2, we examined between-group differences in changes in the primary outcomes from baseline to the 12-week follow-up assessment using linear regression models. We created difference scores (post minus baseline) and conducted each model by regressing the change in each outcome (dependent variable) on study group assignment (independent variable) and interpreting the unstandardized coefficients, represented by the capital letter B. We considered estimates statistically significant based on a 2-sided α of 0.05 and 95% confidence intervals. We included the change in perceived social support on the MSPSS as a covariate in all models for 2 reasons. First, we selected this for use as a covariate a priori, due to the documented relationship between social support and adherence. Second, we observed that there was a marginally significant difference in perceived social support over time on the MSPSS, such that patients assigned to the mobile app intervention reported larger decrements in perceived social support compared with those assigned to the standard care group (Mean_{Diff} = 0.39; SE_{Diff} = 0.20; t_{162} = 1.90; p = .060).

Aim 3: To evaluate the efficacy of the mobile application in improving quality of oncology care. For tests of aim 3, we examined between-group differences in changes in the secondary outcomes, conducted in an identical fashion to tests of aim 2.

Exploratory Aim: To determine whether particular patient demographic and clinical characteristics moderate the effect of the study intervention. We also conducted tests of
treatment response heterogeneity with the goal of determining whether the treatment effect of the mobile app varied among levels of baseline and other factors. We prespecified subgroups of interest in the study design based on our previous research.\textsuperscript{18} To identify moderators of the treatment effect, we first examined demographic and clinical characteristics known to be related to poorer adherence. These factors included being less educated or less health literate, not being married or partnered, having lower perceived social support, having higher anxiety or depression, and reporting memory problems. We also examined demographic and clinical factors that have been inconsistently related to adherence (ie, gender, age, number of concomitant medications, duration of oral therapy treatment), or those that were theoretically believed to influence the treatment effect or overall adherence (ie, type of cancer [hematologic malignancy versus solid tumor], therapy dosing schedule [continuous dosing versus interval dosing], type of oral therapy [targeted therapy versus oral chemotherapy], and functional performance status [ECOG]).

To conduct subgroup analyses, we first created interaction terms (study condition by subgroup characteristic) and regressed each outcome on the interaction term, the subgroup characteristic, and study group assignment, controlling for change in perceived social support (per the MSPSS). Given that tests for interactions usually have limited power, and that the lack of a significant interaction does not definitively eliminate the possibility of treatment heterogeneity, we further probed interaction terms with $\alpha < 0.10$ to examine the effects of study group assignment on the outcome across levels of the moderator.\textsuperscript{60} For categorical moderators, we examined the effect of study group assignment on the outcome for each subgroup. For continuous moderators, we used an empirical cutoff when applicable, or applied the Johnson-Neyman technique in the PROCESS macro for SPSS,\textsuperscript{61} which uses iterative approximation to calculate regions of significance and identify the optimal cutoff.

**Power analyses.** Using the effect size estimates from our prior pilot investigation, we had 80% power to detect a statistically significant improvement in adherence rates from 0.70 to 0.90 with a sample size of 150 patients (75 patients per group). While we originally aimed to enroll 180 participants in the study based on this power analysis, we increased the accrual goal to 220 participants to account for attrition. The larger sample size also helped increase power.
to explore potential moderators (ie, identify subgroups of patients who may respond
differently to the mobile app intervention).

**Missing data analyses.** Data were missing at postassessment for 12 participants.
Reasons for missing data were as follows: withdrawal (n = 7); death (n = 4); lost to follow-up (n
= 1). Due to a clerical error with administering the MDASI, data on this measure were missing
for 31 participants at the baseline assessment. Otherwise, 1 participant did not complete the
baseline survey and therefore had missing data on most baseline measures. We first
conducted statistical analyses using all available baseline and follow-up data and then, to
address missing data concerns, we repeated the analyses with imputed data using the Multiple
Imputation method in SPSS.62

**Conduct of the study.** Over the course of this study we amended the protocol
(Appendix F) to restructure the assessment timeline; add a resource utilization questionnaire;
add the M.D. Anderson Symptom Inventory questionnaire; add an optional pill diary; add
community cancer clinic affiliates in North Shore, Emerson, and MGH West as study sites; add
an app usability questionnaire; and increase accrual from 180 to 220 participants to ensure
that at least 180 patients were randomized.
F. RESULTS

Phase 1

Participant characteristics. We previously described stakeholder involvement, and characteristics of MGH patients and oncology clinicians are presented in Table 1.

Final mobile app intervention. To meet criteria for phase 1, aim 1, we developed a patient-centered mobile app to assess symptoms, side effects, and adherence to oral chemotherapy that is feasible for use with oncology patients. We successfully created the app content with input from key stakeholders, the research team, and technology experts. Summary findings of feedback from the individual interviews with MGH patients and clinicians as well as the 4 stakeholder focus groups during phase 1 are presented in Table 2 and Appendix C. In addition, example feedback in email communication with stakeholders and the research team’s response is presented in Appendix D.

The mobile app, CORA, was written primarily in JavaScript language and developed on the Titanium 3.5 and 5.0 platform to ensure cross-platform functionality on both Apple iOS and Android devices. CORA was supported by a PHP/MySQL database and hosted on a LAMP server that met HIPAA Security Rule requirements. The entire study team participated in code reviews and quality assurance testing with each code release. We included MGH oncology patients in usability testing and beta testing to ensure app usability for implementation in the RCT. Qualitative feedback from interviews with oncology patients, family members, clinicians, and key stakeholders indicated that the app was feasible and acceptable for use in this patient population. Table 4 illustrates examples of how we incorporated feedback from stakeholders into the final mobile app. CORA underwent 7 version updates to address integration with third-party smartphone operating systems (n = 4) and to fix software bugs or make minor improvements (n = 3). The final version of CORA is organized in functional modules (Appendix E), including a medication treatment plan with a timeline and reminder system, reporting features for adherence and symptoms along with graphics, educational resources and recipes, integrated wearable fitness tracking with Fitbit, and a section for notes and questions.
<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>Stakeholder Feedback</th>
<th>Module: Feature</th>
<th>Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients and families</td>
<td>“Connect patients with the same disease type for social support.”</td>
<td>Education Library Module: Resources and Social Networking</td>
<td>CORA includes a list of reputable, disease-specific resources for patients looking to connect with others.</td>
</tr>
<tr>
<td>Health care representatives</td>
<td>“Provide patients with anchors and definitions of symptoms so they can appropriately determine the severity and urgency of their symptoms.”</td>
<td>Symptom Reporting: Frequency and duration</td>
<td>When a patient reports a symptom, CORA asks several questions about the frequency and duration before providing tailored feedback.</td>
</tr>
<tr>
<td>Oncology clinicians</td>
<td>“The weekly symptom reports that are sent to clinicians should be concise and easy to understand.”</td>
<td>Symptom Reporting: Trends</td>
<td>Weekly Symptom Reports provide a list of symptoms reported by the patient, as well as a color and numeric value (1-10) denoting severity.</td>
</tr>
<tr>
<td>Practice administrators</td>
<td>“Provide resources and contact information for patients to use when they miss a dose of their medication.”</td>
<td>Symptom Reporting–“Touch to call clinical team”</td>
<td>Patients receive study team contact information at baseline. Embedded in the symptom reporting feature is a “touch to call” button for their specific clinic.</td>
</tr>
</tbody>
</table>
Phase 2

Participant characteristics. Of the 696 potentially eligible patients screened via the EHR, 196 were not approached for the study because the oncologist denied our request to approach \(n = 64\) or did not respond to our request to approach \(n = 134\) the patient. We therefore approached 500 patients in clinic, 178 (35.6%) of whom did not own a smartphone, and 110 (22.0%) of whom declined to participate. Reasons patients cited for refusal included not interested in the intervention \(n = 43\), not interested in participating in any research \(n = 25\), not comfortable using their smartphone \(n = 25\), belief that the study would be too burdensome/disrupt current treatment \(n = 16\), or concerns about the security of their data \(n = 1\). The remaining 212 enrolled in the study and were scheduled to complete baseline assessments at their next outpatient oncology visit. The baseline visit occurred on average 36 days (SD = 49 days) after enrollment. During this time, 28 participants dropped out of the study, 3 were lost to follow-up (see CONSORT flow diagram, Figure 3), and 181 completed baseline assessments and were then randomized to either the mobile app \(n = 91\) or standard care \(n = 90\). Of this total of 181 patients, we had recruited 173 from MGH and 8 from community affiliate sites. A total of 169 patients completed the postassessment survey at the 12-week follow-up. Reasons for incomplete assessments included patient withdrawal \(n = 7\), death \(n = 4\), and loss to follow-up. MEMSCap data were available on 170 patients; 9 patients did not return their pill bottle, 1 cap was lost in the mail, and 1 did not have available data on the cap. No study-related adverse events occurred over the course of the study. As noted, 1 participant’s MEMSCap data were lost in the mail (Table 5); however, confidentiality was not breached because no identifiable participant information was in the envelope or on the bottle. Table 6 presents Patient Intervention Comparison Outcome (PICOT) descriptors, and Appendix G references results tables submitted to ClinicalTrials.gov.
Figure 3. CONSORT Flow Diagram

Potentially Eligible Per EHR Screen (n=696)

Assessed for Eligibility (n=500)

Enrolled (n=212)

Randomized (n=181)

Mobile App

Baseline Assessment (n=91)

Post Assessment (n=80)

MEMSCap Collected (n=84)

Standard Care

Baseline Assessment (n=90)

Post Assessment (n=89)

MEMSCap Collected (n=86)

Oncologist denied permission to approach (n=62)
Oncologist did not respond to request to approach (n=134)

No Smartphone (n=178)
Declined (n=110)
Association with cancer (92)
Not interested in research (26)
Uncomfortable using smartphones (25)
Study burden (19)
Data security concerns (1)

Dropped out (n=28)
47 declined to continue
Study burden (7)
Lost interest (4)
Travel burden (3)
MEMSCap concerns (2)
Not feeling well (1)
11 became ineligible
Other (6)
Began Taltalice (2)
No longer taking WII (1)

Lost to follow-up (n=3)

Missing Post (n=1)
Deceased (n=1)

Missing MEMS (n=2) Did not return (n=6)
Lost in mail (1)

Missed Post (n=1) Did not return (n=6)
Lost in mail (1)
Table 5. Adverse Events Overview

<table>
<thead>
<tr>
<th>Events</th>
<th>Mobile App (n = 91)</th>
<th>Standard Care (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Affected/At Risk (%)</td>
<td>No. Events</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3 (3.3%)</td>
<td>3</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>0 (0%)</td>
<td>0</td>
</tr>
<tr>
<td>Other adverse event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product issue&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>1 (1.1%)</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adherence data were lost due to the patient’s deidentified MEMSCappill bottle being lost in the mail. There was no breach of confidentiality.

<sup>b</sup> Collection approach: nonsystematic assessment.
<table>
<thead>
<tr>
<th><strong>PICOT Descriptor</strong></th>
<th><strong>Study-specific Description</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient group</strong></td>
<td>Patients with diverse malignancies prescribed oral chemotherapy</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>12-week mobile app intervention to monitor adherence and symptoms</td>
</tr>
<tr>
<td><strong>Control or comparator</strong></td>
<td>Standard oncology care</td>
</tr>
<tr>
<td><strong>Outcomes (main/important outcomes)</strong></td>
<td>Primary outcomes: changes in patient-reported adherence (MMAS-4), electronically monitored adherence (MEMSCap), symptom severity and interference (MDASI), quality of life (FACT-G)</td>
</tr>
<tr>
<td></td>
<td>Secondary outcomes: treatment satisfaction (FACIT-TS-PS), urgent emergency department visits and hospitalizations (RUQ), app usability (percentage of symptom reports completed)</td>
</tr>
<tr>
<td><strong>Timing (duration of follow-up)</strong></td>
<td>12 weeks (+/− 3 weeks)</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Massachusetts General Hospital Cancer Center and community affiliates: outpatient oncology clinics</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Semistructured interviews and 2-arm randomized, parallel assignment, efficacy trial</td>
</tr>
</tbody>
</table>

Within the sample, patients were 53.30 years of age on average (SD = 12.91), half were women (53.6%), the majority were Caucasian (87.8%), and 80.1% were partnered (see Table 3 for demographic characteristics of the sample). Participants were well-educated, with 23.2% having graduated from college, and an additional 44.8% having an advanced degree. Approximately one-third of patients had a hematologic malignancy (33.1%), followed by non-small cell lung cancer (18.2%), breast cancer (14.4%), and high-grade gliomas (11.6%). Most patients (66.9%) were prescribed targeted therapies (ie, agents that specifically target cancer cells with known oncogenic mutations) while the remainder were prescribed other oral chemotherapies (33.1%). Appendix H lists the types of oral therapies patients were prescribed. Patients had been taking oral therapies for an average of 12.70 months (SD = 20.87). At the baseline assessment, 21.5% of patients (n = 39) reported problems with adherence to oral therapies. Of the 170 participants with MEMSCaps data available, 52.9%, 22.4%, and 12.9% of patients were less than 90%, 70%, and 50% adherent over the course of the study, respectively.

**Aim 1: To implement a patient-centered mobile app to assess symptoms, side effects, and adherence to oral chemotherapy that is feasible for use with oncology patients.** In phase 2, tests of aim 1 showed that the feasibility aim was not met, with only 34% of patients assigned to the mobile app completing the adherence and symptom reports on more than 75% of the total possible study weeks. On average, patients assigned to the mobile app condition completed 15.92 (SD = 14.15) reports over the course of the study (median = 14.00; IQR = 5.00 to 21.00). Patients completed the adherence and symptom reports on a mean of 6.43 weeks (SD = 3.86) out of the 12 study weeks (57.1% of possible weeks). The average app usability rating was good (M = 71.22; SD = 17.36), with 23.1% of patients reporting acceptable usability (scores 70-79), 21.2% reporting good usability (scores 80-89), and 15.4% reporting superior usability (scores 90-100). On average, patients used the app for 59 minutes and 32 seconds (SD = 1 hour, 8 minutes, and 15 seconds) over the course of the 12-week study period and accessed the app on 21.75 discrete days (SD = 21.24 days) out of 84 possible days. The medication treatment plan timeline was the most frequently visited page of the app, followed by the educational library, the symptom graph review, the ad hoc symptom reporting module,
and the free notes section. The most frequently reported symptoms in the app were fatigue and disturbed sleep.

Aim 2: To evaluate the efficacy of the mobile application in improving adherence and patient-reported clinical outcomes. Tests of aim 2 evaluated the efficacy of the mobile app in improving adherence as measured by MEMSCap, patient-reported adherence, change in symptom severity and interference, and change in QOL (Table 7). These analyses showed that the mobile app intervention group and usual care control group did not differ with respect to the primary outcomes of MEMSCap adherence rates, self-reported adherence, symptoms, or overall QOL. Specifically, at the postassessment, 23.3% of patients in the standard care group and 13.8% of patients in the mobile app intervention reported poor adherence; however, this difference was not statistically significant. Study groups also did not differ with respect to objective MEMSCap adherence rates, change in symptom severity or interference, or overall QOL. We observed a significant effect of group assignment on change in social and family well-being on the FACT-G; patients in the mobile app intervention had a smaller reduction in social and family well-being from baseline to postassessment (M_{change} = –0.55; SE = 0.53) compared with the standard care group (M_{change} = –2.22, SE = 0.50; M_{diff} = 1.67, SE = 0.74, F_{1161} = 5.13, p = .025, 95% CI [–3.12 to –0.21]).

Aim 3: To evaluate the efficacy of the mobile application in improving quality of oncology care. Tests of aim 3 evaluated the efficacy of the mobile application in improving secondary outcomes of quality of oncology care (Table 8). Study groups did not differ significantly with respect to satisfaction with clinicians and treatment or the number of emergency department visits or hospitalizations. We observed a marginally significant difference in the change in Satisfaction with Interpersonal Treatment subscale on the FACIT-TS-PS; patients in the mobile app intervention had a slight improvement in their satisfaction on average (M_{change} = 0.07; SE = 0.13) compared with those in the standard care group, who had a slight reduction in satisfaction (M_{change} = –0.29, SE = 0.13; M_{diff} = –0.35, SE = 0.18, F_{1159} = 3.67, p = .057, 95% CI [–0.72-0.01].
<table>
<thead>
<tr>
<th>Primary Study Outcome</th>
<th>N</th>
<th>Mean (SE) or N (%)</th>
<th>Mean Difference (SE)</th>
<th>Odds Ratio (SE)</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standard Care</td>
<td>Mobile App</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-report poor adherence (MMAS-4)</td>
<td>162</td>
<td>20/86 (23.3%)</td>
<td>11/80 (13.8%)</td>
<td>–</td>
<td>0.56 (0.46)</td>
<td>.186 [0.23-1.33]</td>
</tr>
<tr>
<td></td>
<td>158</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Objective adherence rate (MEMSCap)</td>
<td>158</td>
<td>79.16 (2.78)</td>
<td>81.50 (2.93)</td>
<td>–2.34 (4.06)</td>
<td>.566</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Δ Symptom severity (MDASI)</td>
<td>138</td>
<td>0.08 (0.15)</td>
<td>–0.30 (0.15)</td>
<td>0.11 (0.21)</td>
<td>–</td>
<td>.603 [–0.31-0.53]</td>
</tr>
<tr>
<td>Δ Symptom interference (MDASI)</td>
<td>137</td>
<td>–0.11 (0.23)</td>
<td>–0.12 (0.23)</td>
<td>0.01 (0.33)</td>
<td>–</td>
<td>.982 [–0.64-0.65]</td>
</tr>
<tr>
<td>Δ Quality of life (FACT-G)</td>
<td>162</td>
<td>–1.93 (1.13)</td>
<td>0.49 (1.19)</td>
<td>–2.42 (1.65)</td>
<td>–</td>
<td>.144 [–5.66-0.83]</td>
</tr>
<tr>
<td>Δ Physical well-being</td>
<td>163</td>
<td>0.11 (0.45)</td>
<td>0.81 (0.48)</td>
<td>–0.70 (0.66)</td>
<td>–</td>
<td>.294 [–2.00-0.61]</td>
</tr>
<tr>
<td>Δ Social/family well-being</td>
<td>164</td>
<td>–2.22 (0.50)</td>
<td>–0.55 (0.53)</td>
<td>–1.67 (0.74)</td>
<td>.025b</td>
<td>0.21 [-3.12 to -0.21]</td>
</tr>
<tr>
<td>Δ Emotional well-being</td>
<td>163</td>
<td>0.53 (0.40)</td>
<td>0.04 (0.41)</td>
<td>0.49 (0.58)</td>
<td>–</td>
<td>.392 [–0.64-1.63]</td>
</tr>
<tr>
<td>Δ Functional well-being</td>
<td>164</td>
<td>–0.40 (0.41)</td>
<td>0.35 (0.43)</td>
<td>–0.75 (0.60)</td>
<td>–</td>
<td>.216 [–1.94-0.44]</td>
</tr>
</tbody>
</table>

Abbreviations: Δ, change from baseline to postassessment; CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy-General; MDASI, M.D. Anderson Symptom Inventory; MEMSCap, Medication Event Monitoring System Caps; MMAS-4, 4-item Morisky Medication Adherence Scale; SE, standard error.

Self-report adherence (MMAS-4) analysis is controlling for baseline self-reported adherence on MMAS-4. All analyses are controlling for change in perceived social support (Multidimensional Scale of Perceived Social Support).

b p < .05.
Table 8. Differences in Secondary Outcomes by Study Group\textsuperscript{a}

<table>
<thead>
<tr>
<th>Secondary Study Outcome</th>
<th>N</th>
<th>Mean (SE) or N (%)</th>
<th>Mean Difference (SE)</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standard Care</td>
<td>Mobile App</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfaction with treatment (FACIT-TS-PS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\Delta) Clinician explanations</td>
<td>163</td>
<td>-0.34 (0.19)</td>
<td>0.04 (0.20)</td>
<td>-0.38 (0.28)</td>
<td>.170 ([-0.93-0.17])</td>
</tr>
<tr>
<td>(\Delta) Interpersonal treatment</td>
<td>162</td>
<td>-0.29 (0.13)</td>
<td>0.07 (0.13)</td>
<td>-0.35 (0.18)</td>
<td>.057 ([-0.72-0.01])</td>
</tr>
<tr>
<td>(\Delta) Comprehensive care</td>
<td>162</td>
<td>-0.89 (0.49)</td>
<td>0.08 (0.52)</td>
<td>-0.97 (0.72)</td>
<td>.178 ([-2.39-0.45])</td>
</tr>
<tr>
<td>(\Delta) Nursing communication</td>
<td>159</td>
<td>-0.26 (0.19)</td>
<td>-0.45 (0.20)</td>
<td>0.20 (0.28)</td>
<td>.481 ([-0.35-0.75])</td>
</tr>
<tr>
<td>(\Delta) Trust and confidence in clinicians</td>
<td>163</td>
<td>-0.24 (0.12)</td>
<td>-0.24 (0.13)</td>
<td>0.01 (0.17)</td>
<td>.970 ([-0.34-0.35])</td>
</tr>
<tr>
<td>Emergency department visits (RUQ)</td>
<td>162</td>
<td>0.14 (0.04)</td>
<td>0.16 (0.04)</td>
<td>-0.03 (0.06)</td>
<td>.682 ([-0.15-0.10])</td>
</tr>
<tr>
<td>Hospitalizations (RUQ)</td>
<td>160</td>
<td>0.15 (0.07)</td>
<td>0.20 (0.07)</td>
<td>-0.05 (0.10)</td>
<td>.640 ([-0.24-0.15])</td>
</tr>
</tbody>
</table>

Abbreviations: \(\Delta\), change from baseline to postassessment; CI, confidence interval; FACIT-TS-PS, Functional Assessment of Chronic Illness Therapy–Treatment Satisfaction–Patient Satisfaction; RUQ, Resource Utilization Questionnaire.

\textsuperscript{a} All analyses are controlling for change in perceived social support (Multidimensional Scale of Perceived Social Support).
**Exploratory Aim:** To determine whether particular patient demographic and clinical characteristics moderate the effect of the study intervention. The exploratory aim addressed treatment heterogeneity by testing efficacy of the mobile app intervention within key patient subgroups. We first examined the presence of an interaction between study group assignment and the proposed baseline moderator factors in predicting primary outcomes. In tests of moderation, we did not find evidence for moderation by the following factors: gender, education, health literacy, relationship status, depression, perceived social support, type of cancer (hematologic malignancy versus solid tumor), type of oral therapy (chemotherapy versus targeted therapy), duration of oral therapy treatment, number of concomitant medications, therapy dosing schedule (continuous dosing versus interval dosing), and functional performance status (ECOG).

We did find evidence of moderation by the following factors: baseline self-reported adherence (MMAS-4), baseline anxiety (HADS-anxiety), and patient age. Linear regression models examining self-reported adherence at baseline as a potential moderator showed a significant interaction between group assignment and baseline self-reported adherence in predicting the MEMSCaps adherence rate ($B = 26.04; SE = 9.65; p = 0.008; 95\% CI, 6.97-45.10$; Table 9). Further examination of the effect of group assignment on the MEMSCaps adherence rate at levels of the moderator (good adherence versus poor adherence) revealed that among patients with poor self-reported adherence at baseline (Table 10), those who were randomized to the mobile app intervention had improved adherence on the MEMSCaps ($M = 86.23; SE = 7.72$) compared with those in the standard care control ($M = 63.94, SE = 6.46; B = 22.30, SE = 10.06, p = .034, 95\% CI [1.78-42.82]; Figure 4). Self-reported adherence at baseline was not a moderator of the other primary study outcomes (all $ps > .10$).

Linear regression models examining anxiety as a potential moderator showed a significant interaction between group assignment and self-reported anxiety (HADS-Anxiety subscale) at the baseline assessment in predicting the MEMSCaps adherence rate ($B = 17.55; SE = 8.84; p = .049; 95\% CI, 0.08-35.02$; Table 11). Probing at the levels of this moderator (low anxiety versus high anxiety) indicated that among patients with high anxiety at baseline (Table 12), those randomized to the mobile app intervention had improved adherence on the
MEMSCaps (M = 85.46; SE = 5.57) compared with those in the standard care control group (M = 69.39, SE = 5.19; B = 16.08, SE = 7.76, p = .044, 95% CI [0.41-31.74]; Figure 5). Baseline anxiety was not a moderator of the other primary outcomes (all p-values > .10).

Finally, in linear regression models to test whether age was a potential moderator, we found a significant interaction between study group assignment and age predicting change in overall QOL on the FACT-G (B = 0.27; SE = 0.13; p = .041; 95% CI, 0.01-0.52; see Table 13).
Table 9. Linear Regression Examining Baseline Self-reported Adherence as a Moderator of the Effect of the Mobile App Intervention on the Objective Adherence Rate per the MEMSCaps (n = 158)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unstandardized</th>
<th>Standardized</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition (mobile app)</td>
<td>–3.67</td>
<td>–0.07</td>
<td>.412</td>
</tr>
<tr>
<td>Perceived social support (MSPSS)</td>
<td>–1.63</td>
<td>–0.08</td>
<td>.290</td>
</tr>
<tr>
<td>Self-reported poor adherence (MMAS-4)</td>
<td>–19.92</td>
<td>–0.33</td>
<td>.002</td>
</tr>
<tr>
<td>Interaction (condition X self-reported adherence)</td>
<td>26.04</td>
<td>0.30</td>
<td>.008a</td>
</tr>
</tbody>
</table>

Total model  Adjusted $R^2 = 0.05$, $F = 3.03$ (4153), $p = .020$

Effect of the mobile app on the adherence rate in patients with poor adherence  $B = 22.30$, $SE = 10.06$, $p = .034$ [1.78, 42.82]

Abbreviations: CI, confidence interval; MEMSCaps, Medication Event Monitoring System Caps; MMAS-4, 4-item Morisky Medication Adherence Scale; MSPSS, Multidimensional Scale of Perceived Social Support; SE, standard error.

*a p < .05.
Table 10. Differences in Primary Outcomes by Study Group in Patients With Self-reported Poor Adherence at the Baseline Assessment on the Morisky Medication Adherence Scale (MMAS-4)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Primary Study Outcome</th>
<th>N</th>
<th>Mean (SE) or N (%)</th>
<th>Mean Difference (SE)</th>
<th>Odds Ratio (SE)</th>
<th>(P) Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Standard Care</td>
<td>Mobile App</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-report poor adherence (MMAS-4)</td>
<td>35</td>
<td>9/21 (40.9%)</td>
<td>7/14 (41.2%)</td>
<td>-</td>
<td>1.33 (0.70)</td>
<td>.683 [0.34–5.21]</td>
</tr>
<tr>
<td>Objective adherence rate (MEMSCaps)</td>
<td>34</td>
<td>63.94 (6.46)</td>
<td>86.23 (7.72)</td>
<td>−22.30 (10.06)</td>
<td>–</td>
<td>.034\textsuperscript{b} [−42.82 to −1.78]</td>
</tr>
<tr>
<td>Δ Symptom severity (MDASI)</td>
<td>29</td>
<td>0.05 (0.29)</td>
<td>−0.04 (0.34)</td>
<td>0.01 (0.45)</td>
<td>–</td>
<td>.836 [−0.84–1.03]</td>
</tr>
<tr>
<td>Δ Symptom interference (MDASI)</td>
<td>29</td>
<td>0.19 (0.49)</td>
<td>0.16 (0.58)</td>
<td>0.03 (0.77)</td>
<td>–</td>
<td>.970 [−1.55–1.60]</td>
</tr>
<tr>
<td>Δ Quality of life (FACT-G)</td>
<td>35</td>
<td>−2.70 (2.48)</td>
<td>1.36 (3.04)</td>
<td>−4.05 (3.92)</td>
<td>–</td>
<td>.309 [−12.04–3.93]</td>
</tr>
<tr>
<td>Δ Physical well-being</td>
<td>35</td>
<td>−0.85 (0.97)</td>
<td>1.46 (1.18)</td>
<td>−2.31 (1.53)</td>
<td>–</td>
<td>.141 [−5.42–0.81]</td>
</tr>
<tr>
<td>Δ Social/family well-being</td>
<td>35</td>
<td>−1.69 (0.90)</td>
<td>−0.53 (1.11)</td>
<td>−1.16 (1.43)</td>
<td>–</td>
<td>.424 [−4.06–1.75]</td>
</tr>
<tr>
<td>Δ Emotional well-being</td>
<td>35</td>
<td>0.14 (0.74)</td>
<td>−0.001 (0.90)</td>
<td>0.15 (1.17)</td>
<td>–</td>
<td>.902 [−2.23–2.52]</td>
</tr>
<tr>
<td>Δ Functional well-being</td>
<td>35</td>
<td>−0.30 (0.81)</td>
<td>0.43 (0.99)</td>
<td>−0.74 (1.27)</td>
<td>–</td>
<td>.567 [−3.33–1.86]</td>
</tr>
</tbody>
</table>

Abbreviations: Δ, change from baseline to postassessment; CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy-General; MDASI, M.D. Anderson Symptom Inventory; MEMSCaps, Medication Event Monitoring System Caps; MMAS-4, 4-item Morisky Medication Adherence Scale; SE, standard error.

\textsuperscript{a} Self-report adherence (MMAS-4) analysis is controlling for baseline self-reported adherence on MMAS-4. All analyses are controlling for change in perceived social support (Multidimensional Scale of Perceived Social Support).

\textsuperscript{b} \(p < .05\).
Figure 4. Differences in MEMSCaps Adherence Rates Between Study Groups Moderated by Self-reported Adherence (Good Versus Poor) at Baseline

MEMCaps Adherence Rate

Study Condition
- Standard Care
- Mobile App Intervention

**Self-Report Adherence at Baseline**

Estimated Marginal Means

Good Adherence  Poor Adherence

a Model adjusts for perceived social support on the Multidimensional Scale of Perceived Social Support.
Table 11. Linear Regression Examining Baseline Anxiety as a Moderator of the Effect of the Mobile App Intervention on the Objective Adherence Rate Measured With the MEMSCap (n = 158)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unstandardized</th>
<th>Standardized</th>
<th>B</th>
<th>SE</th>
<th>[95% CI]</th>
<th>β</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition (mobile app)</td>
<td>−2.63</td>
<td>4.72</td>
<td>−11.96 to 6.70</td>
<td>−0.05</td>
<td>.578</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived social support (MSPSS)</td>
<td>−1.26</td>
<td>1.56</td>
<td>−4.33 to 1.82</td>
<td>−0.07</td>
<td>.422</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High anxiety (HADS-anxiety)</td>
<td>−12.93</td>
<td>6.06</td>
<td>−24.90 to −0.97</td>
<td>−0.23</td>
<td>.034</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction (condition X anxiety)</td>
<td>17.55</td>
<td>8.84</td>
<td>0.08 to 35.02</td>
<td>0.24</td>
<td>.049 a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total Model Adjusted $R^2 = 0.02$, $F = 1.61$ (4153), $p = .175$

Effect of the mobile app on the adherence rate in patients with high anxiety $B = 16.08$, SE = 7.76, $p = .044$, 95% CI [0.41, 31.74]

Abbreviations: CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; MEMSCaps, Medication Event Monitoring System Caps; MSPSS, Multidimensional Scale of Perceived Social Support; SE, standard error.

*a $p < .05$. 
Table 12. Differences in Primary Outcomes by Study Group in Patients With Self-reported High Anxiety on the Baseline Assessment on the Hospital Anxiety and Depression Scale-Anxiety Subscalea

<table>
<thead>
<tr>
<th>Primary Study Outcome</th>
<th>N</th>
<th>Mean (SE) or N (%)</th>
<th>Mean Difference (SE)</th>
<th>Odds Ratio (SE)</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-report poor adherence (MMAS-4)</td>
<td>46</td>
<td>8/25 (32%)</td>
<td>1/21 (4.3%)</td>
<td>–</td>
<td>0.06</td>
<td>1.44 [0.003-0.96]</td>
</tr>
<tr>
<td>Objective adherence rate (MEMSCaps)</td>
<td>45</td>
<td>69.39 (5.19)</td>
<td>85.46 (5.57)</td>
<td>–16.08 (7.76)</td>
<td>–</td>
<td>.044 [-31.74 to –0.41]</td>
</tr>
<tr>
<td>Δ Symptom severity (MDASI)</td>
<td>39</td>
<td>0.02 (0.33)</td>
<td>–0.30 (0.36)</td>
<td>0.33 (0.50)</td>
<td>–</td>
<td>.523 [-0.70-1.35]</td>
</tr>
<tr>
<td>Δ Symptom interference (MDASI)</td>
<td>39</td>
<td>0.19 (0.51)</td>
<td>–0.90 (0.55)</td>
<td>1.09 (0.77)</td>
<td>–</td>
<td>.168 [-0.48-2.65]</td>
</tr>
<tr>
<td>Δ Quality of life (FACT-G)</td>
<td>46</td>
<td>–4.56 (2.37)</td>
<td>2.28 (2.60)</td>
<td>–6.84 (3.58)</td>
<td>–</td>
<td>.063 [-14.05-0.38]</td>
</tr>
<tr>
<td>Δ Physical well-being</td>
<td>46</td>
<td>–0.27 (0.82)</td>
<td>1.92 (0.90)</td>
<td>–2.19 (1.24)</td>
<td>–</td>
<td>.085 [-4.69-0.32]</td>
</tr>
<tr>
<td>Δ Social/family well-being</td>
<td>46</td>
<td>–4.07 (1.07)</td>
<td>–1.36 (1.18)</td>
<td>–2.71 (1.62)</td>
<td>–</td>
<td>.102 [-5.97-0.56]</td>
</tr>
<tr>
<td>Δ Emotional well-being</td>
<td>46</td>
<td>0.63 (0.81)</td>
<td>0.62 (0.89)</td>
<td>0.01 (1.23)</td>
<td>–</td>
<td>.995 [-2.47-2.49]</td>
</tr>
<tr>
<td>Δ Functional well-being</td>
<td>46</td>
<td>–0.85 (0.84)</td>
<td>1.10 (0.92)</td>
<td>–1.95 (1.27)</td>
<td>–</td>
<td>.130 [-4.50-0.60]</td>
</tr>
</tbody>
</table>

Abbreviations: Δ, change from baseline to post-assessment; CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy-General; MDASI, M.D. Anderson Symptom Inventory; MEMSCaps, Medication Event Monitoring System Caps; MMAS-4, 4-item Morisky Medication Adherence Scale; SE, standard error.

a Self-report adherence (MMAS-4) analysis is controlling for baseline self-reported adherence on MMAS-4. All analyses are controlling for change in perceived social support (Multidimensional Scale of Perceived Social Support).

b p < .05.
Figure 5. Differences in MEMSCaps Adherence Rates Between Study Groups Moderated by Anxiety (Low Versus High) at Baseline

MEMSCaps Adherence Rate

Study Condition
- Standard Care
- Mobile App Intervention

Hospital Anxiety and Depression Scale at Baseline

*Model adjusts for perceived social support on the Multidimensional Scale of Perceived Social Support.
Table 13. Linear Regression Examining Patient Age as a Moderator of the Effect of the Mobile App Intervention on Change in Quality of Life on the Functional Assessment of Cancer Therapy-General (n = 162)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unstandardized</th>
<th>Standardized</th>
<th></th>
<th>β</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
<td>[95% CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition (mobile app)</td>
<td>–11.72</td>
<td>7.03</td>
<td>[–25.61–2.18]</td>
<td>–0.56</td>
<td>.098</td>
</tr>
<tr>
<td>Perceived social support (MSPSS)</td>
<td>1.33</td>
<td>0.62</td>
<td>[0.10–2.56]</td>
<td>0.17</td>
<td>.035</td>
</tr>
<tr>
<td>Patient age</td>
<td>–0.16</td>
<td>0.09</td>
<td>[–0.34–0.03]</td>
<td>–0.19</td>
<td>.094</td>
</tr>
<tr>
<td>Interaction (group X patient age)</td>
<td>0.27</td>
<td>0.13</td>
<td>[0.01–0.52]</td>
<td>0.71</td>
<td>.041</td>
</tr>
</tbody>
</table>

Total model  
Adjusted $R^2 = 0.04$, $F = 2.62$ (4132), $p = .037$

Effect of the mobile app on the adherence rate in older patients (> 55 years old) based on Johnson-Neyman Technique:

$B = 5.84$, $SE = 2.57$, $p = .027$, 95% CI [0.70, 10.98]

Abbreviations: CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy-General; MSPSS, Multidimensional Scale of Perceived Social Support; QOL, Quality of Life, SE, standard error.

*p < .05.
Using the Johnson-Neyman technique in the PROCESS macro for SPSS, we identified the optimal cutoff of greater than 55 years of age versus 55 years of age or younger. Patients greater than 55 years old (Table 14) who were randomized to the mobile app intervention reported improved overall QOL ($M = 1.93; \ SE = 1.93$) compared with those in the standard care control ($M = -3.90, \ SE = 1.68$), $B = 5.84, \ SE = 2.57, \ p = .027, \ 95\% \ CI [0.70-10.98]$, Figure 6. Age was not a significant moderator of the effect of group assignment on other primary outcomes (all $ps > .10$).

**Missing data analyses.** The rate of missing data at the postassessment time point was 6.6% for the self-report questionnaires and 6.1% for the MEMSCap data. To account for these missing data, as well as the missing baseline MDASI data due to a clerical error, we conducted all analyses in an identical fashion using Multiple Imputation. Tables 15 to 22 display the findings, which generally corroborate the available case analyses. Specifically, the only significant primary main effect of the intervention was the same: Participants in the mobile app group reported a smaller reduction in social well-being over time than did those receiving standard care. In addition, the marginally significant group difference in satisfaction with interpersonal treatment (secondary outcome) became statistically significant with Multiple Imputation, favoring the intervention. Otherwise, the subgroup analyses were essentially replicated for the effect of the intervention on objective (MEMSCap) adherence in patients who reported adherence problems at baseline. However, the moderator effects of anxiety on adherence and age on quality of life became marginally significant with Multiple Imputation.
<table>
<thead>
<tr>
<th>Primary Study Outcome</th>
<th>N</th>
<th>Mean (SE) or N (%)</th>
<th>Mean Difference (SE)</th>
<th>Odds Ratio (SE)</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standard Care</td>
<td>Mobile App</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-report poor adherence (MMAS-4)</td>
<td>66</td>
<td>8/36 (20.5%)</td>
<td>5/32 (13.2%)</td>
<td>–</td>
<td>0.57 (0.73)</td>
<td>.435 [0.13-2.37]</td>
</tr>
<tr>
<td>Objective adherence rate (MEMSCaps)</td>
<td>66</td>
<td>85.24 (3.38)</td>
<td>86.59 (3.82)</td>
<td>–1.35 (5.11)</td>
<td>–</td>
<td>.792 [-11.56-8.86]</td>
</tr>
<tr>
<td>Δ Symptom severity (MDASI)</td>
<td>58</td>
<td>0.37 (0.17)</td>
<td>0.17 (0.20)</td>
<td>0.20 (0.27)</td>
<td>–</td>
<td>.447 [-0.33-0.73]</td>
</tr>
<tr>
<td>Δ Symptom interference (MDASI)</td>
<td>57</td>
<td>–0.03 (0.29)</td>
<td>0.09 (0.34)</td>
<td>–0.11 (0.44)</td>
<td>–</td>
<td>.797 [-0.10-0.77]</td>
</tr>
<tr>
<td>Δ Quality of life (FACT-G)</td>
<td>67</td>
<td>–3.90 (1.68)</td>
<td>1.93 (1.93)</td>
<td>–5.84 (2.57)</td>
<td>–</td>
<td>.027 [-10.98 to 0.70]</td>
</tr>
<tr>
<td>Δ Physical well-being</td>
<td>67</td>
<td>–0.36 (0.54)</td>
<td>0.84 (0.62)</td>
<td>–1.20 (0.83)</td>
<td>–</td>
<td>.154 [-2.85-0.46]</td>
</tr>
<tr>
<td>Δ Social/family well-being</td>
<td>68</td>
<td>–2.65 (0.84)</td>
<td>0.22 (0.95)</td>
<td>–2.87 (1.28)</td>
<td>–</td>
<td>.028 [-5.42 to 0.32]</td>
</tr>
<tr>
<td>Δ Emotional well-being</td>
<td>68</td>
<td>–0.33 (0.52)</td>
<td>0.35 (0.59)</td>
<td>–0.68 (0.79)</td>
<td>–</td>
<td>.391 [-2.26-0.90]</td>
</tr>
<tr>
<td>Δ Functional well-being</td>
<td>68</td>
<td>–0.58 (0.64)</td>
<td>0.85 (0.72)</td>
<td>–1.43 (0.96)</td>
<td>–</td>
<td>.143 [-3.35-0.50]</td>
</tr>
</tbody>
</table>

Abbreviations: Δ, change from baseline to postassessment; CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy-General; MDASI, M.D. Anderson Symptom Inventory; MEMSCaps, Medication Event Monitoring System Caps; MMAS-4, 4-item Morisky Medication Adherence Scale; SE, standard error.

*a Self-report adherence (MMAS-4) analysis is controlling for baseline self-reported adherence on MMAS-4. All analyses are controlling for change in perceived social support (Multidimensional Scale of Perceived Social Support).

b p < .05.
Figure 6. Differences in the Change in Overall Quality of Life Between Study Groups Moderated by Age\textsuperscript{a}

\textsuperscript{a} Model adjusts for perceived social support on the Multidimensional Scale of Perceived Social Support.
Table 15. Differences in Primary Outcomes by Study Group Using Multiple Imputation (Pooled Results From 10 Data Sets)^a

<table>
<thead>
<tr>
<th>Primary Study Outcome</th>
<th>N</th>
<th>Mean (SE) or N (%)</th>
<th>Mean Difference (SE)</th>
<th>Odds Ratio (SE)</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-report poor adherence (MMAS-4)</td>
<td>181</td>
<td>22.4/90 (24.9%)</td>
<td>17.3/91 (19.0%)</td>
<td>–</td>
<td>0.70 (0.45)</td>
<td>.431 [0.29-1.70]</td>
</tr>
<tr>
<td>Objective adherence rate (MEMSCaps)</td>
<td>181</td>
<td>78.40 (2.95)</td>
<td>78.78 (3.14)</td>
<td>–0.38 (4.23)</td>
<td>–</td>
<td>.929 [-8.68-7.92]</td>
</tr>
<tr>
<td>Δ Symptom severity (MDASI)</td>
<td>181</td>
<td>0.11 (0.14)</td>
<td>0.01 (0.14)</td>
<td>0.10 (0.20)</td>
<td>–</td>
<td>.618 [-0.29-0.48]</td>
</tr>
<tr>
<td>Δ Symptom interference (MDASI)</td>
<td>181</td>
<td>–0.08 (0.21)</td>
<td>–0.10 (0.23)</td>
<td>0.02 (0.31)</td>
<td>–</td>
<td>.947 [-0.59-0.63]</td>
</tr>
<tr>
<td>Δ Quality of life (FACT-G)</td>
<td>181</td>
<td>–2.01 (1.15)</td>
<td>–0.15 (1.21)</td>
<td>–1.86 (1.64)</td>
<td>–</td>
<td>.258 [-5.08-1.36]</td>
</tr>
<tr>
<td>Δ Physical well-being</td>
<td>181</td>
<td>–0.11 (0.45)</td>
<td>0.67 (0.46)</td>
<td>–0.77 (0.65)</td>
<td>–</td>
<td>.233 [-2.05-0.50]</td>
</tr>
<tr>
<td>Δ Social/family well-being</td>
<td>181</td>
<td>–2.30 (0.50)</td>
<td>–0.61 (0.51)</td>
<td>–1.70 (0.72)</td>
<td>.019^b</td>
<td>[-3.12 to –0.28]</td>
</tr>
<tr>
<td>Δ Emotional well-being</td>
<td>181</td>
<td>0.48 (0.39)</td>
<td>–0.13 (0.40)</td>
<td>0.61 (0.57)</td>
<td>–</td>
<td>.285 [-0.51-1.73]</td>
</tr>
<tr>
<td>Δ Functional well-being</td>
<td>181</td>
<td>–0.51 (0.42)</td>
<td>0.15 (0.43)</td>
<td>–0.66 (0.61)</td>
<td>–</td>
<td>.275 [-1.86-0.53]</td>
</tr>
</tbody>
</table>

Abbreviations: Δ, change from baseline to postassessment; CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy-General; MDASI, M.D. Anderson Symptom Inventory; MEMSCaps, Medication Event Monitoring System Caps; MMAS-4, 4-item Morisky Medication Adherence Scale; SE, standard error.

^a Self-report adherence (MMAS-4) analysis is controlling for baseline self-reported adherence on MMAS-4. All analyses are controlling for change in perceived social support (Multidimensional Scale of Perceived Social Support).

^b p < .05.
Table 16. Differences in Secondary Outcomes by Study Group Using Multiple Imputation (Pooled Results From 10 Data Sets)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Secondary Study Outcome</th>
<th>N</th>
<th>Mean (SE) or N (%)</th>
<th>Mean Difference (SE)</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standard Care</td>
<td>Mobile App</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfaction with treatment (FACIT-TS-PS)</td>
<td>181</td>
<td>−0.34 (0.19)</td>
<td>0.06 (0.20)</td>
<td>−0.40 (0.28)</td>
<td>.152 [−0.95−0.15]</td>
</tr>
<tr>
<td>Δ Clinician explanations</td>
<td>181</td>
<td>−0.28 (0.13)</td>
<td>0.10 (0.14)</td>
<td>−0.38 (0.18)</td>
<td>.037\textsuperscript{a} [−0.74−0.02]</td>
</tr>
<tr>
<td>Δ Interpersonal treatment</td>
<td>181</td>
<td>−0.91 (0.50)</td>
<td>0.24 (0.56)</td>
<td>−1.16 (0.74)</td>
<td>.120 [−2.61−0.30]</td>
</tr>
<tr>
<td>Δ Comprehensive care</td>
<td>181</td>
<td>−0.25 (0.19)</td>
<td>−0.46 (0.21)</td>
<td>0.21 (0.27)</td>
<td>.444 [−0.32−0.74]</td>
</tr>
<tr>
<td>Δ Nursing communication</td>
<td>181</td>
<td>−0.25 (0.12)</td>
<td>−0.24 (0.13)</td>
<td>−0.01 (0.18)</td>
<td>.962 [−0.36−0.34]</td>
</tr>
<tr>
<td>Δ Trust and confidence in clinicians</td>
<td>181</td>
<td>0.13 (0.04)</td>
<td>0.17 (0.05)</td>
<td>−0.04 (0.06)</td>
<td>.491 [−0.16−0.08]</td>
</tr>
<tr>
<td>Emergency department visits (RUQ)</td>
<td>181</td>
<td>0.16 (0.07)</td>
<td>0.21 (0.07)</td>
<td>−0.05 (0.10)</td>
<td>.634 [−0.24−0.15]</td>
</tr>
</tbody>
</table>

Abbreviations: Δ, change from baseline to postassessment; CI, confidence interval; FACIT-TS-PS, Functional Assessment of Chronic Illness Therapy–Treatment Satisfaction–Patient Satisfaction; RUQ, Resource Utilization Questionnaire.

\textsuperscript{a} All analyses are controlling for change in perceived social support (Multidimensional Scale of Perceived Social Support).
### Table 17. Linear Regression With Multiple Imputation Examining Baseline Self-reported Adherence as a Moderator of the Effect of the Mobile App Intervention on the Objective Adherence Rate per MEMSCaps (Pooled N = 181)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unstandardized</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
<td>95% CI</td>
<td>t</td>
<td>p</td>
</tr>
<tr>
<td>Δ Perceived social support (MSPSS)</td>
<td>–1.21</td>
<td>1.93</td>
<td>[–5.07-2.65]</td>
<td>–0.63</td>
<td>.533</td>
</tr>
<tr>
<td>Baseline self-reported poor adherence (MMAS-4)</td>
<td>–19.29</td>
<td>6.73</td>
<td>[–32.50 to –6.09]</td>
<td>–2.87</td>
<td>.004</td>
</tr>
<tr>
<td>Interaction (group X baseline self-reported MMAS-4)</td>
<td>26.53</td>
<td>10.53</td>
<td>[5.83-47.24]</td>
<td>2.52</td>
<td>.012a</td>
</tr>
</tbody>
</table>

Effect of the mobile app on objective adherence rate in patients with poor baseline adherence (per MMAS-4):

B = −20.63; SE = 10.04; p = .040; 95% CI [−40.41 to −0.94]

**Abbreviations:** CI, confidence interval; MEMSCaps, Medication Event Monitoring System Caps; MMAS-4, 4-item Morisky Medication Adherence Scale; MSPSS, Multidimensional Scale of Perceived Social Support; SE, standard error.

a p < .05.
Table 18. Differences in Primary Outcomes by Study Group (Using Multiple Imputation) in Patients With Self-reported Poor Adherence at the Baseline Assessment on the Morisky Medication Adherence Scale\(^a\)

<table>
<thead>
<tr>
<th>Primary Study Outcome</th>
<th>Pooled N</th>
<th>Mean (SE) or N (%)</th>
<th>Mean Difference (SE)</th>
<th>Odds Ratio (SE)</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Care</td>
<td>Mobile App</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-report poor adherence (MMAS-4)</td>
<td>40.2</td>
<td>9.6/22 (43.6%)</td>
<td>9.4/18.2 (51.6%)</td>
<td>–</td>
<td>1.38 (0.73)</td>
<td>0.657</td>
</tr>
<tr>
<td>Objective adherence rate (MEMSCaps)</td>
<td>40.2</td>
<td>63.79 (6.40)</td>
<td>84.47 (8.07)</td>
<td>–20.63 (10.04)</td>
<td>–</td>
<td>0.040(^b)</td>
</tr>
<tr>
<td>Δ Symptom severity (MDASI)</td>
<td>40.2</td>
<td>0.002 (0.29)</td>
<td>0.04 (0.32)</td>
<td>–0.04 (0.42)</td>
<td>–</td>
<td>0.931</td>
</tr>
<tr>
<td>Δ Symptom interference (MDASI)</td>
<td>40.2</td>
<td>0.03 (0.43)</td>
<td>0.24 (0.54)</td>
<td>–0.21 (0.68)</td>
<td>–</td>
<td>0.754</td>
</tr>
<tr>
<td>Δ Quality of life (FACT-G)</td>
<td>40.2</td>
<td>–2.96 (2.43)</td>
<td>0.35 (2.99)</td>
<td>–3.31 (3.92)</td>
<td>–</td>
<td>0.399</td>
</tr>
<tr>
<td>Δ Physical well-being</td>
<td>40.2</td>
<td>–1.02 (0.97)</td>
<td>0.84 (1.24)</td>
<td>–1.86 (1.55)</td>
<td>–</td>
<td>0.230</td>
</tr>
<tr>
<td>Δ Social/family well-being</td>
<td>40.2</td>
<td>–1.88 (0.91)</td>
<td>–0.67 (1.25)</td>
<td>–1.21 (1.50)</td>
<td>–</td>
<td>0.419</td>
</tr>
<tr>
<td>Δ Emotional well-being</td>
<td>40.2</td>
<td>0.04 (0.77)</td>
<td>–0.36 (0.93)</td>
<td>0.40 (1.24)</td>
<td>–</td>
<td>0.749</td>
</tr>
<tr>
<td>Δ Functional well-being</td>
<td>40.2</td>
<td>–0.43 (0.80)</td>
<td>0.29 (1.02)</td>
<td>–0.73 (1.27)</td>
<td>–</td>
<td>0.568</td>
</tr>
</tbody>
</table>

Abbreviations: Δ, change from baseline to postassessment; CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy-General; MDASI, M.D. Anderson Symptom Inventory; MEMSCaps, Medication Event Monitoring System Caps; MMAS-4, 4-item Morisky Medication Adherence Scale; SE, standard error.

\(^a\) Self-report adherence (MMAS-4) analysis is controlling for baseline self-reported adherence on MMAS-4. All analyses are controlling for change in perceived social support (Multidimensional Scale of Perceived Social Support).

\(^b\) \(p < .05\).
Table 19. Linear Regression With Multiple Imputation Examining Baseline Anxiety as a Moderator of the Effect of the Mobile App Intervention on the Objective Adherence Rate per MEMSCaps (Pooled N = 181)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unstandardized</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
<td>[95% CI]</td>
<td>t</td>
<td>p</td>
</tr>
<tr>
<td>Study group (mobile app)</td>
<td>–4.41</td>
<td>4.94</td>
<td>[–14.11-5.29]</td>
<td>–0.89</td>
<td>.373</td>
</tr>
<tr>
<td>Δ Perceived social support (MSPSS)</td>
<td>–0.81</td>
<td>1.91</td>
<td>[–4.61-2.99]</td>
<td>–0.43</td>
<td>.672</td>
</tr>
<tr>
<td>High anxiety (HADS-anxiety)</td>
<td>–13.51</td>
<td>6.44</td>
<td>[–26.12 to –0.89]</td>
<td>–2.10</td>
<td>.036</td>
</tr>
<tr>
<td>Interaction (group X baseline HADS-anxiety)</td>
<td>17.11</td>
<td>9.35</td>
<td>[–1.24-35.45]</td>
<td>1.83</td>
<td>.068</td>
</tr>
</tbody>
</table>

Effect of the mobile app on the objective adherence rate in patients with high baseline anxiety (per HADS-anxiety):
B = –14.47; SE = 8.11; p = .074; 95% CI [–30.36, 1.43]

Abbreviations: Δ, change from baseline to postassessment; CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; MEMSCaps, Medication Event Monitoring System Caps; MSPSS, Multidimensional Scale of Perceived Social Support; SE, standard error.

*p < .05.
Table 20. Differences in Primary Outcomes by Study Group (Using Multiple Imputation) in Patients With Self-reported High Anxiety on the Baseline Assessment per the Hospital Anxiety and Depression Scale-Anxiety Subscale (HADS-Anxiety)\(^a\)

<table>
<thead>
<tr>
<th>Primary Study Outcome</th>
<th>Pooled N</th>
<th>Mean (SE) or N (%)</th>
<th>Mean Difference (SE)</th>
<th>Odds Ratio (SE)</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-report poor adherence (MMAS-4)</td>
<td>48.1</td>
<td>8/25 (32.0%)</td>
<td>2/23.1 (8.7%)</td>
<td>–</td>
<td>0.11 (1.40)</td>
<td>.110 [0.007-1.67]</td>
</tr>
<tr>
<td>Objective adherence rate (MEMSCaps)</td>
<td>48.1</td>
<td>67.78 (5.51)</td>
<td>82.25 (5.62)</td>
<td>–14.47 (8.11)</td>
<td>–</td>
<td>.074 [-30.36-1.43]</td>
</tr>
<tr>
<td>Δ Symptom severity (MDASI)</td>
<td>48.1</td>
<td>0.04 (0.31)</td>
<td>–0.25 (0.33)</td>
<td>0.29 (0.46)</td>
<td>–</td>
<td>.522 [-0.60-1.19]</td>
</tr>
<tr>
<td>Δ Symptom interference (MDASI)</td>
<td>48.1</td>
<td>0.15 (0.47)</td>
<td>–0.67 (0.52)</td>
<td>0.82 (0.71)</td>
<td>–</td>
<td>.250 [-0.58-2.22]</td>
</tr>
<tr>
<td>Δ Quality of life (FACT-G)</td>
<td>48.1</td>
<td>–4.67 (2.37)</td>
<td>1.81 (2.61)</td>
<td>–6.48 (3.59)</td>
<td>–</td>
<td>.071 [-13.52-0.57]</td>
</tr>
<tr>
<td>Δ Physical well-being</td>
<td>48.1</td>
<td>–0.30 (0.83)</td>
<td>1.82 (0.90)</td>
<td>–2.12 (1.26)</td>
<td>–</td>
<td>.092 [-4.58-0.34]</td>
</tr>
<tr>
<td>Δ Social/family well-being</td>
<td>48.1</td>
<td>–4.10 (1.08)</td>
<td>–1.61 (1.18)</td>
<td>–2.49 (1.63)</td>
<td>–</td>
<td>.128 [-5.69-0.72]</td>
</tr>
<tr>
<td>Δ Emotional well-being</td>
<td>48.1</td>
<td>0.60 (0.82)</td>
<td>0.47 (0.89)</td>
<td>0.13 (1.24)</td>
<td>–</td>
<td>.916 [-2.30-2.56]</td>
</tr>
<tr>
<td>Δ Functional well-being</td>
<td>48.1</td>
<td>–0.86 (0.85)</td>
<td>0.97 (0.94)</td>
<td>–1.83 (1.28)</td>
<td>–</td>
<td>.153 [-4.34-0.68]</td>
</tr>
</tbody>
</table>

Abbreviations: Δ, change from baseline to postassessment; CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy-General; MDASI, M.D. Anderson Symptom Inventory; MEMSCaps, Medication Event Monitoring System Caps; MMAS-4, 4-item Morisky Medication Adherence Scale; SE, standard error.

\(^{a}\) Self-report adherence (MMAS-4) analysis is controlling for baseline self-reported adherence on MMAS-4. All analyses are controlling for change in perceived social support (Multidimensional Scale of Perceived Social Support).

\(^{b}\) p < .05.
Table 21. Linear Regression With Multiple Imputation Examining Patient Age as Moderator of the Effect of the Mobile App Intervention on Change in Quality of Life on the Functional Assessment of Cancer Therapy-General (Pooled N = 181)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unstandardized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Study group (mobile app)</td>
<td>-11.46</td>
</tr>
<tr>
<td>Δ Perceived social support (MSPSS)</td>
<td>1.31</td>
</tr>
<tr>
<td>Patent age</td>
<td>-0.16</td>
</tr>
<tr>
<td>Interaction (group X patient age)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Effect of the mobile app on the adherence rate in older patients (> 55 years old) based on Johnson-Neyman Technique:
B = , SE = , p = , [95% CI: ]

Abbreviations: CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy-General; MSPSS, Multidimensional Scale of Perceived Social Support; SE, standard error.

* p < .05.
Table 22. Differences in Primary Outcomes by Study Group (With Multiple Imputation) in Patients > 55 Years of Agea

<table>
<thead>
<tr>
<th>Primary Study Outcome</th>
<th>Pooled N</th>
<th>Mean (SE) or N (%) Standard Care</th>
<th>Mean Difference (SE)</th>
<th>Odds Ratio (SE)</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-report poor adherence (MMAS-4)</td>
<td>77</td>
<td>9.8/39 (25.1%)</td>
<td></td>
<td>0.70 (0.67)</td>
<td>.591</td>
<td>[0.19-2.58]</td>
</tr>
<tr>
<td>Objective adherence rate (MEMSCaps)</td>
<td>77</td>
<td>83.99 (4.20)</td>
<td>80.38 (4.34)</td>
<td>3.60 (6.02)</td>
<td>.550</td>
<td>[-8.20-15.40]</td>
</tr>
<tr>
<td>Δ Symptom severity (MDASI)</td>
<td>77</td>
<td>0.37 (0.17)</td>
<td>0.14 (0.21)</td>
<td>0.23 (0.27)</td>
<td>.397</td>
<td>[-0.30-0.75]</td>
</tr>
<tr>
<td>Δ Symptom interference (MDASI)</td>
<td>77</td>
<td>0.02 (0.28)</td>
<td>0.03 (0.32)</td>
<td>-0.004 (0.43)</td>
<td>.992</td>
<td>[-0.86-0.85]</td>
</tr>
<tr>
<td>Δ Quality of life (FACT-G)</td>
<td>77</td>
<td>-4.02 (1.70)</td>
<td>0.61 (1.84)</td>
<td>-4.63 (2.55)</td>
<td>.070</td>
<td>[-9.64-0.38]</td>
</tr>
<tr>
<td>Δ Physical well-being</td>
<td>77</td>
<td>-0.47 (0.56)</td>
<td>0.59 (0.59)</td>
<td>-1.05 (0.79)</td>
<td>.185</td>
<td>[-2.61-0.50]</td>
</tr>
<tr>
<td>Δ Social/family well-being</td>
<td>77</td>
<td>-2.75 (0.84)</td>
<td>-0.02 (0.91)</td>
<td>-2.74 (1.22)</td>
<td>.025b</td>
<td>[-5.13 to -0.34]</td>
</tr>
<tr>
<td>Δ Emotional well-being</td>
<td>77</td>
<td>-0.39 (0.54)</td>
<td>0.07 (0.57)</td>
<td>-0.46 (0.79)</td>
<td>.566</td>
<td>[-2.01-1.10]</td>
</tr>
<tr>
<td>Δ Functional well-being</td>
<td>77</td>
<td>-0.64 (0.64)</td>
<td>0.45 (0.75)</td>
<td>-1.09 (0.97)</td>
<td>.264</td>
<td>[-3.00-0.82]</td>
</tr>
</tbody>
</table>

Abbreviations: Δ, change from baseline to postassessment; CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy-General; MDASI, M.D. Anderson Symptom Inventory; MEMSCaps, Medication Event Monitoring System Caps; MMAS-4, 4-item Morisky Medication Adherence Scale; SE, standard error.

a Self-report adherence (MMAS-4) analysis is controlling for baseline self-reported adherence on MMAS-4. All analyses are controlling for change in perceived social support (Multidimensional Scale of Perceived Social Support).

b p < .05.
G. DISCUSSION

In this study, we developed an acceptable, patient-centered mobile app for adherence and symptom management for patients with diverse malignancies who were prescribed oral chemotherapy. However, patients assigned to the intervention group did not meet the a priori feasibility criterion for completing the weekly reports of adherence and symptoms. Moreover, the mobile app did not lead to significant improvements in the primary and secondary outcomes of adherence per MEMSCaps, symptoms, overall QOL, perceptions of quality of care, and health care utilization as hypothesized. Patients in the mobile app intervention reported a smaller reduction in social and family well-being over the course of the study than did those in the usual care control condition. It is possible that the app relieved some of the burden that caregivers generally experience in the context of home-based care, and this may have resulted in improvements in QOL of the patient in the social domain. Furthermore, patients who are struggling with medication adherence or have elevated anxiety may benefit from such an app to improve oral chemotherapy adherence, which may, in turn, improve therapeutic efficacy and influence treatment outcomes. Finally, older patients may find this mobile app helpful for their overall QOL, potentially by connecting them with resources for managing symptoms and by providing education about their illness and resources for improving health (eg, recipes, activity tracking).

Decisional Context

The study results underscore the importance of clinicians proactively assessing adherence to treatment in the modern era of oral cancer therapeutics—22.0% of patients reported difficulties taking these medications at baseline. However, only 13.8% of patients in the mobile app group reported adherence problems at postassessment, while 23.3% of patients in the standard care group continued to report difficulties. Although not a statistically significant change, proactive and systematic monitoring of adherence and symptoms through mobile technologies not only emphasizes the value and importance of adherence for patients but also may serve as an extra layer of support for the care team and patients to communicate effectively about the administration of oral chemotherapy and management of symptoms.
Treatment adherence is significant for public health and is a challenge for the health care system, which aims to optimize treatment outcomes. Health care decision makers may find these study results beneficial in that they suggest the potential for improving treatment outcomes for specific populations of patients who may be at greater risk. A mobile app provides a minimally burdensome, cost-effective, low-resource approach for patients who are receiving care outside of the hospital or infusion center. Such an approach could be offered to patients who endorse difficulties taking oral chemotherapy as instructed, have anxiety symptoms, or are older. The mobile app intervention reduces variation in practice by administering validated instruments to assess adherence and symptoms in a systematic manner. Moreover, using this intervention to target patients at greater risk for adherence problems would ideally reduce variation in treatment outcomes across patient subpopulations.

**The study results in context**

The current study results highlight the potential for an adherence intervention to promote medication taking in patients at greater risk for nonadherence. However, we did not observe a significant benefit of the mobile app intervention in improving the outcomes of adherence, symptoms, QOL, or perceptions of quality of care overall between the 2 study groups. Several factors may have contributed to the null findings: (1) most patients had high self-reported adherence at baseline and therefore had little or no room for improvement; (2) the app included multiple features to enhance patient engagement, which perhaps diffused its target focus on adherence and symptoms; (3) the sample was quite heterogeneous with respect to cancer types, stages, and oral treatments; (4) the use of MEMSCaps to assess adherence to oral chemotherapy regimens that have multiple intermittent breaks between cycles is challenging; and (5) oncology clinicians were not required to follow up with patients regarding their weekly adherence and symptom reports but rather could respond based on their clinical judgment. Further rigorous qualitative study with the intervention patients who participated in this study and their oncology clinicians would help elucidate the possible reasons the mobile app did not have its intended benefits on the outcomes.
In our recently published systematic review, we identified only 12 adherence intervention studies for patients with cancer, and most of them had a high risk of bias due to methodological limitations such as a small sample size or nonrandomized designs.\(^{18}\) To overcome these prior limitations, we implemented an adequately powered, randomized trial with 181 patients diagnosed with diverse malignancies. Furthermore, we employed a more robust measure of adherence, including both objective monitoring with MEMSCaps and self-reported adherence, methods utilized in only 2 previous adherence intervention studies.\(^{41,63}\) Finally, in our clinical trial, we examined clinically meaningful outcomes relevant to the patient experience, such as quality of life, symptoms and side effects, and satisfaction with treatment\(^{18,64}\) in addition to adherence.

Studies to date have not targeted multiple adherence factors at the patient, provider, and systems levels, with the few intervention trials mostly focused on reminder systems. For example, a randomized 3-group pilot study by Spoelstra and colleagues\(^{42}\) showed no differences in adherence rates following an Automated Voice Response (AVR) system alone compared with AVR combined with adherence management or with AVR combined with adherence and symptom management. In another randomized 3-arm trial, investigators did find differences in adherence when effects from 2 patient information program interventions were pooled in comparison with the control group.\(^{65}\) Otherwise, the few intervention studies with improved outcomes for adherence were nonrandomized. Specifically, in one nonrandomized study of patients with advanced non–small cell lung cancer who were prescribed oral chemotherapy, participants in the treatment monitoring program had higher rates of adherence as recorded by pill count and self-report than did a retrospective standard care control group.\(^{66}\) In addition, a nonrandomized study involving intensified multidisciplinary pharmaceutical care showed that patients with colorectal and breast cancer had higher daily adherence rates than did a standard care comparison group.\(^{41}\) Within this context, the advances of our clinical trial are reflected not only in the randomized design, sample size, and selection of outcomes, but also the intervention components. That is, we designed the mobile app to target patient factors (ie, reminder system, education library, energy tracking),
treatment factors (ie, symptom monitoring and management strategies), and clinician factors (ie, proactive communication with cancer care clinicians).

With respect to mobile health (mHealth) interventions, most studies have focused on management of long-term conditions such as diabetes, HIV, and asthma. For example, findings from a recent meta-analysis revealed improvements in treatment adherence following mobile text messaging for patients with chronic illness, but this review did not include studies with oncology patients and is therefore limited in generalizability. The authors of another meta-analysis of mHealth interventions concluded that certain mobile phone messaging interventions may improve the self-management of long-term illness; however, significant gaps exist in this work, requiring further research. While we observed no intervention effects overall in our study sample, our findings extend the growing literature suggesting that an adherence intervention delivered through mobile modalities may be beneficial for disease self-management among patients with cancer who are at greater risk for nonadherence. However, prospective follow-up study is needed to confirm that the app is indeed effective for those with poor baseline adherence and higher anxiety prior to broader dissemination and implementation of the intervention.

**Implementation of study results**

The key to successful implementation of the mobile app intervention in this study was incorporating the voices of patients, family members, clinicians, cancer practice administrators, and health care representatives throughout every phase of development and testing. While stakeholder engagement is common in earlier stages of research, we incorporated stakeholders throughout the research process, including dissemination and implementation, which occurs less frequently. For example, our final stakeholder focus groups proved to be instrumental in brainstorming the next steps for this study and how to disseminate results to audiences outside the scientific community. Moreover, the stakeholders were enthusiastic and willing to participate, and many did not want reimbursement but rather sought to help make the research more meaningful, relevant, and feasible in real-world care settings. The positive experiences with our stakeholder engagement in this study informed the development of a Patient/Family Advisory Council specifically for supportive care research at
the MGH Cancer Center, which meets 3 to 4 times per year. Investigators from our Cancer Outcomes Research Program now present studies to and gather feedback from the council about clinical relevance, whether interventions are timed effectively, and how to optimize delivery to patients, families, and the care team.

As an example of how stakeholder feedback enhanced acceptability and implementation of the mobile app intervention by MGH oncology clinicians, we drew on qualitative feedback from clinician stakeholders. Specifically, we learned that the optimal frequency for the care team to receive patient reports of adherence and symptoms would be no more than weekly. To translate this intervention successfully in typical care settings, such patient symptom reports would ideally be integrated seamlessly with the electronic health record for ongoing tracking and documentation. Unfortunately, we were unable to deliver the reports in this manner as our institution was in the process of converting to a new EHR system at the time of study implementation. Regardless, it is also important to note that we did not achieve our a priori feasibility threshold of most participants in the intervention group completing 75% of the weekly adherence and symptom reports during the study period. Perhaps the proposed feasibility criterion was not the most appropriate measure for how patients engaged with the mobile app, as some patients may have chosen not to complete the adherence and symptom reports on weeks they were feeling well or had nothing to endorse. Follow-up qualitative study is needed with patients assigned to the intervention, to discern the optimal frequency of communication with the cancer care team and whether reports should be recommended at certain time intervals, in tandem with clinically meaningful triggers, or whether the reports should be delivered primarily at the patient’s discretion.

Another primary concern for implementation across care settings relates to maintaining the mobile app functionality over time. Specifically, because mobile devices and operating systems are constantly evolving and continuously upgraded, the application software must also be adjusted and maintained. During our trial, we occasionally needed to loan backup tablet devices to participants when we encountered glitches in the system due to smartphone upgrades, for example.
A final key barrier to implementation of the intervention would be the extent to which the patient populations, or those at risk for poor medication adherence, own smartphones since the intervention was specifically designed for use on mobile technology. Given that many people keep their smartphone on their person most of the day, this technology represents an ideal modality, particularly for real-time reporting of symptoms with responsive logic to teach behavioral strategies for management. Although not all patients in the oncology setting have access to smartphones, ownership continues to grow at a rapid pace across populations, including older patients and those of lower socioeconomic status. Within our study, of the 500 patients approached to assess for eligibility, 322 (64.4%) had access to a smartphone.

**Generalizability**

As noted in the Results section, the patient sample was predominantly white and married (or partnered), approximately equally distributed across genders, and very well educated, with a wide range in age and representation of hematologic and solid tumor cancer types. The study findings would therefore likely generalize to similar patients who seek care at an urban comprehensive cancer center like Massachusetts General Hospital. Further study is needed to test the efficacy of the intervention in larger, more racially and ethnically diverse samples in both community and rural cancer care settings. Moreover, the extent to which patients’ high education levels may have selected for a more knowledgeable and motivated sample, and perhaps contributed to the high adherence rates and null findings overall, requires further research.

**Subpopulation Considerations**

Although we must interpret subgroup analyses with caution given the reduction in sample sizes, the mobile app intervention appeared to be more efficacious for patients with certain risk factors. Specifically, based on prior theory and evidence, we examined particular subgroups likely to have adherence problems, such as patients who reported poor adherence or heightened anxiety at baseline. Analyses of these subgroups revealed that those assigned to the mobile app intervention had significantly higher objective adherence estimates (per the MEMSCaps) over the study period than did those who received standard care alone. Such findings are theoretically consistent and would be meaningful to consider for potential
translation into patient care. We also observed that older patients who received the mobile app intervention reported significantly higher quality of life (per the FACT-G) than did older patients in the standard care group. These findings certainly warrant further investigation for confirmation prior to broader dissemination and implementation of the intervention.

**Study Limitations**

The study has several limitations that may have influenced the results. First, an unfortunate clerical error resulted in loss of data on the MDASI, one of the main study outcomes. However, analyses with imputed data on the full sample did not reveal a different pattern of findings from the available case analyses with respect to intervention effects on symptom severity or interference. In addition, although we used the current “gold standard” for measuring medication adherence with the MEMSCaps as the primary outcome, such monitoring in the control group likely raised awareness and improved adherence,70 potentially diluting the effect of the intervention. Moreover, using MEMSCaps to monitor medication adherence for patients with interval dosing schedules (eg, 2 weeks on, 1 week off) was challenging, especially in defining critical periods for when the patient was supposed to be taking the medication. The study team therefore had to compare data from the MEMSCaps against EHR documentation of planned breaks in the medications to ensure patients were not penalized for missing doses those days. Again, any error in adherence measurement would likely bias against intervention effects. Finally, the study took place at an academic institution with a fairly homogenous patient population with respect to race, ethnicity, level of education, and socio-economic status, which may limit generalizability of findings to other care settings and populations.

**Future Research**

Follow-up research is needed to test the benefit of the mobile app in populations at high risk for poor adherence as well as across both academic and community oncology care settings. Ideally, future studies should sample patients who are poorly adherent at baseline, therefore minimizing type 2 error. A hybrid efficacy-effectiveness study would be a useful design for further intervention testing and implementation. In addition, to augment the utility of the intervention, investigators may want to examine whether integrating patient-reported
data from the mobile app into the EHR helps enhance communication with the care team versus employing a primary triage clinician (eg, oncology nurse) to review and respond to the patient reports versus having a completely stand-alone app that records and stores data natively on the smartphone, which patients can choose to share with clinicians at their discretion. Moreover, a follow-up study could explore how oncology clinicians utilized the weekly adherence and symptom reports to inform care in their patient encounters as well as patient perceptions of why the app did not affect the primary and secondary outcomes. Expanding the mobile app to help patients monitor and manage multiple medications simultaneously may also enhance its usefulness. Finally, in future studies, the inclusion of multiple longitudinal assessments of adherence and symptoms would be needed to discern the impact of the intervention over longer follow-up periods, especially given prior research showing that medication adherence tends to wane over time.18

H. CONCLUSIONS

To our knowledge, this study represents the first examination of the development and testing of a mobile application to improve adherence to oral chemotherapy. With critical feedback from key constituent stakeholders throughout every phase of the project, we first successfully created a patient-centered mobile application, incorporating features to support adherence, symptom management, and communication with the oncology care team. We then conducted a randomized clinical trial to test the benefits of the mobile app versus standard care for improving symptoms and adherence to oral chemotherapy, in a sample of 181 patients with diverse malignancies. Although the mobile app did not have significant effects on the primary and secondary outcomes in the entire sample overall, subgroup analyses demonstrated that the intervention shows promise for patients who may be at risk for poor adherence, such as those who report having problems with medication adherence or anxiety. In addition, the mobile app may positively impact quality of life among older patients. Further work is needed to confirm the effectiveness of the intervention in these subpopulations across oncology care settings and to explore the utility of the mobile app in sustaining optimal adherence over longer periods of time. A key factor to ensure successful
dissemination and implementation of the mobile app will be the seamless integration of patient-reported data with existing electronic health record systems. As cancer care continues to evolve with orally administered agents, the innovative use of technology through this mobile app may foster communication with the care team and serve as an extra layer of support for patients to understand and adhere to their recommended treatments.
I. REFERENCES


J. PUBLICATION LIST


Appendix A: Phase 1 Semi-structured Interview Guide for Pre-Trial Focus Groups with Stakeholders

Topic 1: Perceived importance of monitoring of adherence to oral chemotherapy
   1) What are the potential problems and benefits of monitoring oral chemotherapy practices?
   2) What do you believe are the patient, clinician, and healthcare system factors that impact adherence to oral chemotherapy?
   3) To what extent does the proposed study and intervention address those factors?

Topic 2: Barriers to communication between patients and the oncology team regarding management of side effects and medication adherence
   1) What are the most important aspects of communication between patients and clinicians to ensure effective adherence to oral chemotherapy?
   2) How might communication breakdown overtime between patients and the oncology team?
   3) To what extent does the proposed study intervention address these communication barriers?

Topic 3: Potential role of the mobile application to address barriers to quality cancer care
   1) What are your impressions of the three components of the mobile application to improve symptom monitoring and adherence to oral chemotherapy:
      a. Creation of chemotherapy treatment plan
      b. Weekly self-report surveys (via the app) of symptoms and medication adherence
      c. Immediate results feedback to patients and oncology team
   2) Would you make any changes to any of these three components? In what ways could the app be improved to meet the needs of patients and clinicians?
   3) What additional resources would be helpful for managing symptoms and medications at home?

Topic 4: Feasibility, acceptability and utility of electronic intervention
   1) When would be the ideal time to start the mobile app intervention during cancer care?
   2) What types of problems, if any, do you foresee with the process of creating a chemotherapy treatment plan?
   3) To what extent does the results feedback seem personal, relevant, and helpful?
   4) Under what circumstances do you think patients or clinicians would not want to use the app?
   5) In what ways could we change or improve the app to help make it more user-friendly and acceptable to patients and clinicians?

Topic 5: System barriers and facilitators to implementation
   1) Given the components of the proposed mobile app, do you foresee any problems or barriers to implementing the intervention as we proposed?
   2) Do you have any suggestions for changing the protocol to improve the study process and flow?
   3) What recommendations do you have to ensure patient recruitment and retention?

Any final thoughts, comments or recommendations about the study that we have not yet discussed? This brings us to the end of the interview. We greatly appreciate your participation. Thank you.
Appendix B: Phase 1 Semi-structured Interview Guide for MGH Patients & Oncology Clinicians

**Topic 1: Content of Mobile Application**
1) What are your impressions of the three components of the mobile application to improve symptom monitoring and adherence to oral chemotherapy:
   a. Creation of chemotherapy treatment plan
   b. Weekly self-report surveys (via the app) of symptoms and medication adherence
   c. Immediate results feedback to patients and oncology team
2) Would you make any changes to any of these three components? In what ways could the app be improved to meet the needs of patients and clinicians?
3) Were there any parts of the app that didn’t make sense to you?
4) How likely would patients refer to educational links from organizations, like the National Cancer Institute, or use suggestions from the mobile app for coping with symptoms and side effects?
5) What additional resources would be helpful for managing symptoms and medications at home?

**Topic 2: Feasibility and Acceptability of the Mobile Application**
6) When would be the ideal time to start the mobile app intervention during cancer care?
7) What types of problems, if any, do you foresee with the process of creating a chemotherapy treatment plan?
8) To what extent does the results feedback seem personal, relevant, and helpful?
9) How comfortable would you feel using this mobile app (at home or in your practice)?
10) Under what circumstances do you think patients or clinicians would not want to use the app?
11) In what ways could we change or improve the app to help make it more user-friendly and acceptable to patients and clinicians?

**Topic 3: Weekly Assessments**
1) What are your thoughts about the app surveys of symptoms and medication adherence?
2) Are there any problems with the wording or was there anything you did no understand?
3) How often should patients complete the app surveys?
4) Are the surveys too long to complete on a weekly basis?
5) At what cutoff value for each scale would it make sense to notify the oncology team of the survey results?
6) Should we add any other questions to the surveys to make the app more useful for patients and clinicians?

Anything else you would like to add or suggest? This brings us to the end of the interview. Thank you very much for your time and participation.
Appendix C. Summary of Feedback from Phase 1 Interviews with MGH Patients, Clinicians, and Stakeholders

Personalized Chemotherapy Plan/Medication Reminders
- Identify patients who are taking the same oral chemotherapy/disease cohort and connect them to serve a support system
- Stratify patients by line of chemotherapy if variation exists in the patient populations
  - Example: oral chemotherapy as a first line of therapy versus not first line or first time taking oral chemotherapy versus treated with oral chemotherapy previously
- Allow patients to create a window of time (i.e. 7am-9am) during which they can take their medication, rather than an exact time (on the hour)
- Give patients the ability to alter the frequency of medication reminders (i.e. daily/weekly/x per week)
- Make sure that treatment plan is editable
- Include patient/treatment information in treatment plan: primary clinician, NP, who to contact on weekends, general contact info
- Specify “since your last visit to the application...”
  - Ask once every ~30 days – ask every time patient opens the app until they answer it

Symptom Management
- One goal for this section should be to empower patients to report symptoms and hopefully speak up more during clinic visits regarding symptom management
- Establish a method of tracking patient phone calls to clinic regarding symptoms and compare between study arms
- List only the common/ “red flag” side effects
- Use a slider scale for symptom support frequency and severity (0-10 for each symptom)
- Have the symptoms reorder according to endorsement
- Give specific definitions and anchors for symptoms
- Option for stable patients: “my symptoms have not changed over the last week/since my last report”
- Add sexual symptoms – sexual dysfunction
- Notify clinician when a symptom is unacceptable

Daily Tips
- Give patients the option to receive daily or weekly tips

Resources
- Track patient hits on educational resources
- Consider collaborating/partnering with a pharmaceutical company to provide relevant and reliable information to patients – many companies have portals for patients and partners, as well
• Drive educational content based on common side effects of the patient’s specific disease/drug
• Provide links to inspire.com for each disease message board(s)
• Provide information for PFAC
• Include link to website and location of Cancer Resource Room

Patient/Physician Communication
• The study can serve as an opportunity to foster communication between the patient and the care team (i.e. MD, PA, NP, etc...)
• This could be an opportunity to measure patient satisfaction on an ongoing basis, as well as satisfaction with care team communication
• Provide patients with information on how to communicate with their care team effectively
• Promote patient advocacy through this app
• Capture patient-physician communication as an outcome
• Have a point person to triage patient messages via app – NP, RN, PA
• Collect data on MDs who follow up on patient symptom reports and how (i.e. EMR)
• Look at past information on how MDs act upon new or worsening symptoms
• Make sure that communication is non-judgmental in regards to feedback on adherence

Usability, Acceptability, and Feasibility
• Ensure that this program is rewarding for patients
• Collect baseline data on patient’s beliefs and expectations regarding oral chemotherapy, as well as coping styles
• Assess whether patients see oral chemotherapy as a quality of life treatment or burdensome
• Inquire about patient’s unmet needs and gather them throughout the study
• Provide patients with feedback on how their adherence is compared to other patients using the mobile app
• Examine subgroups/cohorts of patients who might benefit more than others – compare their data – examine age/meds/age
• It is important to recognize that patients’ symptoms can be debilitating so they might have a hard time reporting some days
• Pilot the actual application with patients and clinicians before the RCT
• Assess how much the app has enhanced or burdened care for patients
  o What proportion of patients in RCT liked or disliked the application – this section could be called “Patient Engagement”
  o Ask questions like “does reading about side effects make you more anxious?”
• Incentivize patients – for every survey, give them $20
• Find an alternative way to measure ED/Urgent Care visits because if patients do not go to MGH ED/UC, then it will not show up in their electronic medical record
• Flesh out “point person” for app in great depth – some barriers could arise if this is not organized
• What will a patient do if they report a severe symptom on a Friday afternoon when no one is there to receive the message?
• What is the point person is on vacation?
• Ensure that there is a clear disclaimer that the app does not replace when patient should call their doctor regarding severe symptoms

• Conduct clinician assessments on how acceptable the app is for them
  • Clinicians might think it’s a great idea during a focus group, but once they actually have a busy schedule, during the RCT, they could neglect it
  • Clinicians who are not researchers might have a hard time accepting this

• Stratify for different oral agents
• Not necessary to exclude by line of chemotherapy, but worth collecting and noting/stratifying
• Exclude patients who are enrolled in a clinical trial – clinical trial patients at MGH do not receive “standard care”
• Thus, exclude trial/experimental drugs

**General Suggestions**
• Train Research Assistants and study staff in the app to give an instructional seminar for participants using the app
• Possibly include a training video in the app on how to use the app
• Assess if patients are taking oral chemotherapy for a short period of time or indefinitely – engage both of these populations and get feedback on how to make this app ongoing for both populations
• MD referrals are not ideal for RCT – query electronic medical records, then approach physicians regarding eligible patients – develop a cross-Cancer Center protocol for recruitment in various disease groups
• Involve clinicians throughout app development and RCT so that they are interested and invested in the project, thus more likely to dedicate time to utilizing the patient/physician features on the mobile app
• Ensure that clinicians are addressing patient-reported symptoms on the app during clinic
• Make sure that patients are reminded to refill their medication ahead of time so they don’t run out and miss doses because of this reason
• Attempt to forward patient symptom reports to EMR
• Gather information from pharmaceutical or insurance companies that might have their own cell phone call system regarding medication adherence and instructions
• Look into liability of symptom reporting – important for fever, neutropenia, etc...
• Change exclusion criteria language from “owns a smartphone” to “uses a smartphone” – some people will own an iPhone/Android, as well as an incompatible phone – could be confusing
• Make certain parts of the app email/print friendly
• Add a “notes” section for patients to store information regarding their next clinic visit, etc.
• Best time to start app is at beginning of oral chemo prescription
• Include a disclaimer that this app is not an emergency service app and that patients should call 911 if they feel their symptoms/situation is urgent
• Provide patients with contact information if they are struggling with the app’s technical features
• Use the term “oncology clinician” rather than “doctor”
• Utilize drop down menus when possible
Appendix D. Example Email Communication with Stakeholder Groups

Dear Stakeholders,

Thank you for providing feedback for Dr. Greer’s Oral Chemotherapy Mobile Application Study. Your feedback is integral to the development and implementation of this study. We have consolidated your feedback below and included plans of how we will incorporate your suggestions into this project.

1. We asked you...
_What kinds of things could we highlight about the control arm to reassure those participants that their participation is equally important, and to ensure that they stay motivated?_

You suggested that we...

- Emphasize the high-tech characteristics of the pill bottles
- Let participants know that in the future the app may be accessible to all patients
- Be honest – the control group is important in order to see the effects of the mobile app
- Schedule check-ins with the control group participants to ensure that they feel appreciated throughout their participation

What we have changed...
Thank you for your suggestions! We have begun to inform participants of the high-tech aspects of the pill bottles, and we now inform them that the app could eventually be available for all patients. We emphasize the importance of the control group in research and communicate more frequently to ensure that all control participants feel valued and appreciated.

2. We asked you...
_We also want to encourage the oncology clinicians to be engaged with this study. When we send clinicians these weekly reports, what kinds of messages would be helpful for getting the clinicians motivated?_

You suggested that we...

- Include information about adherence in the weekly symptom reports
- Include a brief report on symptoms that impact quality of life in between clinic visits
- Set up a forum for clinicians to post comments about their experience receiving the reports
- Disseminate information on how other clinicians respond to the reports
- Ensure that the weekly symptom reports are simple, easy to interpret, and brief, with a way for clinicians to provide feedback directly
What we have changed...
This is very helpful feedback! In the current weekly symptom report format, we disseminate personalized information on the participants’ adherence and symptoms to clinicians. This is an effective way for clinicians to be informed of patients’ symptoms in between clinic visits, particularly for participants who come to clinic less frequently. We are currently restructuring our weekly symptom report format to include easily interpretable and comprehensive graphics that will allow clinicians to see what the participant endorses over a longer period of time, rather than only the current week’s data.

We asked you...
Is there any one specific feature not currently in CORA that you think would greatly improve it if it were added?

You suggested that we...
• Create a competitive incentive by allowing participants to see how adherent they are compared to other app users. This could work for both the Fitbit and mobile app.
• Provide a section for participants to submit information about their emotional well-being
• Create a feature that allow participants to share comments on their experience with the app, as well as tips on managing adherence and symptoms
• Create a patient portal
• Provide specific information about medication

These are excellent and thoughtful recommendations. In future iterations of the app, we hope to create new features that engage the app users. Creating a method to allow participants to compare their adherence with each other and share tips on their experience would be an excellent feature that we will keep in mind for the future. Participants currently have the ability to record notes and questions in the app and are encouraged to share this information with their clinician in clinic. This is a great outlet for questions and comments about emotional well-being. Participants are also given the opportunity to submit information related to emotional well-being in the adhoc and weekly symptom reports. Additionally, the app includes an extensive education library with information on medication, adherence, symptoms and side effects, as well as emotional well-being and mood symptoms.

Thank you for providing us with your ideas! Your ongoing feedback is essential to the success of this study and we are grateful for your support. Please do not hesitate to reach out with any additional suggestions and feedback that come up in between Stakeholder newsletters.

Sincerely,

Joseph Greer and the Study Team
Appendix E. Mobile App Features

1. Treatment Plan: As part of routine clinical care, participants had an initial consultation with their oncology clinician (i.e., oncologist or nurse practitioner) to review their personalized chemotherapy treatment plans. These treatment plans were uploaded into the mobile app so that patients had access to them throughout the study period. The chemotherapy treatment plan included the patient’s medication name, dosage, administration schedule, break schedule, and prompts for medication reminders.

2. Medication adherence: Within the app, participants could set up daily alerts to take their medication. In addition, they were asked to complete a weekly, two-item questionnaire assessing how well they took their oral chemotherapy medication in the last week. Specifically, these questions asked: 1) what percent of the time did you take your prescribed oral chemotherapy medication(s)? (0%-100%); and 2) on average, how would rate your ability to take all of your oral chemotherapy medication(s) as your doctor prescribed? (“very poor” to “excellent”). Patients were reminded to take their medications and complete weekly adherence reports via push notifications sent directly from the server. Push notifications are pop-up messages that appear on the mobile device and serve to remind the user to engage with the app. The patient could accept the notification on the screen which directly opened the app to the adherence report page. In addition, if the patient ignored the notification but entered the app at a later date, a banner would appear on the home screen serving as a reminder to complete the weekly report. Finally, a badge would display on the app icon itself (known as a badge app icon), serving as an additional reminder for the patient to enter the app and complete the weekly report. The adherence reports were then emailed to the patient’s oncology clinicians on a weekly basis.

3. Symptom and side effect reporting: The mobile app contained features for symptom and side effect reporting to participants’ care team. Patients completed an abbreviated version of M.D. Anderson Symptom Inventory (MDASI) within the app. At a minimum, patients were required to complete symptom reports on a weekly basis, and were
prompted with push notifications (as described above) to complete the symptom and side effect survey on the app. Participants were also able to go into the app at any time and report any bothersome symptoms or side effects. For any extreme, new (or worsening) symptoms, patients were instructed through the app to call their oncology clinician directly. The symptom reports were also displayed in a graph format showing symptoms over time. Compiled results from these symptom reports were emailed to the patients’ oncology clinicians on a weekly basis.

4. **Education library:** To enhance patient engagement with the app, the study team compiled a library of educational materials that could be accessed by patients within the app. The library included descriptions of symptom self-management strategies, skills for communicating effectively with providers, and links to reputable websites (i.e., American Society of Clinical Oncology and American Cancer Society websites) where educational material about specific cancer types is available. There was also a page devoted to connecting participants with reputable sources that provide advice about managing finances and financial assistance during cancer care.

5. **Social networking:** The mobile app contained a social networking component that provided patients with relevant websites with disease-specific forums and support groups. In addition to specific resources, all patients had access to general oncology forums and support groups from reputable websites (e.g., inspire.com, cancer.net, patientslikeme.com, etc.). Patients were also given contact information for the Cancer Resource Center at the MGH and the Patient and Family Advisory Board to gain information, resources, and support throughout their time at the MGH.

6. **Nutrition education:** The mobile app had a page that provided participants with helpful nutritional information as well as suggestions for healthy recipes. This page contained specific information on nutrition that work well for patients undergoing treatment for cancer.

7. **Fitbit integration:** We provided intervention participants with Fitbit devices that connected directly to the mobile app. Patients were able to keep track of steps taken each day and create activity goals for themselves.
Appendix F. Summary of Protocol Changes

On March 6, 2015, our study team submitted an amendment to the IRB proposing to restructure the timeline for study participants. We clarified that the 3-month enrollment period would begin on the date of orientation rather than the date of consent. We made this change to accommodate patients with spaced out clinic schedules. The IRB approved this amendment on March 16, 2015.

We submitted an amendment on March 20, 2015, proposing to add a resource questionnaire that gathered information on emergency department visits outside of MGH. We also added a psych resource questionnaire to inquire about patient's recent mental health services and an ECOG Performance Status questionnaire so that patients could self-report their performance status if it is not listed in their electronic medical record. Lastly, this amendment added a question to the patient qualitative interview to inquire if doctors brought up adherence and symptom reports from the mobile application during clinic visits. This amendment was approved by the IRB on April 14, 2015.

On July 12, 2015, our team submitted an amendment to replace the Memorial Symptom Assessment Scale (MSAS) with the M.D. Anderson Symptom Inventory (MDASI) to collect participant self-report data at baseline and post-assessment. Due to an administrative error, we had not collected any data using the MSAS or full MDASI at the baseline or post assessments prior to the submission of this amendment. Participants assigned to the intervention group who utilized the mobile app had been completing an abbreviated MDASI on a weekly basis. This amendment was approved by the IRB on July 30, 2015.

We submitted an amendment on August 14, 2015, proposing to add a pill diary that would be given to all participants when they enrolled in the study. The pill diary was an optional tool, and was not an official measure of adherence. Rather, it was given to participants to use in the case that they had notes they would like to take regarding their adherence on any particular day. This amendment was approved by the IRB on August 26, 2015.
On October 19, 2015, our study team submitted an amendment to add Mass General West (MGH West) as a study site to aid in our enrollment efforts. Additionally, we proposed to change our adherence monitor (GlowCap to MEMS). This amendment was approved by the IRB on November 4, 2015.

On December 2, 2015, we submitted an amendment proposing to add an “app usability questionnaire” to the post-assessment with the intervention group. This questionnaire gathered information about the usability of the app. This amendment was approved by the IRB on December 4, 2015.

We submitted an amendment on March 23, 2016, proposing to increase the overall study accrual from 180 to 200 participants. This amendment was approved on March 29, 2016. On June 3, 2016, we submitted an additional amendment to increase the accrual once again from 200 to 220 participants. This amendment was approved by the IRB on June 20, 2016. By increasing accrual to 220 participants, we were able to enroll more than 180 participants to account for those who dropped out or expired after randomization.

Appendix G. ClinicalTrials.gov Results Weblink:
https://clinicaltrials.gov/ct2/show/study/NCT02157519?term=greer+oral+chemotherapy&draw=1&rank=1
Appendix H. List of Generic Oral Chemotherapy and Targeted Therapy Drugs

Afatinib
Axitinib
Bosutinib
Capecitabine
Ceritinib
Crizotinib
Dabrafenib
Dasatinib
Erlotinib
Everolimus
Gefitinib
Ibrutinib
Imatinib
Nilotinib
Lapatinib
Lenalidomide
Osimertinib
Palbociclib
Pazopanib
Pomalidomide
Sorafenib
Sunitinib
Temozolomide
Copyright© 2019. Massachusetts General Hospital (The General Hospital Corp.). All Rights Reserved.

Disclaimer:

The [views, statements, opinions] presented in this report are solely the responsibility of the author(s) and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute® (PCORI®), its Board of Governors or Methodology Committee.

Acknowledgement:

Research reported in this report was [partially] funded through a Patient-Centered Outcomes Research Institute® (PCORI®) Award (#IHS-1306-03616) Further information available at: https://www.pcori.org/research-results/2013/does-smartphone-app-help-patients-cancer-take-oral-chemotherapy-planned