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Improving Palbociclib adherence among women with metastatic breast cancer using a CONnected CUstomized Treatment Platform (CONCURxP): A Pilot Study

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Abstract

Objective: To pilot test a mobile health intervention using a CONnected CUstomized Treatment Platform (CONCURxP) that integrates a connected electronic adherence monitoring smartbox and an early warning system of non-adherence with bidirectional automated texting feature and provider alerts.

Methods: 29 adult women with hormone-receptor positive, human epidermal growth factor receptor 2–negative metastatic breast cancer and a prescription for palbociclib were asked to complete a survey and participate in a CONCURxP intervention, including use of a smartbox for real-time adherence monitoring, which triggered text message reminders for any missed or extra dose, and referrals to (a) participant's oncology provider after three missed doses or an episode of over-adherence, or (b) a financial navigation program for any cost-related missed dose. Use of

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Ethics Approval: This study was conducted according to the guidelines in the Declaration of Helsinki. Procedures for obtaining informed consent and protecting participants were approved and monitored by the Emory Institutional Review Board (IRB# STUDY00001515).

Consent to Participate: The study was Health Insurance Portability and Accountability Act compliant. Written informed consent was obtained from all participants.

Consent for Publication: Given no identifiable data is being published, consent for publication was not required.

smartbox, number of referrals, palbociclib adherence, CONCURxP usability measured by System Usability Scale, and changes in symptom burden and quality of life (QOL) were assessed.

Results: Mean age was 57.6 and 69% were white. The smartbox was used by 72.4% of participants, with palbociclib adherence rate of 95.8%±7.6%. One participant was referred to oncology provider due to missed doses and one was referred to financial navigation. At baseline, 33.3% reported at least one adherence barrier including inconvenience to get prescription filled, forgetfulness, cost, and side effects. There were no changes in self-reported adherence, symptom burden or QOL over 3 months. CONCURxP usability score was 61.9±14.2.

Conclusion: The CONCURxP interventions is feasible, resulting in high palbociclib adherence rate without any decline overtime. Future efforts should focus on improving usability.

Keywords

Metastatic breast cancer; mHealth; adherence; palbociclib

Introduction

For women with hormone receptor-positive (HR+) and human epidermal growth factor receptor 2–negative (HER2-) metastatic breast cancer (MBC), palbociclib, the most commonly used cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), leads to a doubling of progression-free survival from 14.5 to 24.8 months[1, 2], an increase in 5-year overall survival from 16.8% to 23.2%, and a reduction in symptom burden when added to endocrine therapy[3, 4]. The single published study of palbociclib adherence used claims data and found that adherence ranged from 65% to 81%[5]. The complex schedule of palbociclib and high cost (an average wholesale cost per cycle of $13K)[6], together with side effects, likely contribute to non-adherence. Prior research suggests that for palbociclib to have a survival benefit, the relative dose intensity needed is 94%[1, 2].

The increasing penetration of mobile phones across every segment of the population can be leveraged by the healthcare community to engage patients between visits and improve medication adherence[7]. We aimed to address the clinical need to optimize medication adherence in MBC to prolong survival by pilot testing a multilevel mobile health (mHealth) intervention. Specifically, we evaluated a CONnected CUstomized Treatment Platform (CONCURxP) that integrates an electronic adherence monitoring smartbox and an early warning system of non-adherence with bidirectional automated texting and provider alerts. Feasibility of the intervention, palbociclib adherence, changes in patient-reported outcomes over 3 months enrollment period, and participants' experience with the intervention were assessed.

Methods:

This study was conducted according to the guidelines in the Declaration of Helsinki. Procedures for obtaining informed consent and protecting participants were approved and monitored by the Institutional Review Board (IRB# STUDY00001515). The study was Health Insurance Portability and Accountability Act compliant. Written informed consent was obtained from all participants.

Study Population

Women were eligible if they were English speaking, 18 years or older, of any menopausal status with pathology proven HR+ HER2− MBC, were treated as an outpatient at a single comprehensive cancer center in a metropolitan area, and had a new or existing prescription for palbociclib, a smartphone with data plan, and the capacity to consent. Women with an ECOG performance status > 2 were excluded.

Smartbox

The Wisepill RT2000 Medication Dispenser, also called the smartbox, is 4G LTE enabled, allowing remote, real-time medication management (Figure 1). It automatically tracked when the box was opened and marked the dose as “taken.” In the case of a refill, participants were instructed to open the smartbox at the time of their scheduled dose to avoid false double or off-cycle dose tracking. Adherence data were automatically sent to the web portal through cellular service and linked to the study ID. Study coordinators and participants could view the history of doses taken on web portal.

Enrollment

Between January and November 2021, eligible women were identified, introduced to the study, and consented via phone by the study coordinator. After consenting, participants were asked to complete an online 30-minute baseline survey and were mailed their smartbox. Next, the study coordinator confirmed the receipt of the smartbox, first day of cycle, and preferred time for taking their palbociclib (enrollment call). The study coordinator used this information to set up the initial medication schedule for participants. Participants were asked to use the smartbox exclusively with their prescribed palbociclib for 3 cycles starting from the enrollment call or first day of their next cycle (if the enrollment call was during off-cycle).

A person-specific login account was set up for access to the smartbox web portal. On the web portal, participants could review their adherence and modify their scheduled time of palbociclib and the first day of their cycle. Participants received training on the use of smartbox and on navigating the web portal using a step-by-step instruction sheet and a link to an instructional video.

All participants received usual care which included routine oncology visits, access to ancillary staff, and internal or external resources for financial assistance per normal clinic procedures.

CONCURxP.

The CONCURxP intervention consisted of use of the smartbox and web portal to provide:

1. *Smart reminders,* including personalized text messages (a) to remind of the missed dose, if the smartbox was not opened within 30 minutes after scheduled dose time; (b) to inquire about reason for non-adherence using a link to a single multiple-choice question if the participants did not take the medication within 11 hours after scheduled dose time (Supplemental Table 1); and (c) to

confirm over-adherence immediately after a double if more than one opening was recorded within that same 24-hour period or an off-cycle dose if an opening was recorded during the off-cycle.

2. *Smart referrals* to (a) the oncologist to initiate contact with participant after three non-consecutive missed doses in a 28 day cycle or incidence of confirmed over-adherence; and (b) Patient Advocate Foundation (PAF), a national nonprofit financial navigation organization, when a missed dose was reported to be due to cost.

3. *Adherence monitoring via* logging into the study web portal to review medication doses recorded using the smartbox.

Data Collection

Baseline and 3-month follow-up assessment included self-reported adherence, symptom burden, quality of life (QOL), patient-provider communication, and financial worry plus usability questions at follow up only. Survey data was collected electronically, by mail, or over the phone based on participant preference. Participants received $20 gift cards upon completion of each survey.

To better understand the participants' experience with the usability of CONCURxP, we conducted phone interviews with five study participants between October and November 2021. Participants who completed the interviews received an additional $20 gift card.

Outcomes

The primary outcome was feasibility defined as participants' use of smartbox. Other feasibility outcomes included number of smart reminders, notification to oncologists, and referral to PAF and reasons for non-adherence.

We measured palbociclib adherence using the smartbox, defined as the proportion of times each participant took scheduled palbociclib during the 3-cycles after initiation. Off-cycle day, and days when providers advised to temporarily or permanently stop the medication were deducted from the total days in the study.

Patient-reported outcomes measured were CONCURxP usability using a modified 10-item System usability scale (score 0–100; higher score = higher usability; average usability = 68)[8], palbociclib adherence using the Patient Reported Outcomes Measurement Information System (PROMIS) Medication Adherence Scale (PMAS) (score 9–45; higher score= higher adherence)[9], symptom burden using a modified Functional Assessment of Cancer Therapy-Breast (FACT-B) (score 0–64; higher score=less symptom burden)[10], QOL using 10-item PROMIS-10, and converted to t-scores[11], patient-provider communication using modified validated American Board of Internal Medicine's Patient Assessment survey (score 10–50; higher score=better communication)[12], and financial worry using the 11-item Comprehensive Score for Financial Toxicity (COST) survey (score 0–44; higher score=less worry)[13, 14].

At baseline, participants were queried on age, race, ethnicity, marital status, education, employment status, income, health literacy[15], frequency of internet use, self-reported barriers to palbociclib adherence, at least one emergency department visit or inpatient hospitalization in the last 3 months.

Data analyses

Descriptive statistics were used to report baseline characteristics and health outcomes with categorical variables reported as frequency and percentage, and the continuous variables reported as mean and standard deviation (SD) or median and interquartile range (IQR), where appropriate. For self-reported adherence, symptom burden, QOL, and financial worry we used paired *t*-tests to assess changes in outcomes at enrollment and 3 months. All statistical tests were performed using the STATA software package (Stata/MP 17.0 for Mac; StataCorp, TX). A p value < 0.05 was set as significant.

Results

Of the 135 HR+ HER2− MBC patients assessed for eligibility and approached, 32 did not meet the eligibility criteria. Of the remaining 104 patients, 29 were enrolled and completed the baseline survey (Figure 2).

Baseline Demographics and Clinical Characteristics

Mean age at enrollment was 57.6±10.5 years (range 41–84), 69% (n=20) were White, and 3.8% (n=1) were Hispanic (Table 1). A majority (57.2%, n=16) had commercial primary insurance, followed by 32.1% (n=9) who had Medicare. Overall, 63% (n=17) reported having a concurrent prescription for endocrine therapy, and 33.3% (n=9) reported at least one barrier to palbociclib adherence.

Feasibility and Adherence

Two of the 29 enrolled withdrew from the study prior to receipt of CONCURxP. For 6 participants no or limited adherence data was recorded, due to technical issues or user errors. Overall, eight participants were lost to follow-up at 3 months, resulting in 21 participants who were included in the analyses.

The smartbox was used by 72.4% (n=21) of participants over a mean of 50 days (SD 18.6; range 13–73 days). The variable usage is due to whether they paused or discontinued the medication. Two participants used the smartbox more than the expected 3 cycles. Overall, palbociclib adherence rate was 95.8% (SD 7.6%), and ranged between 75% and 100% with two participants reporting adherence rates of less than 80%.

All 21 participants received a mean of 8.8 (SD 8.6; range 1–35) reminders 30-minutes after their missed dose, and 15 participants received a mean of 2.9 (SD 3.0; range 0–10) reminder question inquiring reason for non-adherence 11 hours after a missed dose. Overall 14 participants responded to 35 of 65 reason question. Episodes participants reported as discontinuing the medication permanently (n=2), or temporarily due to side effects (n=2) as advised by provider, or taking the medication at a later time (n=29) were not counted

as non-adherence. Episodes where participants reported as not filling the prescription on time and starting the cycle late (n=2) or participants did not respond to the questionnaire were counted as non-adherence (n=32). Overall, one participant was referred to oncologist. A second participant with non-adherence more than 3 dose was not referred as her non-adherence was due to delay in prescription refill. Additionally, one patient was referred to PAF. This referral was due to participant's request as opposed to direct result of a missed dose due to cost-related non-adherence.

Ten participants received a mean of 0.7 (SD 1.0; range 1–4) reminders for double or off-cycle dose. However, all incidents were due to opening the smartbox for refill or charging battery.

Changes in patient-reported outcomes

No significant changes were seen in patient-reported adherence, symptom burden, QOL, and patient-provider communication during 3 months study (Table 2). However, participants' financial worry significantly increased (i.e, COST score decreased) at 3 months (COST score, 25.1 ± 9.5) when compared to enrollment (COST score, 28.1 ± 10.1 (p=0.02).

Patient Experience with CONCURxP

The usability score of CONCURxP was 61.9 (SD, 14.2). In interviews, participants reported being satisfied with the frequency and method of delivery of the smart reminders. With other aspects of the CONCURxP intervention, however, participants described the following challenges. First, the bulky design of the smartbox led to inconsistent use. One participant explained, "If I had an occasion when I wasn't at home at dinner time [which is when I usually take my pills], I didn't want to take the whole box with me. Normally if I want to take the pills with me when I'm out, I put them in a small container, so it's not so obvious that I'm taking pills at dinner." Second, participants reported that the smart reminders would occasionally send incorrect notifications, because the smartbox was programmed to associate any opening the smartbox, even if it was to charge it or to place new pills, with the participant taking the medication. Participants shared that receiving incorrect notifications felt "frustrating" as they would receive alarming messages even though they were "doing everything I was supposed to." Lastly, participants who self-reported high medication adherence did not perceive a need for adherence monitoring. One participant said that "I am conscious of taking my medication at the same time every day. I am able to do it without having any reminders."

To improve usability, participants suggested enhancing the video tutorials so that they include clear instructions on "what to do with it and how it works" as well as "how it sends a signal" in terms of transmitting the information on adherence based on opening of the box.

Discussion

In this pilot study, we found that a mHealth intervention using smartbox to provide real-time palbociclib adherence monitoring and bidirectional messages complemented with smart referral is feasible, with 72.4% consistently using the intervention as intended. The average palbociclib adherence rate using CONCURxP was 95.8% (SD 7.6%), which is higher

than what was reported in prior studies based on claims data and in the absence of any intervention (65–81%)[5].

One third of participants reported facing a barrier to palbociclib adherence, with inconvenience and side effects being most commonly cited. According to a prior survey of MBC patients, across all oral treatment medications, forgetfulness (41.3%) was the most common reason for non-adherence, followed by side-effects (36.5%)[16]. Medications with complex dosing schedules such as palbociclib are more difficult to manage and can increase adherence issues, especially in those with forgetfulness. The most common CDK4/6i adverse event is hematologic toxicities, primarily neutropenia; but this is usually uncomplicated and managed with dose interruption and/or reduction. While patients with MBC are often willing to accept additional side effects such as fatigue or nausea for survival gains[16, 17], 20.1% of patients reduce dose within the first 6 cycles of treatment initiation predominantly due to side effects[18]. Permanent discontinuation of CDK4/6i due to grade 3–4 treatment-related adverse events were reported in 6 to 7.5% of patients[19, 20]. CDK4/6is are expensive, with an average of $13K in wholesale price per cycle, and a monthly out-of-pocket copay ranging between $0-$12,056 among those with commercial insurance[5]. High cost of CDK4/6 inhibitors has been described as a potential barrier to adherence in prior study[17]. In the current study, 11% reported cost being a barrier to adherence. Our intervention aimed to address these barriers: (1) forgetfulness via text reminders; (2) medication side effects via notifying oncology providers to contact patients; and (3) cost concerns via referral to the Patient Advocate Foundation. Although the high adherence rate observed in the current study is partially related to the receipt of our multi-level intervention addressing barriers to adherence, it is also possible that our enrolled patients have higher adherence rate compared to average population, as majority of our participants had demographics that are generally associated with higher adherence rates (e.g., insured, non-minority, English speaking)[21, 22]. Of note, majority of enrollees (more than 50%) were receiving their medication from our healthcare specialty pharmacy which also facilitated higher adherence rates.

The effectiveness of prior mHealth interventions to improve adherence has been mixed. A recent trial of early-stage breast cancer with biweekly unidirectional text messages focusing on overcoming barriers to adherence did not improve aromatase inhibitor adherence[23]. However, a study of multiple myeloma patients with a new prescription for oral anticancer therapy using a similar 28-day cycle as palbociclib, combining reminders from smart pill bottle with personalized pharmacy follow-ups improved adherence[24]. This suggests that a more personalized and hands-on interventions may be needed. In a pilot study of breast cancer patients on endocrine therapy, a bidirectional text messaging system including daily medication reminders, weekly medication adverse event questions, and provider alerts to call patients if they report severe symptoms or missed doses found a self-reported adherence rate of 85%, with the intervention described easy to use and tolerable for patients with minimal clinical impact on daily clinical interactions[25].

Although our study was limited due to lack of a control group, we did not observe any changes in self-reported adherence, symptom burden, QOL, or patient-provider communication. This is likely due to the small sample size and a short follow-up period.

However, prior longitudinal studies have shown that oral anticancer therapy adherence generally decline over time[26]. Lack of decline in palbociclib adherence in the current study is a promising finding.

We observed an increase in patients' financial worry, which is expected given the high cost of treatment. Prior studies have shown worsening financial hardship as over a 12 month period among patients with metastatic colorectal cancer[27]. Although our study attempted to address non-adherence due to cost via referrals to the PAF, financial hardship usually impacts material conditions (e.g., medical debt) and psychosocial domain before impacting adherence, and we did not refer adherent patients expressing financial worry due to cancer cost to the PAF.

The reported usability of CONCURxP intervention was below average (61 in current study vs. 68 reported as average in literature)[28]. The bulky design of the smartbox, incorrect smart reminders, and lack of a perceived need for an adherence-monitoring device emerged as barriers to use in interviews. Because palbociclib changed its packaging from pills to blister packs at the beginning of this study, we had to quickly find alternative solutions for devices that would provide real-time adherence monitoring and accommodate the size of the redesigned blister packs. Wisepill was willing to accommodate this change and quickly developed a new smartbox using the specific dimensions of the palbociclib blisterpacks. With more time and usability testing, we believe that the smartbox design can be improved to be more user-friendly. Further, the smartbox was programmed to associate opening of the box with taking doses, even if it were for reasons other than taking a dose (e.g., for charging or refilling the box). This issue is common for many available electronic monitoring devices and may be avoided by educating the user on how the smartbox works through video or manual tutorials as suggested by our interviewees. Additionally, some participants received missed dose reminders in response to doses taken later or when changes in medication schedule were not communicated to the team beforehand. This can be improved by increasing the window for the first reminder (e.g., sending the first reminder 2 hours after scheduled dose as opposed to 30 minutes) as well as giving patients ability to adjust their medication schedule on the patient portal.

Our study had challenges and limitations. The small sample size, a non-randomized design, and a short follow-up period limited assessment of CONCURxP intervention effectiveness on adherence and other health outcomes. Given the change in palbociclib packaging our options in optimizing the smartbox design were limited, which resulted in several patients not using the smartbox. Lastly, study participants were recruited from a single clinic and were required to communicate in English which may limit the generalizability of our findings.

Conclusion

Our study showed that a personalized intervention using smartbox to monitor palbociclib adherence and bi-directional reminders complemented with smart referral is feasible and can result in a high palbociclib adherence rates without a decline in adherence over time. The usability of the intervention can be improved by redesigning the smartbox to make it more user friendly and increasing awareness of how the reminders are triggered.

Larger randomized controlled trials are needed to assess the effectiveness of the proposed intervention on improving adherence and outcomes and in a more diverse patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest:

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Abbreviations:

CDK4/6i	Cyclin-dependent kinase 4/6 inhibitors
COST	Comprehensive Score for Financial Toxicity
CONCURxP	CONnected CUstomized Treatment Platform
FACT-B	Functional Assessment of Cancer Therapy-Breast
HER2−	Human epidermal growth factor receptor 2–negative
HR+	Hormone receptor-positive
IQR	Interquartile range
MBC	Metastatic breast cancer
mHealth	Mobile health
PROMIS	Patient Reported Outcomes Measurement Information System
PMAS	PROMIS Medication Adherence Scale
QOL	Quality of life
SD	Standard Deviation

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Figure 1.
Smartbox

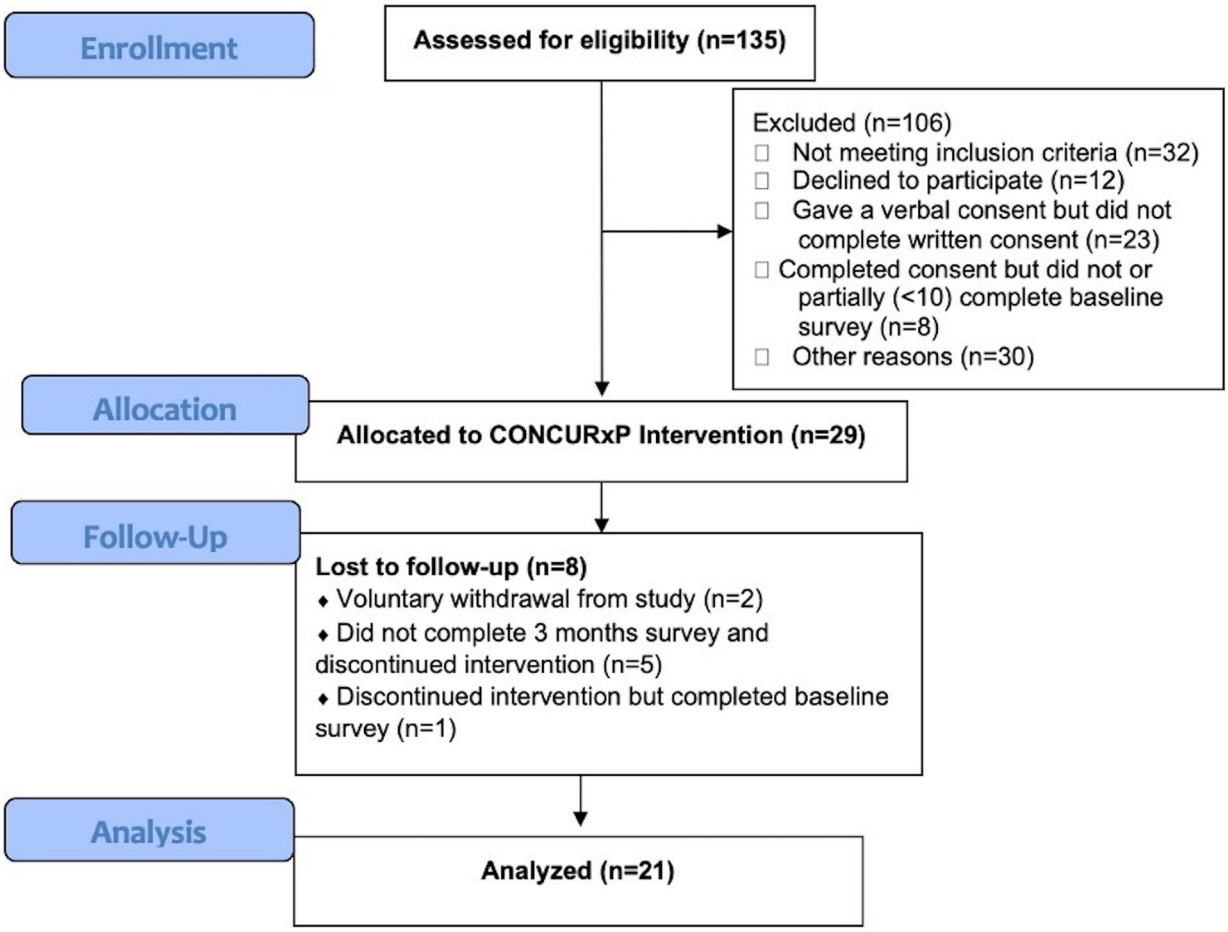

Figure 2.
Study Flowchart

Table 1.

Baseline characteristics of participants.

	Total (n=29)
Demographics	
Age, years (mean ±SD)	57.6±10.5
Race, n (%) (Missing = 0)	
White	20 (69.0)
Black	8 (27.6)
Others	1 (0.4)
Ethnicity , n (%) (Missing = 3)	
Hispanic, Latino or Spanish	1 (3.8)
Not Hispanic, Latino or Spanish	25 (96.2)
Marital Status, n (%) (Missing = 0)	
Married or living with partner	16 (55.2)
Single, Separated, Divorced, Widowed	13 (44.8)
Education, n (%) (Missing = 1)	
High school graduate or less	2 (7.1)
More than high school graduate	26 (92.9)
Employment status, n (%) (Missing = 1)	
Full-time or part-time	12 (42.9)
Unemployed, Retired, Disabled	16 (57.1)
Income, n (%) (Missing = 2)	
<$60k	10 (37.0)
>=$60k	17 (62.9)
Insurance, n (%) (Missing = 1)	
Medicare	9 (32.1)
Medicaid	3 (10.7)
Commercial	16 (57.2)
Adequate health literacy, n (%) (Missing = 1)	21 (75)
Daily Internet use, n (%) (Missing = 1)	27 (96.4)
At least one barrier to Palbociclib Adherence, n (%)	9 (33.3)
Inconvenient to get prescription filled (Missing = 3)	4 (15.4)
Forgetfulness (Missing =2)	2 (7.4)
Cost (Missing = 3)	2 (7.7)
Side effect (Missing = 2)	3 (11.1)
At least one ER visit in the last 3 months, n (%) (Missing = 0)	11 (37.9)
At least one hospital admission in the last 3 months, n (%) (Missing = 0)	9 (31.0)

Table 2.

Changes in patients' health outcomes among participants with a follow-up.

For all outcomes higher score = better outcome.

	Pre-CONCURxP (enrollment)	Post-CONCURxP (3 months)	P value
Self-reported Adherence	41.5 ± 3.7	42.3 ± 4.9	0.43
Symptom burden	17.4 ± 10.6	20.4 ± 10.9	0.11
Quality of Life (Mental Health)	48.4 ± 10.9	47.7 ± 10.7	0.51
Quality of Life (Physical Health)	45.6 ± 7.1	45.5 ± 7.7	0.91
Patient-provider communication	46.3 ± 5.4	46.5 ± 4.8	0.83
Financial worry COST score	28.1 ± 10.1	25.1 ± 9.5	0.02