FINAL PROGRESS REPORT

1. **TITLE PAGE**

Title: Toward safer opioid prescribing for chronic pain in high risk populations: implementing the Centers for Disease Control Guideline (CDC) guideline in the primary care HIV clinic.

Principal Investigator: Jessica Robinson-Papp, MD, MS

Team Members: *Core team*: Gabriela Cedillo, Mary Catherine George, Richa Deshpande, Emma K. T. Been, Allison Navis, Alexandra Nmashie, Linda Weiss, Maya Scherer, Alexandra Kamler, Judith A. Aberg, Barbara G. Vickrey; *Collaborators*: Alina Siddiqui, Bridget R. Mueller, Yosuke Chikamoto, Angela Bryan, Bradh Horn, Angela Starkweather, Jeffrey Fisher

Organization: Icahn School of Medicine at Mount Sinai

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Federal Project Officer: Eileen Hogan, MPA

2. STRUCTURED ABSTRACT

Purpose: To develop and pilot test an intervention to increase HIV primary care providers' (PCP) adherence to the U.S. Centers for Disease Control Opioid Prescribing Guideline (CDCOPG).

Scope: Chronic pain is common among people with HIV (PWH) and has often been treated with long term opioid therapy (LTOT). The 2016 CDCOPG provided a framework for the care of patients on LTOT, but required translation into an implementable format. To do so without causing harm, particularly in populations at risk for disparities such as PWH and chronic pain, we took an iterative approach including stakeholder input, and development and testing of a provider-focused intervention designed to improve CDCOPG-adherence while maintaining or improving patient-centered outcomes.

Methods: Using the Information, Motivation and Behavioral Skills (IMB) model of behavior change, this project was conducted in five steps: 1) provider engagement; 2) response to provider IMB needs; 3) patient engagement; 4) intervention finalization; 5) feasibility trial. In steps 1-4, we developed the TOWard SafER Opioid Prescribing (TOWER) intervention which was comprised of: 1) a patient-facing opioid management app; 2) a progress note template to guide the office visit; and 3) provider training. In step 5, we measured CDCOPG adherence and patient outcomes in a 9-month pilot, cluster-randomized, trial of TOWER vs. usual care.

Results: PCPs randomized to TOWER were 48% more CDCOPG-adherent (p<0.0001) with significant improvements in use of: non-pharmacologic treatments, functional treatment goals, opioid agreements, prescription drug monitoring programs, opioid benefit/harm assessment, and naloxone prescribing.

Key Words: chronic pain; HIV; opioids; opioid prescribing guidelines

3. PURPOSE

Chronic pain is common among people with HIV (PWH), and often results in a significant negative impact on quality of life. Beginning early in the HIV epidemic, PWH with chronic pain were often treated using the "cancer model" in which opioids were more liberally prescribed. This has resulted in a large group of PWH who have been maintained on long-term opioid therapy (LTOT) to this day. The U.S. opioid epidemic and the publication of the U.S. Centers for Disease Control Opioid Prescribing Guideline (CDCOPG) enhanced scrutiny on opioid prescribing practices and produced a sense of pressure among providers to reduce prescribing. However subsequent research and clinical experience highlighted the potential dangers of non-consensual opioid tapers particularly in otherwise stable chronic pain patients of LTOT. Moreover given pre-existing disparities in pain management, including opioid prescribing, it was important to be cognizant of the potential for changes in opioid prescribing practices to be applied unevenly.

This project had two Specific Aims:

Aim 1: To collaborate with stakeholders to develop an algorithmic "testable" version of the CDCOPG, which incorporates communication and implementation strategies tailored for the HIV primary care setting.

Aim 2: To assess the feasibility of the CDCOPG intervention (developed in Aim 1) in the HIV primary care setting.

These Aims, their execution, and the results are detailed in this report.

4. SCOPE

Background
Chronic pain (CP) is a significant problem for many Americans. According to data from the CDC approximately 20% of U.S. adults experience CP, defined as pain lasting for more than three months. High impact CP which interferes with daily activity and quality of life affects 8% of US adults. Chronic pain is a source of healthcare disparities, disproportionally affecting those of lower socioeconomic status. It is also one of the most common reasons for healthcare utilization and is estimated to cost $560 billion annually due to treatment costs and lost

productivity. Current treatments for CP are only modestly effective and some, such as opioids, carry significant risks.

The current U.S. opioid epidemic has greatly increased scrutiny on opioid prescribing practices, however the link between opioid prescribing for CP patients and opioid morbidity and mortality is complex and incompletely understood. Approximately 2.1 million Americans have opioid use disorder (OUD), and drug overdoses (the majority involving opioids) are still at epidemic levels with ~85,516 overdose deaths in 2020. Although opioid prescription rates have been declining since 2010, they are still quite high with ~17% of Americans receiving one or more opioid prescriptions annually. A systematic review of the literature published in 2015 estimated a prevalence of OUD of 8-12% in CP patients treated with opioids; these data demonstrate that opioids are too high risk to be considered a first-line treatment for CP, and initiating opioids for this indication should be discouraged. However, they do not provide insight into the best path forward for CP patients who are already prescribed LTOT. Some such patients have experienced poor outcomes, including precipitation of OUD when their access to prescription opioids was lost.

Context

In March 2016, the CDCOPG was published as a guide for front-line providers such as those in primary care. The CDCOPG recommendations are summarized in the Box. Some recommendations (indicated in bold) are relatively specific, however the CDCOPG also emphasizes the importance of assessment of benefit, harm, and risk of harm from prescription opioids (underlined) which is a nuanced process that presents implementation challenges. TOWER sought to improve provider adherence to the CDCOPG and improve patient outcomes without requiring additional personnel so as to be broadly generalizable to settings with limited resources.

Box. Summary of CDCG Guideline for Prescribing Opioids for Chronic Pain (CDCOPG)

1. **Nonpharmacologic and nonopioid pharmacologic therapy** are preferred.
2. Establish and measure **goals for pain and function**.
3. Discuss <u>benefits and risks</u> and clinician and **patient responsibilities for managing opioid therapy**.
4. Use immediate-release opioids when starting.
5. Carefully reassess <u>benefit/risk</u> when considering increasing dosage to **≥50 morphine milligram equivalents** (MME)/day; avoid increasing dosage to **≥90 MME/day**.
6. When opioids are needed **for acute pain, 3 days or less will often be sufficient**; more than seven days will rarely be needed.
7. Follow-up and re-evaluate <u>risk of harm</u> within **1-4 weeks** of a dose increase and at least **every 3 months** otherwise; reduce dose or taper and discontinue if <u>harm outweighs benefit</u>.
8. Evaluate <u>risk factors</u> for opioid-related harms. Consider offering **naloxone**.
9. Check **Prescription Drug Monitoring Programs (PDMP)**.
10. Use **urine drug testing at least annually**.
11. Avoid concurrent **benzodiazepine** and opioid prescribing.
12. Arrange **treatment for opioid use disorder** if needed.

Settings

The project was conducted within the Mount Sinai Health System (MSHS). Structured around seven hospital campuses and a single medical school, the MSHS has an extensive ambulatory network and a range of inpatient and outpatient services—from community-based facilities to tertiary and quaternary care. The MSHS includes approximately 7,100 primary and specialty care physicians; 12 joint-venture ambulatory surgery centers; more than 140 ambulatory practices throughout the five boroughs of New York City, Westchester, and Long Island; and 31 affiliated community health centers. Within the MSHS, the latter parts of this project were conducted within Institute for Advanced Medicine (IAM), a network of five large primary care clinics specializing in HIV care. Collectively these clinics provide primary care services for approximately 10,000 PWH.

Participants

There were different groups of participants for different steps of this project. Step 1 was initial provider engagement. In this step we engaged nine physician stakeholders of diverse specialties and backgrounds in one-on-one interviews to understand their needs for successful CDCOPG implementation. Step 2 was a preliminary intervention design step and did not have participants. Step 3 was a patient-engagement step in which 43 PWH participated. Step 4 involved feedback on the planned TOWard SafER Opioid Prescribing

(TOWER) intervention; 12 providers participated. Step 5 was the feasibility trial; 11 providers and 40 PWH participated.

Incidence
The incidence of CP in PWH, and more specifically the incidence of new opioid prescriptions for its treatment, is not known. For this study we focused on PLW with prevalent chronic pain and LTOT.

Prevalence
The prevalence of CP among PWH varies based on the population under study. In our work, which is reflective of the population under study in this project the prevalence of CP among PWH was 40% and the prevalence of an active opioid prescription was 12%.

5. METHODS

Study Design
Aim 1 (which included Steps 1-4 of the study) was a multistep intervention development phase, which used mostly qualitative methodology and was guided by the IMB model of behavior change as the theoretical framework. The provider-focused work generally used one-on-one interactions. The most formalized step of this process was Step 1 in which the interview protocol followed a "think aloud" structure whereby the physicians were provided with a printed copy of an early operationalized version of the CDCOPG. The transcribed interviews were analyzed using NVivo, a software package for the management and analysis of qualitative data. Inductive and deductive processes were employed, considering pre-identified and emerging themes. The patient-focused work (Step 3) employed the method of public deliberation (PD) which is a means of stakeholder engagement used to gather informed public input on decisions that cannot be addressed with technical information alone. Forty-three PWH (with and without chronic pain) participated in one of two day-long sessions that included interactions with experts in chronic pain, opioid prescribing and other relevant topics; discussion of case studies; and development of recommendations.

Aim 2 was a cluster-randomized feasibility study. PCPs were randomized 1:1 to TOWER versus control (described further in the *Intervention* section). Patient-participants had four visits with the research team (baseline, 3, 6, and 9 months) at which patient-reported outcome measures (PROMs) were administered.

Data Sources/Collection
Data was collected directly from participants and from the electronic health record (EHR). Data collected from participants included audiotaped qualitative data and notes from interviews, demographic information, validated PROMs (see below in the measures section), and laboratory testing (blood and urine). The EHR was used to collect clinical information about patient-participants and also to determine CDCOPG adherence using the Safer Opioid Prescribing Evaluation Tool (SOPET), a validated tool developed for this project.

Intervention
The TOWER intervention is comprised of: an opioid management app (OM-App), opioid management progress note template (OM-Note), and PCP training.

OM-App was developed for this study based on provider feedback obtained in Step 1, that performing all the care processes required by the CDCOPG would be prohibitively time consuming without some automation. Its purpose is to collect data for the opioid risk-benefit assessment directly from the patient, focusing on data not usually in the EHR and/or data that are likely to change over time. OM-App delivers a daily text message to the patient containing a link to a rotating survey of 2–3 questions each day. The OM-App questions were derived from the CDCOPG and ancillary materials on the CDC website, and query: 1) pain intensity and interference (PEG questionnaire); 2) progress toward a pain treatment goal; 3) opioid side effects (constipation, nausea, vomiting, cognitive symptoms, breathing interruptions in sleep); 4) opioid risk behaviors/misuse (alcohol or other drug use, getting opioids from alternative sources, sharing opioids with others); 5) symptoms of OUD; 6) opioid medication adherence; and 7) non-pharmacologic pain management techniques used.

The OM-Note is a progress note template intended to help PCPs conduct an efficient CDCOPG-adherent opioid management visit by providing decision support for the opioid risk-benefit assessment and organizing

the data needed to perform this assessment, including opioid-relevant data from the OM-App, the EHR, and external websites, e.g., prescription drug monitoring programs (PDMP) and opioid dose calculators.

The PCP training was a single, ~90 minute, one-on-one session which addressed IMB barriers to CDCOPG adherence and included: review of the CDCOPG, training in OM-App/OM-Note, non-opioid and non-pharmacologic pain treatments, calculation of morphine equivalents (MME), interpreting urine drug testing (UDT), naloxone training, referring for OUD treatment, use of the PDMP, opioid risk/benefit assessment, opioid tapering, patient responsibilities for opioid management, and communication strategies including motivational interviewing (MI) techniques. PCPs were instructed to use what they learned at their clinic visits with patient-participants.

Control PCPs received no training, no decision support materials, and no access to OM-App data. They were instructed to follow their usual care practices with their patient-participants.

Measures
The following PROMs were administered in the clinical trial (Aim 2):
- Brief Pain Inventory (BPI)
- Hospital Anxiety and Depression Scale (HADS)
- World Mental Health Composite International Diagnostic Interview (CIDI) substance use disorders module
- Current Opioid Misuse Measure (COMM)
- Self-Reported Misuse, Abuse, and Diversion (SR-MAD)
- Quantitative Analgesic Questionnaire (QAQ)
- AIDS Clinical Trials Group (ACTG) antiretroviral adherence questionnaire
- Trust in Provider Scale (TIPS)
- Clinician & Group Consumer Assessment of Healthcare Providers and Systems (CG-CAHPS) survey (selected questions)
- HIV Stigma Scale (HSS)
- Internalized Stigma of Chronic Pain (ISCP)
- Brief Perceived Ethnic Discrimination Questionnaire-Community Version (BPEDQ-CV)

Limitations
The limitations of the study design are as follows:
- Small sample size, single health system, and limited to patients who spoke English with their PCP.
- Patients were free to refuse participation and we had a relatively low enrollment rate (40 out of 136 eligible patients). This may have biased our sample. For example, "compliant" patients may have been more likely to enroll.
- The PCP training was conducted live and one-on-one by the study PI which would not be possible in a large trial.
- Some opioid prescribing information is inherently local, e.g. resources for non-pharmacologic treatments, and could not be part of a disseminated training.
- We incentivized OM-App adherence, and so adherence in a real world setting may be lower.
- The primary outcome measure, the SOPET which is EHR-based, does not capture decay of intervention effect well because data tends to copied forward in subsequent notes.
- OM-App data were likely underutilized by intervention-PCP-participants because of lack of EHR-integration.
- OM-App is not currently commercially available.

6. RESULTS

Principal Findings
The principal finding from the project overall is that the TOWER intervention significantly increases PCP CDCOPG adherence and was not associated with any adverse outcomes among patient-participants. This is described in greater detail in the *Outcomes* section below.

The main findings from the developmental stages of the work (Aim 1, Steps 1-4) were qualitative and were used to inform the development of the TOWER intervention.

Provider-generated experiences and recommendations included:
- Some providers find open communication with patients about opioids difficult and at times unpleasant but recognize its importance and have developed communication strategies which they share with colleagues.
- Provider-identified knowledge gaps regarding opioid prescribing included patient-specific topics (e.g., availability of/insurance coverage for non-opioid treatments) and more general areas (e.g., opioid dosing/equivalencies, prescribing naloxone).
- Innovation in information technology, focusing on the EHR for decision support, would support safer opioid prescribing within the time constraints of clinical practice.

Patient-generated recommendations included:
- Physicians should engage in an open conversation with patients, to build needed trust and to avoid assumptions about patient risk based on stereotypes—including those related to race and ethnicity—and stigmatized behavior.
- An extensive patient history was considered to be essential for opioid prescribing decisions so that physicians could fully understand issues that contributed to healthcare behaviors and the potential for behavioral change.
- Decisions related to opioid prescription and management should be communicated honestly and transparently; providers should be prepared to explain the rationale for their actions.
- PLW recognize the risks of opioid use. Recommended actions to reduce patient risk included patient education on the dangers associated with opioid misuse and safe storage practices. They also recognized the value and importance of monitoring prescribed opioids.

Other findings from the clinical trial (Aim 2, Step 5) were as follows:

- The patient OM-App experience was positive overall; 39 of the 40 patient-participants used OM-App over the course of the study with an overall response rate of 70%. Patient-participants typically required less than 1 minute to enter their responses. Patient-participants used OM-App to report important opioid side effects and risk behaviors, including medication overuse. They also (n=37; 92.5%) used OM-App to report positive non-pharmacologic pain self-management strategies, suggesting a potential for OM-App to be used to reinforce positive pain behaviors.
- The PCP experience with OM-App was mixed. All PCPs were able to access the OM-App data, however its lack of integration within the EHR and the need for a second login was perceived as burdensome. This would be important to remedy prior to any larger study.

Outcomes
The primary quantitative outcome for the clinical trial (Aim 2, Step 5) was the score from the Safer Opioid Prescribing Evaluation Tool (SOPET). The intervention group exhibited a 48% increase in SOPET scores, which was significantly different from the control group (p=<0.0001, see table).

Primary outcome: SOPET scores, mean (SD)		
	Baseline	Follow-up
Control (n=18)	8.3 (SD=1.8)	8.7 (SD=1.8)
Intervention (n=19)	8.1 (SD=2.5)	12.0 (SD=1.1)

Since the SOPET is based on EHR documentation (which may not accurately reflect the content of the encounter) we also performed and published qualitative analyses of audiotaped clinic visits between patients and PCPs which confirmed greater alignment with the CDCOPG in the spoken content of the intervention PCPs' visits with their enrolled patient-participants. With regard to individual aspects of the CDCOPG, improvements were noted in: use of non-pharmacologic treatments, establishing a functional treatment goal and opioid agreement, assessment of opioid benefit/harm, use of the PDMP, and appropriate naloxone prescribing.

With regard to patient outcomes there was no evidence of intervention-associated change in any of the PROMs we used. We also employed an exploratory dichotomous outcome defined as the presence of all three of the following: stable or improved pain and function; no OUD or overdose; and undetectable viral load. Intervention patients met this criteria more commonly than controls (47% vs. 33%, OR=1.80) suggesting that our intervention did not appear to cause adverse patient outcomes, but the difference was not statistically significant (p=0.6).

Discussion
We found that PCPs randomized to TOWER were more CDCOPG-adherent overall than those randomized to control. With regard to individual CDCOPG items, some already had high levels of adherence at baseline, (e.g., assessment for opioid related risks/harms, and avoidance of opioid dose escalation or co-prescription of benzodiazepines). These high-adherence items could perhaps be de-emphasized in the future. Several other items showed significant improvement in the intervention group, some to very high (≥90%) adherence levels (e.g. non-pharmacologic treatment, review of PDMP, assessment for a high risk situation). Others, while significantly improved (47-79%), still had room to improve further (e.g. functional treatment goals, opioid agreements, assessment of opioid benefit, naloxone prescription), and so the TOWER tools and/or training could be modified further to better support PCPs in this second group of tasks.

The TOWER intervention had no effect on MME, which is unsurprising since in keeping with the original language of the CDCOPG, PCPs were not instructed to taper opioids per se but rather to make tapering decisions based on their assessment of risk-benefit. An emerging literature suggests that opioid tapers are mainly successful when patients are motivated. Otherwise opioid taper can be associated with poor outcomes including mental health crises. Thus efforts to explicitly reduce opioid prescribing, if adopted, should be done within a well-planned implementation framework.

We employed numerous PROMs in our study and found that no single measure or small group of measures sufficiently captured the constructs that might be impacted by changes in opioid prescribing which included: pain intensity and interference, mental health, substance use, trust, stigma, perceived discrimination and adherence to other aspects of care. Our study was not powered to detect differences in these outcomes. However, it is reassuring that none of them appeared to worsen. We also piloted a relatively simple composite dichotomous outcome, specific to HIV, which included stable or improved pain and function, no OUD or overdose, and undetectable viral load. We found that participants in our intervention group more often met these criteria (47% vs. 33%). Thus, although the difference was not statistically significant, this outcome may warrant further exploration.

The issue of which outcomes should be measured is an important one. The great majority of past studies relied exclusively on EHR-based outcomes such as MME and the presence of urine drug testing and/or opioid contracts in the EHR. But these "outcomes" are not directly relevant to the health and wellbeing of the patient or the larger community. Moreover, should guideline adherence even be expected to improve outcomes for people with CP-LTOT? Our study, although small, showed no evidence of intervention-associated change in any of the PROMs we used, and at least one other larger study has had similar results. A more realistic goal may be to reduce risk of community exposure to prescription opioids without worsening outcomes for people with CP-LTOT. The MME and COMM, both measured in this study, could, respectively, be used to quantify the amount of opioids dispensed to patients and the presence of behaviors which could lead to opioid diversion in the community. However, if benefit is societal rather than individual, it is even more important to guard against harm to people with CP-LTOT by collecting comprehensive outcome measures.

Conclusions
Based on our findings we conclude that the TOWER intervention has the potential to improve CDCOPG among HIV-PCPs in their treatment of patients with CP on LTOT. It is uncertain and perhaps doubtful whether such adherence will improve outcomes for the individual patients to whom they are applied, and this study design does not provide insight into the larger public health effect of CDCOPG.

Significance
In summary, the TOWER pilot study demonstrates that a relatively simple and sustainable intervention (involving direct data collection from patients using a mobile health technology, a PCP decision support tool,

and a PCP training) can assist HIV-PCPs to deliver more guideline-adherent care to PWH and CP-LTOT. Moreover, doing so does not appear to compromise the patient-PCP relationship nor lead to worsening of other patient-centered outcomes. Despite our relatively small sample size, these findings are important because, to our knowledge, TOWER is the first randomized, controlled study demonstrating the successful implementation of national opioid prescribing guidelines without the use of ancillary personnel, and which included extensive collection of PROMs. Future work is needed to establish consensus on a pragmatic patient-centered primary outcome measure, and to design definitive trials to establish evidence-based, sustainable and broadly achievable standards of care for people with CP-LTOT.

Implications
Over the intervening years since this project began, an increasingly negative view of the CDCOPG has emerged. In a particularly visible recent example (July 2021), the American Medical Association (AMA) addressed a letter to the CDC stating that "the 2016 Guideline is hurting patients" and that this is "a direct result of the arbitrary thresholds on dose and quantity contained in the 2016 CDC Guideline."

To be more precise, the harm to some pain patients that occurred following the CDCOPG is actually the direct result the actions of providers, health insurers, pharmacies, pharmacy benefit managers, and other policy makers who used content from the CDCOPG to justify restrictions in prescription opioid access. Our study, although small, suggests that when carefully and faithfully implemented the CDCOPG does not harm patients.

Whether the CDCOPG should be held accountable for actions not included in its recommendations because such actions are (as stated in the AMA letter) "not unforeseeable," is an interesting and provocative question. It certainly is foreseeable that the opioid pendulum will swing, and that people and institutions will sometimes use guidelines to achieve purposes other than optimizing patient outcomes. However, it does not clearly follow that the guideline is responsible, or perhaps more importantly, that revision of the guideline will improve the situation. The missteps in CDCOPG implementation are the more direct cause of patient harm, but their study and remediation is a much more complex problem. The revision of the CDCOPG is indeed underway and is expected to be available in draft form toward the end of 2021. We remain hopeful that this will be coupled with the hard work of careful implementation and monitoring of outcomes.

7. LIST OF PUBLICATIONS and PRODUCTS

The following manuscripts have been published describing this project and its results. The final manuscript describing the quantitative outcome from Aim 2 is still under peer review. There are no products associated with this project.

1. Navis A, George MC, Scherer M, Weiss L, Chikamoto Y, Robinson-Papp J. What physicians need to implement safer opioid prescribing: a qualitative study. J Opioid Manag 2019, 15(6):479-485.

2. Robinson-Papp, J, Aberg J, Benn EKT, Bryan A, Cedillo G, Chikamoto Y, George MC, Horn B, Kamler A, Navis A, Nmashie A, Scherer M, Starkweather A, Vickrey B, Weiss L, Yang Q, Fisher J. Decreasing risk among HIV patients on opioid therapy for chronic pain: Development of the TOWER Intervention for HIV Care Providers. Contemporary Clinical Trials Communications 2019, 12;16:100468.

3. Scherer, M, Weiss, L, Kamler, A, George, MC, Navis, A, Gebhardt, Y, Robinson-Papp, J. Patient Recommendations for Opioid Prescribing in the Context of HIV Care: Findings from a Set of Public Deliberations. AIDS Care 2020, Nov;32(11):1471-1478.

4. Navis A, George MC, Nmashie A, Hoang E, Cedillo G, Robinson-Papp J. Validation of the Safer Opioid Prescribing Evaluation Tool (SOPET) for Assessing Adherence to the Centers for Disease Control Opioid Prescribing Guidelines. Pain Med. 2020, 21(12):3655-3659.

5. Scherer M, Kamler A, Weiss L, George MC, Cedillo G, Robinson-Papp, J. Toward Safer Opioid Prescribing: Effects of the TOWER Intervention on HIV Care Providers. AIDS Care. 2021, Mar 9:1-6.