Research Paper

Stratified care to prevent chronic low back pain in high-risk patients: The TARGET trial. A multi-site pragmatic cluster randomized trial

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ABSTRACT

Background: Many patients with acute low back pain (LBP) first seek care from primary care physicians. Evidence is lacking for interventions to prevent transition to chronic LBP in this setting. We aimed to test if implementation of a risk-stratified approach to care would result in lower rates of chronic LBP and improved self-reported disability.

Methods: We conducted a pragmatic, cluster randomized trial using 77 primary care clinics in four health care systems across the United States. Practices were randomly assigned to a stratified approach to care (intervention) or usual care (control). Using the STarTBack screening tool, adults with acute LBP were screened low, medium, and high-risk. Patients screened as high-risk were eligible. The intervention included electronic best practice alerts triggering referrals for psychologically informed physical therapy (PIPT). PIPT education was targeted to community clinics geographically close to intervention primary care clinics. Primary outcomes were transition to chronic LBP and self-reported disability at six months. Trial Registry: ClinicalTrials.gov NCT02647658

Findings: Between May 2016 and June 2018, 1207 patients from 38 intervention and 1093 from 37 control practices were followed. In the intervention arm, around 50% of patients were referred for physical therapy (36% for PIPT) compared to 30% in the control. At 6 months, 47% of patients reported transition to chronic LBP in the intervention arm (38 practices, n = 658) versus 51% of patients in the control arm (35 practices, n = 635; OR=0.83 95% CI 0.64, 1.09; p = 0.18). No differences in disability were detected (difference -2·1, 95% CI -4.9−0.6; p = 0.12). Opioids and imaging were prescribed in 22%−25% and 23%−26% of initial visits, for intervention and control, respectively. Twelve-month LBP utilization was similar in the two groups.

Interpretation: There were no differences detected in transition to chronic LBP among patients presenting with acute LBP using a stratified approach to care. Opioid and imaging prescribing rates were non-concordant with clinical guidelines.

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Research in context

Evidence before this study

Before undertaking this trial, we used the most comprehensive systematic review and practice guidelines for low back pain to date, issued in 2007 by the American College of Physicians and the American Pain Society in Annals of Internal Medicine, which reported insufficient data to support any specific approach to prevent the transition from acute to chronic LBP. Our own literature search did not identify any definitive prospective clinical trials comparing different patient-oriented interventions with enough long-term follow-up to determine effectiveness for the prevention of the transition from acute to chronic LBP.

Added value of this study

Given differences in United States versus European health care delivery, we assessed whether the stratified approach: (1) was feasible to implement in the US; (2) had the potential to prevent high-risk patients with acute LBP from transitioning to chronic LBP; and (3) reduced patient exposure to unnecessary, expensive, and potentially harmful tests (e.g., MRIs), medications (e.g., opioids), and procedures (e.g., epidural steroid injections).

Implications of all the available evidence

By evaluating the stratified approach to LBP in a large pragmatic RCT conducted in the United States, we assessed implementation as well as effectiveness in US primary care settings. Primary care physicians in the United States will be better able to judge the potential effectiveness of the stratified approach in reducing the risk of acute LBP leading to persistent disability due to chronic LBP.

1. Introduction

Internationally, low back pain (LBP) is one of the most prevalent, potentially disabling, and costly conditions for which people seek health care [1–3]. In the United States (US), up to 80% of adults will experience at least one episode of LBP in their lifetime [4,5] with close to one-quarter reporting an acute episode of LBP (e.g., an incident within previous month) [6]. In terms of cost, spinal pain represents the most costly health care condition in the US with estimates exceeding $134 billion [7]. Approximately 70% of these costs come from the vast majority of patients receiving non-surgical care [8].

A large proportion of patients experiencing acute LBP initially seek care from primary care physicians (PCPs) [9–11]. The prognosis of acute LBP is generally purported to be good [12]. Systematic reviews of studies in primary care settings [13] and general patient populations [14], however, indicate that on average, only 33% of patients seen in primary care settings recover in three months, approximately 65 percent of patients still experience pain after 12 months, and 33 percent have relapses of work absence. These findings suggest that the general attitude of uncomplicated, spontaneous recovery is overestimated.

Recent studies report equivocal results using a LBP-specific, stratified approach in primary care, which entails using a nine-item prognostic screening tool (i.e., the STarTBack tool) [15] to assess risk factors for disabling chronic LBP, coupled with matched intervention pathways that include combined physical and biobehavioral interventions. The approach has shown promise in European-based studies [16,17] but was unsuccessful in a one-site US-based study [18]. Subsequent qualitative analyses suggested the negative result was

attributable to providers (i.e., physicians and physical therapists) failing to implement the recommended matched treatments [19].

The Targeted Interventions to Prevent Chronic Low Back Pain in High-Risk Patients (TARGET) Trial was a cluster randomized large pragmatic trial designed to comprehensively assess whether the stratified approach to LBP was effective in US-based PCP clinics. Specifically, we targeted high risk patients with aLBP and sought to test if the stratified approach, defined as Usual Care (UC) supplemented with referral to Psychologically Informed Physical Therapy (UC+PIPT), is superior to UC alone as demonstrated by lower rates of transition to chronic LBP, lower self-reported disability, and lower healthcare utilization.

2. Methods

2.1. Study design and participants

TARGET was a multi-site, pragmatic cluster randomized trial with 1:1 allocation ratio. The protocol is included in Supplement 1 and has been previously published [20]. Clusters were primary care clinics in five health care systems (University of Pittsburgh Medical Center [UPMC], Boston Medical Center [BMC], Johns Hopkins Medicine [JHM], Intermountain Health [IH], Medical University of South Carolina[MUSC]) with eligibility criteria of willingness to participate and presence of a minimal number ($N \geq 12$) of networked, busy primary care clinics working with a common electronic medical record (EMR). There were no changes in clinic or patient eligibility criteria after the trial began. A trial steering committee oversaw the study. Approval of the study protocol by all site institutional research ethics boards specified: (1) for processes conducted at the primary care clinics, the study was viewed as a quality improvement initiative, (2) for the follow-up assessments at six months, the study was viewed as research requiring patient informed consent for collection of patient-reported primary outcomes, and (3) for the 12-month EMR review patient consent or waiver of HIPAA authorization and patient consent was required.

Sites had varying approaches to obtaining consent for the six-month survey follow-up and 12-month EMR review: (1) BMC obtained consent at the time of the six-month follow-up and EMR data for the 12 months after the index visit were extracted only for those who consented. (2) JHM required consent at the index visit for 6-month follow-up but had a HIPAA waiver and waiver of consent for the 12-month limited data set from the EMR for all patients screened as acute. (3) The University of Pittsburgh was the IRB of record for UPMC and IH. UPMC and IH required consent for six-month follow-up but had a waiver of HIPAA authorization and consent for the 12-month EMR review, with both sites obtaining consent for the six-month follow-up at the time of the follow-up. During the implementation phase of the study, full protocol implementation and data collection were not successful at MUSC, therefore, they were excluded from primary analysis.

All adult patients (18 years or older) who presented at a participating primary care clinic with a primary complaint of LBP were eligible for screening. Patients who endorsed chronic symptoms based on a two-item LBP Questionnaire derived from the NIH Chronic LBP task force were ineligible [21]. The questions included: 1) How long has low back pain interfered with your ability to do regular daily activities, and 2) How often has low back pain interfered with your ability to do regular daily activities? A response of "more than three months" to question one, and a response of "half the days or more than half the days" to question two defined chronic LBP. All remaining patients completed the nine-item STarTBack Tool, which produces two scores: an overall score and a distress subscale score, the latter of which focusses on five psychological obstacles to recovery (e.g., fear, anxiety, catastrophizing, etc.). Scoring four of five defined the high-risk group and coupled with a confirmatory primary

encounter or ordering diagnosis of back pain in the EMR completed eligibility. Patients were excluded retrospectively if they presented with specific non-musculoskeletal causes of LBP (examples: cauda equina syndrome, cancer-related back pain, epidural abscess, or vertebral fracture). There were no changes to the eligibility criteria for patients after the trial began.

2.2. Interventions

For all participating primary care clinics, prior to recruitment we used educational outreach through grand rounds, staff meetings, and online modules to review acute LBP guidelines without monitoring or incentivizing adherence. Education was based on the most up to date guidelines [22] and included recommendations for a focused history and physical examination, with diagnostic imaging and testing not indicated unless signs of severe or progressive neurologic deficits or serious non-musculoskeletal conditions were present/ suspected [20].

Clinics randomized to the intervention received enhanced usual care with specific instructions for immediate referral of high-risk patients to a stratified approach to care [15−17]. In all study locations except one (BMC), referrals occurred through an automatic best practice alert (BPA) in the EMR triggered by scores from the STartBack tool. For two study sites (UPMC and IH), the order was electronically linked to an in-network, centralized physical therapy service or to an administrator who followed up with the patient to schedule the physical therapy. At the remaining sites, the referral was either printed in the patient's after visit summary to be given to the physical therapist or a patient navigator followed up with the patient to schedule physical therapy.

In keeping with the pragmatic nature of the trial, additional resources used for implementation included: (1) monetary support for PCP staff time to detect patients eligible for screening (both groups); (2) EMR programming for tablets and web portals (baseline data input; both groups); (3) EMR programming support for detection of high-risk patients and initiation of BPA in the EMR (intervention group); and (4) patient navigator support (both groups, BMC site only).

Once intervention clinics were established, we identified common physical therapy referral sites and specifically targeted sites through letters from PCPs that included their desire to implement the stratified approach and strong encouragement to attend the courses. A training program for PIPT [23] was delivered to physical therapists who commonly receive referrals from the primary care clinics randomized to the intervention. More information on the training program has been published elsewhere [20,23]. Briefly, the course content provided an overview of the theoretical rationale and supporting data for the approach, specific management principles and skills, with demonstration and practice, and treatment monitoring components. The approach focused on educating patients about their condition, reducing fear of movement, and improving coping skills, as well as addressing physical impairments, such as mobility deficits and pain. In all, we trained 329 physical therapists, 77 in Pittsburgh, 61 in Boston, 80 in Salt Lake City and 111 in Baltimore.

Due to the pragmatic nature of the trial, standardization of the PIPT delivery was not closely monitored. However, we developed a PIPT checklist to be included with the PT referral that included key components of PIPT [20].

2.3. Randomization and masking

Primary care clinics were the unit of allocation instead of patients due to: (1) the overwhelmingly negative PCP stakeholder feedback about burden of individual randomization in busy primary care settings and (2) our concerns about cross contamination of the PIPT intervention if PCPs were referring both intervention and control

patients to the same physical therapy clinic, especially when considering the open layout of many physical therapy practices and the proximity of therapists when treating patients. Primary care clinics were randomized 1:1 to UC+PIPT (intervention) or UC (control) using a stratified permuted block randomization with block size of four. A study biostatistician blinded to clinic names generated the allocation list in Rx64 3.3.2 . The unidentified clinics were stratified by site (health care system), then sorted by the number of annual back pain encounters and payer mix (i.e., percentage of patients covered by Medicaid or self-pay). Once sorted, the allocation list was applied and sent to the lead coordinator who added the clinic names, then sent the lists to their respective site coordinator. The site coordinators were responsible for communicating with the clinics, the training teams, and the information technology specialists to ensure the correct training and referrals were available. After randomization was implemented, any patient presenting with LBP as the primary reason for the primary care visit was eligible for screening. After allocation implementation, site personnel, clinical staff at the clinics, and the TARGET study team were not blinded to intervention arms. Staff conducting the 6-month follow-ups and personnel retrieving the electronic medical record data were masked to intervention arms. Patients were not blinded to the intervention.

2.4. Outcomes

The primary outcomes were patient-reported (1) transition to chronic LBP and (2) back-related disability at six months. We chose six months follow-up duration given the NIH Task Force definition, the six months duration immediately after the portal of entry would best capture the transition to chronic that could most plausibly be linked to the initial acute LBP visit [24]. Chronicity was determined through the patients' answers to a simple two-item questionnaire adapted from the NIH Task Force on research standards for chronic LBP [21]. Functional disability outcome was measured with the Oswestry Disability Index (ODI) [25], which is a reliable, well-validated patient reported legacy instrument that assesses the functional impact of the back pain on the patient. The primary outcomes were obtained by the University Center for Social and Urban Research (UCSUR) at the University of Pittsburgh for patients at the UPMC, BMC and JHM health systems, while the research team at IH obtained 6-month follow-up data using well-established internal protocols. Six-month data collection processes were standardized and collected by one of three methods: (1) trained interviewers using a computer-assisted telephone interview (CATI) version of the questionnaires, (2) web-based responses via a link sent in email, and (3) return-mail responses to questionnaires mailed at 6 months to the participant's home address.

The secondary outcomes of the study extracted from the EMR were LBP-related processes of care and medical utilization over 12 months from the index visit as documented in the EMR. Process of care measures were defined as LBP-related referral to physical therapy (PT) or PIPT, referral to medical specialists, diagnostic imaging, and orders for opioid prescriptions and other LBP-related pain medications. Medical utilization outcomes were defined as outpatient visits (primary care and specialists), receipt of diagnostic imaging, interventional pain procedures (e.g., epidural injections), electrodiagnostic tests (e.g., nerve conduction velocity), surgeries, hospitalizations, and ED visits for back pain. Twelve-month all source utilization data were extracted directly from the EMRs for BMC, IH, and JHM systems, while 12-month utilization data for UPMC were extracted from the PCORnet [26].

Due to the pragmatic nature of the trial (i.e., a quality improvement comparison of two standards of care, UC or UC+PIPT), and the low-risk nature of the intervention, no adverse event data were collected.

2.5. Statistical analysis

We assumed a 6-month transition rate from acute to chronic of 25−30% [27,28] and a priori hypothesized that the acute to chronic transition rate at 6 months for patients seen at stratified care clinics would be reduced by 40% (i.e., 10−12 absolute percent) compared to those seen at usual care clinics. The originally proposed sample size of N = 60 clinics and 48 patients per clinic was based on 90% power, 12.5% cluster size variation and 10% non-response rate at 6 months (two-sided α = 0.05, intraclass correlation coefficient = 0.05) [27,29−31]. During the third year of the trial, the funder requested an assessment of feasible sample size due to slow recruitment and higher than expected non-response rates. The number of required clinics had been enrolled at that time. With 60 PCP clinics and fixed m = 10−14 patient completers for the 6-month assessment, we were projected to have over 80% power to detect the original 40% relative reduction. We therefore modified the targeted enrollment to an average of m = 31 high-risk patients per clinic (60*31 = 1860) in the QI phase of the study to account for the high variation in cluster sizes (assuming coefficient of variation = 0.65) and a 40% non-response rate at 6 months [32].

Analysis was by intention to treat where group assignment is based on the clinic of the patient's index visit. The unit of analysis was the patient. We estimated and compared the rates of transition to chronic LBP at six months between patients from the UC and UC+PIPT clinics using a generalized linear mixed model with a logit link controlling for site, a fixed effect for intervention, and a random clinic effect to account for clustering. For the second primary outcome, we estimated and compared the average back-related functional disability (Oswestry) at six months using linear mixed models controlling for baseline Oswestry and site as fixed effects and random clinic effects to account for the cluster randomized design. Corresponding 95% confidence intervals were calculated for each estimate of the intervention effect (odds ratios for six-month transition, mean difference for Oswestry). Analyses for the primary outcomes of transition to chronic LBP and disability were initially conducted only in those individuals with six-month survey data. We conducted sensitivity analysis using multiple imputation under ignorable and non-ignorable assumptions. We explored the effect of referral to a stratified approach to care by conducting an 'as treated' analysis comparing those patients who received a referral to PIPT, referral to PT, or received no PIPT/PT referral using the same models. We used generalized linear mixed models with logit link controlling for the cluster randomized trial design with random effects for clinics and fixed effect for site to compare all explanatory and secondary measures of processes of care and utilization over 12 months. We conducted all analyses using SAS version 9.4 (SAS Institute). All tests were two-sided α = 0.05.

2.6. Role of the funding source

The sponsor of the study had no role in the design, in the collection, analysis, and interpretation of data in the writing of the report and in the decision to submit the paper for publication. Also, the corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

3. Results

Seventy-seven clinics were randomized across four sites. Shortly after randomization and during the implementation phase for the UPMC sites, one clinic failed to successfully implement the approach and was eliminated prior to screening of patients. Patients were screened in 76 clinics from May 2016 until June 2018 with six-month follow-up ending in February 2019 and 12-month utilization outcomes retrieved through June 2019. Of interest, almost 50% of

patients initially seen for LBP were already chronic, far exceeding epidemiological estimates for chronicity in PCP environments. Of the nearly 10,000 patients with acute LBP who were screened, 36% were classified as low risk, 40% as medium risk, and 24% as high-risk. For the high-risk group that were randomized, 55% had 6-month patient reported outcomes, of which we were able to capture 95−96% of 12-month healthcare utilization data in both intervention arms (Fig. 1).

Volume of LBP in the past 12 months and payer mix were similar between clinics randomized to UC and UC+PIPT (Table 1). The baseline characteristics of the patients, including STarT Back total score and subscores, were also similar between intervention arms (Table 1).

At the index visit, 57% of patients in the intervention group received either a "general" PT or a specific PIPT order (Table 2). About 30% received a referral to PT in the usual care group. Very few patients were referred to a specialist in either group with 5% being referred to non-surgical medical specialists and 5%-6% to spine surgeons. Non-surgical medical specialists include physical medicine & rehabilitation, anesthesiology, primary care sports medicine, or pain medicine. About one in six received a referral for x-ray and only 6−7% for magnetic resonance/computerized tomography (MR/CT). With respect to medication, 22−25% of patients received a prescription for opioids, around 36−44% muscle relaxants, and 30% NSAIDs. Other medication prescriptions were rare (acetaminophen, benzodiazepines).
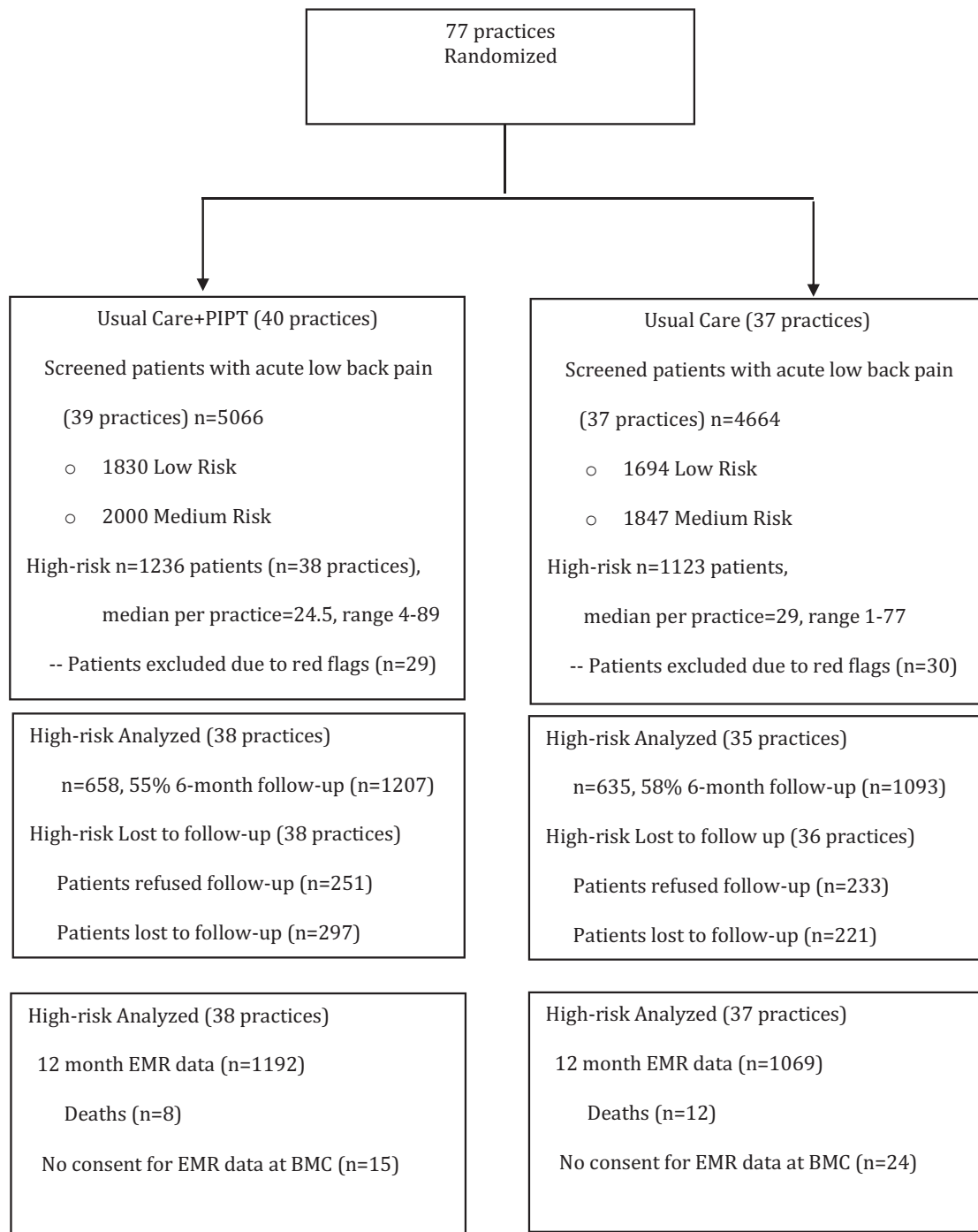
The six-month follow-up non-response rate (44%) did not differ between the intervention and usual care group but was higher than anticipated. Those with completed follow-up were younger and were slightly more likely to be women (61% versus 56%), have private health insurance (50% versus 44% among those with information), be obese (51% versus 46%) and white (77% versus 71%). There were no differences detected on the baseline ODI or STarTBack between those with and without six-month follow-up data and those with follow-up data were slightly less likely to report back pain duration < one month (58% versus 64%).

About half of patients in both groups reported transition to chronic LBP at 6 months (Fig. 2A). Just over 70% stated that LBP had interfered with their ability to do regular daily activities for more than 3 months. Among them about 70% responded the frequency of LBP interference was half or more than half the days in the previous six months. Both groups were lower on functional disability showing scores indicative of moderate disability rather than severe disability, which was the average at baseline (Fig. 2B). In the exploratory "as treated" analysis, rates of chronic LBP at 6 months for patients who received referral to PIPT, referral to PT, or no referral to either were 51%, 48%, and 48%, respectively, p = 0.92. The results and inference did not change using multiple imputation assuming missingness at random. Imputation under non-ignorable missingness showed no group differences except under extreme, highly unlikely scenarios where the proportion that transitioned to chronic among non-responders was double in the intervention compared to the control.

Up to 12 months after the index visit, less than 10% of patients received additional referral to PIPT or PT for LBP from any physician type (Table 3). Very few patients received referral to non-surgical or surgical specialists (2−4%) and roughly 7−8% received an opioid prescription, 6−8% a prescription for muscle relaxants, and 5−8% a prescription for NSAIDs (Table 3).

4. Discussion

The stratified management approach in this pragmatic trial consisted of identifying high-risk patients using prognostic screening and coupling it with immediate referral for PIPT treatment. This intervention did not result in decreasing the rate of transitioning from acute to chronic LBP. Stratified care also failed to demonstrate effectiveness in self-reported disability, nor did it make a difference

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                        │     77 practices    │
                        │     Randomized      │
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Usual Care+PIPT (40 practices)

Screened patients with acute low back pain

(39 practices) n=5066

- 1830 Low Risk

- 2000 Medium Risk

High-risk n=1236 patients (n=38 practices),

    median per practice=24.5, range 4-89

-- Patients excluded due to red flags (n=29)

Usual Care (37 practices)

Screened patients with acute low back pain

(37 practices) n=4664

- 1694 Low Risk

- 1847 Medium Risk

High-risk n=1123 patients,

    median per practice=29, range 1-77

-- Patients excluded due to red flags (n=30)

High-risk Analyzed (38 practices)

    n=658, 55% 6-month follow-up (n=1207)

High-risk Lost to follow-up (38 practices)

    Patients refused follow-up (n=251)

    Patients lost to follow-up (n=297)

High-risk Analyzed (35 practices)

    n=635, 58% 6-month follow-up (n=1093)

High-risk Lost to follow up (36 practices)

    Patients refused follow-up (n=233)

    Patients lost to follow-up (n=221)

High-risk Analyzed (38 practices)

  12 month EMR data (n=1192)

    Deaths (n=8)

  No consent for EMR data at BMC (n=15)

High-risk Analyzed (37 practices)

  12 month EMR data (n=1069)

    Deaths (n=12)

  No consent for EMR data at BMC (n=24)

Fig. 1. Trial profile. PIPT=Psychologically Informed Physical Therapy. EMR=Electronic Medical Record. BMC=Boston Medical Center.

in process-based measures of utilization derived from the EMR. Ultimately, approximately half of high-risk patients reported transition to chronic LBP at six months. The "as treated" analyses demonstrated very similar results, with 51% and 48% of patients transitioning to chronic in the intervention and usual care groups, respectively.

Almost half the entire sample transitioned to chronic LBP, a figure that far exceeds most previous reports in primary care. We used the NIH Consensus Panel [21] definition of chronic LBP, which is new to the literature, thus difficult to gauge comparatively. However, the definition was created through a comprehensive consensus process with the goal of addressing previous gaps in literature, namely, that definitions used for chronic LBP were highly variable.

Patients with LBP commonly enter the health care system through primary care settings. Clinical guidelines for initial uncomplicated LBP management in primary care consistently include avoiding diagnostic imaging and minimizing opioid prescribing [33]. Systematic reviews of primary care management reflect low adherence to these guidelines [34,35]. Similarly, in our study we found lack of full adherence to clinical guidelines: one in four acute, high-risk patients received opioid prescriptions at the index visit. One in five patients received orders for diagnostic imaging.

Despite creating an automated process of identifying high-risk patients and generating referrals for matching PIPT, only half received a referral to PIPT in the stratified group compared to a third

Table 1
Baseline characteristics by intervention group.

	Usual Care+PIPT (n = 1207)	Usual Care (n = 1093)
Age (years)	49·3 (16·2)	50.6 (17.1)
Sex, female	721 (60%)	635 (58%)
Health Insurance		
Private	539 (45%)	450 (41%)
Medicare	212 (18%)	208 (19%)
Medicaid (proxy for underserved)	163 (14%)	137 (13%)
Self-pay	106 (9%)	92 (8%)
Other	52 (4%)	58 (5%)
Missing/Unknown	135 (11%)	148 (14%)
Psychological Comorbidities		
Depression	51 (4%)	34 (3%)
Anxiety	66 (5%)	36 (3%)
BMI, mean ± SD	31·0 (7·3)	31·0 (7·0)
n (%) with BMI data	1067 (88%)	954 (87%)
Obese	516 (48%)	476 (50%)
Smoking	221 (18%)	171 (16%)
Current smoker	717 (59%)	678 (62%)
Not current smoker	269 (22%)	244 (22%)
Missing/Unknown		
Race		
White	949 (79)	769 (70)
Black	181 (15)	224 (20)
Other	25 (2)	57 (5)
Missing/Unknown/ Declined	52 (4)	43 (4)
Ethnicity		
Hispanic	75 (6)	72 (7)
Non-Hispanic	1087 (90)	995 (91)
Missing/Unknown/ Declined	45 (4)	26 (2)
Eligible Diagnosis		
Axial back pain	823 (68)	737 (67)
Back pain and legs symptoms	383 (32)	356 (33)
Oswestry Disability Index	48.0 (17·4)	48.3 (17·5)
n (%) with ODI data	1161 (96)	1063 (97)
Chronic LBP Question- naire Duration of LBP		
Less than 1 month	754 (62)	644 (59)
1 − 3 months	342 (28)	328 (30)
More than 3 months	111 (9)	121 (11)
STarT Back score (range 0−9)	7·2 (1·1)	7·2 (1·1)
STarT Back subscore (range 0−5)	4·4 (0·5)	4·3 (0·5)
Participating clinics	**38**	**37**
Regional site		
UPMC	17	16
BMC	6	6
IH	9	9
JHM	6	6
Clinic volume LBP past 12 months	535 (383, 690)	485·0 (398·0, 832·0)
Clinic percent Medicaid and self-pay	8.0 (6·6, 26·3)	8.5 (6·7, 15·7)

Data are mean (SD), median (p25, p75) or number (%). BMI=Body Mass Index. LBP=Low Back Pain. Depression includes any diagnosis of ICD-10 codes: F32.0, F32.1, F32.2, F32.4, F32.8, F32.89, F32.9, F33.0, F33.1, F33.2, F33.3, F33.4, F33.40, F33.41, F33.8, F33.9; Anxiety includes any diagnosis of ICD-10 codes: F06.4, F41.1, F41.3, F41.8, F41.9. STarT=Subgroups for Targeted Treatment. UPMC=University of Pittsburgh Medical Center. BMC=Boston Medical Center. IH=Intermountain Health. JHM=Johns Hopkins Medical.

of patients receiving a referral to PT in the usual care group. Adherence to initiating PIPT referrals was far below expectations of the study team as well as our PCP stakeholder groups. We engaged with key stakeholders prior to and during the study, which included key participating primary care physicians and representative national primary care professional groups. The implementation strategies executed were mutually agreed upon prior to the study and included a twofold process: (1) automatically generating a BPA in the EMR for the medical assistants and/or PCPs for all high-risk patients, with specific instructions for immediate referral to PIPT, and (2) once the referrals were executed and processed by the PCP, expedited mechanisms to notify participating PT clinics.

The implementation shortfall in the BPA-PIPT referral linkage was a major limitation in the TARGET Trial and demonstrates significant challenges that remain in present primary care environments. Though the BPA approach was favored by PCP stakeholders, subsequent discussion with PCPs along with more recent reports describe "alert fatigue," which is blamed for the high override rates that hamper decision-support systems [36], suggesting that BPA effectiveness may be overestimated. Causes of alert fatigue, which include cognitive overload from very busy EMR environments and desensitization from too many alerts, have been proposed. Regardless of the cause, overestimating the BPA effect may serve to decrease expectations, as evidenced by the interpretation of our result from our PCP stakeholders, characterized by the quote, "a 60% adherence to a BPA is 'pretty good.'" Though we were able to almost double the rate of PT referral in the stratified approach over usual care, we still missed 40% of the high-risk cohort. There is existing evidence indicating this issue is not simply a reflection of participating TARGET trial sites. An analysis of 2.5 million individuals in the US with newly diagnosed LBP indicated that 55% with new episode of LBP received no treatment, and about 33% received care that was inconsistent with clinical guidelines [8].

Funding guidelines prohibiting funds to pay for physical therapy treatments led the study team to balance the pragmatic-explanatory continuum more toward pragmatic with regard to *flexibility adherence and delivery* of the intervention [37]. Our approach to PIPT delivery, though highly generalizable, was without additional resources to assure clinical implementation, particularly when considering the barriers in PIPT delivery. With more recent guidelines advocating for "non-pharmacologic-first" approaches to pain [38], it remains to be seen if payers will explore payment reform that includes reducing barriers to non-pharmacologic care such as physical therapy (whether it be psychologically informed or not).

One major limitation of this study was the limited treatment fidelity reflected in the low rate of PIPT referrals. We attempted to implement a new protocol in already busy primary care clinics. Despite its simplicity, the protocol required changes in workflow and staff commitment. Clearly, overcoming implementation barriers would be critical before another attempt at a PCP-based pragmatic trial of the stratified approach to LBP. A second major limitation was the 40% non-response of the primary outcome at 6 months. Standards for non-response rates have not been established for pragmatic trials, which often use different follow up procedures than explanatory trials [39]. In the TARGET trial "best practices" for capturing patient reported outcomes in pragmatic trials were incorporated, including options for phone, web-based, and mail follow up capture [40]. Even with this 40% non-response rate, there were similar rates between treatment arms and we captured follow-up on over 500 patients per treatment arm, which limits measurement error when modeled across different imputation approaches [41]. Indeed, in our own imputation models the primary analyses were robust to several different approaches and scenarios. Data on our secondary outcomes were much more complete as we were able to ascertain process of care measures and utilization in the EMR for over 90 percent of our sample. One limitation to these measures, however, is that they only capture healthcare use within the healthcare system. Any care sought outside the system would be missed. Additional analyses of our data will supplement the EMR data with claims data which may provide additional information for comparisons.

Table 2
Processes of Care at the Index Visit up to 21 Days.

	Usual Care + PIPT (n = 1207) % (95% CI)	Usual Care (n = 1093) % (95% CI)	Odds Ratio (95% CI)	p-value
PIPT Checklist in medical record	7.8 (5.4, 10.4)	0.0 (0.0, 0.0)	–	–
Referral to PIPT or PT	56.8 (49.9, 63.5)	29.3 (23.5, 35.8)	–	–
Referral to PIPT	35.9 (26.2, 46.8)	0.4 (0.2, 1.2)	–	–
Referral to Specialist				
Complementary and Integrative Health	1.8 (0.9, 3.3)	1.1 (0.5, 2.3)	1.60 (0.59, 4.20)	0.36
Behavioral Health/Counseling[$]	1.2 (0.6, 2.1)	0.9 (0.4, 1.8)	1.34 (0.53, 3.42)	0.53
Non-Surgical Medical Specialist	5.0 (3.8, 6.6)	5.0 (3.7, 6.6)	1.00 (0.66, 1.52)	0.99
Spine Surgery	5.0 (3.6, 7.0)	6.4 (4.6, 8.9)	0.76 (0.47, 1.25)	0.28
Diagnostic Imaging Order				
X-ray MR/CT	15.0 (11.5, 19.2) 7.2 (5.3, 9.7)	18.1 (14.1, 23.0) 6.1 (4.4, 8.5)	0.80 (0.53, 1.21) 1.19 (0.74, 1.91)	0.28 0.47
Opioid Prescription	22.3 (18.3, 26.9)	24.5 (20.1, 29.5)	0.89 (0.62, 1.26)	0.50
Other Prescriptions				
Acetaminophen	1.0 (0.44, 2.1)	1.6 (0.8, 3.4)	0.57 (0.20, 1.64)	0.29
Benzodiazepines	2.5 (1.6, 3.8)	2.6 (1.7, 4.1)	0.95 (0.51, 1.79)	0.87
Muscle relaxants	44.0 (39.3, 48.7)	36.2 (31.6, 41.0)	1.38 (1.05, 1.83)	0.024
NSAIDs	29.0 (25.3, 32.9)	31.2 (27.3, 35.5)	0.90 (0.69, 1.17)	0.41

PIPT=Psychologically informed physical therapy. PT=Physical therapy. MR=Magnetic resonance. CT=computerized tomography. NSAIDs=non-steroidal anti-inflammatory including topical.
All proportions, odds ratios and confidence intervals estimated using generalized linear mixed models with random effects for clinic adjusted for site.
[$] did no adjust for site due to convergence issues

When considering LBP in general, numerous trials and RCTs have been performed so far, comparing dozens of interventions, including stratified approaches. These research findings have been synthesized for more than 25 years into LBP practice guidelines. Given the rate of non-concordance with LBP practice guidelines, there remains doubt as to whether available evidence can be effectively translated into everyday practice [8]. Pragmatic trials, such as TARGET, that combine research rigor with treatment delivery in real world settings will often clearly reveal this harsh reality [42]. Though disappointing, the

Fig. 2. **Primary outcomes of the TARGET Trial at 6 months.** (A) Transition to chronic low back pain (B) Change in Oswestry Disability Index represented by mean ± standard error.

results of the TARGET trial illustrate the implementation challenge in translating evidence to practice [43]. Some may respond to a negative pragmatic trial by calling for a more explanatory trial whereby treatment fidelity is emphasized and more thoroughly assessed. This may be necessary to isolate PIPT efficacy; however, we cannot lose sight of the fact that additional explanatory trials will not address the implementation challenges that come with establishing effectiveness in everyday practice settings.

Future work should focus on solving implementation challenges, perhaps by considering hybrid designs (e.g., Type III Implementation/Effectiveness), which would allow testing the feasibility and acceptance of more active approaches to implementing stratified care. Implementation strategies that could be compared include: (1) EMR "forced function" strategies (e.g., administrative approaches that automate choices or prevent further steps if a BPA is not considered) whereby selected patients with LBP are almost immediately directed to alternative care providers that can provide immediate access to evidence-based, non-pharmacologic interventions; (2) aligned payment models (e.g., shared savings) whereby evidence-based care is incentivized and non-guideline-concordant care (e.g., x-rays, opioid prescriptions) are dis-incentivized similar to other chronic conditions (e.g., diabetes or hypertension); (3) primary care co-management models with Advanced Practice Providers (nurse practitioners, physicians assistants) to support PCPs by using protocolized approaches such as stratified care for LBP; (4) integrated models of care where other health professionals (e.g., physiotherapists, behavioral health professionals) with specific training in musculoskeletal/mental health approaches are co-located in the PCP environment; (5) models of care that promote alternatives to primary care as the portal of entry for people with a primary complaint of LBP.

In a large pragmatic trial in acute LBP, we did not find reduction in transition to chronic LBP using a stratified approach to care. Overall, US primary care practices involved with this trial had difficulty implementing the stratified approach targeting high-risk patients in the intervention arm. In both treatment arms, opioid prescribing and diagnostic imaging rates were not concordant with clinical guidelines for acute LBP. Future investigations of the stratified approach should focus on the challenges of implementing the referral in primary care and in the delivery of appropriate care by providers such as physical therapists.
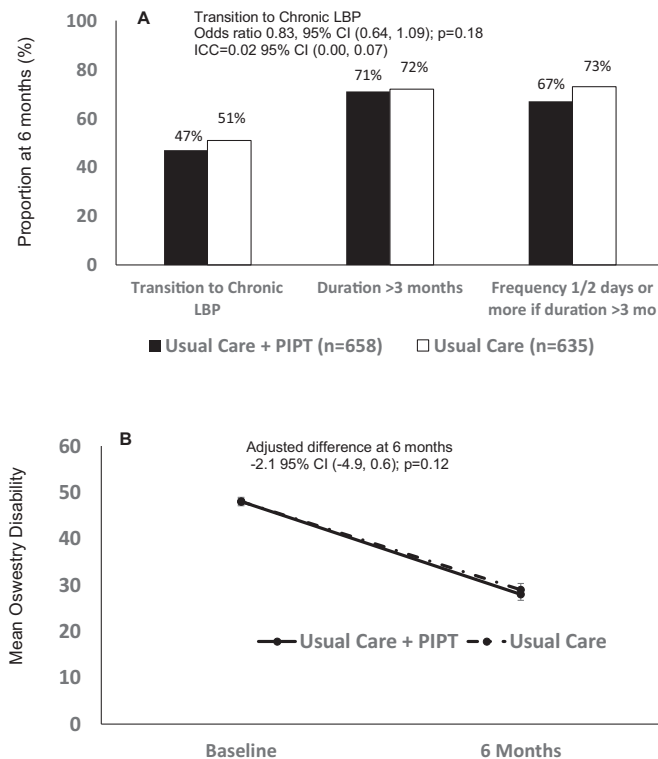
Table 3
Secondary outcomes of processes of care and health care utilization over 12 months.

	Usual Care+PIPT (*n* = 1192) % (95% CI)	Usual Care (*n* = 1069) % (95% CI)	Odds Ratio (95% CI)	p-value
Process of Care after Index Visit up to 12 Months				
Referral to PIPT or PT	8.1 (6.4, 10.2)	7.0 (5.4, 9.1)	1.17 (0.81, 1.70)	0.40
Referral to PIPT	3.4 (1.9, 4.8)	0.0 (0.0, 0.0)	—	—
Referral to Specialist				
Complementary and	0.4 (0.2, 1.02)	0.6 (0.2, 1.3)	0.75 (0.2, 0.46)	0.63
Integrative Health	0.5 (0.2, 1.1)	0.9 (0.4, 1.8)	0.55 (0.17, 1.76)	0.31
Behavioral Health/	3.3 (2.4, 4.7)	1.9 (1.3, 3.0)	1.75 (1.02, 3.01)	0.0425
Counseling$	3·2 (2·1, 4·9)	3·8 (2·5, 5·7)	0·84 (0·46, 1·54)	0·57
Non-Surgical Medical				
Specialist				
Spine Surgery				
Diagnostic Imaging Order				
X-ray	2.5 (1.7, 3.8)	2.5 (1.7, 3.9)	0.99 (0.60, 1.65)	0.98
MR/CT$	2.9 (1.9, 4.3)	3.4 (2.3, 5.1)	0.83 (0.46, 1.50)	0.54
Opioid Prescription	7.0 (5.3, 9.1)	7.5 (5.7, 9.9)	0.92 (0.61, 1.40)	0.69
Other Prescriptions				
Acetaminophen$	0.4 (0.2, 1.1)	0.7 (0.3, 1.6)	0.58 (0.16, 2.12)	0.41
Benzodiazepines$	1·4 (0·8, 2·6)	1·8 (1·0, 3·2)	0·80 (0·55, 1·16)	0·58
Muscle relaxants	6.7 (5.2, 8.5)	8.2 (6.4, 10.4)	0.78 (0.54, 1.12)	0.23
NSAIDs	5.6 (4.1, 7.6)	7.7 (5.7, 10.2)	0.72 (0.46, 1.12)	0.14
12 Month Utilization				
Primary Care Visit	46.7 (42.3, 51.0)	49.5 (45.0, 54.1)	0.89 (0.69, 1.15)	0.37
Specialist Visits (Any)	14.6 (11.9, 17.6)	17.2 (14.02, 20.8)	0.82 (0.59, 1.13)	0.22
	3.3 (2.2, 5.2)	2.9 (1.8, 4.7)	1.15 (0.59, 2.23)	0.68
Orthopedic Surgery$	0.2 (0.04, 0.7)	0.6 (0.2, 1.5)	0.27 (0.05, 1.53)	0.14
Neurosurgery$	1.8 (1.0, 3.3)	1.3 (0.6, 2.6)	1.37 (0.53, 3.55)	0.51
Physical Medicine &	1.9 (1.1, 3.2)	2.4 (1.4, 4.1)	0.79 (0.36, 1.75)	0.56
Rehabilitation$	7.7 (5.8, 10.1)	11.2 (8.7, 14.4)	0.66 (0.44, 0.99)	0.044
Anesthesiology/Pain				
Management$				
Other				
Imaging (Any)	15.3 (12.4, 18.7)	17.1 (13.8, 20.9)	0.88 (0.62, 1.24)	0.45
X-ray	8.9 (6.7, 11.6)	9.5 (7.1, 12.5)	0.93 (0.61,1.44)	0.75
CT/MRI	8.3 (6.6, 10.5)	9.7 (7.6, 12.2)	0.85 (0.61, 1.19)	0.33
Advanced studies#	0.08 (0, 0.25)	0 (−,−)	—	—
Interventional Pain Procedures$	2.3 (1.4, 3.7)	3.3 (2.1, 5.1)	0.70 (0.36, 1.38)	0.30
Electrodiagnostic Testing$	0.2 (0.1, 0.8)	0.3 (0.1, 1.0)	0.65 (0.11, 3.88)	0.63
Surgery (Any)	1.7 (1.0, 2.8)	1.2 (0.7, 2.2)	1.37 (0.74, 2.53)	0.31
Fusion	1.5 (0.0, 32.6)	1.2 (0.0, 35.4)	1.24 (0.02, 66.7)	0.62
Non-fusion#	0·08 (0, 0·25)	0·09 (0, 0·27)	—	—
Red flag#	0.08 (0, 0.25)	0 (−,−)	—	—
Other#	0.17 (0, 0.40)	0 (−,−)	—	—
Hospitalizations#	0.17 (0, 0.41)	0.19 (0, 0.44)	—	—
ED visits	5.2 (3.7, 7.2)	7.0 (5.1, 9.5)	0.74 (0.45, 1.19)	0.21

PIPT=Psychologically informed physical therapy. PT=Physical therapy. MR=Magnetic resonance. CT=computerized tomography. NSAIDs=non-steroidal anti-inflammatory including topical. ED=Emergency department. All proportions, odds ratios, and confidence intervals are estimated from generalized linear mixed models with random effect for clinic adjusting for site.

$ did not adjust for site due to convergence issues from small cell counts

estimates using survey sampling approach to adjust for clustering

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Data Sharing

The study is registered with ClinicalTrials.gov, number NCT02647658, and select data from the Figures and Table 1, Table 2, Table 3 have been added to the registration. In accordance with the protocol, no investigators will have access to participant data with identifiers. De-identified data will be shared with external investigators and the funder upon request. Requests for data Inter-university Consortium for Political and Social Research (ICPSR) at the University of Michigan — to provide access to de-identified data by no later than July 01, 2021. Requests for access to the data can be made via the ICPSR website: https://www.icpsr.umich.edu/.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.100795.

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