

## Original Investigation

# Oral Steroids for Acute Radiculopathy Due to a Herniated Lumbar Disk

## A Randomized Clinical Trial

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**IMPORTANCE** Oral steroids are commonly used to treat acute sciatica due to a herniated disk but have not been evaluated in an appropriately powered clinical trial.

**OBJECTIVE** To determine if oral prednisone is more effective than placebo in improving function and pain among patients with acute sciatica.

**DESIGN, SETTING, AND PARTICIPANTS** Randomized, double-blind, placebo-controlled clinical trial conducted from 2008 to 2013 in a large integrated health care delivery system in Northern California. Adults (n=269) with radicular pain for 3 months or less, an Oswestry Disability Index (ODI) score of 30 or higher (range, 0-100; higher scores indicate greater dysfunction), and a herniated disk confirmed by magnetic resonance imaging were eligible.

**INTERVENTIONS** Participants were randomly assigned in a 2:1 ratio to receive a tapering 15-day course of oral prednisone (5 days each of 60 mg, 40 mg, and 20 mg; total cumulative dose = 600 mg; n = 181) or matching placebo (n = 88).

**MAIN OUTCOMES AND MEASURES** The primary outcome was ODI change at 3 weeks; secondary outcomes were ODI change at 1 year, change in lower extremity pain (measured on a 0-10 scale; higher scores indicate more pain), spine surgery, and Short Form 36 Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) scores (0-100 scale; higher scores better).

**RESULTS** Observed baseline and 3-week mean ODI scores were 51.2 and 32.2 for the prednisone group and 51.1 and 37.5 for the placebo group, respectively. The prednisone-treated group showed an adjusted mean 6.4-point (95% CI, 1.9-10.9;  $P = .006$ ) greater improvement in ODI scores at 3 weeks than the placebo group and a mean 7.4-point (95% CI, 2.2-12.5;  $P = .005$ ) greater improvement at 52 weeks. Compared with the placebo group, the prednisone group showed an adjusted mean 0.3-point (95% CI, -0.4 to 1.0;  $P = .34$ ) greater reduction in pain at 3 weeks and a mean 0.6-point (95% CI, -0.2 to 1.3;  $P = .15$ ) greater reduction at 52 weeks. The prednisone group showed an adjusted mean 3.3-point (95% CI, 1.3-5.2;  $P = .001$ ) greater improvement in the SF-36 PCS score at 3 weeks, no difference in the SF-36 PCS score at 52 weeks (mean, 2.5; 95% CI, -0.3 to 5.4;  $P = .08$ ), no change in the SF-36 MCS score at 3 weeks (mean, 2.2; 95% CI, -0.4 to 4.8;  $P = .10$ ), and an adjusted 3.6-point (95% CI, 0.6-6.7;  $P = .02$ ) greater improvement in the SF-36 MCS score at 52 weeks. There were no differences in surgery rates at 52-week follow-up. Having 1 or more adverse events at 3-week follow-up was more common in the prednisone group than in the placebo group (49.2% vs 23.9%;  $P < .001$ ).

**CONCLUSIONS AND RELEVANCE** Among patients with acute radiculopathy due to a herniated lumbar disk, a short course of oral steroids, compared with placebo, resulted in modestly improved function and no improvement in pain.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00668434

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**A**cute lumbar radiculopathy (sciatica) is characterized by radiating buttock and leg pain in a lumbar nerve root distribution.<sup>1,2</sup> It is commonly associated with the herniation of the nucleus pulposus<sup>3,4</sup> and has a lifetime prevalence exceeding 10%.<sup>5</sup> Spontaneous recovery occurs in most patients; however, many endure substantial pain and disability.<sup>2,3,6</sup> For those who do not recover quickly, invasive procedures such as epidural steroid injections (ESIs) and lumbar discectomy are commonly performed.<sup>3,7,8</sup> Accelerating the process of recovery would provide substantial benefits to affected patients and potentially reduce the need for expensive invasive procedures.

**ESI** epidural steroid injection

**MRI** magnetic resonance imaging

**NRS** numerical rating scale

**ODI** Oswestry Disability Index

Despite conflicting evidence, ESIs are frequently offered under the assumption that radicular symptoms are caused by inflammation of the affected lumbar nerve root.<sup>4,9-11</sup> Epidural steroid injections are invasive, generally require a preprocedure magnetic resonance imaging (MRI) study, and expose patients to fluoroscopic radiation. In addition, the US Food and Drug Administration recently warned of rare but serious neurologic sequelae from ESIs.<sup>12,13</sup> Oral administration of steroid medication may provide similar anti-inflammatory activity, does not require an MRI or radiation exposure, can be delivered quickly by primary care physicians, carries less risk, and would be much less expensive than an ESI. Oral steroids are used by many community physicians, have been included in some clinical guidelines,<sup>14</sup> and are noted as a treatment option by some authors.<sup>15,16</sup> However, no appropriately powered clinical trials of oral steroids for radiculopathy have been conducted to date.<sup>17</sup>

To address this issue, we performed a parallel-group, double-blind randomized clinical trial of a 15-day tapering course of oral prednisone vs placebo for patients with an acute lumbar radiculopathy associated with a herniated lumbar disk. The trial protocol is available in the Supplement.

## Methods

### Participants

Eligible patients (**Figure 1**) were members of Kaiser Permanente Northern California, were aged 18 to 70 years, reported leg pain extending below the knee in a nerve root distribution, had a herniated disk confirmed by MRI, and scored 30 points or higher on the Oswestry Disability Index<sup>18</sup> (ODI; this cut point was chosen from a pilot study as the approximate median ODI score among similar patients). Exclusion criteria included onset of radicular pain more than 3 months prior, previous lumbar surgery, oral or epidural steroid treatment in the prior 3 months, diabetes, substantial or progressive motor loss, and/or ongoing litigation or workers compensation claim. A positive straight-leg raise test result was initially an inclusion criterion that was eliminated after 14 months to improve recruitment and allow interaction analyses with this characteristic. Participants were recruited from primary care practices at 3 Kaiser Permanente Northern

California facilities and from a daily extract of the electronic medical record. Race/ethnicity data were self-reported. (This National Institutes of Health-funded study was required to collect and annually report data on race and ethnicity for all participants. We used these data in preplanned subgroup analyses examining potential interaction with demographic variables; see section 2.3 of the trial protocol in the Supplement.)

### Intervention

Participants randomized to the active treatment group took three 20-mg capsules of prednisone daily for 5 days, then 2 capsules daily for 5 days, then 1 capsule daily for 5 days (this cumulative dose of 600 mg was thought to provide sufficient anti-inflammatory effect and was in common use in local practice). Participants in the placebo group received identical-appearing capsules and instructions. Nonsteroidal anti-inflammatory drugs were not allowed for 3 weeks after randomization, but otherwise all patients in both treatment groups received usual care for their symptoms.

### Outcomes

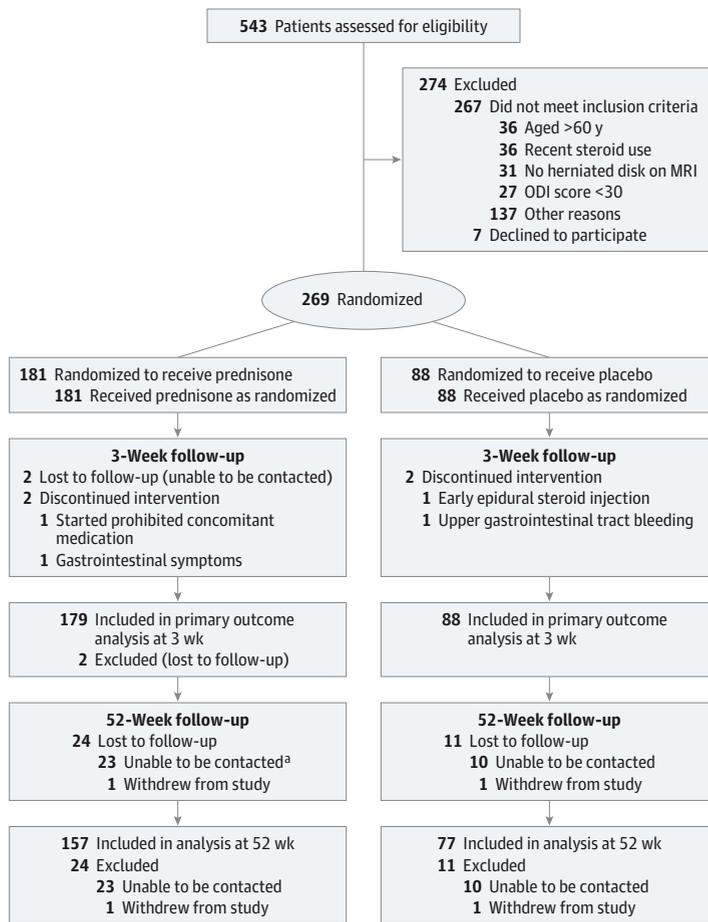
The primary outcome was self-reported score on the ODI, version 2.0 (measured on a 0- to 100-point scale, with higher scores indicating greater dysfunction)<sup>18</sup> measured 3 weeks after randomization. We chose this time point for the primary outcome because we were most interested in testing whether oral steroids could more rapidly return patients to higher functioning and less pain in the early, more symptomatic weeks of an acute sciatica episode. Predefined secondary outcomes were a pain numerical rating scale (NRS) scored on a 0- to 10-point scale (higher numbers indicating more pain) that inquired about participants' average, best, and worst levels of pain below the waist over the prior 3 days and participants' average pain levels above the waist, the Short Form 36 Health Survey Physical Component Summary and Mental Component Summary subscale scores (each measured on 0- to 100-point scales, with higher scores indicating better health status),<sup>19</sup> and incidence of lumbar spine surgery. An additional measure assessed participants' global assessment of improvement by asking participants to rate how much their leg pain had changed since taking the study medication (measured on a Likert scale from 1 [very much better] to 7 [very much worse]).

### Study Procedures

After providing informed consent, patients were reviewed for eligibility by a spine-specialist physician. The presence of a herniated lumbar disk was established by concordance between 2 independent readings of the patient's lumbar spine MRI by 2 spine physicians or a spine physician and a neuroradiologist.

Randomization was performed using variable block sizes and implemented by the University of California, San Francisco Compounding Pharmacy, which provided pre-filled medication bottles according to a randomization list generated by nonstudy personnel. Study investigators, staff, and participants were blinded to treatment assignment.

Figure 1. Flow of Participants in Randomized, Double-Blind Trial of Oral Prednisone vs Placebo Through 3-Week (Primary) and 52-Week (Secondary) Follow-up



MRI indicates magnetic resonance imaging; ODI, Oswestry Disability Index.

<sup>a</sup> One of the 2 participants lost to 3-week follow-up visits was lost to follow-up for the entire study after the baseline visit. The other participant was contacted and included in the final 52-week follow-up.

Participants were seen in the clinic at 3 weeks and 24 weeks after randomization and were telephoned at 6, 12, and 52 weeks. By protocol, patients who did not describe themselves as at least “much better” on the patient global assessment item and whose ODI score remained higher than 30 points were offered ESIs at 3 and 6 weeks after randomization but could also be referred for an ESI by their physician at any time.

The occurrence of adverse events was ascertained at each study contact. Study progress was reviewed regularly by a data and safety monitoring board constituted by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. All study procedures were approved by the institutional review board of the Kaiser Foundation Research Institute; written informed consent was obtained from all participants.

The first participant was randomized in November 2008; the last participant assessment occurred in August 2013.

**Statistical Analysis**

The trial had sufficient statistical power for a 90% probability of detecting a difference of 7.0 points or more on the ODI at 3 weeks, assuming a standard deviation in ODI scores of 15.1, with a randomization ratio of 2:1 and a 2-sided  $\alpha=.047$  (to allow for up to 2 interim analyses).<sup>29</sup> The intergroup difference

of 7.0 points was within the range of published estimates of the minimum clinically important difference for the ODI.<sup>21-28</sup> These calculations required an evaluable sample of 226 participants; assuming a potential 20% withdrawal rate, the final intended sample size was 270 participants.

Unadjusted analyses were conducted using the *t* test for continuous and ordinal variables and were consistent with the corresponding Wilcoxon rank sum tests. Categorical variables (including the responder analyses) were analyzed with the Fisher exact test or its generalization for more than 2 levels.<sup>29</sup> Adjusted analyses for continuous and ordinal variables were conducted with multivariable linear regression models, assessed for model fit and departures from the modeling assumptions. For dichotomous outcome variables, adjusted risk ratios were obtained from multivariable Poisson regression models using robust (Huber-White) standard errors.<sup>30</sup> The final models included adjustments for baseline demographics, study site, presence of a positive straight-leg raise test result at baseline, and elapsed time between symptom onset and randomization. Continuous outcomes were dichotomized at several cut points for a set of exploratory, post hoc responder analyses. All analyses were conducted under the principle of intention to treat in that all participants were analyzed in the

Table 1. Baseline Demographic and Clinical Characteristics Overall and by Study Group

Characteristics	All Participants (N = 269)	Prednisone Group (n = 181)	Placebo Group (n = 88)
Age, mean (SD), y	46.0 (12.1)	45.6 (11.8)	46.7 (12.6)
Male, No. (%)	149 (55.4)	98 (54.1)	51 (58.0)
Race, No. (%) <sup>a</sup>			
Native American	5 (1.9)	1 (0.6)	4 (4.6)
Asian	32 (11.9)	24 (13.3)	8 (9.1)
African American	6 (2.2)	3 (1.7)	3 (3.4)
Pacific Islander	2 (0.7)	2 (1.1)	0
White	179 (66.5)	129 (71.3)	50 (56.8)
>1 Race	19 (7.1)	10 (5.5)	9 (10.2)
Declined to state race	26 (9.7)	12 (6.6)	14 (15.9)
Ethnicity, No. (%) <sup>b</sup>			
Hispanic	62 (23.1)	34 (18.8)	28 (31.8)
Education, No. (%)			
High school graduate or lower	68 (25.3)	46 (25.4)	22 (25.0)
Some college	95 (35.3)	65 (35.9)	30 (34.1)
College graduate or higher	106 (39.4)	70 (38.7)	36 (40.9)
Oswestry Disability Index score, mean (SD) <sup>c</sup>	51.1 (13.5)	51.2 (14.5)	51.1 (11.5)
Below-waist pain numerical rating scale score, mean (SD) <sup>d</sup>	6.7 (1.9)	6.6 (2.0)	6.9 (1.8)
Time from pain onset to randomization, d			
Mean (SD)	30.4 (21.4)	29.7 (20.8)	31.7 (22.7)
Median (interquartile range)	25 (14-42)	25 (14-38)	27 (12-48)
Positive straight-leg raise test result, No. (%)	224 (88.4)	154 (85.1)	70 (79.6)
Muscle weakness at baseline, No. (%) <sup>e</sup>	14 (5.2)	8 (4.4)	6 (6.8)
Short Form 36 Health Survey score, mean (SD)			
Physical Component Summary <sup>f</sup>	30.6 (6.6)	30.4 (6.8)	30.9 (6.2)
Mental Component Summary <sup>g</sup>	48.7 (11.8)	48.5 (11.6)	49.3 (12.3)

<sup>a</sup>  $P=.009$  for prednisone group vs placebo group.

<sup>b</sup>  $P=.02$  for prednisone group vs placebo group.

<sup>c</sup> Score range, 0-100; higher scores indicate greater dysfunction.

<sup>d</sup> Score range, 0-10; higher scores indicate more pain.

<sup>e</sup> Defined as score  $\leq 3$  on 0- to 5-point scale for lower extremity motor strength scoring.

<sup>f</sup> Score range, 0-100; higher scores indicate better physical health status.

<sup>g</sup> Score range, 0-100; higher scores indicate better mental health status.

group to which they were randomized, regardless of adherence. For the 52-week data, all models were fit to 50 multiple-imputed data sets using a Markov chain Monte Carlo method.<sup>31</sup> All reported  $P$  values are 2-sided, with  $P < .05$  signifying statistical significance, and no adjustments were made for multiple hypothesis testing. All analyses were conducted with Stata software, version 13.1.<sup>31</sup>

Seven subgroup analyses were prespecified (numbers in each group shown in brackets): median baseline severity of symptoms (ODI score  $\leq 48$  vs  $>48$  [ $n=140$  vs  $n=129$ ]), presence of baseline ipsilateral motor weakness (muscle strength score 0-3 vs 4-5 on a 0- to 5-point scale, with higher scores indicating greater strength [ $n=14$  vs  $n=255$ ]), median time between onset of symptoms and randomization ( $\leq 25$  days vs  $>25$  days [ $n=137$  vs  $n=132$ ]), median age ( $\leq 46$  vs  $>46$  years [ $n=137$  vs  $n=132$ ]), sex (male vs female [ $n=149$  vs  $n=120$ ]), race (white vs nonwhite [ $n=179$  vs  $n=90$ ]), and ethnicity (Hispanic vs non-Hispanic [ $n=62$  vs  $n=207$ ]). Other subgroups examined were median baseline pain score ( $\leq 6$  vs  $>6$  [ $n=107$  vs  $n=162$ ]) and straight-leg raise test (positive vs negative result [ $n=224$  vs  $n=45$ ]). All subgroup analyses were performed using interaction terms in the multivariable regression models.

## Results

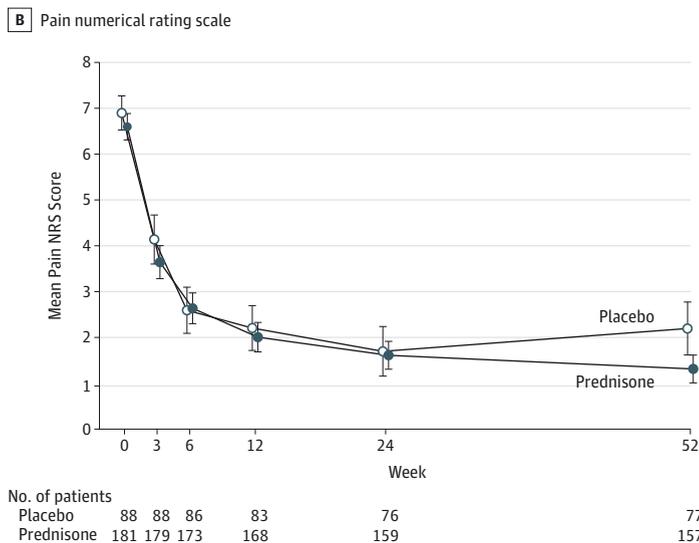
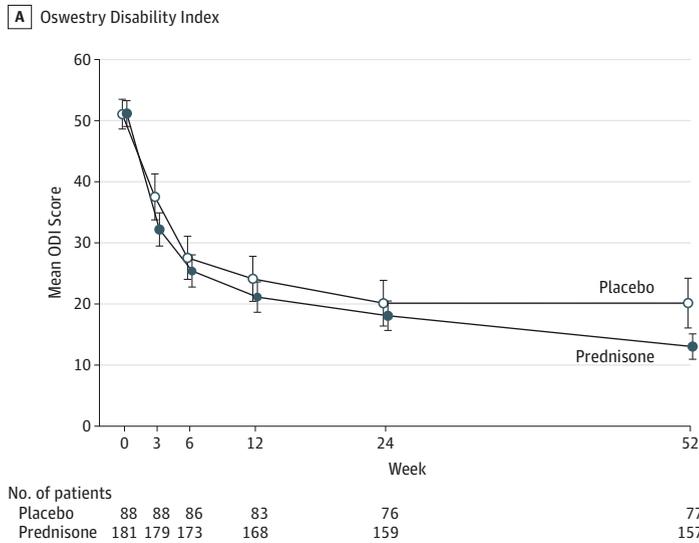
Of the 543 individuals screened, 269 met eligibility criteria and were enrolled (Figure 1). The most common reasons for ineligibility were related to age, radiographic findings, severity or duration of symptoms, or current steroid treatment.

Treatment groups were generally well matched at baseline (Table 1), although participants randomized to prednisone included a higher prevalence of white patients and a lower prevalence of reporting more than 1 race, declining to state a race, and Hispanic ethnicity.

The primary outcome visit at 3 weeks was attended by 267 participants (99.3%), and the secondary 52-week outcome assessment was completed by 234 participants (87.0%). Two hundred fifty-four (95.5%) of 266 participants for whom adherence data were available took all their study medication and 263 (98.9%) took at least 75% of their study medication.

Participants in both blinded treatment groups showed an improvement in symptoms over the initial 6 weeks, with more gradual reductions until the 24-week visit, after which changes were more variable (Figure 2). Baseline ODI scores were 51.2

Figure 2. Scores on the Oswestry Disability Index and Pain Numerical Rating Scale



Observed mean values for the (A) Oswestry Disability Index (ODI) and (B) pain numerical rating scale (NRS) for average pain below the waist in the prior 3 days in the prednisone-treated and placebo-treated groups. The ODI is measured on a 0- to 100-point scale, with higher numbers indicating more functional disability. The pain NRS is measured on a 0- to 10-point scale, with higher numbers indicating more pain. Treatment occurred during the first 15 days after randomization. Errors bars indicate 95% CIs.

and 51.1 in the prednisone and placebo groups, respectively; corresponding ODI scores at 3 weeks were 32.2 and 37.5. At 3 weeks, participants in the prednisone-treated group showed an unadjusted mean 5.6-point (95% CI, 1.1-10.1;  $P = .01$ ) greater reduction in ODI scores compared with participants in the placebo group (Figure 2A). At 52 weeks, the mean between-group difference was 7.6 points (95% CI, 2.6-12.7;  $P = .003$ ). After statistical adjustment, the between-group differences also favored prednisone at 3 weeks (mean difference, 6.4 points; 95% CI, 1.9-10.9;  $P = .006$ ) and at 52 weeks (mean difference, 7.4 points; 95% CI, 2.2-12.5;  $P = .005$ ) (Table 2).

In a responder analysis, the prednisone-treated group showed a significantly greater relative likelihood of achieving at least a 30-point or 50% improvement in the ODI at 3 weeks (relative risk [RR], 1.7; 95% CI, 1.1-2.9; number needed to treat [NNT], 10.6 and RR, 1.8; 95% CI, 1.1-2.9; NNT, 7.6, respectively) and at 52 weeks (RR, 1.3; 95% CI, 1.0-1.6; NNT, 7.1 and RR, 1.2; 95% CI, 1.1-1.5; NNT, 5.5, respectively) (Table 2).

Unlike the ODI, there was no statistically significant difference between groups in changes in the below-waist pain NRS at either the 3-week or 52-week time points (Table 2 and Figure 2B). Similarly, there were no significant differences between groups in the proportion of participants achieving at least a 2-, 3-, or 5-point improvement in the pain NRS scores at either time point (Table 2).

Participants randomized to prednisone had a significantly greater improvement in the Physical Component Summary score of the Short Form 36 at 3 weeks (by a mean of 3.3 points; 95% CI, 1.3-5.2;  $P = .001$ ) and the Mental Component Summary score at 1 year (by a mean of 3.6 points; 95% CI, 0.6-6.7;  $P = .02$ ) (Table 2).

Over the 1-year follow-up period, there was no significant between-group difference in the likelihood of undergoing spine surgery (9.9% vs 9.1%; RR, 1.2; 95% CI, 0.5-2.6;  $P = .68$ ) (Table 2).

The global patient assessment outcome, an exploratory outcome, was measured with a dynamic perceived change in

Table 2. Changes in Outcome Measures From Baseline to 3-Week and 52-Week Follow-up

Outcomes	3-Week Follow-up			52-Week Follow-up			
	Prednisone Group (n = 179)	Placebo Group (n = 88)	Adjusted Difference Between Groups (95% CI) <sup>a</sup>	Prednisone Group (n = 157)	Placebo Group (n = 77)	Adjusted Difference Between Groups (95% CI) <sup>a</sup>	P Value
Primary outcome, mean (95% CI)							
Oswestry Disability Index score <sup>b</sup>	-19.0 (-21.6 to -16.3)	-13.3 (-16.7 to -10.0)	-6.4 (-10.9 to -1.9)	-37.8 (-40.7 to -35.0)	-30.4 (-34.8 to -25.9)	-7.4 (-12.5 to -2.2)	.005
Other continuous outcomes, mean (95% CI)							
Pain numerical rating scale score <sup>c</sup>							
Below waist, average	-3.0 (-3.3 to -2.6)	-2.8 (-3.3 to -2.2)	-0.3 (-1.0 to 0.4)	-5.2 (-5.6 to -4.7)	-4.6 (-5.2 to -4.0)	-0.6 (-1.3 to 0.2)	.15
Below waist, worst	-3.6 (-4.0 to -3.1)	-3.2 (-3.8 to -2.6)	-0.5 (-1.3 to 0.3)	-6.5 (-7.0 to -6.1)	-5.7 (-6.4 to -5.0)	-0.7 (-1.6 to 0.1)	.09
Below waist, least	-2.0 (-2.4 to -1.6)	-1.5 (-2.1 to -1.0)	-0.5 (-1.2 to 0.2)	-3.4 (-3.8 to -2.9)	-3.0 (-3.6 to -2.3)	-0.4 (-1.1 to 0.4)	.33
Above waist, average	-1.0 (-1.3 to -0.6)	-0.8 (-1.3 to -0.3)	-0.2 (-0.8 to 0.5)	-1.5 (-2.0 to -1.0)	-1.4 (-2.0 to -0.7)	-0.2 (-1.0 to 0.6)	.61
Short Form 36 Health Survey score <sup>d</sup>							
Physical Component Summary	5.8 (4.7 to 7.0)	2.8 (1.3 to 4.2)	3.3 (1.3 to 5.2)	18.0 (16.5 to 19.5)	15.7 (13.2 to 18.2)	2.5 (-0.3 to 5.4)	.08
Mental Component Summary	1.2 (-0.2 to 2.6)	-0.7 (-3.0 to 1.6)	2.2 (-0.4 to 4.8)	6.9 (5.1 to 8.7)	3.1 (0.7 to 5.4)	3.6 (0.6 to 6.7)	.02
Categorical outcomes, No. (%) [95% CI]							
Improvement in Oswestry Disability Index score							
≥10 points	119 (66.5) [59.5-73.4]	47 (54.7) [43.9-65.4]	1.3 (1.0-1.6) <sup>e</sup>	148 (94.3) [90.6-97.9]	67 (88.2) [80.7-95.6]	1.1 (1.0-1.1) <sup>e</sup>	.24
≥15 points	97 (54.2) [46.8-61.6]	39 (45.3) [34.6-56.1]	1.2 (0.9-1.6) <sup>e</sup>	145 (92.4) [88.1-96.6]	62 (81.6) [72.7-90.5]	1.1 (1.0-1.3) <sup>e</sup>	.05
≥30 points	48 (26.8) [20.2-33.4]	15 (17.4) [9.3-25.6]	1.7 (1.1-2.9) <sup>e</sup>	111 (70.7) [63.5-77.9]	43 (56.6) [45.2-68.0]	1.3 (1.0-1.6) <sup>e</sup>	.04
≥50%	59 (33.0) [26.0-39.9]	17 (19.8) [11.2-28.4]	1.8 (1.1-2.9) <sup>e</sup>	136 (86.6) [81.2-92.0]	52 (68.4) [57.7-79.1]	1.2 (1.1-1.5) <sup>e</sup>	.01
Improvement in pain numerical rating scale score							
≥2 points	120 (67.0) [60.1-74.0]	57 (64.8) [54.6-75.0]	1.1 (0.9-1.3) <sup>e</sup>	141 (89.8) [85.0-94.6]	66 (85.7) [77.7-93.7]	1.0 (0.9-1.2) <sup>e</sup>	.45
≥3 points	92 (51.4) [44.0-58.8]	45 (51.1) [40.5-61.8]	1.0 (0.8-1.3) <sup>e</sup>	131 (83.4) [77.6-89.3]	60 (77.9) [68.4-87.4]	1.1 (0.9-1.2) <sup>e</sup>	.39
≥5 points	51 (28.4) [21.8-35.2]	23 (26.1) [16.8-35.5]	1.1 (0.8-1.7) <sup>e</sup>	106 (67.5) [60.1-74.9]	44 (57.1) [45.8-68.4]	1.2 (0.9-1.4) <sup>e</sup>	.19
Back surgery, any	147 (82.1) [76-88]	61 (69.3) [60-79]	1.2 (1.0-1.4) <sup>e</sup>	18 (9.9) [5.5-14.3]	8 (9.1) [3.0-15.2]	1.2 (0.5-2.6) <sup>e</sup>	.68
Global patient assessment at least "somewhat better" <sup>f</sup>	147 (82.1) [76-88]	61 (69.3) [60-79]	1.2 (1.0-1.4) <sup>e</sup>	143 (91.1) [86.6-95.6]	66 (85.7) [77.7-93.7]	1.1 (1.0-1.2) <sup>e</sup>	.30

<sup>a</sup> Between-group differences are adjusted for baseline age, sex, race, ethnicity, study site, presence of a positive straight-leg raise test result at baseline, and elapsed time between symptom onset and randomization.

<sup>b</sup> Score range, 0-10; higher scores indicate greater dysfunction.

<sup>c</sup> Score range, 0-10; higher scores indicate more pain. Average = pain on average over past 3 days; worst = pain at its worst over past 3 days; least = pain at its least (best) over past 3 days.

<sup>d</sup> Score range, 0-100; higher scores indicate better physical/mental health status.

<sup>e</sup> Data are relative risk (95% CI).

<sup>f</sup> Global patient assessment was queried as "How has your leg pain changed since you started taking your study medication?" using the following ordered response categories: very much better, much better, somewhat better, about the same, somewhat worse, much worse, or very much worse.

Table 3. Adverse Events Reported by Participants Up to the 3-Week Follow-up Visit

Adverse Events <sup>a</sup>	All Participants, No. (%) (n = 267) <sup>b</sup>	Prednisone Group, No. (%) (n = 179) <sup>c</sup>	Placebo Group, No. (%) (n = 88) <sup>c</sup>
Insomnia	55 (15.9)	46 (25.7)	9 (10.2) <sup>d</sup>
Nervousness	40 (11.5)	33 (18.4)	7 (8.0) <sup>e</sup>
Increased appetite	49 (14.1)	40 (22.3)	9 (10.2) <sup>f</sup>
Indigestion	26 (7.5)	20 (11.2)	6 (6.8)
Headache	45 (13.0)	32 (17.9)	13 (14.8)
Joint pain	20 (5.8)	10 (5.6)	10 (11.4)
Sweating	50 (14.4)	35 (19.6)	15 (17.0)
Other	62 (17.9)	46 (25.7)	16 (18.2)
Total reporting ≥1 adverse event	106 (39.7)	88 (49.2)	21 (23.9) <sup>g</sup>

<sup>a</sup> Participants could report more than 1 event at a time. All events except "other" were assessed with a questionnaire; events noted as "other" were volunteered by participants.

<sup>b</sup> Percentage of all reported adverse events.

<sup>c</sup> Percentages of individual adverse events reported in each treatment group.

<sup>d</sup>  $P = .003$  for prednisone group vs placebo group.

<sup>e</sup>  $P = .03$  for prednisone group vs placebo group.

<sup>f</sup>  $P = .02$  for prednisone group vs placebo group.

<sup>g</sup>  $P < .001$  for prednisone group vs placebo group.

leg pain score. Between-group differences favored the prednisone group, in whom the change was significantly greater at the 3-week visit (Table 2).

Subgroup analyses revealed no statistically significant interactions at either the 3-week or 52-week time points in the between-group changes in the ODI or pain NRS with baseline age, sex, race, ethnicity, elapsed time between onset of symptoms and randomization, lower extremity motor weakness, or presence of a positive straight-leg raise test result.

By the 3-week visit, 88 participants (49.2%) in the prednisone group reported at least 1 adverse event compared with 21 (23.9%) randomized to placebo ( $P < .001$ ). The majority (82.1%) of these were minor, expected adverse effects commonly associated with short courses of prednisone, such as insomnia, nervousness, and increased appetite (Table 3). By the 52-week visit, 208 participants (77.3%) reported a total of 723 adverse events; there were no significant differences in the mean number of adverse events per person in the active- and placebo-treated groups (2.70 vs 2.69;  $P = .98$ ) or in the proportion of participants in each group reporting at least 1 adverse event (80.1% vs 71.6%;  $P = .12$ ). Overall, 5 serious adverse events occurred over the 52-week follow-up period, 3 in the prednisone group (appendectomy, suicide attempt, and deep venous thrombosis) and 2 in the placebo group (upper gastrointestinal tract hemorrhage and partial nephrectomy for renal cell carcinoma); none was judged to be likely due to the study medication.

At the 3-week time point, 130 (74.7%) participants in the prednisone group believed that they had been given the active treatment compared with 48 (52.8%) of placebo-assigned participants ( $P = .001$ ).

## Discussion

Acute lumbar radiculopathy associated with a herniated nucleus pulposus commonly causes substantial pain and disability and generates significant costs.<sup>3,4,32</sup> Treatment options include advice, education, self care, and medica-

tions (including oral steroids), followed by various physical modalities (eg, physical therapy, ultrasound, electrical stimulation), epidural steroids, and microdiscectomy if pain persists.<sup>3,7,8,33,34</sup>

Over the past 35 years, 6 comparative trials have studied the use of nonepidural steroids in patients with sciatica.<sup>35-40</sup> These trials were generally small with low statistical power (3 enrolled fewer than 40 patients<sup>36,37,39</sup>). Most of these studies did not find evidence of efficacy of steroid treatment, although 1 recent trial (which enrolled the greatest number of participants) found a trend toward improvement in pain and a significant benefit in function 1 month after a single intramuscular injection of methylprednisolone.<sup>40</sup> To date, however, no study has examined the effectiveness of a full course of oral steroids in addition to usual care in a well-powered clinical trial.

In this trial of oral prednisone for patients with acute lumbar radiculopathy, we found a small, statistically significant improvement in function (as measured by the ODI) at both 3 weeks and 52 weeks favoring the prednisone-treated group but no difference in lower extremity pain scores at any time point. Several secondary outcomes showed small but inconsistent improvements in the active treatment group relative to the placebo group. Interaction analyses did not reveal any subgroup response that might explain these results. There was no significant difference in the likelihood of undergoing spine surgery up to 52 weeks. While there were significantly more adverse effects in the treatment group noted at 3 weeks, these were primarily transient, expected adverse effects associated with short courses of oral prednisone and there was no difference in adverse events at 1 year; no serious adverse events related to treatment were observed.

The adjusted mean improvement for the primary functional outcome, the ODI, was 6.4 points on a 100-point scale 3 weeks following randomization. This degree of benefit must be interpreted in the context of the clinical setting, as there is no clear consensus regarding the patient-relevant minimum clinically important difference for the ODI, with most published estimates in the range of 5 to 15 points.<sup>21-28</sup>

We designed the study power calculations around a minimum clinically important difference of 7 points, which was chosen to be in the lower end of this interval, although this choice was arbitrary, given the lack of published consensus. Whether the observed improvement in function (without concomitant improvement in pain) merits use of oral steroids for patients with an acute radiculopathy is a difficult decision and, ultimately, becomes a personal one that must be weighed by individual patients and their physicians. In addition, pain may limit function, so as pain decreases, function (ODI) may increase until pain again limits functional capacity. This may explain the improved function without measurable improvement in pain.

Examination of the response curves (Figure 2) for both the ODI and pain NRS show that the small between-group differences observed 3 weeks after randomization were not observed at the 6-week time point. However, between-group differences were statistically significant again at the 52-week follow-up. The magnitude of the difference at the 52-week follow-up is greater than the magnitude of the difference at the 3-week follow-up. We know of no physiological explanation for a potential delayed effect of prednisone. The observed difference at the 52-week follow-up may be due to chance.

An important rationale for using oral steroids is the potential to decrease the need for more invasive interventions.

However, in this trial, the use of prednisone did not decrease the likelihood of undergoing surgery.

Our study had several strengths, including effective randomization, high adherence to the intervention, high follow-up rates, and use of standardized patient-reported outcomes. Several potential limitations should also be noted. While it is possible that allowing up to 3 months after onset of symptoms was too long, we did not find any significant difference in response based on the time to treatment. We chose what we considered to be an adequate dosage for the prednisone treatment, but it may be argued that this dosage was insufficient. Blinding was only partially successful, probably because of the common adverse effects of oral steroids. Although we had multiple secondary outcomes, we did not adjust for multiple comparisons. In addition, generalizability of our results may be limited by the requirement for a positive MRI finding and a baseline ODI score of 30 points or higher.

## Conclusions

Among patients with acute radiculopathy due to a herniated lumbar disk, a short course of oral steroids, compared with placebo, resulted in modest improvement in function and no significant improvement in pain.

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# **ACT FAST**

## ***A Corticosteroid Taper For Acute Sciatica Treatment***

A Double-Blind Randomized Clinical Trial of Oral Prednisone for  
Treatment of Acute Sciatica due to a Herniated Lumbar Disc

Conducted at:

Northern California Kaiser Permanente

Sponsored by:

National Institute of Arthritis, Musculoskeletal Disease and Skin Diseases  
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**TITLE:** A Corticosteroid Taper For Acute Sciatica Treatment (ACT FAST)

**PRIMARY**

**OBJECTIVE:** Determine if treatment with a 15-day tapering course of oral prednisone results in differences in changes in physical functioning compared to treatment with an oral placebo after three weeks follow-up.

**SECONDARY OBJECTIVES:**

1) Determine if treatment with a 15-day tapering course of oral prednisone results in differences in changes in pain compared to treatment with an oral placebo after three weeks follow-up.

2) Determine if treatment with a 15-day tapering course of oral prednisone results in differences in changes in physical functioning compared to treatment with an oral placebo after 24 weeks follow-up.

3) Determine if treatment with a 15-day tapering course of oral prednisone results in differences in changes in pain compared to treatment with an oral placebo after 24 weeks follow-up.

4) Determine if the efficacy of a 15-day tapering course of oral prednisone is associated with the

- a) severity of functional impairment at baseline
- b) degree of lower-extremity weakness at baseline.
- c) length of time between the onset of sciatica symptoms and the initiation of prednisone therapy.
- d) presence of multi-level (vs. single-level) disease

**DESIGN:** Randomized, double-blind, placebo-controlled two-arm parallel-comparison trial

**POPULATION:** Adults aged 18 - 70 years with functionally incapacitating leg pain, extending below the knee, and an Oswestry Disability Index score  $\geq 30$  and an MRI showing a herniated nucleus pulposus compatible with the patient's clinical presentation.

**INTERVENTION:** Participants will be randomized to one of two treatment arms:

- Prednisone:
  - For participants  $\geq 50$  kg, the dose is 60 mg daily for 5 days, then 40 mg daily for 5 days, then 20 mg daily for 5 days
  - For participants  $< 50$  kg, the dose is 40 mg daily for 10 days, then 20 mg daily for 5 days
- Placebo for 15 days.

**DURATION:** The medication-treatment phase will last 15 days; the primary outcome will be measured at 3 weeks and all participants will be followed for 52 weeks

**SAMPLE SIZE:** 270 participants randomized in a 2:1 allocation to prednisone or placebo.

## **0.1 ACRONYMS USED IN THIS PROTOCOL**

AE = Adverse Event

DOR = Division of Research

DSMB = Data Safety Monitoring Board

ESI = Epidural Steroid Injection

FDA = Food and Drug Administration

HNP = Herniated Nucleus Pulposus

ICH = International Committee on Harmonization

IND = Investigational New Drug

IRB = Institutional Review Board

KPNC = Kaiser Permanente, Northern California

LBP = Low Back Pain

MCID = Minimum Clinically Important Difference

MRI = Magnetic Resonance Imaging

NSAID = Nonsteroidal Anti-Inflammatory Drug

NRS = Numerical Rating Scale

ODI = Oswestry Disability Index

PHI = Protected Health Information

RCT = Randomized Clinical Trial

SAE = Serious Adverse Event

SF-36 = Short-Form 36

SLR = Straight Leg Raising

## **1.0 INTRODUCTION**

### **1.1 STUDY RATIONALE**

Acute radiculopathy associated with herniated lumbar nucleus pulposus (HNP), also referred to as sciatica, is a significant cause of pain, loss of function, and work absenteeism in the industrialized world. Though nerve-root compression has been previously thought to be the primary etiology of the symptoms associated with HNP, recent basic-science evidence indicates that inflammation may be a prerequisite or the dominant cause of the pain and dysfunction.

Epidural steroid injections (ESI's) are commonly used to decrease pain and return patients to normal function; the rationale for their use is to decrease the inflammatory component of the radicular syndrome. However, the literature on the effectiveness of ESI is inconsistent and many methodologic problems exist in the published studies.

Given the plausible rationale of a dominant inflammatory cause of sciatica, and conflicting literature on effectiveness of ESI's, it is rational to consider oral delivery of the steroid; this is a strategy frequently used anecdotally in clinical practice. Despite the compelling logic and low risk, to date there have been no published clinical trials to evaluate the effectiveness of oral steroids compared to placebo.

The purpose of this proposal is to formally test, in a fully powered, phase III clinical trial, the benefits and side effects associated with a short tapering course of oral steroids compared to placebo. Should oral steroids prove effective, patients and clinicians will have access to a simple, inexpensive therapy that can be used by primary care physicians without delay.

### **1.2 BACKGROUND**

Low back pain is one of the most common reasons for visits to a doctor (1) and the most common cause of work absenteeism (2-4). The lifetime prevalence of back pain exceeds 70% in most industrialized countries (5). In the National Health and Nutrition Examination Survey (NHANES) II, the cumulative lifetime prevalence of LBP lasting at least 2 weeks was 13.8%. Sciatica was reported by 12% of those with back pain and 1.6% of the entire sample (6).

A common cause of sciatica is an acute HNP (7). The incidence and prevalence of radiculopathy associated with HNP must be considered in the context of the study from which it is derived, and the definitions used. It is estimated in various studies to be between 1% point prevalence (8) and 42%-59% life time prevalence (9), and many intermediate estimates exist (10-12). The majority of patients with radiculopathy associated with acute herniated nucleus pulposus recover with conservative care management, although 10-20% require surgery by some estimates (13, 14).

Sciatica due to a HNP is an important medical and socioeconomic problem (1). Sciatica is defined as pain radiating into the leg in a specific nerve root distribution, associated with nerve root tension signs and neurologic findings (15). Radiculopathy is a neurologic condition in which conduction is blocked in the axons of a spinal nerve or its roots (16). Conduction block in sensory axons result in numbness; conduction block in motor axons results in weakness (16). It had been thought for many years that radicular pain was due entirely to compression of the nerve root by the extravasated nucleus pulposus. However, neurophysiologic experiments have demonstrated that compression of the nerve root does not invoke nociceptive activity (17, 18). Clinical experiments intra-operatively have also demonstrated that direct compression or traction of the nerve root may evoke paresthesia and numbness, but does not evoke pain (19, 20). It has been questioned whether radiculopathy is due to mechanical compression, chemical inflammation, or both (21). Disc herniation is the single most common cause of radicular pain, and there is increasing evidence that this condition causes pain by mechanisms other than simple compression (22). Numerous imaging studies demonstrate nerve root compression among patients who have no symptoms (23-26). In addition, patients who have been symptomatic, but whose symptoms have resolved, continue to have compression on imaging studies (27, 28). This observation argues for a mechanism of pain other than compression.

Inflammatory changes have been observed intra-operatively (29, 30). Studies have demonstrated that intervertebral disc nuclear material is both inflammatory (29-34) and capable of eliciting an auto-immune response (35-40). Application of nuclear material to nerve roots without compression induces inflammatory changes including edema, increased vascular permeability, and intravascular coagulation (41-44). The inflammation damages nerve roots, blocks nerve conduction, (43, 45-47) and produces hyperalgesia and pain behavior (48-50). The mediators of this inflammatory response are phospholipase A2, nitric oxide, and tumor necrosis factor  $\alpha$  (43, 46, 48, 49, 51-55). Human studies have demonstrated that HNP attracts macrophages, fibroblasts, and lymphocytes (56-62) and inflammatory mediators are produced by these cells and/or the disc itself. These mediators include phospholipase A2 (63, 64), metalloproteinases (63-65), prostaglandin E2 (61, 63-65), leukotriene B4 and thromboxane (66) nitric oxide (54, 64-66), interleukin 8 (67, 68), interleukin 12 and interferon  $\gamma$  (59), and TNF- $\alpha$  (67). The disc material stimulates the production of IgM and IgG antibodies (69), particularly to the glycosphingolipid of the nerve roots (70).

There is compelling evidence that an inflammatory mechanism may at least partially account for radicular symptoms in acute sciatica associated with an acute herniated disc (17, 18) and epidural steroid injections have been used to treat sciatica since the 1950s (71, 72). However, the clinical trials of epidural steroid injections have met with mixed results (73-85). The indications for which they have been applied is varied: several trials have evaluated ESIs for low back pain (LBP) (83, 86), others for post

laminectomy syndrome (82, 87, 88), or during lumbar discectomy (89). However, given the physiologic evidence cited above, the putative effect of an ESI would be to control the inflammatory changes and presumptively the pain and dysfunction associated with the inflammation. Green (90) showed relief of pain using intramuscular dexamethasone. This suggests that steroid delivery may be effective in differing routes. The North American Spine Society (NASS) and American Academy of Orthopaedic Surgeons Phase III Clinical Guidelines for Multidisciplinary Spine Care Specialists for treatment of LBP with radicular syndrome in the acute phase includes oral corticosteroids in the treatment algorithm (91).

ESI's require advanced treatment referral, although they remain unsubstantiated by clinical trials. Oral corticosteroid tapers have not been adequately assessed by clinical trials. If oral corticosteroid treatment is found to be effective, the treatment of acute radiculopathy associated with HNP may be moved to the primary care setting, creating more rapid access to treatment, and possibly improved resolution of the radicular syndrome with decreased costs. If it is not effective, removal of this treatment course from clinical guidelines will decrease unnecessary risk. Either outcome will produce an important improvement in clinical care of this condition.

Given the conflicting evidence for effectiveness of ESI's in the management of pain and dysfunction from radiculopathy associated with herniated nucleus pulposus, we propose to evaluate whether the oral corticosteroid treatment of this condition is effective in increasing function and decreasing pain associated with this condition. As part of this trial, we will also evaluate the oral corticosteroid delivery compared to ESI, contributing a high-quality investigation and literature on this common intervention.

### **1.3 STUDY DESIGN**

This is a randomized, double-blind, placebo-controlled, two-arm, parallel-comparison clinical trial of a 15-day tapering course of oral prednisone vs. placebo for treatment of patients with an acute radicular syndrome caused by a herniated lumbar disc.

All patients presenting to the Physical Medicine Department Spine Clinic at one of the three clinical KPNC sites (San Jose, Roseville, or Redwood City, California) will be screened for eligibility. Those patients who present with the clinical syndrome of radiculopathy and meet preliminary eligibility requirements, will undergo an MRI scan. MRI confirmation will be obtained by two study physicians, and in the event of disparity, adjudicated by a third study physician. Those patients who have an MRI compatible with the clinical presentation will undergo informed consent and be randomized in a 2:1

fashion favoring prednisone. The primary outcome is change in functional status at three weeks as measured by the modified Oswestry Disability Index (ODI); several secondary outcomes are defined.

All participants will be assessed at three weeks for the primary outcome; those participants who show insufficient improvement (defined as failing to report “better” or “much better” global improvement in symptoms on a seven-level Likert-like response scale and continue to have an ODI score > 30, as defined by Carette, et al. (14)) will then receive an ESI, regardless of the arm to which they were originally randomized. All participants will again be assessed at six weeks post-randomization. Those participants who continue to show insufficient improvement will receive another study-mandated ESI. No protocol-mandated interventions will be conducted after the 6-week telephone interview. All participants will then be re-assessed at 12 weeks, at 24 weeks, and at 52 weeks, at which time the follow-up will be terminated. Note that once a participant achieves sufficient improvement, they will enter follow-up and all subsequent interventions will be considered non-study interventions (e.g., if a participant improves at 3 weeks, so that no ESI is given, then worsens and his/her physician orders a later ESI, this latter procedure will be considered a concomitant intervention, not a study intervention). While the efficacy of the ESI is not a fundamental research question in this trial, we have attempted to bring some consistency to the follow-up interventions so that comparisons between the treatment arms is more meaningful.

The primary outcome is measured at three weeks; we are primarily interested in the short-term efficacy of steroids and their ability to return patients to improved function quickly. As noted, patients who achieve insufficient relief from their initially allocated intervention will then receive up to two ESI’s at three-week intervals with assessment of outcomes. The rationale for this design is that, within KPNC (and, we believe, in most modern practices), it is standard of care, and consistent with published guidelines (91), to provide ESI for patients who do not improve from initial conservative therapy, despite the inconsistent literature on the efficacy of ESI; therefore, we believe that this intervention could not be ethically withheld from study patients who remain symptomatic. However, we will continue to collect outcome data for 52 weeks on all patients in both arms, in order to examine efficacy trends.

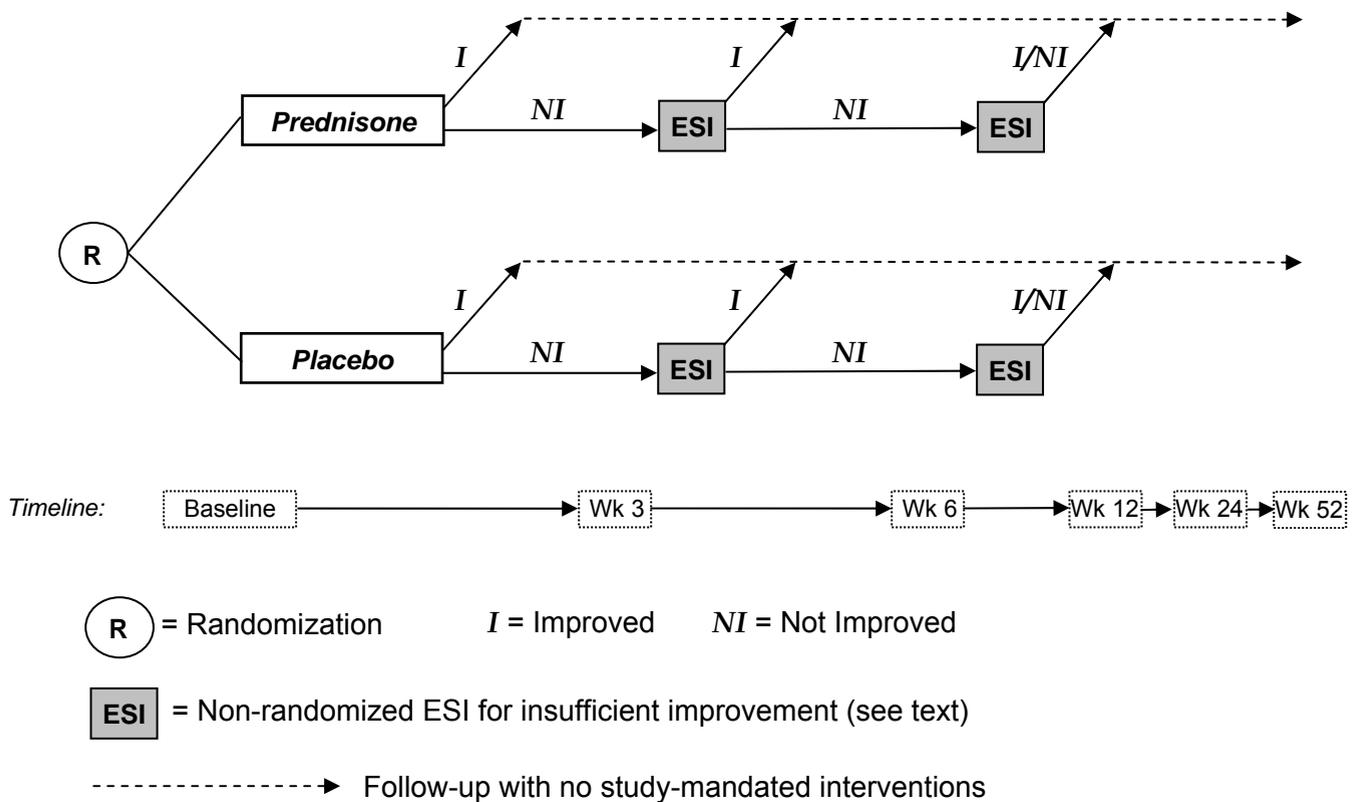


Figure: Study Design Schema

## 2.0 OBJECTIVES

### 2.1 PRIMARY OBJECTIVE

Determine if treatment with a 15-day tapering course of oral prednisone results in differences in changes in physical functioning compared to treatment with an oral placebo after three weeks follow-up.

### 2.2 SECONDARY OBJECTIVES

1) Determine if treatment with a 15-day tapering course of oral prednisone results in differences in changes in pain compared to treatment with an oral placebo after three weeks follow-up.

2) Determine if treatment with a 15-day tapering course of oral prednisone results in differences in changes in physical functioning compared to treatment with an oral placebo after 52 weeks follow-up.

3) Determine if treatment with a 15-day tapering course of oral prednisone results in differences in changes in pain compared to treatment with an oral placebo after 52 weeks follow-up.

4) Determine if the efficacy of a 15-day tapering course of oral prednisone is associated with the

a) severity of functional impairment at baseline

b) degree of lower-extremity weakness at baseline.

c) length of time between the onset of sciatica symptoms and the initiation of prednisone therapy.

d) presence of multi-level (vs. single-level) disease

## 2.3 PROPOSED SUBGROUPS

We define five subgroup analyses a priori.

First, we will examine differential response to therapy by baseline severity of symptoms. This analysis will be performed by stratification on baseline ODI scores, dichotomized at the median. Technically, these analyses will be performed by including an additional covariate for the binary baseline ODI score in the ANCOVA model or using higher-order interaction terms in the mixed linear models.

Second, we will examine differential response to therapy by the presence of baseline weakness. “Weakness” will be defined on a 6-point ordinal scale by neurologic testing. The six levels will be defined as follows (British Medical Research Council scale):

5/5 - Normal strength

4/5 - Weakness against resistance

3/5 - Able to move against gravity, but not against resistance

2/5 - Able to move with gravity eliminated (perpendicular to gravity)

1/5 - Unable to move but trace of muscle contraction present

0/5 - No sign of muscle contraction

These interaction analyses will be performed using increasing cut-off's of 3, 4, and 5 by including an additional covariate for the binary baseline weakness score in the ANCOVA model or using higher-order interaction terms in the mixed linear models. Lower-level cut-off's will not be used as fewer than 5% of acute sciatica patients in the Spine Clinics have levels of weakness less than 3.

The third pre-defined subgroup analysis will examine differential response to therapy according to time between first onset of symptoms and randomization. The concept is that patients provided steroid therapy may elicit a less favorable response if their symptoms are long-standing compared to patients whose symptoms are very acute. This subgroup analysis will be exploratory in nature, since a priori dichotomization cannot be specified. The time interval between the onset of symptoms and

randomization will be initially modeled as a continuous variable for these subgroup analyses and examinations for a threshold effect will be undertaken, by examining a range of cutpoints for these interactions.

The fourth pre-specified subgroup analysis will be a test of interaction with the presence of single-level vs. multi-level disease, as determined by the baseline MRI reading. This analysis will be performed as described above for baseline weakness using a simple dichotomous variable for multi-level disease (yes/no). The motivation for this analysis derives from the fact that systemic oral steroids may provide a particularly effective therapy for patients with multi-level disease, since an ESI directed at a single intervertebral level may fail to fully treat inflammatory reactions at adjacent levels that may also be contributing to a patient's symptoms.

Finally, we will also examine our data for interactions with gender, race/ethnicity, and age, as specified in the NIH Phase III clinical trial guidelines (92).

## **2.4 SUBSTUDIES**

### **2.4.1 LUMBAR SPINE MRI READING INSTRUMENT SUBSTUDY**

All radiologists reading study MRIs will use a structured instrument on which to record their findings. Despite extensive inquiry, we have been unable to identify a relevant instrument for this purpose. Therefore, as part of the study start-up activities, we will develop a structured instrument for recording MRI findings relevant to research on acute low-back pain and sciatica, using a modified Delphi technique (93, 94).

For this process, we will involve the three KPNC study neuroradiologists and several academic neuroradiologists with expertise and an interest in lumbar spine MRI (participating radiologists will be paid for their involvement). We will generate a candidate list of attributes of potential importance from each of the Delphi participants by asking for a comprehensive inventory of potentially important findings; a master list of findings will then be created and distributed to all panel members. The characterizations of the items will follow those recently defined by the Combined Task Forces of the North American Spine Society, the American Society of Spine Radiology, and the American Society of Neuroradiology, February 2003 Update (95).

Consensus will be defined as  $\geq 80\%$  of members declaring that the current version of the form is acceptable for use in clinical research. We will also use Cronbach's alpha as a secondary measure of consensus, with the expectation of achieving a level at least 0.9 (96).

Finally, we will pilot the form with all members, to uncover any problems with the use and implementation of the instrument, to estimate the mean time it takes to complete the form, and to

examine consistency across members. Any problems uncovered during the pilot phase will be relayed to the panel members for potential revision of the form. The final instrument will be placed in the public domain and made freely available to other investigators for their use, testing, and continued development.

### 2.4.2 PREDICTION OF RESPONSE TO THERAPY

If evidence of treatment efficacy is found, we will examine a wide range of predictor variables in an attempt to understand the characteristics of patients who are likely to respond to therapy (with the potential for development of a clinical prediction rule). Candidate predictors include demographics, severity of symptoms, length of symptom period prior to initiation of therapy, characteristics of pain patterns, evidence of weakness or sensory deficit, past history of back pain, past history of steroid exposure, and specific MRI findings.

## 3.0 STUDY PARTICIPANTS

### 3.1 INCLUSION CRITERIA

All study participants will be active members of the KPNC health plan, since all recruitment activities and interventions will take place in KPNC medical facilities.

The inclusion criteria for the ACT FAST study, and their rationales, are:

1. Adult patients, male or female, age 18 - 70 years of age	1. HNP occurs most commonly between the ages of 18-70 in both sexes
2. Presenting to a KPNC spine-care specialist in one of the three clinical sites (San Jose Redwood City, or Roseville California)	2. The Directors of these clinics are investigators participating in this study. Most patients with severe sciatica are referred to these clinics for management
3. Complaining of functionally incapacitating leg pain, extending below the knee, in a nerve-root distribution with or without low back pain.	3. This is the clinical presentation of patients who are likely to have an inflamed nerve root
3. Score $\geq 30$ on the modified Oswestry Disability Index	3. Ensure minimum level of dysfunction and avoid the "floor phenomenon" in the primary outcome instrument
4. Confirming imaging study (MRI) that shows a HNP consistent with the presenting symptoms and signs	4. To confirm the presumptive etiology

### 3.2 EXCLUSION CRITERIA

The exclusion criteria for the ACT FAST study, and their rationales, are:

1. Onset of sciatica symptoms more than 3 months prior to presentation to the clinic	1. Emphasis of this trial is on acute sciatica.
2. Cauda equina syndrome	2. This condition is a surgical emergency
3. Active cancer	3. These patients have a higher likelihood of occult metastatic disease that requires specific investigation and for which steroids may not be appropriate
4. Active spinal infection	4. This condition requires specific treatment and steroids may be contraindicated
5. Acute spinal fracture	5. This condition is not appropriately treated with steroids
6. Taken oral steroids within 3 months of randomization.	6. Recent steroid treatment may confound assessment.
7. Diabetes mellitus	7. Oral steroid therapy may cause severe hyperglycemia
8. Systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg within 30 days of randomization date.	8. Oral steroid therapy may cause further increase in blood pressure
9. Pregnant or lactating	9. Oral steroid therapy may be hazardous to the fetus or newborn
10. Active peptic ulcer disease	10. Oral steroid therapy may predispose to exacerbation or perforation
11. History of intolerance to steroid therapy	11. Steroid therapy contraindicated
12. History of allergy to local anesthetic or intravenous contrast	12. Local anesthetics and intravenous contrast are used in the ESI
13. Bleeding diathesis or anticoagulant therapy	13. Epidural injections may be hazardous in these patients
14. Ongoing litigation or workers compensation claim for LBP or sciatica	14. Strong predictor of poor response to therapy with issues of secondary gain (97)
15. Prior lumbar surgery	15. Cicatrix associated with prior surgery complicates interpretation of findings
16. ESI in prior 3 months	16. Recent prior ESI confounds assessment
17. Inability to read/understand English	17. Consent, study forms and data-collection instruments are in English
18. Active tuberculosis infection, systemic fungal infection	18. Oral steroid therapy relatively contraindicated
19. Does not undergo MRI scanning within 14 days	19. Unable to characterize nature of any anatomic lesion
20. Significant or progressive motor loss (<3/5 knee extension or ankle dorsi- or plantar flexion)	20. These patients have high risk of need for urgent surgery

These exclusion criteria are established for safety and to ensure consistency in the participant sample. While most of these criteria would be consistent with routine clinical practice, there will be some modest compromise in generalizability. For example, diabetics might still be candidates for oral steroid

therapy in the clinical setting (with close monitoring of blood glucose) but are excluded from this trial for safety reasons.

### **3.3 RANDOMIZATION AND STRATIFICATION**

Randomization will be unbalanced in a ratio of 2:1, favoring active prednisone (i.e., twice as many participants will be randomized to active prednisone than placebo), blocked (using randomly chosen block sizes of 3, 6, and 9) and stratified by clinical site and ODI score. The purpose of the former stratification criterion is to ensure approximately equivalent distributions in treatment arms between the two centers; the purpose of the latter stratification is to prevent a disproportionate number of participants of either high or low functional impairment being preferentially randomized to the active-prednisone arm.

Unbalanced randomization will be used for two reasons. First, we believe recruitment will be more successful when patients are offered a greater likelihood of receiving the active therapy. Second, in the context of this study, in which there exists a reasonable chance that the active treatment will be beneficial, the risks are low, and many patients may enter the trial for the opportunity to receive a new intervention for their symptoms, unbalancing randomization in favor of the active treatment arm provides a design that is more consistent with the best interests and likely preferences of the participants (98).

The randomization list will be generated by a DOR Project Coordinator not affiliated with this study, using the “ralloc.ado” procedure in Stata, version 9 (this procedure creates a blocked, stratified, and self-documenting randomization list) (99). The randomization list will then be taken by this Project Coordinator (always in a sealed envelope) to the compounding pharmacy of the UCSF Drug Product Services Laboratory in San Francisco, so that the study medications can be processed correctly. A second copy will be taken to the chief Research Pharmacist at the KPNC San Jose facility (which will serve as the central research pharmacy for this study), so that the randomization code can be broken at any time in case of a medical emergency. No other personnel associated with the study will see this randomization list at any time during the study.

### **3.4 REFUSAL/REJECT LOG**

A log of potential participants who decline to enter the study or who are deemed ineligible by the application of entry inclusion and exclusion criteria will be kept to judge the representativeness of those who consent to be randomized, consistent with CONSORT guidelines (100). If the individual permits, data collected in the refusal/reject log will include the individual’s age, gender, race/ethnicity, ODI score, NRS pain score, and reason for rejection or refusal.

### **3.5 RECRUITMENT**

Patients will be recruited from the primary care departments to the integrated Spine Clinics at the participating Kaiser Permanente Medical Centers at San Jose, Redwood City, and Roseville, as well as neighboring facilities, including Santa Clara, South San Francisco, Fremont, and Hayward. Primary care departments (including internal medicine, urgent care, and the emergency department) at these medical centers will be oriented to the study design and will be asked to refer all patients with the clinical syndrome of acute radiculopathy (sciatica) directly to the Physical Medicine and Rehabilitation Spine Clinic (note that we will ask primary care providers to refer all patients with acute sciatica to the Spine Clinics: those patients who are ineligible or decline to enter the study will still be managed by the spine-clinic physicians). Primary care providers will have an incentive to refer all patients with sciatica as this will relieve them of the burden of managing these patients themselves. Periodic reminder e-mails will be sent to all relevant providers. If recruitment problems arise, those primary care providers who designate visit diagnoses consistent with lumbar radiculopathy but who do not refer patients to the Spine Clinics will be identified through the KPNC clinical databases and contacted personally by study investigators to encourage them to refer their patients. Grand rounds presentations will be provided to each of these primary care departments reviewing the clinical condition, typical diagnosis and treatment strategies, the rationale for this study, and the patients who are potentially eligible. Recruitment will be monitored bi-weekly through the Velos electronic-data capture and project-management system (see Section 7.3) and the KPNC databases.

In addition to this passive strategy, we will also employ more active recruitment strategies, as needed. First, study personnel at the San Jose, Redwood City, and Roseville facilities will monitor the "reason for visit" fields in HealthConnect and for the emergency room to identify potentially eligible patients. The providers seen these patients will be reminded about the existence of the ACT FAST study with a paper reminder prior to the clinic visit. Second, the Kaiser clinical databases will be monitored on a daily basis for patients with a relevant diagnosis who have not been prescribed prednisone. If a patient appears potentially eligible (after review of their medical record), the patient's primary care physician will be contacted for permission to contact the patient. If the primary care physician does not decline to have their patient contacted within 48 hours, an overnight letter with study information will be sent to the patient's home. The recruitment letter will include a telephone number for the patient to call study personnel if they want to learn more about the study right away or if they prefer not to be contacted about the study. If the patient does not opt out of being called within 72 hours, a qualified study staff member will call the patient at home to explain more about the study, assess the patient's interest in participating, assess the likelihood that the patient has true sciatica symptoms, and telephone screen the patient, if the patient appears to be potentially eligible and expresses interest in participation. If the patient passes the telephone screen, he/she will be invited to the clinic for a full screening visit.

### **3.6 PARTICIPANT COMPENSATION**

Participants will be compensated \$20 for each of the follow-up interviews following the initial three-week study period (i.e., at the six, 12, 24, and 52-week timepoints), for a total of \$80 for participants who complete all appropriate study interviews.

## **4.0 MEASUREMENTS**

### **4.1 PRIMARY OUTCOME**

The primary outcome measurement for this study is the Oswestry Disability Index (ODI), version 2.0. The ODI is a widely used functional status measurement specifically developed for patients with disorders of the spine (101) and has been widely used in both clinical practice and clinical trials. The ODI is a ten-item questionnaire with ordered 6-response-item (0 - 5) scales for each question. The questions address physical functioning, sleeping, home/work functioning and impact on social life (102). The scores are summed and the percentage of the maximum possible score calculated (up to one missing item is allowed) (103), so the final range of scores is 0 - 100.

### **4.2 SECONDARY OUTCOMES**

The secondary outcomes include:

- a) a numeric rating scale (which will be used both as a visit-collected instrument and as a daily diary for the first three weeks post-randomization)
- b) the Short-Form 36 v2
- c) concomitant medication use for sciatica and back pain
- d) incidence of low-back surgery over the follow-up period

### **4.3 OTHER MEASUREMENTS**

Several other measurements will be obtained. These include:

- a) an assessment of participants' perception of global change in their symptoms, using a seven-item Likert-like scale, as in Carette, et al. (14) (this measurement will also serve, along with the ODI, as the determinant for the non-randomized protocol-driven ESI's for participants who show insufficient improvement in symptoms).
  - b) number of work days lost due to back pain and limitations in activities of daily living
  - c) a directed physical exam: all participants will undergo a physical exam at baseline and closeout. The specific data items collected include the neurologic elements: an acute tension sign

represented by the straight leg raising; motor loss, toe and heel walk capacity; patellar and Achilles deep tendon reflexes; and sensory loss (assessed in the usual dermatomal distributions).

#### **4.4 PLAIN-FILM LUMBAR SPINE X-RAYS**

Lumbar spine anterior-posterior and lateral x-rays will be obtained on all patients prior to referral to the Spine Clinic when an MRI is not performed; this is routine practice at KPNC. These films will be used to identify osseous abnormalities that may indicate exclusion criteria, such as a fracture.

#### **4.5 LUMBAR SPINE MRI**

Lumbar spine MRI will be obtained on all potential study participants within fourteen days of the eligibility visit to confirm the presence of a herniated lumbar disc. Criteria for the location and characterization of the herniation will be assigned in the study MRI reading instrument. The MRI will confirm the inclusion criteria of a herniated nucleus pulposus, and will also be used to confirm exclusion criteria of cauda equina syndrome, active cancer, or fracture (not seen on the plain-film X-ray). HNP characteristics will include location of the herniation (central, paracentral, lateral, far lateral), as well as other degenerative changes (central, lateral recess, and neuroforaminal spinal stenosis).

### **5.0 INTERVENTIONS**

#### **5.1 STUDY MEDICATIONS**

##### **5.1.1 ACTIVE AND CONTROL MEDICATIONS**

The active study medication is prednisone, a synthetic corticosteroid preparation with little mineralocorticoid activity. Prednisone is the most widely used oral steroid preparation (104) and is used frequently in local and systemic inflammatory and autoimmune conditions affecting nearly all organ systems. The risk of hypothalamic-pituitary-adrenal axis suppression is minimal with supraphysiologic doses of prednisone taken for less than three weeks (105).

The control medication is an identical-appearing placebo capsule with the same excipients but none of the active prednisone medication.

Since prednisone, as used in this trial, satisfies the requirements of 21 CFR 312.2a, an Investigational New Drug approval from the FDA is not required; an IND exemption has been granted by the FDA.

##### **5.1.2 DOSING**

We have chosen a weight-dependent dosing scheme for the oral steroid preparation for this trial. The purpose for this more complex dosing method is that we intend to provide a strong dose of oral steroid to ensure that we test the study hypotheses well (i.e., we wish to avoid under-dosing as a potential explanation, should the trial produce negative results). However, because some of the potential

adverse effects of prednisone are dose-related, it is rational to reduce the highest dose in lower-weight participants. Furthermore, it is known that the metabolism and volume of distribution of prednisone are also weight-related (106), so that higher doses should be used for heavier patients.

Those participants who weigh at least 50 kg will be instructed to take 60 mg (three capsules) daily for five days, then 40 mg (two capsules) daily for five days, then 20 mg (one capsule) daily for five days. Those participants who weigh less than 50 kg will be instructed to take 40 mg (two capsules) daily for ten days then 20 mg (one capsule) daily for five days.

The active study-medication capsules contain 20 mg of prednisone powder each. Participants will be told to take all doses of the study medication in the morning (to avoid sleep interference by potentially activating side effects of prednisone). The pharmacokinetics of prednisone make once-daily dosing appropriate (106).

The placebo capsules will be dosed in an identical manner.

### **5.1.3 SOURCE AND PACKAGING OF MEDICATIONS**

The active prednisone and the placebo capsules will be formulated by the Drug Product Services Laboratory of the University of California, San Francisco. This compounding pharmacy, in the Department of Clinical Pharmacy at UCSF, has a long history of experience supplying active and placebo compounds to double-blind clinical trials.

The medications will be provided in sealed bottles labeled with the study information and the coded randomization number. At the randomization visit, the site Research Assistant will remove the capsules from the bottle and place them in a pill organizer with the correct number of pills put in the correct day-labeled compartments. This method insures that participants will have immediate visual cues for assessing the need for taking medications and will not have to rely on their memories.

### **5.1.4 CONCOMITANT MEDICATIONS AND RESTRICTIONS**

Patients will be provided analgesics and muscle relaxants as needed, which will be quantified by both pill count and participant-completed medication diary. Analgesics include acetaminophen and opioids (including hydrocodone with acetaminophen or codeine with acetaminophen); muscle relaxants include diazepam and cyclobenzaprine. However, nonsteroidal anti-inflammatory drugs (NSAIDs) will be restricted for the first three weeks post-randomization. As the putative mechanism being studied is the effectiveness of steroidal anti-inflammatory medication through an oral delivery, the use of other medication with a similar mechanism of action may confound the analysis of effect. Therefore NSAIDs will be restricted from use during the first three weeks of follow-up.

### **5.1.5 BREAKING THE STUDY BLIND**

In the event of a serious medical emergency during which a treating physician must know whether a participant is taking active prednisone or placebo, the randomization code may be broken for that participant. Each participant will be given a wallet-sized card on which an emergency contact number is printed. The contact will be the primary study research pharmacy at each medical center which will be staffed 24 hours a day. The pharmacist will fill out an "ACT FAST Treatment Assignment Disclosure" form and provide the treating physician with the participant's randomization assignment (the pharmacist will encourage the treating physician not to disclose the treatment assignment to the patient, unless he/she insists). The participant will then be withdrawn from study medication though he/she will be encouraged to keep all remaining study visits.

#### **5.1.6 ADHERENCE MEASURES**

Medication adherence will be measured by simple pill counts at the three-week study visit (participants will be asked and reminded to bring their pill bottles and medication organizers to the three-week appointment).

#### **5.2 EPIDURAL STEROID INJECTIONS**

Prior to beginning the study, Dr. Bill Firtch will certify all physicians who will do ESI's on study patients to ensure that they follow the protocol precisely. Dr. Firtch will recertify all physicians doing study-related ESI's on an annual basis.

A standard fluoroscopically guided technique is performed. The specific technique (transforaminal vs. intralaminar) is chosen based on patient anatomical considerations, MRI findings, and physician experience.

Full informed consent for the procedure is obtained. Prior to the procedure, an intravenous line is placed. Procedural sedation is provided on an as-needed basis for patient discomfort. Pulse oximetry and cardiac monitoring are utilized throughout the procedure. The participant is placed on the procedure table in the prone position. Fluoroscopy is utilized to visualize spinal anatomy. Following sterile preparation, the area overlying the target is identified. Local cutaneous anesthesia is administered. For transforaminal injections, an appropriate spinal needle is then advanced towards the inferior mid-point of the corresponding pedicle. Needle placement is confirmed with anteroposterior and lateral fluoroscopic views. Contrast is then instilled and flow along the nerve sheath is confirmed. An aliquot of 1 ml 2% lidocaine is instilled and allowed to sit for 60 seconds. 1 ml Kenalog (triamcinolone 40 mg/ml) is then instilled. For interlaminar injections, an appropriate needle is advanced into the epidural space using loss-of-resistance technique. Needle placement is confirmed with anteroposterior and lateral fluoroscopic views. Contrast is then instilled and flow within the epidural space is confirmed. An aliquot of 2 ml Kenalog (triamcinolone 40 mg/ml) and 3 ml 1% lidocaine without epinephrine is instilled. The

precise amount of injected medications may be adjusted by the physician performing the ESI based on his/her clinical judgment at the time of the procedure; all changes will be recorded. The patient is observed until stable and then discharged from the recovery area in the presence of their chaperone. An electronic or hard copy of AP and lateral fluoroscopic images documenting contrast flow is retained. In addition to the standard procedure note documentation in the physician records, the following variables will be collected: procedure performed (including side and site of needle entry), description of final contrast pattern, presence or absence of concordant pain provocation, and straight-leg raise test pre-procedure and at discharge. The Research Assistant then ensures that all study-related protocols are observed and that the participant understands his/her tasks over the ensuing follow-up period.

## **6.0 STUDY PROCEDURES**

### **6.1 FIRST CONTACT**

For patients referred directly from a primary care clinic, the clinic staff will first be notified of a potential participant by a call to the SpectraLink BACK phone. The physician accepting the call will quickly assess if the patient might be appropriate for the study and, if so, fill out the patient's contact information on the study-provided 3x5 card and hand the card to the Clinic Research Assistant (RA). The RA will then conduct an electronic pre-screen, searching for exclusion criteria present in the patient's chart. The RA will identify the patient as potentially eligible or ineligible on the Physician Communication Contact Sheet and place it in the box (along with the electronic pre-screen form) behind the receptionist. The receptionist will schedule the patient to be seen either later that day (if an opening with a study physician is available) or the next day and order the patient's L/S spine x-ray.

### **6.2 ELIGIBILITY VISIT**

The patient will be seen for their initial spine-clinic visit and fill out the usual clinic intake forms which includes the ODI. The RA will retrieve the ODI and correct the Physician Communication Contact sheet if necessary (i.e., if participant was previously listed as "potentially eligible" but has an ODI score <30). The patient will then see the study physician who will complete the Physician Pre-Screen Form. The physician will assess additional eligibility criteria and, if the patient appears to be eligible, introduce the study to the patient. If the patient expresses an interest in participating, the study physician will then transfer the patient to the RA.

The RA will then escort the patient to a private examine room, where the videoconference consent will be administered. Once the patient has signed the consent form, the RA will conduct the eligibility interview. If no exclusions are identified at this point, the participant will be scheduled for an L/S spine MRI as soon as possible, but no later than fourteen days from the eligibility interview. Once the

MRI is completed, the RA will contact a spine-clinic physician and the designated radiologist to read the MRI. If a compatible disc lesion is observed, the participant will return to the clinic that day for the randomization visit.

### **6.3 RANDOMIZATION VISIT**

At this visit, all eligibility criteria will be checked and, if the patient is still interested in participating, the study medications will be provided at this time. The clinic RA will retrieve the next sequentially numbered study-medication bottle from the pharmacy, along with all of the patient's concomitant medications (acetaminophen, narcotic analgesic (typically Vicodin), and, if ordered by the physician, a muscle relaxant). Participant will be instructed in how to fill out the pain/medication diary, and study procedures and calendars will be reviewed with the participant. The study medication will then be placed in the provided Medi-set, according to the patient's weight and day of the week. The RA will then give the study Medi-set to a study physician or nurse who will then hand it to the participant.

### **6.4 3-WEEK PRIMARY OUTCOME VISIT**

The participant will return to the clinic three weeks from the randomization visit in order to access all of the primary outcome variables. The participant will have been instructed (and reminded) to bring their pain diary and medications with them to their clinic visit. At this visit, all of the 3-week study instruments will be administered and the participant will see a study physician for further outcome measurements and to assess their clinical status. In addition, an assessment of the need for a study-mandated ESI will be done. If an ESI is indicated, the participant will be given an appointment to see the interventional pain specialist; if it is not indicated, all future study-mandated ESI appointments and ESI follow-up visits will be cancelled (note: a participant may still receive an ESI if they do not meet study criteria, if the study physician feels it is indicated; similarly, a participant who meets criteria for an ESI may not undergo the procedure if the study physician does not feel it is indicated). Finally, the participant will be given a medication log to complete over the following four-to-six week follow-up period.

### **6.5 6-WEEK FOLLOW-UP TELEPHONE CALL**

At six weeks from the point of randomization, the participant will be called at home and all 6-week follow-up instruments will be administered during the call. In addition, an assessment of the need for a study-mandated ESI will be done. If an ESI is indicated, the participant will be given an appointment to see the interventional pain specialist; if it is not indicated, all future study-mandated ESI appointments and ESI follow-up visits will be cancelled (note: a participant may still receive an ESI if they do not meet

study criteria, if the study physician feels it is indicated; similarly, a participant who meets criteria for an ESI may not undergo the procedure if the study physician does not feel it is indicated).

## **6.6 12-WEEK FOLLOW-UP TELEPHONE CALL**

At 12 weeks from the point of randomization, the participant will be called at home and all 12-week follow-up instruments will be administered during the call.

## **6.7 24-WEEK VISIT**

At 24 weeks from the point of randomization, the participant will return to the study clinic where he/she will complete all 24-week study follow-up instruments and undergo a final physical examination by a study physician.

## **6.8 52-WEEK FOLLOW-UP TELEPHONE CALL**

At 52 weeks from the point of randomization, the participant will be called at home and all 52-week follow-up instruments will be administered during the call. The participant will be thanked for their contributions to the study.

## **7.0 ADVERSE EVENT REPORTING**

### **7.1 CLASSIFICATION OF ADVERSE EVENTS**

The ACT FAST study uses the definitions of an adverse event (AE) and a serious adverse event (SAE) established in the International Conference on Harmonization (ICH) guidelines on Clinical Safety Data Management. These definitions are:

**An adverse event** (also known as “non-serious adverse event”) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Note that changes in the outcomes measures of the study (e.g., the ODI, pain and scores) are not considered adverse events and will not be reported as such. Symptoms or other abnormalities that were present prior to a participant’s starting study medication will not be considered adverse events; similarly, therapies (e.g., surgery) to treat a pre-existing condition are not reportable

adverse events. Note that clinically meaningful *worsening* of a pre-existing condition is considered an adverse event and should be reported as such.

**A serious adverse event** is any untoward medical occurrence that at any dose:

- 1) results in death
- 2) is life-threatening
- 3) requires inpatient hospitalization or prolongation of existing hospitalization
- 4) results in persistent or significant disability/incapacity
- 5) is a congenital abnormality or birth defect
- 6) is a cancer
- 7) is an important medical event that may not result in death, be life-threatening or require inpatient hospitalization if, based on appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent a serious adverse event.

## **7.2 REPORTING OF SERIOUS ADVERSE EVENTS**

While the ACT FAST study will not be conducted under an FDA IND, we will observe similar reporting requirements for SAE's. For fatal or life-threatening SAE's, the IRB will be notified (e.g. by telephone, fax, or in writing) within 24 hours and the DSMB (via KAI) within 48 hours after first knowledge of a fatal or life-threatening SAE. A complete report with any additional details will follow within 8 additional calendar days. For all other SAE's, (those that are not fatal or life-threatening) a report will be filed as soon as possible but no later than 15 calendar days after the first knowledge of the event. Reporting will use the standard KFRI IRB form along with any supporting documentation. All SAE's will also be recorded on the ACT FAST study SAE form in the Velos system.

## **7.3 REPORTING OF NON-SERIOUS ADVERSE EVENTS**

All non-serious AE's will be recorded on the AE study form. All AE's will be reported in aggregate and individually to the IRB annually and to the DSMB on a schedule that will be determined by the DSMB.

## **7.4 CRITERIA FOR TREATMENT DISCONTINUATION**

Any participant who exhibits a serious untoward reaction to a study intervention that, in the opinion of the investigators or the participant's treating physician, would render study continuation contrary to the best interest of the participant will be withdrawn from study medications or further interventions. This determination will be made without knowledge of the randomization assignment and the randomization code will not be broken for that participant (unless necessary for safety reasons; in this case, the Research Pharmacist will communicate the unblinded randomization assignment to the relevant

individuals and the study investigators and staff will remain blind). Any participant who is withdrawn from study interventions will be encouraged to continue to keep all study visits and interviews, in order to permit an intention-to-treat analysis with minimal data imputation. Given the short duration of the intended treatment period (15 days), re-challenge with the study medication will, in general, not be attempted.

## **7.5 CRITERIA FOR STUDY DISCONTINUATION**

All participants will be encouraged to keep all study visits even if they discontinue study medications, in order to permit an intention-to-treat analysis. If a participant expresses an intention to withdraw from the study, he/she will be questioned about the reasons for their intended withdrawal and attempts at resolving barriers to continued participation will be made (e.g., providing transportation, increasing contact with study investigators, shortening questionnaire time). Any participant may withdraw entirely from the study at any time.

## **8.0 STATISTICAL AND DATA CONSIDERATIONS**

### **8.1 POWER CALCULATIONS**

As noted, the primary endpoint is participants' functional status at three weeks post-randomization (measured by the ODI). In order to ensure that this trial is adequately powered, we have made several conservative assumptions.

First, we have adjusted the final alpha level down to 0.0471 in order to allow for up to two interim analyses, if requested by the DSMB. This alpha value was determined using the O'Brien-Fleming group sequential design that allows for interim analyses while constraining the overall experimentwise alpha to 0.05 (107, 108).

Second, we used only literature-based estimates for the variance of the change in ODI scores and took the mean, not the smallest, value for this parameter (102, 109-111).

Third, we have assumed a 20% drop-out rate. While we expect fewer than this for the short-term primary endpoint, we have used this larger figure in order to account for potential drop-outs in the long-term (24-week) follow-up component.

Finally, we have chosen a value of 7.0 points for the minimum clinically important difference (MCID) in ODI scores. This value is consistent with an extensive review of the literature (109-116).

The following describes the methods and assumptions used for calculation of the necessary sample size for this study (power calculations were performed with the PASS power-analysis package (117)):

Ho: There is no difference in the change in the ODI scores between two treatment groups.

Alpha: 0.0471 (two-tailed)

Beta: 0.1 (Power=90%)

Clinically relevant difference in ODI change scores: 7.0

Standard deviation of change in ODI scores: 15.1

Randomization ratio: 2:1

Statistical test on which calculations are based: Student's t-test

Number of participants required to demonstrate statistical significance = 151 in the active-treatment group and 75 in the placebo group; Total number required (two arms) = 226

Number of participants required after accounting for 20% withdrawals = 270

Based on a projected accrual rate of 8-10 participants per month, we anticipate that we will require approximately 2.25 - 2.5 years to fully recruit to this trial.

## **8.2 STATISTICAL ANALYSIS PLANS**

The primary analysis is a comparison of the difference in change scores (from randomization to the three-week follow-up visit) on the ODI between two treatment groups. With 100 potential levels, the ODI score will be treated as a continuous variable (118) (though we will verify the validity of this assumption by repeating the major analyses using rank-order statistics).

The primary analytic strategy will be an analysis of covariance model, always including adjustment for the two baseline stratification variables (clinical site and participant's weight). In practical terms, we will use a multivariable linear regression model in which the dependent variable is the three-week ODI score and the independent variables include the baseline ODI score, a treatment group indicator, the clinical site, and a dichotomous variable indicating the participant's weight (above or below the 65 kg cutoff value).

All analyses will be checked for violations of the modeling assumptions. The linearity assumption will be checked by creating scatterplots of each continuous independent variable against each continuous outcome. If a plot indicates significant deviation from linearity, appropriate transformations will be employed in order to achieve acceptable model fit for that particular independent-dependent variable combination. From a purely frequentist perspective, it is not necessary to adjust for imbalances in baseline variables in the setting of randomization; however, we will include adjustment for any baseline covariates that show substantial imbalance (note: these will include all significant baseline differences and any other variables that appear substantially imbalanced, even if not statistically significantly different). We will also examine the models for evidence of multicollinearity and the presence of outliers or highly influential observations.

Those secondary endpoints that are measured as the difference in values between baseline and the three-week visit will be analyzed in a manner analogous to the primary endpoint (i.e., three-week changes in the SF-36, amount of concomitant pain medication).

All other endpoints have more than two determinations: these include the NRS pain diary during the initial three-week follow-up period and all outcome measurements over the 52-week follow-up period (over which each participant will contribute up to six observations for each outcome). These outcomes will be analyzed with linear mixed-effects models (119) that include terms for the effects of time, study group and the group-by-time interaction which will serve as the primary statistical test of the study hypotheses. Subjects will be included as random effects, and the within-subject correlation modeled appropriately. The most appropriate error structure will be chosen by comparing model fit using Akaike's Information Criterion (120). The overall difference between two total response curves will be tested with likelihood-ratio tests. We will also examine the assumption of linear time effects of these models by creating profile plots, and make appropriate transformations as necessary. The predicted (modeled) change in each outcome over the relevant follow-up period will be obtained from each model along with the associated standard errors from which 95% confidence intervals will be constructed.

The linear mixed models have several advantages for these analyses. First, it is straightforward to implement an intention-to-treat analysis in that each participant contributes to the analysis all data collected from them with no need to impute missing data; those who complete more outcome assessments will contribute proportionally more information. Second, the models will permit analysis of the *course* of response to each treatment, not simply a comparison of the simple change scores for each arm. This ability is particularly important as the time course of response to each therapy may differ between study arms.

Finally, a comparison of the incidence of back surgery between each of the arms will be carried out with survival-analytic techniques. The basic, unadjusted analysis will consist of creating Kaplan-Meier survival curves for two treatment groups, then comparing them using log-rank tests (121). These analyses are robust and make few assumptions about the data structure. If multivariate analyses are required (e.g., if there are baseline differences in covariates between treatment groups), we will use Cox proportional-hazards models. Overall assessments of model fit will be performed using the test described by May and Hosmer (122). In this procedure, each observation is assigned a predicted risk based on its covariate values. Observations are then placed in groups of approximately equal size (with the number of groups being at least 6 to less than the number of events divided by 5 (123)). Next, a set of dummy variables is created for the grouping variable and each observation is assigned to the appropriate group. Finally, the model is re-fit using the new dummy variables and compared to the original model with a likelihood ratio test.

Importantly, we have defined a large number of secondary comparisons and the possibility of a Type I error must be explicitly considered; we have not adjusted the alpha level for the total number of comparisons to be tested in this study. While this is an area of some controversy (124), we believe that the analysis of these data would be best served not by stringent overall alpha adjustments or by elimination of important clinical comparisons, but by careful evaluation and cautious interpretation of the analyses, with the full recognition of the problems inherent in multiple-hypothesis testing.

All analyses will be performed under the principle of intention-to-treat, in which participants will remain in the groups to which they were randomized for the purpose of analysis. Because there are only two time-points for the primary endpoint, a final value must be imputed for each withdrawal. We will use a multiple-imputation procedure (118) for this process.

Whether or not interim analyses will be performed will be decided by the DSMB. We have powered this study to permit two interim analyses so an adequate sample size will be available should the DSMB request unblinded interim looks at the data. If unblinded interim analyses are requested, they will be performed by an analyst who is not associated with the study and the results forwarded to the DSMB without access by the study staff and investigators.

### **8.3 DATA QUALITY CONTROL**

All data collected for this trial will be stored in Velos™, a secure, web-based data collection application that employs full range and logic checking (and that is currently in use at KPNC DOR); the application uses an Oracle® backend database. The advantages of computer-based data-collection systems include more complete data collection (since it is not possible to inadvertently skip a question), more accurate data collection (since illogical and impossible responses are identified and “cleaned” in real time), the ability to permit entirely current data assessments, and strong protection of study data security and confidentiality. Study investigators and staff will review data reports bi-weekly to ensure that data collection is proceeding appropriately.

To ensure integrity and consistency of recruitment, randomization, interventions, data collection, and follow-up procedures, a detailed Manual of Operations and Procedures will be prepared and distributed to all study personnel. Pretesting of the procedures manual will be carried out in the pilot phase to ensure that instructions are complete, lucid, and precise. Extensive pilot testing of all procedures (from recruitment to data entry) will be completed prior to enrolling participants into the full trial.

Dr. Harley Goldberg, as the PI, is responsible for the overall implementation and conduct of the study and takes primary responsibility for all clinic-related activities. Dr. Avins, who is based at the KPNC DOR, will take primary responsibility for all data coordination and reporting. All study staff will have regular face-to-face meetings (at the clinical sites) at which time all issues related to study progress

will be discussed and procedures refined and documented. The study programmer/analyst will prepare bi-weekly reports of all critical information including recruitment rates and targets, visit and intervention adherence, completeness of data collection, serious and non-serious adverse events, and all protocol violations and deviations. Reports of incomplete data will be reviewed by the study team on a regular basis to ensure that data acquisition is complete, accurate, and proceeding on schedule. Any evidence of systemic problems in data collection will be resolved quickly.

#### **8.4 DATA AND SAFETY MONITORING PLAN**

All data and safety issues will be reviewed by all study investigators and study staff at each biweekly staff meeting.

A Data and Safety Monitoring Board (DSMB) has been established by the NIAMS for this trial and will be coordinated by KAI, Inc. The composition of the DSMB has been determined by NIAMS program officials. The DSMB met May 20, 2008 and June 20, 2008, and approved the protocol and approximately every six months will review study progress and safety data. A DSMB report will be prepared prior to each meeting; this report will include both blinded and unblinded data if requested by the DSMB (if unblinded data are requested, these data will be prepared by an analyst not associated with the study). Adverse-event monitoring and withdrawal of participants are discussed above (Sections 6.1 - 6.5).

#### **9.0 ETHICAL CONSIDERATIONS**

##### **9.1 INFORMED CONSENT**

The principles of informed consent described in Food and Drug Administration (FDA) regulations (21CFR part 50) will be followed. IRB approval of the protocol and the consent form will be given in writing. This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB. Written informed consent will be obtained from the participant, who will be given ample time to study the document and encouraged to ask questions. The informed consent will describe the purpose of the study, the procedures to be followed and the risks and benefits of participation. A copy of the consent form and the Research Subject's Bill of Rights will be given to the participant.

##### **9.2 CONFIDENTIALITY**

Data will be collected using the Velos electronic data capture and clinical-trial management system. The Velos application is fully HIPAA and 21CFR Part 11 compliant and maintains a high level of security and confidentiality for the study data. Access to the study data is limited to study personnel only, and can only be accessed through a highly secure password-protected interface. All accessing of and

changes to the data are audited and recorded. Data will be stored on secure servers located behind a firewall at the KPNC DOR with nightly redundant backups. All study-related data will be stored on secure servers, not on personal computers. All computers used to access the KPNC intranet will follow standard access-protection procedures, including regular changing of passwords and formation of an audit trail; prior to conduct of the study, all procedures will be tested to ensure that the implemented security procedures cannot be circumvented or defeated. All study personnel will undergo required HIPAA training (certification of successful completion of HIPAA training is a requirement for employment at KPNC).

The minimal study data collected on paper forms (e.g., consent forms, source documentation for serious adverse events, etc.) will be stored in locked file cabinets in a secure location at the KPNC Division of Research. Only authorized study personnel will have access to the file cabinets, which are located in secure sections of the DOR, behind locked doors requiring electronic card access.

Protected Health Information (PHI) will be closely guarded and never shared with individuals outside of the research staff, unless compelled to do so by regulation or law. Such data include any study-related forms that contain any of the 18 HIPAA identifiers. No PHI will be disclosed in any publications or presentations as a result of the work from this study. No PHI will be used in the analysis datasets, as it is not necessary (conforming to the “minimum necessary” standard).

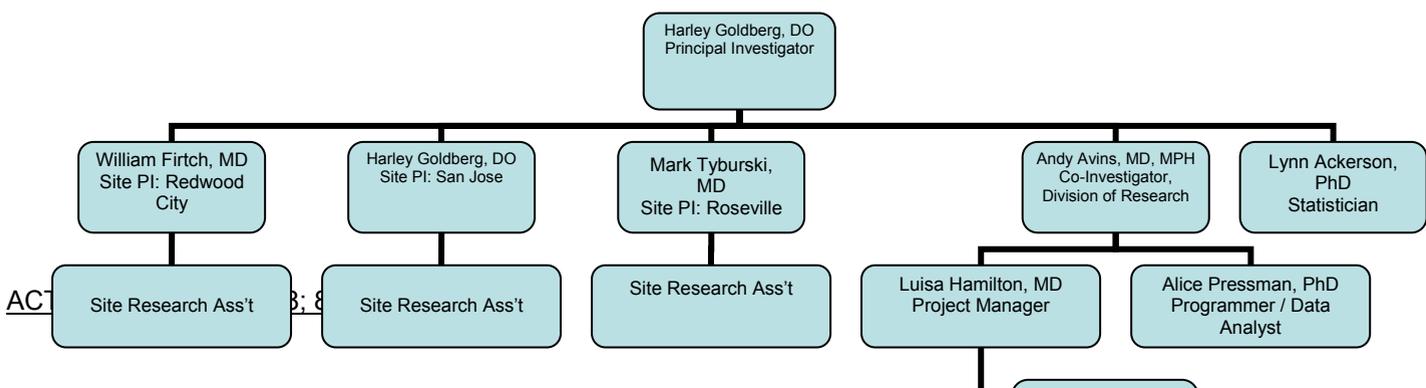
### 9.3 GENDER AND MINORITY INCLUSION

Based on KPNC administrative data and member health surveys of patients reporting a history of back pain, it is anticipated that our final sample will be approximately 58% women, 12% Latino, 10% African-American, 12% Asian, 3% Native American, and less than 1% Native Hawaiian or Pacific Islander. Therefore, we predict that the majority of our participants will be women and that approximately one-third of our sample will belong to a minority group.

## 10.0 STUDY ADMINISTRATION

### 10.1 ORGANIZATIONAL CHART

The organizational and reporting structure of the project is shown below:



## **10.2 CLINICAL SITES**

### **10.2.1 THE KPNC, SAN JOSE CLINICAL SITE**

The Physical Medicine and Rehabilitation Department in the San Jose Medical Center is located in Suite 310, 275 Hospital Parkway, San Jose, CA. It consists of offices for 5 full-time physicians, 4 part-time physicians, and 4 medical assistants, as well as the nurse manager. It is conjoined with the Department of Orthopedic Spine Surgery, which is of similar size and configuration. Thirty to forty patients per day are routinely seen for a variety of conditions within the scope of physical medicine and rehabilitation. Spine care is the primary focus of clinical care. All spine diagnostic and treatment procedures are included in the scope of practice, including appropriate medications and interventional procedures. Close working relationships exist with the Departments of Orthopedic Spine Surgery, Radiology, and Pain.

### **10.2.1 THE KPNC, REDWOOD CITY CLINICAL SITE**

The Physical Medicine and Rehabilitation Department in Redwood City is a full scope-of-practice department, with inpatient neurorehabilitation services, and outpatient services. The greatest volume of outpatient services are Spine Clinic services, which include all interventional procedures for the spine. The department is located proximal to the Physical Therapy program, and on campus with the Neurosurgery services program. There are 5 full-time physiatrists with a full complement of support staff seeing approximately 30 patients per day.

### **10.2.3 THE KPNC, ROSEVILLE CLINICAL SITE**

The Physical Medicine and Rehabilitation (PM&R) Department in Roseville/Sacramento has eight PM&R specialists and one anesthesiologist and provides the full scope of PM&R services. The PM&R department has two main branches, one in physical medicine and one in neurological rehabilitation. The greatest volume of outpatient visits are non surgical spine care patients. In addition services include non-spine musculoskeletal care, amputee clinic, rehabilitation of brain injuries, stroke rehabilitation,

rehabilitation of spinal cord injuries, rehabilitation of other neurological conditions such as MS and Guillain Barré syndrome, spasticity management, and electrodiagnostic medicine. All spine diagnostic and treatment procedures are included in the scope of practice.

### **10.3 DATA COORDINATING CENTER**

The Data Coordinating Center resides at the Division of Research, Northern California Kaiser Permanente in Oakland, California. The data-related activities of the ACT FAST trial will be supervised by Drs. Avins and Ackerson, with the assistance of Dr. Hamilton and Dr. Pressman. The Coordinating Center will take responsibility for monitoring recruitment and data quality and regular reports of recruitment and issues related to data quality will be produced for monthly project meetings. In addition, the Data Coordinating Center will have responsibility for ensuring timely reporting of adverse event data, preparation of reports for the DSMB, and IRB renewals. As all data collection will be conducted with the Velos system which is housed at the Division of Research, the Coordinating Center will ensure that all data collection forms and systems are working appropriately.

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## APPENDIX 1: SCHEDULE OF EVALUATIONS

<b><u>VISIT:</u></b>	Elig Visit	Rand Visit	3 Wk Visit	6 Wk Tel Intvw	12 Wk Tel Intvw	24 Wk Visit	52 Wk Tel Intvw*
<b><u>PROCEDURE:</u></b>							
Informed Consent	•						
Eligibility Screening	•						
In-clinic administered forms	•		•			•	
Plain L/S spine X-rays	•						
Directed physical/neuro exam	•		•			•	
Randomization (meds dispensed)		•					
L/S Spine MRI (between elig and rand visits)	•						
Telephone Interview				•	•		•
<b><u>DATA COLLECTED</u></b>							
Demographics	•						
Oswestry Disability Index	•		•	•	•	•	•
Numerical Rating Pain Scale	•		•	•	•	•	•
Global Participant Assessment			•	•	•	•	•
SF-36	•		•	•	•	•	•
Work Absence / Disability			•	•	•	•	•
Surgery History			•	•	•	•	•
Analgesic Medication Assessment			•	•			
Epidural Steroid Injection Assessment			•	•			
Participant Randomization Perception			•	•	•	•	•
Adverse Event Assessment			•	•	•	•	•

**Key:**

Elig/Rand Visit = Eligibility / Randomization Visit

Interim = 3-week interim period between Elig/Rand Visit and 3-Week Visit

Wk = Week

Tel Intvw = Telephone Interview

L/S = Lumbosacral

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