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Implementation of Treat-to-Target in Rheumatoid Arthritis Through a Learning Collaborative

Results of a Randomized Controlled Trial

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Objective. **Treat-to-target (TTT) is an accepted paradigm for the management of rheumatoid arthritis (RA), but some evidence suggests poor adherence. The purpose of this study was to test the effects of a group-based multisite improvement learning collaborative on adherence to TTT.**

Methods. **We conducted a cluster-randomized quality-improvement trial with waitlist control across 11 rheumatology sites in the US. The intervention entailed a 9-month group-based learning collaborative that incorporated rapid-cycle improvement methods. A composite TTT implementation score was calculated as the percentage of 4 required items documented in the visit notes for each patient at 2 time points, as evaluated by trained staff. The mean change in the implementation score for TTT across all patients for the intervention sites was compared with that for the control sites after accounting for intracluster correlation using linear mixed models.**

Results. **Five sites with a total of 23 participating rheumatology providers were randomized to intervention and 6 sites with 23 participating rheumatology providers were randomized to the waitlist control. The intervention included 320 patients, and the control included 321 patients. At baseline, the mean TTT implementation score was 11% in both arms; after the 9-month intervention, the mean TTT implementation score was 57% in the intervention group and 25% in the control group (change in score of 46% for intervention and 14% for control; $P = 0.004$). We did not observe excessive use of resources or excessive occurrence of adverse events in the intervention arm.**

Conclusion. **A learning collaborative resulted in substantial improvements in adherence to TTT for the management of RA. This study supports the use of an educational collaborative to improve quality.**

Randomized controlled clinical trials have consistently demonstrated that a strategy of treating to target (TTT) results in better outcomes compared with usual care in rheumatoid arthritis (RA). Specifically, this strategy is implemented by using disease activity measures at every visit and escalating therapy in eligible patients with disease activity above the target level (1–8). This strategy is similar to those recommended for diabetes mellitus and hypertension: setting a target for treatment, measuring progress toward achieving the target regularly, altering treatments until reaching the target, and maintaining the target. The TTT strategy for RA is based on a number of principles and recommendations articulated by an international working group and embraced by a US-based professional

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society (9–11). These include identification of a disease activity target, recording of a disease activity score using a validated measure, and when appropriate, documentation of shared decision-making and reasons why TTT was not implemented.

Several lines of evidence suggest that TTT is not practiced consistently across rheumatology settings. The Consortium of Rheumatology Researchers of North America (CORRONA), the largest US-based RA registry, examined the management of patients at high risk of poor outcomes (i.e., with moderate disease activity and a poor prognosis or with high disease activity) (12,13). Despite having active disease, only one-third to one-half of patients, depending on their level of disease activity, received treatment changes over the subsequent 6–12 months. A large Australian cross-sectional study identified various reasons rheumatologists do not adjust RA treatments at visits where patients were found to have moderate or high levels of disease activity, such as irreversible joint damage and patient preferences (14).

Most attempts to align physician behavior with recommended management in chronic illnesses have demonstrated marginal benefits (15). While many studies have evaluated educational interventions for providers, methods are generally weak, and studies rarely report on adherence to guideline-based treatment (16). However, there is some limited evidence that quality collaboratives produce improvement (17). These collaboratives often include setting out principles that characterize best practices, forming teams that include health care providers and staff, rapid-cycle testing of changes in care that align with the agreed upon principles, frequent measurement of key indicators for care improvement, and collaboration across practice sites to share best practices (18). This process has been tested in many clinical settings and is often conducted as part of a group-based multisite educational collaborative, often described as a learning collaborative (19). Despite prior success with the care of diabetes mellitus (20), HIV (21), and childhood asthma (22), learning collaboratives have not been widely pursued in subspecialty medical care. We designed a learning collaborative for the purpose of improving care in patients with RA.

Since implementing TTT broadly requires health care delivery redesign across practices with different workflows and team members, we pursued a trial of a learning collaborative across 11 practices, the Treat-to-Target in RA: Collaboration to Improve Adoption and Adherence (TRACTION) trial. The goal of the TRACTION trial was to test the effectiveness of a learning collaborative for improving implementation of TTT principles in RA.

PATIENTS AND METHODS

Trial design. We conducted a cluster-randomized waitlist-controlled clinical trial to test the effects of the learning collaborative for TTT between January 2014 and October 2015. (The waitlist control sites received the intervention subsequent to October 2015.) We made contact with over 70 sites by e-mail and then interviewed 25 sites by telephone. Eleven US rheumatology practice sites were recruited to participate (see Appendix A); 9 were affiliated with academic medical centers, and 5 participated in rheumatology fellowship training programs. The 11 sites were diverse in geography, patient populations, and organization (for further site details, see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40111/abstract). None was actively engaged in TTT at baseline according to a baseline interview of the team leaders by the Principal Investigator (DHS), who asked about the 4 aspects of the outcome measure (see below).

Sites were randomized to active intervention or waitlist control. Four sites described using disease activity measures at baseline, and these were evenly distributed across arms through stratified randomization, which was achieved through a random-number generator provided by the study statistician (BL). Randomization occurred at the site level since the intervention targeted practice sites, not patients or individual providers. Sites and providers were not blinded with regard to their treatment assignment.

Research activities were approved by the Institutional Review Board of Partners Healthcare.

Patient sample. All study sites were given the same instructions for selecting patients. A sample of at least 40 patients with RA was provided by each site, representing patients from providers who attended at least 1 learning session and contributed to the monthly medical record review. A minimum of 5 patients per provider was required. Visits had to have occurred within the baseline and follow-up periods described below. The medical records of these patients were included in the final review by study staff, not local site personnel. Baseline visits were defined as the first visit during the 4-month period prior to the start of the intervention: September 1, 2014 to December 31, 2014. The follow-up visits were defined as the first visit during the last 4 months of the study period: September 1, 2015 to December 31, 2015.

Intervention. The intervention consisted of a learning collaborative, which we have described elsewhere (23). Briefly, the learning collaborative involved the faculty developing a set of principles and associated concepts that describe the goals for implementing TTT principles, referred to herein as just TTT (see Supplementary Figure 1, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40111/abstract). The concepts were used by the study sites to guide rapid-cycle tests of change. The principles and concepts were taught in the first learning session, which was conducted as a face-to-face 1-day meeting. The first learning session also aimed to facilitate team building by sites and cross-site collaborative relationships, and 8 subsequent monthly learning sessions were conducted via webinar. Each learning session included sites sharing a set of agreed upon metrics collected through a local medical record review. As well, a learning collaborative faculty member presented a question-and-answer session regarding the principles and concepts of TTT. More details of the learning sessions are provided in Supplementary Table 2 (available at http://onlinelibrary.wiley.com/doi/10.1002/art.40111/abstract).

We asked all team members from each site to attend all learning sessions, but this was not always possible. All learning sessions were recorded and made available on a web-based collaborative tool. The tool was developed using commercially available software (SharePoint by Microsoft) that helped manage contents being shared across teams (i.e., key resources, rapid-cycle tests of change), displayed monthly improvement metrics, and provided a discussion board with conversation "threads."

We reviewed the medical records (including visit notes, laboratory and radiology orders, and medication lists) of RA patients seen at the rheumatology practices involved in the learning collaborative from each site.

Outcome assessments. The primary trial outcome was the change in the composite TTT implementation score. The score included 4 items directly stemming from the principles and concepts of TTT: 1) specifying a disease activity target; 2) recording RA disease activity using 1 of 4 recommended measures (e.g., the Disease Activity Score in 28 joints, Simplified Disease Activity Index, Clinical Disease Activity Index [CDAI], or Routine Assessment of Patient Index Data 3 [RAPID3]), with results described numerically or by category (i.e., remission, low, moderate, or high) (24); 3) documenting shared decision-making when a decision was made (i.e., change in target or change in treatment); and 4) basing treatment decisions on the target and disease activity measure or describing reasons why TTT was not adhered to. Each item was recorded as absent or present based on a medical record review by trained study staff (interrater reliability $\kappa = 94\%$ [95% confidence interval (95% CI) 90–99], and intrarater reliability $\kappa = 98\%$ [95% CI 95–99]). We calculated the TTT implementation score for each patient as a percentage of TTT items noted in the visit notes at the baseline and follow-up visits.

Secondary outcomes were as follows: 1) percentage of patients with any positive change in implementation score between baseline and follow-up, and 2) proportion of patients with full implementation of all TTT items at follow-up. We assessed resource use by examining all visits for RA by patients in the sample over the 9-month study period. We examined the RA treatments used, the monitoring laboratory tests performed (i.e., complete blood cell count, liver function tests, or serum creatinine level), the levels of acute-phase reactants measured (i.e., erythrocyte sedimentation rate or C-reactive protein), and the diagnostic imaging performed (i.e., dual x-ray absorptiometry, plain radiographs, computed tomography scans, or magnetic resonance imaging). We also examined all visits during the study period for possible medication-related adverse events, such as rashes, oral ulcers, alopecia, infections requiring antibiotics, liver toxicity as manifested by abnormal findings on liver function tests and/or liver imaging studies, cytopenias as manifested by complete blood cell counts below the lower limits of normal, renal insufficiency as defined by a 50% decrease in creatinine clearance, cancer, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, unexplained weight loss/gain, abdominal pain, or dyspepsia), and other miscellaneous side effects.

Post hoc secondary outcomes included the percentage of visits at which there was a change in disease-modifying antirheumatic drug and the percentage of patients in the different disease activity categories at follow-up.

Statistical power considerations. This trial was powered based on the primary outcome: the estimated difference in change in the TTT implementation score between the intervention sites and the control sites. Several assumptions underpinned our sample size calculations. First, we assumed that the control group would have no or only a small change (5%) in the TTT implementation score during the 9-month period compared with a change in the intervention group of ~20%. These assumptions were based on the improvement level observed in a similar trial using a learning collaborative (25). Second, we knew that the average number of providers at each of the 11 practice sites would be 4 and that there would be moderate intracluster correlation among patients within a given provider and site; we assumed an intracluster correlation of ~0.2 based on previous work (26). Finally, the statistically significant alpha level was set at a 2-sided P value of 0.05. Based on these assumptions, we estimated that to ensure 80% power, the required number of patients per provider would be 5.

Statistical analysis. We hypothesized that adherence to the TTT would improve to a greater extent in patients seen at rheumatology sites randomized to the learning collaborative intervention as compared with control patients seen at the waitlist sites. Thus, the primary analysis compared the mean change in the TTT implementation score over 9 months across patients in the intervention sites as compared with the mean change for the patients in the control sites after accounting for intrasite and intraprovider correlation using linear mixed models (27). Any patient covariates that were imbalanced at the baseline visit were considered for the model, including age, sex, baseline disease activity, baseline RA drugs, and disease duration. For the secondary binary outcomes (e.g., improvement versus no improvement

Table 1. Baseline characteristics of the patients included in the TRACTION trial*

	Control (n = 321)	Intervention (n = 320)
Age, mean ± SD years	59.7 ± 14.3	60.2 ± 27.5
BMI, mean ± SD kg/m^2	30.1 ± 7.5	29.4 ± 7.5
Female	250 (77.9)	253 (79.1)
RA duration, years		
≤2	22 (16.1)	50 (25.6)
2–5	39 (28.5)	49 (25.1)
6–10	30 (21.9)	47 (24.1)
>10	46 (33.6)	49 (25.1)
Serologic status		
Positive	193 (76.3)	216 (81.5)
Negative	60 (23.7)	49 (18.5)
Use of DMARDs		
Synthetic	248 (77.3)	259 (80.9)
Biologic	131 (40.8)	148 (46.3)
Comorbidity index, mean ± SD	1.33 ± 0.6	1.28 ± 0.5
Joint erosion		
Yes	109 (53.4)	142 (59.7)
No	95 (46.6)	96 (40.3)
Total medications		
0	0 (0)	1 (0.3)
1–5	42 (13.1)	53 (16.6)
6–10	104 (32.4)	117 (36.6)
10+	175 (54.5)	149 (46.6)

* Except where indicated otherwise, values are the number (%). Data were missing for the following variables (similar distribution across treatment arms): age (n = 64), body mass index (BMI; n = 52), rheumatoid arthritis (RA) duration (n = 309), serologic status (n = 123), and joint erosions (n = 199). TRACTION = Treat-to-Target in RA: Collaboration to Improve Adoption and Adherence; DMARDs = disease-modifying antirheumatic drugs.

Table 2. Implementation of treat-to-target and components at patient visits in the TRACTION trial*

	Control (n = 321)			Intervention (n = 320)			*P* for difference in change
	Baseline	Follow-up	Change	Baseline	Follow-up	Change	
Primary outcome							
Implementation score	11.0	24.7	13.7	11.1	57.1	46.0	0.004
Visits with components present							
Treatment target	0	12.5	12.5	0.6	45.6	45.0	0.065
Disease activity measure	30.2	52.3	22.1	20.0	89.1	69.1	0.002
Shared decision-making†	24.5	43.0	18.5	51.3	85.9	34.6	<0.001
Treatment decision‡	0	8.4	8.4	0.6	27.8	27.2	0.064

* Values are the percentage. *P* values were calculated using linear mixed models for the primary outcome and generalized linear mixed models for binary outcomes for the components; both sets of models accounted for clustering within sites and within providers (28). TRACTION = Treat-to-Target in RA: Collaboration to Improve Adoption and Adherence.
† The shared decision-making criteria did not apply to all visits when no decisions were being made about changing targets or changing treatments. The number of visits when shared decision-making applied was 102 baseline visits and 100 follow-up visits for the control group and 115 baseline visits and 184 follow-up visits for the intervention group.
‡ Treatment decision based on target and disease activity measure.

and complete implementation versus incomplete implementation), we used generalized linear mixed models for binary outcomes that accounted for clustering within sites and within providers (28). Analysis of adverse events and resource utilization was performed using Poisson regressions for resource use and adverse events as the outcome variables. Similar to the primary analyses, we adjusted for intrasite and intraprovider correlations.

RESULTS

Study population. The Consolidated Standards of Reporting Trials (CONSORT) diagram in Supplementary Figure 2 (available at http://onlinelibrary.wiley.com/doi/10.1002/art.40111/abstract) shows that 1 site dropped out after randomization but before any activities began, leaving a total of 11 participating sites. The characteristics of the 641 patients with RA included in the trial are shown in Table 1. They represent a typical RA population, with a mean age of 60 years, 78% female, and 79% with at least 1 positive serologic test for RA. Patient characteristics were well-balanced across treatment arms. The structure, staff, and insurance mix were diverse and also well-balanced (see Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40111/abstract).

Trial outcomes. At baseline, the mean TTT implementation score was 11% in both arms. After the 9-month intervention, the TTT implementation score was 57% in the intervention arm and 25% in the control arm. The mean change was 46% in the intervention arm and 14% in control (*P* for difference in change = 0.004 from a linear mixed model) (Table 2). Each component of the TTT implementation score improved in the intervention arm, but not all improved to the same extent (Table 2). The proportion of participants for whom the presence of a treatment target was documented went from 0.6% at baseline to 45.6% at follow-up in the intervention arm. Recording of the disease activity increased from 20.0% to 89.1%; all sites used the CDAI or RAPID3 instrument. Shared decision-making started out at 51.3% in the intervention group and increased to 85.9%. While there was some improvement noted over time in the waitlist control arm, the improvement in implementation of each component of the TTT was not as large as it was in the intervention arm.

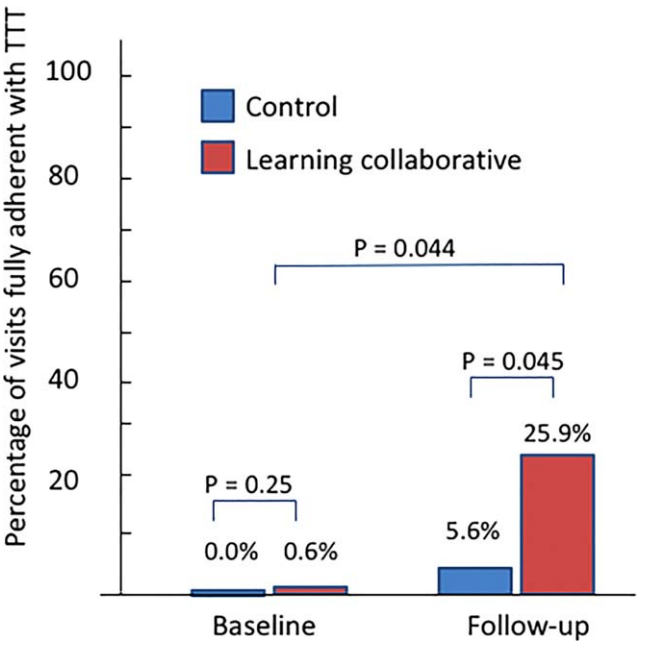

Figure 1. Percentage of visits at baseline and follow-up that were in full adherence to the treat-to-target (TTT) protocol, the secondary outcome of the Treat-to-Target in RA: Collaboration to Improve Adoption and Adherence (TRACTION) trial.

Table 3. Resource use and adverse events during the TRACTION trial*

	No. of tests or adverse events (mean no. per patient)	
	Control group (n = 321)	Intervention group (n = 320)
Monitoring laboratory tests†	2,614 (8.14)	2,591 (8.10)
C-reactive protein or erythrocyte sedimentation rate	788 (2.45)	607 (1.90)
Plain radiography of the musculoskeletal system	308 (0.96)	247 (0.77)
Computed tomography of the musculoskeletal system	6 (0.019)	12 (0.038)
Magnetic resonance imaging of the musculoskeletal system	14 (0.044)	16 (0.050)
Rheumatology visits	922 (2.87)	753 (2.35)
Adverse events‡	138 (0.43)	83 (0.26)

* *P* values were calculated using Poisson regression for the count data after accounting for clustering within sites and within providers (28). None of the *P* values were significant. TRACTION = Treat-to-Target in RA: Collaboration to Improve Adoption and Adherence.
† Consisted of a complete blood cell count and/or a basic metabolic panel and/or liver function tests.
‡ Adverse events in the intervention group and the control group included infections (n = 14 and n = 34, respectively), cutaneous reactions (n = 13 and n = 21, respectively), liver test abnormalities (n = 9 and n = 10, respectively), renal test abnormalities (n = 1 in the intervention group), gastrointestinal symptoms (n = 22 and n = 28, respectively), and other miscellaneous (n = 24 and n = 45, respectively).

Secondary outcomes differed across treatment arms. A positive change (of any magnitude) in the TTT adherence score was noted in 83.8% of patients in the intervention arm sites (268 of 320) and 36.8% in the control arm sites (118 of 321) ($P = 0.0001$). A similar trend was observed when visits were analyzed for having all components of TTT present versus fewer than all components (Figure 1). At baseline, almost no patient visits in either arm were adherent to all components of the TTT. At follow-up, the percentage of visits adherent to all 4 components was 25.9% in the intervention arm and 5.6% in the control arm ($P = 0.045$).

The number of orders for drug-monitoring laboratory tests was similar across the control (8.14 tests per patient) and intervention (8.10 tests per patient) arms ($P = 0.67$) (Table 3). Radiology orders were also very similar between the control (0.96 per patient) and intervention (0.77 per patient) arms ($P = 0.96$). Patients in the intervention arm were noted to have fewer adverse events (0.26 per patient) than those in the control arm (0.43 per patient) ($P = 0.043$) (Table 3).

We abstracted information on disease activity measures at follow-up visits from medical records when available and found that a numerically greater percentage of patients in the intervention arm were in remission: 40.5% in the intervention arm versus 26.1% in the control arm ($P = 0.07$). However, since the control arm was not instructed on disease activity measurement, this was measured in only 69 patients in the control arm but 284 patients in the intervention arm.

DISCUSSION

Treatment for RA does not always follow the recommended TTT approach. The TRACTION trial focused on improving implementation of TTT principles for RA using a learning collaborative approach to adopting new strategies and improving workflow. While TTT is a proven strategy in the care of RA, many areas of health care require a similar team approach for effective care. In this study, we found large benefits, despite using a relatively low-intensity approach to the learning collaborative, with only 1 face-to-face meeting.

The success of the TRACTION trial has potential implications beyond the care of RA. Effective management of diabetes mellitus and hypertension also requires a similar treatment approach: setting a treatment target (i.e., hemoglobin A_{1c} or blood pressure), with patient involvement, regular measurement of progress toward the target, and modification of treatments until the target is reached and maintained. While our learning collaborative focused on RA, it seems clear that the principles and concepts underlying this approach could be transferred to other chronic diseases. In fact, our model is consistent with the goals and strategy of the Million Hearts campaign to reduce cardiovascular disease burden across the US by targeting 5 areas of goal-based therapy (29). The program we used for this learning collaborative included only 1 face-to-face meeting but still produced excellent results. Further evaluation of learning collaboratives of different intensities will improve our understanding of how to best fit these improvement programs into the lives of busy health care workers.

While the TRACTION learning collaborative improved the use of TTT for RA, implementation remained far lower than desired, and several previous studies suggest potential reasons. A survey of Australian rheumatologists found that they preferred not to adjust medications for symptoms when they were perceived to be associated with irreversible joint damage (14). Some might argue that this is a defensible position that could avoid overtreatment. They also cited patient preferences as justification for not adjusting treatments. It may be the case that more engagement of patients regarding the choosing

of targets and identifying the best treatments would affect patient preferences.

The TRACTION trial was a pragmatic cluster-randomized controlled trial, with a waitlist for the control arm. This design is often used in quality improvement, and it has associated strengths and limitations. While the trial was appropriately powered, it included only 11 rheumatology practice sites in the US. The sites were geographically diverse and represented different types of practices (academic and non-academic); however, the ability of the TRACTION learning collaborative to produce similar changes in other settings requires further testing. The majority of TRACTION sites were affiliated with an academic medical center, and the results may not be generalizable across all types of practices. In addition, the intervention required ~20 hours per provider over 9 months, which may limit its generalizability.

The primary outcome of the TRACTION trial was a process measure and does not reflect clinical outcomes. The process measure appears to be valid, however, as at least 7 prior trials have demonstrated improved outcomes in RA using a TTT approach (30). We appreciate that the outcome measure for implementation of TTT was developed for this trial since no valid measures for TTT have been published. However, the 4 items were based on the original TTT recommendations to ensure face validity. The developer of the TTT recommendations (JSS) agreed that the 4 aspects of TTT that we were able to measure from chart review were essential to assuring content validity (i.e., the extent that a measure represents the full range of the construct). The measure had good reliability, as indicated by the interrater and intrarater kappa values ($\kappa > 0.9$), but it is a clear limitation that the primary outcome of the trial was not based on a previously validated measure. Disease activity was measured at baseline in only a minority of patients, which limits our understanding of whether implementation of TTT significantly improved disease activity over the course of the trial.

The TRACTION trial staff reviewed medical records to avoid the potential bias of self-assessment. However, the staff was not blinded with regard to the assignment of sites to the intervention or control arms. The high intrarater and interrater reliability values suggest that the outcomes measure, which was assessed at 2 visits, was highly reproducible. A final limitation is that adverse events were collected from chart review and thus could have been biased if providers in different treatment arms differentially reported adverse events. Since providers were not aware of our hypotheses regarding adverse events, this seems unlikely.

In summary, we found significant improvements in adherence to TTT principles in rheumatology practices participating in a learning collaborative. Future work will include dissemination activities with professional organizations to make this opportunity more widely available for other interested rheumatology practice sites. Similar efforts with learning collaboratives for RA are ongoing (31), and our results support considering this approach for other chronic diseases that benefit from TTT strategies.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Solomon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Solomon, Losina, Lu, Agosti, Bitton, Harrold, Pincus, Radner, Smolen, Fraenkel, Katz.

Acquisition of data. Solomon, Zak, Corrigan, Lee, Agosti, Bitton, Pincus, Radner, Smolen, Fraenkel, Katz.

Analysis and interpretation of data. Solomon, Losina, Lu, Yu, Katz.

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APPENDIX A: RHEUMATOLOGY SITES PARTICIPATING IN THE TRACTION TRIAL

The following rheumatology sites and their teams participated in the TRACTION trial: Cedars Sinai Medical Center (Los Angeles, CA): Venturapali, Gaggi, Uy, Bustos, and Vasquez; Loyola University Medical Center (Maywood, IL): Tehrani, Ostrowski, Briones, and Murphy; NorthShore University Health System (Evanston, IL): Grober, Malik, Woodrick, Lynn, Sun, Drevlow, Zaacks, Bilbrey, Chavez, Casey, Gan, and Myers; Park Nicollet Health Services (St. Louis Park, MN): Paisansinsup, Shousboe, Glickstein, and Steele; University of Texas (Houston, TX): Scholz, McCray, Barnes, Tan, and Homann; Kansas University Medical Center (Kansas City, KS): Lindsley, Schmidt, Colbert, Springer, Bhadbhade, Parker, Estephan, McMillian, and Heneghan; University of Kentucky (Lexington, KY): Lohr, Hanaoka, Lightfoot, Jenkins, Baker, Bisono, Wafford, Wiard, Lenert, and Howard; University of Vermont (Burlington, VT): Hynes, Bethina, Kennedy, Lau, Edwards, Libman, and Farely; University of Virginia (Charlottesville, VA): Kimpel, Lewis, D'Souza, Potter, Carlson, Mosteanu, Khalique, Khurana, and Swamy; University of Texas Medical Branch (Galveston, TX): Murthy, Musty, Rudrangi, Ganti, Gonzalez, and McCullum; and Vanderbilt University (Nashville, TN): Annapureddy, Kroop, and Hayden.