TITLE: Phase III Trials of Enhanced Versus Usual Care Physical Therapy for Patients at Risk for Poor Outcome Following Knee Arthroplasty: A Perspective on Meaning and a Way Forward

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[H1]**Abstract**

Physical therapy is routinely delivered to patients after discharge from the hospital following knee arthroplasty (KA). Posthospitalization physical therapy is thought to be beneficial, particularly for those patients most at risk for poor outcome, the subgroup with persistent function-limiting pain despite an apparently successful surgery. Research teams have undertaken 3 large-scale multicenter Phase III randomized

clinical trials designed specifically for patients at risk for poor outcome following KA. All 3 trials screened for poor outcome risk using different methods and investigated different physical therapist interventions delivered in different ways. Despite the variety of types of physical therapy and mode of delivery, all trials found no effects of the enhanced treatment as compared with usual care. In all cases, usual care required a lower dosage of physical therapy as compared with the enhanced interventions. This Perspective compares and contrasts the 3 trials, speculates on factors that may explain the no-effect findings, and proposes areas for future study designed to benefit the poor outcome phenotype.

[H1]Introduction

Knee arthroplasty (KA) is regarded worldwide as being both a highly effective and cost effective surgical procedure.[1] Cohort studies consistently show reductions in knee pain and improvements in self-reported function on the order of 50% to 85%, from preoperatively to 1-year following surgery.[2,3]

Despite being a highly effective pain-relieving procedure when considering large samples of patients, a substantial number of individuals experience poor outcome despite an apparently successful surgery. While definitions vary,[4] poor outcome has generally been defined as persistent function-limiting knee pain, or compromised everyday life activity following surgical recovery.[5] Estimates indicate that approximately 20% of patients undergoing KA experience poor outcome.[6,7] In the US, for example,

assuming 20% of patients experience a poor outcome, this equates to 200,000 patients with poor KA outcome, assuming approximately 1 million KAs per year.[8]

This poor outcome phenotype is a substantial challenge for clinical management and is a high research priority. For example, identification of effective treatments for persistent pain following KA was ranked in 2020 as the highest research priority by the British Association for Surgery of the Knee and the James Lind Alliance.[9]

The focus of this Perspective is on clinical trials that have tested potentially effective physical therapist treatments for the poor outcome phenotype. These trials are likely of strong interest to orthopedic surgeons, rheumatologists, other physicians treating patients with knee pain and physical therapists because patients with persistent pain are challenging to treat, a driver of care seeking and likely contributors to high costs. Well-designed pragmatic trials of physical therapy for the persistent pain population have potential to define the type and dosage of physical therapy that benefit these patients.

Our research teams have recently published 3 multicenter Phase III randomized clinical trials of physical therapist interventions specifically targeting patients with KA at risk for poor pain/function outcome.[10–12] We are not aware of other Phase III physical therapy trials that specifically targeted the poor outcome phenotype but we did not systematically search all potential databases. Rather, the focus of this Perspective is on our recently published trials. Our 3 trials, known by the acronyms COmmunity based Rehabilitation after Knee Arthroplasty (CORKA),[10] Knee Arthroplasty pain coping Skills Training (KASTPain)[12] and Targeted Rehabilitation to Improve Outcome (TRIO)[11] found no differences in outcome among the treatment arms, despite strong theoretical

foundations,[13,14] and pilot data[15] endorsing the potential benefit of enhanced physical therapy. The enhanced interventions in our trials were compared to usual outpatient physical therapy[10] usual outpatient and home-based physical therapy[12] or minimally supervised home exercise.[11]

The consistent no-effect finding of enhanced physical therapy in our trials was a surprise for 2 reasons: (1) there were strong theoretical arguments for therapeutic effects of the interventions of interest and; (2) the samples studied represented those with the greatest need and were likely to demonstrate substantial benefit from the enhanced intervention relative to usual care physical therapy. Our purpose is to compare and contrast our 3 clinical trials of enhanced physical therapy designed specifically for the poor outcome phenotype, to suggest factors that may explain the no-effect findings, and to propose areas for future research directed toward improving poor outcome prediction and physical therapist treatment benefit for the clinically challenging and relatively common KA poor outcome phenotype.

[H1]Methods for Predicting Poor Outcome Risk

Poor outcome is generally defined as persistent function-limiting pain following recovery from apparently successful surgery.[6] Ideally, poor outcome prediction should rely on preoperative data to allow patients and surgeons to consider the surgical decision in the face of a poor outcome risk. Our trials relied either on 6-week postoperative data[11] or pre-operative data[10,12] to recruit patients. The TRIO trial[11] investigators required patients to have Oxford Knee Scores (OKS)[16] of ≤26 points at the 6-week postoperative time point. The OKS ranges from 0 to 48 with lower scores

indicating poorer daily activity and worse knee pain. Patients with OKS of 26 or less would report at least moderate difficulty and pain with most routinely performed daily activities. The TRIO trial relied on prognostic data by Rothwell et al[17] for the OKS cut point. Rothwell and colleagues used New Zealand joint registry data and found that patients with OKSs of ≤26 points 6 months post-surgery were at a ten-fold increased risk of revision during the following 2 years as compared to patients with OKS > 41 points.

The CORKA trial investigators developed a "poor outcome" clinical prediction prognostic model from preoperative data collected in the Knee Arthroplasty Trials (KAT), a series of 3 no-effect randomized trials of surgical implant comparisons (total *N* = 2352).[18] The KAT trial used OKS as the primary outcome. Because these were no-effect trials, data from all subjects were combined into 1 large group to generate a poor outcome prediction model.

The OKS cut point for poor outcome was defined as ≤26 points, 1-year following surgery. Of the 1708 patients with 1-year follow-up data, 389 (22.8%) were classified as having poor outcome. Potential poor outcome predictor variables were obtained preoperatively. After excluding non-significant predictor variables, the final predictive model included the following: body mass index, knee pain severity, American Society of Anesthesiologists (ASA) score, and extent of limitation in daily activities. Multivariable logistic regression odds ratios for each statistically significant predictor were rounded to the nearest integer and a cut point differentiating good versus poor outcome was based on the summed score of each predictor. The predictive model had a fair discriminatory

ability to predict a poor outcome from KAT, as measured by the area under the curve of 0.66 (95% CI = 0.64-0.69) in a receiver operating curve analysis.

Predictor variables from multivariable models like the one used in CORKA are designed to identify outcome predictors at the group level and not at the individual patient level. When using predictor variables to guide treatment, it would not be appropriate, for example, to attempt to reduce body weight in someone classified as poor outcome risk but with normal body weight. With this said, the CORKA and TRIO trial interventions were specifically designed for pain reduction and functional improvement, the 2 major poor outcome indicators.

Riddle and colleagues determined the prognostic significance of the Pain Catastrophizing Scale (PCS) by recruiting 140 patients with KA and following them for 6 months.[19] The study found that persons with PCS scores of >16 were 2.67 times more likely to have <50 improvement in WOMAC Pain scores 6-months post-surgery. The PCS ranges from 0 to 52 with higher scores equating to worse pain catastrophizing. Multiple studies have found that higher pain catastrophizing associates with poor outcome.[20–22] The KASTPain study investigators recruited 384 patients with KA who had moderate to high pain catastrophizing preoperatively, scoring ≥ 16 points on the Pain Catastrophizing Scale (PCS).[23] Mean preoperative PCS scores were 30 (SD = 9.3).

[H1]Interventions Used in Our Trials

Our trials were primarily pragmatic in design because they compared an enhanced physical therapist intervention to usual care physical therapy. The interest

was therefore on effectiveness over efficacy. A limitation of our trials is that there was no sham intervention arm to account for placebo and non-specific effects. Without a sham arm, the true effects of physical therapy cannot be determined. We also did not include a control (ie, no physical therapist treatment) group though it has been argued that it is unethical to provide no treatment to patients at risk for poor outcome.[11] The trial designs allowed us to determine whether the enhanced interventions were more effective than usual care physical therapy. The CORKA and TRIO trial enhanced interventions focused primarily on physical impairments (eg, knee range of motion, pain and strength) while the KASTPain trial focused primarily on psychologically based impairment (eg, pain catastrophizing).

The type of physical therapy in the 3 trials differed, as did the mode of delivery. The enhanced interventions in CORKA and TRIO[10,11] provided similar types of physical therapist care in that they were patient goal-driven and addressed key knee-related impairments known to be affected in persons following KA, including knee range-of-motion, strengthening, proprioception, pain and walking gait, balance training and functional task performance. In addition, both trials allowed for customization to address additional patient-specific impairments identified by the physical therapists. Mode of delivery differed for CORKA and TRIO. The enhanced intervention in CORKA was delivered in the patients' homes and included patient-guided home exercise while in TRIO the enhanced intervention was delivered in physical therapy clinics with additional instruction for exercise at-home. Patients in CORKA received 7 at-home sessions. In TRIO, patients underwent 6 sessions of outpatient physical therapy with individualized home exercise between sessions. In the CORKA and TRIO trials, usual care consisted

of instructions for at-home range-of-motion and strengthening exercise and, in addition, to up to 6 visits with a physical therapist.

KASTPain provided enhanced physical therapy via pain coping skills training, grounded in cognitive behavioral therapy principles. The intent was to reduce pain catastrophizing by providing patients with coping skills they could apply in daily life. Physical therapists were trained by highly experienced pain psychologists to deliver pain coping content and were monitored over the course of the study. Pain coping skills training was delivered in 8 sessions either in-person or via telephone. In addition, patients in all study arms (ie, pain coping skills, arthritis education attention control and usual care) underwent usual care physical therapy either at home, or in an outpatient clinic as is customary after KA. A brief summary of the interventions and recruitment criteria for each trial is provided in Table 1. Detailed characteristics of the interventions can be found in the published protocols.[13,14,24,25]

Several evidence syntheses and clinical practice guidelines have been published to guide the delivery of physical therapy for the population of patients undergoing KA[26–28]. No evidence syntheses were found that specifically examined evidence for treatment of the poor outcome phenotype. Evidence defining characteristics of persons experiencing poor outcome following KA is relatively new which may explain why guidance is lacking for treatment specifically targeting persons experiencing poor outcome. The current paper is, to our knowledge, a first attempt to summarize intervention evidence targeting the poor outcome phenotype.

[H1]Trial Findings and Potential Reasons for the No-effect Findings

Our trials found no differences between the enhanced interventions, and the usual care arms (see Fig. 1 for primary outcomes for each trial). These findings occurred despite methodologic similarities in the fundamental research questions across the trials but with added benefit of diversity in method of delivery, content, and settings. In our view, the two most likely explanations for a consistent no-effect were: (1) our prognostic approaches for selecting patients at risk for poor outcome were inadequate; or (2) the enhanced interventions were unable to lead to additional therapeutic benefit.

[H1]Criteria for Defining Poor Outcome May Have Missed the Target

Methods we used to screen potential participants may have missed patients from the population of interest. Alternatively, these methods may have falsely identified persons as being at risk for poor outcome. The end-result could have been that our samples were not adequately reflective of patients experiencing poor outcome. These possibilities would be supported to the extent that 12-month outcomes approximated outcomes reported for heterogeneous samples of patients with KA who were not selectively screened for poor outcome. If 1-year outcomes in our trials were equivalent to or better than that reported for large cohorts of patients not screened for poor outcome risk, it is likely that our screening methods for poor outcome were not successful.

In the CORKA trial, 12-month mean OKS scores were 37.3 for the usual care arm and 37.8 for the enhanced physical therapy arm. In the TRIO trial, 12-month OKS mean scores were 33.6 for the enhanced physical therapy arm and 31.6 for the usual care arm. The mean 12-month OKS score in England over the period of 2018-2019 was

36.[11] In the KASTPain trial, 12-month mean WOMAC Pain scores ranged from 2.9 to 3.3 for the 3 treatment arms. These mean scores were similar to 12-month mean WOMAC Pain scores for large sample cohort studies of heterogeneous samples of patients.[2,3]

TRIO was the only trial that appeared to successfully enroll a sample of patients at risk for poor outcome, given that mean 1-year postoperative OKS scores were 2 to 4 OKS points lower than the population mean. When considering groups of patients (not individual patients) in CORKA and KASTPain, poor outcomes for the study arms did not appear to occur given group means. In total, our CORKA and KASTPain trial data suggest preoperative data may be inadequate for accurate prognostication of poor outcome. Preoperative screening data are ideal because these data would allow for surgical decisions to be reconsidered in light of a poor outcome risk. However, postoperative data appear to be the more powerful outcome predictors. Postoperative prognostic data, as evidenced by TRIO, appear to show potential for identifying poor outcome samples though a prior systematic review of postoperative prognostic evidence up to 2016 suggests the quality of this evidence is poor.[29] More recent evidence, however, also supports the use of postoperative data to prognose poor outcome.[7,30]

[H1]**Interventions Missed the Target**

It is clear from our 3 trials that the enhanced physical therapist intervention we tested were not effective in improving outcome beyond that provided by usual care approaches. Causal explanations for these no-effect findings cannot be confirmed from our studies but we can speculate on factors that may have played a role.

The enhanced intervention in CORKA and TRIO focused on physical impairment and provided a substantially greater number of physical therapist visits as compared to the usual care arms. While both enhanced and usual care arms improved in CORKA and TRIO, patients did not demonstrate additional benefit from an intervention designed to improve patient engagement, knee strength, pain, range of motion and daily activity performance. The number of supervised treatment sessions delivered in the CORKA and TRIO enhanced physical therapy arms was greater than the usual care arms but still relatively low in number (6 or 7 sessions, respectively) and approximately half that typically seen in comparison to KA patients in the USA, as measured up to approximately 60 days after surgery.[31] In the KASTPain trial, patients averaged 33 (SD = 23.3) visits to a physical therapist over the year of follow-up and patients in the pain coping skills arm had more visits with a physical therapist, when including coping skills visits, as compared to usual care. In a follow-up cross lagged panel analysis of KASTPain data, we found reciprocal positive associations between pain and number of physical therapy visits over time, suggesting that additional physical therapy provided minimal or no benefit.[32] Because additional visits led to no additional benefit, we contend that these enhanced physical therapist interventions “missed the target.”

In KASTPain, the psychologically based pain coping skills intervention was designed to produce greater improvements in pain catastrophizing and subsequently improved outcomes as compared to usual care or arthritis education (attention control). We found that PCS and WOMAC scores showed dramatic improvement over time with no differences among the 3 treatment arms. It appeared that pain-relieving benefits from the KA surgery were so substantial that there was little room for additional improvement

from pain coping skill acquisition. Substantial improvements in OKS scores for all treatment arms also occurred in CORKA and TRIO. These findings, in total, raise questions about the benefits of enhanced postoperative outpatient physical therapy for the poor outcome phenotype. While none of our trials included a control (no treatment or sham) arm, our combined evidence indicates that a dosage of physical therapy on the order of only a few to several visits is equivalent to higher dosages of enhanced physical therapy for patients at risk for poor outcome. For patients at high risk of poor outcome, pain-relieving benefits of surgery far outweigh any benefit attributable to physical therapy. Alternatively, some patients at risk for poor outcome experience very small improvement,[7] which, in our opinion, begs the question of whether surgery should have been conducted given that rehabilitation appears to offer little benefit.

[H1]What is the Way Forward With the Poor Outcome Phenotype?

Our 3 trials suggest that alternative methods for prognosing poor outcome and alternative interventions have potential to advance the science of rehabilitation for a substantial population of patients at risk for poor outcome.

[H1]Improving Prognostic Judgments of Poor Outcome Risk

In our opinion, greater emphasis should be placed on use of early postoperative data over preoperative data to drive prognostic judgments. TRIO was the only trial to use postoperative data to select subjects for study and found worse group-based mean outcomes compared to population estimates. Postoperative data appear to provide more accurate estimates of likely outcome, particularly when combined with latent class modeling,[7,30] as compared to preoperative prognostic algorithms.[10] We argued that a

non-biased statistical approach such as latent class modeling has several advantages over arbitrary cut points such as minimal clinically important difference (MCID) estimates, which are known to rely on arbitrary cut points and to vary substantially.[4] Latent class growth modeling is a statistical method for grouping similar trajectories of recovery (eg, postoperative WOMAC Pain scores) together to better differentiate patients who demonstrate substantial improvement from patients with minimal improvement.[7,33] Figure 2 illustrates how latent class growth analysis modeling used pre- and postoperative WOMAC Pain scores from the KASTPain trial to differentiate among patients with good versus poor outcome.[7] Preoperative predictors of belonging to the poor outcome group were lower income, very high pain catastrophizing and a greater number of painful body regions. [7]

[H1]Alternative Forms of Treatment

Two of our 3 trials (CORKA and TRIO)[10,11] indicate that enhanced physical therapy does not provide additional benefit beyond an intervention consisting of only a few physical therapist visits combined with a home exercise program. The third trial (KASTPain)[34] found no additional benefit of up to 8 additional pain coping visits beyond usual care physical therapy. These data suggest that for the poor outcome group, a higher number of physical therapist visits may not produce additional benefit, but more work is needed to confirm these findings on the poor outcome phenotype. Our 3 trials did not demonstrate the benefits of enhanced physical therapy designed primarily to target knee related impairment[10,11] or pain catastrophizing.[12]

An alternative approach to the treatment of the poor outcome phenotype appears to have potential and involves a stepped/stratified care approach. More targeted

resource intensive interventions are delivered by specialists to those who need it and less intensive care is provided to those who are improving and do not need specialized care.[35] Wylde and colleagues are completing a trial of a stepped care intervention designed to target persons with KA at risk for poor outcome.[36] Patients are assigned to interventions customized to the type of impairment or diagnosis that is believed to increase poor outcome risk.

In our opinion, it is likely that the poor outcome phenotype experiences poor outcome for a variety of reasons. For example, depression may be the main driver of poor outcome for some and for others, poor pain processing, while for other patients, undiagnosed infection or a poorly functioning implant may be the problem. A stepped approach would allow for a targeted intervention for the likely prognostic indicator believed to be the primary driver of poor outcome. For example, if the patient had high levels of depression, the treatment would focus on depression medication or referral to a psychologist whereas if the prognostic indicator of relevance were neuropathic pain, medication and referral to a pain specialist might be appropriate. This is essentially a personalized care approach that none of our 3 trials examined. A personalized stepped approach is, in our view, a potential method for more effectively treating the poor outcome phenotype. This customized stepped/stratified care approach appears to have potential for patients with KA and persistent pain and we await the trial results.[36]

Our 3 trials included over 1300 patients judged to be at risk for poor outcome. The trials each recruited patients from multiple sites and were conducted in 2 countries. While we believe these data provide rigorous and strong evidence supporting the lack of effect of enhanced physical therapy relative to usual care (as delivered in US and Great

Britain) there are some limitations to our evidence. In KASTPain, the physical therapists delivering pain coping were different from the physical therapists delivering usual care rehabilitation. It may be that effects would have been different if the same physical therapist delivered both pain coping and usual care. Our trials did not include either a no-physical therapy arm or a sham physical therapy arm. Future work should consider inclusion of either a sham or no physical therapy arm to determine true effects for the poor outcome phenotype though this approach may be challenging given ethical considerations. A high intensity physical therapist intervention[37] was not tested in our 3 trials and may have potential for the poor outcome phenotype. Finally, usual care was, by definition, unstandardized in our trials and we did not collect data to clarify the various component of usual care physical therapy.

In conclusion, KA leads to substantial pain relief for 80% of patients but the rehabilitation of patients at risk for poor outcome following KA remains a management challenge. Despite rigorous and broad scope amalgamated evidence and theory guiding treatment, enhanced physical therapy appears no more effective than a minimal number of physical therapist visits and home exercise. Additional study, potentially relying on a stepped care model targeting specific impairments that likely lead to poor outcome as well as improvements in the science of outcome prediction should be considered. The clinical message is that the optimal type and number of post-hospitalization visits to a physical therapist after KA remains undecided for the patient at risk for poor outcome.

Author Contributions

Concept/idea/research design: D.L. Riddle, D.F. Hamilton, D.J. Beard

Writing: D.L. Riddle, D.F. Hamilton, L. Dumenci, D.J. Beard

Project management: D.L. Riddle

Consultation (including review of manuscript before submitting): D.F. Hamilton, L. Dumenci

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FIGURE CAPTIONS:

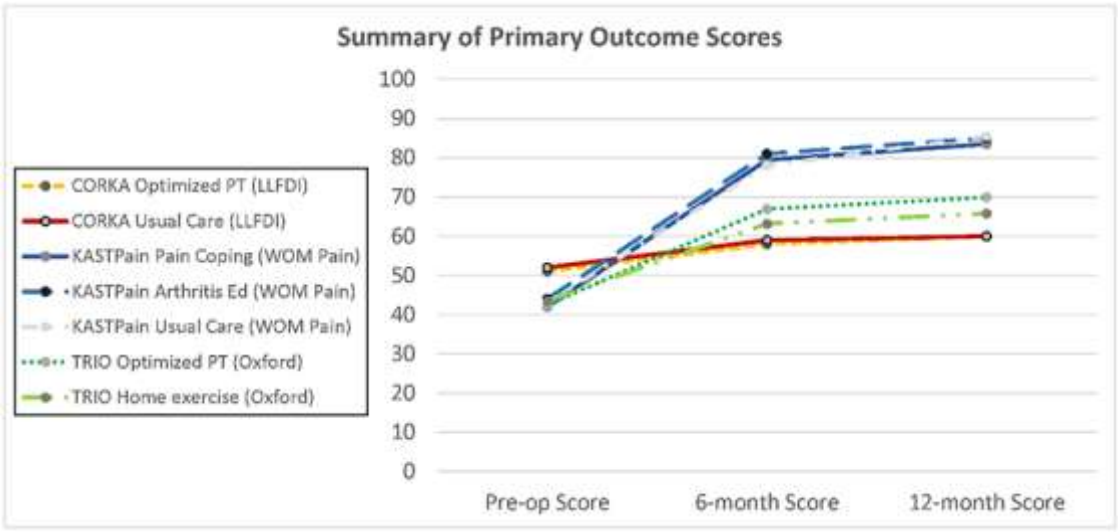

Figure 1. The figure illustrates scores for the primary outcome in each trial. All scores are transformed to a 0 to 100 scale with higher scores equating to better outcomes. CORKA = COmmunity-based Rehabilitation after Knee Arthroplasty trial; KASTPain = Knee Arthroplasty Pain Coping Skills Training trial; LLFDI = Late Life Function and Disability Instrument; Oxford = Oxford Knee Score; and TRIO = Targeted Rehabilitation to Improve Outcome trial; WOM Pain = WOMAC Pain Scale.

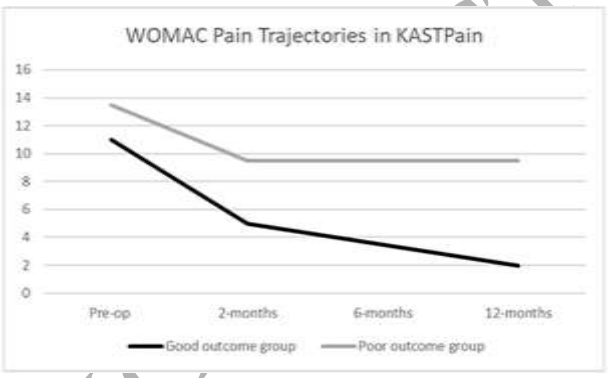

Figure 2. Latent classes of patients experiencing either a good or a poor WOMAC Pain outcome in the KASTPain trial.

Table 1. Summary of the CORKA, KASTPain and TRIO Randomized Clinical Trials[a]

	Main Aim of Active Intervention	Comparator Intervention(s)	Method for Identifying Poor Outcome Risk	Intervention Elements	Number and Timing of Sessions	Method of Delivery
CORKA (2-arm trial with 620 subjects)	Improve knee-related function and activity participation	Usual care outpatient physical therapy of between 1 and 6 visits	Prognostic model using preoperative scores for body mass index, ASA score, and single items from the Oxford knee score and the SF-12	Knee range-of-motion and strengthening exercise with progression, functional task and gait training, balance, information booklet, goal setting, at-home exercise	7 sessions beginning within 4 weeks following surgery	In-person delivered by a physiotherapist in the patient's home and via unsupervised home exercise
KASTPain (3-arm trial with 384 subjects)	Improve thoughts, feelings, and behaviors that contribute to pain	Usual care outpatient/home-based physical therapy or usual care combined with arthritis education designed to be an attention control arm	Preoperative Pain Catastrophizing Scale score of 16 or higher	Pain processing training, Cognitive restructuring, Self-Instructional training, Relaxation training, Imagery, Distraction, Relapse prevention training	8 sessions beginning 2 weeks prior to surgery and ending 2 months following surgery	In-person and at-home via telephone delivered by a physical therapist
TRIO (2-arm trial with 334 subjects)	Improve knee-related pain, function and activity participation	Home-based unsupervised exercise with one physical therapist visit	Oxford Knee Score of 26 or less, 6 weeks following surgery	Knee range-of-motion, and strengthening, joint proprioception exercise, balance/gait training, at-home exercise	6 weekly sessions beginning 6 weeks after surgery and 12 sessions of at-home unsupervised exercise over a 6-week period	In-person delivered by a physiotherapist in an outpatient clinic and via unsupervised home exercise

[a] ASA = American Society of Anesthesiologists; CORKA = COmmunity-based Rehabilitation after Knee Arthroplasty trial; KASTPain = Knee Arthroplasty Pain Coping Skills Training trial; TRIO = Targeted Rehabilitation to Improve Outcome trial.