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Improving the Value of Primary Total Knee Arthroplasty: the ATTUNE® Knee System

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EXECUTIVE SUMMARY

Total Knee Arthroplasty (TKA) is a successful and common procedure that provides pain relief and improved function in patients with osteoarthritis of the knee. Despite the globally reported success of this procedure, studies have shown that up to 20% of patients are dissatisfied with the results of their TKA. Given the increasing incidence in osteoarthritis worldwide, changing patient demographics, and the corresponding demand for TKAs, there is a need for meaningful innovation that continues to raise the bar to improve quality outcomes and meet the expectations of all stakeholders in a cost-constrained environment.

The ATTUNE® Knee System was designed to help address some of these shortcomings and improve patient outcomes. Early clinical results with the ATTUNE Knee provide insights into how this knee implant could help provide value as demonstrated by survivorship, improved patient reported outcomes scores and reduced secondary procedures for complications such as patellofemoral pain. Additionally, real world evidence from one study that included a sample of U.S. hospitals has shown that those patients treated with the ATTUNE Knee experienced a shorter length of stay, and a higher percentage of those patients with the ATTUNE Knee were discharged directly home, compared to another leading knee system. These outcomes may bring benefits to clinicians, patients, providers, and payors.

The purpose of this report is to summarize the burden of osteoarthritis, primary TKA as a treatment option for those patients, approaches for evaluating TKA from a clinical and health economic perspective, and assess the available data on the primary ATTUNE Knee.

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1 OSTEOARTHRITIS AND TOTAL KNEE ARTHROPLASTY

1.1 The Burden of Disease: Knee Osteoarthritis

Osteoarthritis of the knee is one of the five leading causes of disability among non-institutionalized adults in the United States.[1] According to the Centers for Disease Control and Prevention, osteoarthritis affects 13.9% of adults over 25 years of age, and 33.6% of those over 65. In the United Kingdom, it is estimated that 18.2% of those over age 45 have knee osteoarthritis.[4] Patients with knee osteoarthritis generally experience pain, swelling, and unpredictable buckling of the knee; about 80% of patients have difficulties with mobility, including 25% who cannot perform major activities of daily living, such as dressing themselves.[46]

The direct health care costs of nonsurgical management of knee osteoarthritis, which include medication, physical therapy, and pain center visits, are relatively low, but there are large indirect costs in the form of lost earnings, reduced work productivity, and disability benefit payments.[41,58] In addition, there are personal health costs in terms of decreased activity level, increasing weight and obesity with related health conditions, and chronic pain management concerns including potential narcotic abuse. Interventions that alleviate the burden associated with osteoarthritis are therefore valued across multiple stakeholders.

1.2 Primary Total Knee Arthroplasty: A Surgical Treatment

In patients whose knees have become excessively worn or degenerated due to osteoarthritis, a Total Knee Arthroplasty (TKA) to replace the damaged bone and cartilage is a viable option. Modern TKA can be traced back to the 1970s when John Insall implanted the first total condylar knee system.[33] Despite limited offerings with this and other early TKA implants and instruments, with strict indications and careful surgical technique, the potential success of this operation became evident as durable pain relief and improved function were benefits patients could enjoy. With the hope of providing better solutions for patients with knee osteoarthritis, newer implants were needed to deal with the wide variety of human knee anatomy as well as more complex primary procedures and revision TKAs. This led to much research into implant and instrumentation design in an attempt to improve outcomes. By 1990, much of this work had come to fruition, and the results of total knee arthroplasty now demonstrate long-term survivorship. In a recent report from the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR), the durability of total knee implants including more than 350,000 implants showed 93.5% implant survivorship at 12 years, meaning 93.5% of these implants were still functioning well at 12 years.[5]

The long-term effectiveness of TKA means that morbidity is reduced and as a result, so is the indirect cost burden. However, in the short term, TKA is more expensive than nonsurgical management, leading to increases in overall short-term medical costs. For example, in the U.S. nearly 800,000 knee procedures are performed annually,[2] at a cost of over $24.8 billion.[6]

> The expansion in the number of total knee procedures is projected to increase for the next 20 years as longevity increases, patients seek earlier remedy from arthritic conditions, and access to care improves. This increase in numbers of procedures and the attendant costs will put increasing financial stress on health care systems.[38]

The increased economic burden needs to be weighed against the cost of not undertaking the procedure – to both payors and patients alike.

1.3 Outcomes Assessment

There are different ways to measure outcomes after TKA. Outcomes related to the procedure and associated health care services include readmissions, reoperations, and revision surgery rates that can be measured over time. Patient reported outcomes include patient satisfaction, improvements in knee function, return to productive employment and improvements in quality of life.

In general, outcomes of TKA have improved over the past 50 years. National joint implant registries have been in place for many years in the U.K., Australia, New Zealand and, more recently, the U.S. These registries track the performance of specific total joint implants in the different countries. Failure of an implant is reported as a revision, and implant survivorship curves are used to describe the

success in terms of the number of implants remaining in service over time. The good longevity of contemporary TKA has been reported in all joint registries with 10-year revision rates of 4-5% (or 95% implant survivorship).[9,11] Revision rates, however, may vary among different implant types, with some implants performing better than others. Differences between patient age groups have also been noted with younger patients (under 55 years of age) having a fivefold increased risk of revision in the first 10 years compared with older patients (over 80 years).[36] This difference may be due to increased activity levels of younger patients leading to wear and loosening of the implants, or to higher expectations in the younger group, which could lead to greater dissatisfaction and more revision procedures.

Patient reported outcomes show improved patient satisfaction, function and quality of life after TKA.[60] Yet, 10-20% of total knee replacement patients may be dissatisfied with their procedure.[18] Issues that remain for these patients include ongoing pain or discomfort, stiffness, crepitation (noise or vibration with movement), and difficulty squatting, kneeling, or negotiating stairs.[19,47,59,61] Research has been conducted to help identify patient risk factors for complications and poor clinical results. Patient factors that may contribute to a higher risk of poor outcomes include a history of depression or mental illness, morbid obesity, diabetes and chronic narcotic use.[34,35] Furthermore, some of these risk factors are potentially modifiable conditions, and efforts are underway to try to improve outcomes by optimizing comorbid conditions prior to surgery. Some of these programs include smoking cessation, weight loss for morbid obesity, improved diabetes management, narcotic cessation, and pre-operative physical therapy to improve muscle strength and coordination.[17,64] While the hope is that better outcomes or at least lower episodic costs can be obtained in these patients, the evidence is not complete.

TKA is a highly technical procedure, requiring surgical skills to obtain adequate bone preparation and implant fixation, but also soft tissue balancing to replicate knee function. With such a major surgical procedure, patient and surgeon satisfaction are linked. For the surgeon, the ability to implant the device efficiently and reproducibly is extremely important. Achieving optimal harmony of implant positioning/alignment and soft tissue balance during the procedure can affect the long-term satisfaction for the patient and is part of the art of TKA.[30] Furthermore, the longevity of the reconstructed knee may be directly related to the design and quality of initial fixation. Patient satisfaction and outcome are at least partly determined by specific implant design features including sizing options, implant kinematics (how the implants track relative to the native knee), the patellofemoral articulation, as well as surgical techniques of implant rotation, soft tissue balancing and alignment.

1.4 Measuring Patient Reported Outcomes

Improving patients' health or preventing its decline is of course the major aim of any health care intervention, and an important feature of modern health service provision is the ability to measure such improvements via validated tools.

> While objective physiological and functional measures can tell us much about the effectiveness of health care interventions, an important test is patients' perceptions of their health. This has led to the establishment of Patient Reported Outcome Measures (PROMs) as a key factor in evaluating the effectiveness and cost-effectiveness of health care technologies.[13]

In 2006, the U.S. Food & Drug Administration stated, "The use of PRO instruments is part of a general movement toward the idea that the patient, properly queried, is the best source of information about how he or she feels."[12]

It is important to recognize that the objective of PROMs is to measure patients' perceptions of their health, not their experiences of health care delivery. Health care delivery surveys measure patients' experience of, or satisfaction with, the care that they receive, including such factors as whether they are treated with respect and compassion, they have a comfortable environment for their care, and they are provided with enough information about their care. While these are important quality measures in their own right, and while PROMs may be influenced by patients' experience of health care delivery, the two are separate and measured in different ways.

PROMs are validated questionnaires that ask patients to assess their own health and their quality of life as a result of their health, usually capturing changes over time – especially pre- and post-intervention at specified time points. The responses to the different questions are usually processed to generate either a "profile" of health – a combined summary of the responses that gives a picture of health in different dimensions – or a number that gives an overall score. There are many thousands of such PROMs

available in multiple languages. Some of them are related to a particular condition, treatment or symptom, and are generally known as condition-specific or disease-specific measures. Others are intended to be applicable, in principle, to any condition and are usually called generic measures.

The specialty of orthopaedics has been a leader in the development and adoption of PROMs. The main generic measures used to measure a person's state of health with knee problems are the EQ-5D and the SF-36.[22,63] As well as generating a "profile" in five and 12 dimensions respectively, these enable a score to be calculated that can be interpreted as the value of a patient's health state relative to best and worst possible health states.

The most widely used condition-specific PROMs for knee osteoarthritis are the Oxford Knee Score (OKS)[44] and the Knee injury and Osteoarthritis Outcome Score (KOOS).[56] The OKS has 12 questions, each of which generates a score between zero and four. These are added together to give an overall score between zero, meaning as severe knee arthritis as possible, to 48, representing no knee problems at all. KOOS by contrast does not calculate an overall score, but generates scores from zero (extreme symptoms) to 100 (no symptoms) in five subscales: pain, other symptoms, daily living, sport and recreation, and knee related quality of life. It is an extension of another widely used measure, the Western Ontario and McMaster University Osteoarthritis Index (WOMAC),[16] which is applicable to both hip and knee problems; a WOMAC score can be derived from the KOOS questionnaire.

The Patient's Knee Implant Performance (PKIP) is a relatively newer condition-specific PROM that has been specifically developed to assess the functional status of a patient's knee from their own perspective, before and after TKA.[40] It was developed to address gaps in other common PROMs by assessing a patient's satisfaction with their implant, which represents an innovative approach to better understand the nuances involved in outcomes for TKA patients.

PKIP has four subscales (Confidence, Stability, Modify Activities and Satisfaction), each of which generates a score from zero to 10, where higher scores indicate better knee function, and an overall score which ranges from zero to 100. This has been shown in initial studies to perform well in terms of key psychometric criteria such as reliability, validity and responsiveness, which may help discriminate the impact of different implant designs and surgical techniques.[25] It is important to note that "satisfaction" here refers to the implant, which enables a proper assessment of the procedure itself, rather than more general patient satisfaction with the care that they receive, which will be influenced by the environment in which care is provided.

PROMs have many uses, but assessing the results of a health care intervention usually requires changes in health to assess outcome measures. Typically, this requires patients to complete PROMs questionnaires both before and after the intervention. For TKA, this may be referred to as pre-operative and post-operative health states, or baseline and follow-up. It is important to ensure that these assessments are carried out at times that will properly reflect the period over which improvements will be realized and that there are further assessments for possible longer term effects. For example, a common post-operative PROMs assessment for TKA is six months, but, in some cases, the follow-up will also be at one year or longer, enabling a profile of changes over time to be assessed.

PROMs are widely used in clinical trials, but are also increasingly used routinely in practice, for example in joint registries. Since 2009 the National Health Service (NHS) in England has required all health care providers, both publicly and privately owned, to collect specified PROMs for all patients funded by the NHS.[13] PROMs are collected before and after undergoing surgery for four elective procedures, including hip and knee replacements. Around 250,000 patients are invited each year to complete questionnaires, which include both the EQ-5D and the OKS, and the response rates are good: on average 95% of knee replacement patients complete the pre-operative and 75% the post-operative questionnaire. In New Zealand, TKA patients are also invited to complete OKS questionnaires and their data have established that each one-unit drop in the OKS at six months predicts a 9.9% increase in revision rates over two years,[57] which demonstrates the importance of PROMs data from a wider health care perspective.

The English PROMs data are especially useful for examining the overall effects of TKA in real world practice, rather than in the experimental conditions required by clinical trials. Averaging over all NHS providers in England in 2014-2015,[8] 93.2% of knee replacement patients had improved health specific to their condition, measured by the OKS, and 80.5% had improved health more generally, measured by the EQ-5D. The average PROMs scores for primary knee replacement patients pre-operatively were 19/48 according to the OKS and 0.425 for the EQ-5D index. At six months post-operative, primary knee replacement patients reported OKS scores of 35 and EQ-5D index scores of 0.739. The measured outcome of TKAs in the NHS in England was therefore an average improvement per patient of 16 in the OKS and 0.315 in the EQ-5D index.

PROMs that, like the EQ-5D and the SF-36, generate a single score representing the value of a health state can be used to calculate Quality Adjusted Life Years (QALYs). QALYs are a measure that combine length and health-related quality of life into a single score. For example, a person who enjoys a year without any health problems would generate one QALY; someone who had a quality of life value of 80% would have 0.8 QALYs for that year. If there were an intervention that would cure the second person's health problem, they would gain 0.2 QALYs each year. If that improvement lasted for 10 years, they would gain two QALYs, the equivalent of two additional life years with no health problems.

QALYs are a particularly useful measure to ensure that procedures, like TKA, that do more to improve people's quality of life than reduce mortality are judged fairly in comparison with procedures that extend life expectancy.

For example, the reported gain from TKA of 0.315 in the EQ-5D index in the NHS in England suggests that if the improvement is maintained over 10 years, there is a gain of over three QALYs per patient. QALYs, combined with costs, provide the building blocks to the formal economic analysis of a given intervention used by organizations like the National Institute for Health and Care Excellence (NICE), in England.

1.5 The Economics of Total Knee Arthroplasty

Within the hospital, there are fixed costs, and costs associated with the surgical procedure itself, including operating room staff, physicians, implants, and disposable items to perform the procedure. There are also costs of providing nursing care and therapy after surgery. Upon discharge, patients usually continue rehabilitation that can last for weeks or months, with the attendant costs of ongoing treatments. Some of these patients require placement in skilled nursing facilities or rehabilitation units. Post discharge costs are a significant portion (up to 50%)[7] of the overall episode of care. Bozic *et al.* found that up to 35% of the episodic costs were related to care after discharge.[20] Unpredictable events such as complications and readmissions can also add considerably to the episode of care costs.

In many countries, a global evaluation of the episode of care is a major focus. The mandatory bundled payment initiatives in the U.S. are one example. These involve a 90-day window of time where all associated costs are included with the procedure. This process creates incentives for hospital systems to better manage patient care following total joint replacement procedures. Hospitals must manage the total costs for a given procedure, including post-acute care. Any complications and/or readmissions will greatly increase chances of the hospital exceeding this fixed price and therefore owing a penalty payment back to Medicare (CMS). This puts additional risk on the providing hospital but allows the payor, e.g., Medicare, better forecasting of the cost of care to a given population.

In the NHS in England, health care providers are reimbursed by health care commissioners under the "Payment by Results" system. Each patient treated is assigned to a Healthcare Resource Group (HRG), similar to the Diagnosis Related Group (DRG) classification found in the U.S. and other countries' health care systems, for which there is a "tariff" payment covering all inpatient services. Knee replacements are one of a few procedures that are reimbursed using a "Best Practice Tariff," which offers a much larger payment to providers who provide a high standard of performance, such as minimum average improvements in PROMs scores and good data provision, including rates of registration with the National Joint Registry (NJR). They also attract a special additional tariff for post discharge rehabilitation care that follows a defined clinical pathway, including specified numbers of nurse, physiotherapist and occupational therapy appointments, and consultant-led clinic visits.

With the growing population of patients needing TKAs, it is critically important to minimize the total cost of this procedure, subject to maintaining quality of care. Globally, each element of cost for the episode of care is under review for potential cost savings by hospital systems. Length of hospital stay and post-discharge disposition are two areas under review by payors and providers. Decreasing length of stay clearly reduces the cost of inpatient care and can be done safely, with many patients now being discharged directly home within 48 hours and, in some cases, on the day of surgery.[37] The use of skilled nursing and rehabilitation units has also been identified as high cost items associated with 35%[20] -50%[7] of the episode of care cost, and efforts to minimize the use of these facilities are underway. The benefits of post-discharge therapy (either in home or in outpatient) are under review and at least one paper suggests it may be unnecessary following TKA.[23] Further study of this topic will likely be forthcoming.

TKA is widely accepted as a highly cost effective means of generating improvements in patients' quality of life. The cost of a health care intervention can be measured by comparison with the next best alternative way of managing the condition that it deals with. This gives an estimate of the additional or "incremental" cost of the intervention. The cost is compared with the improvements in patient outcomes, measured as gains in QALYS, that the intervention generates compared with the best alternative treatment option. Dividing additional costs by QALY gains gives a cost-effectiveness ratio, an estimate of the cost of generating an additional QALY using that intervention. The inverse of this, Porter's "Value" measure, shows the amount of improved outcome generated by each dollar spent on the intervention.[52]

A number of scientific studies in countries including the U.S., U.K., Finland and Spain, have concluded that TKA is the most cost-effective means of managing osteoarthritis, according to standards that are widely accepted in developed countries.[27,39,42,45,48,54,55]

In the U.S., Losina *et al*. analyzed Medicare data using a modelling approach comparing lifetime costs and quality of life for patients aged 65 and over who had end-stage knee osteoarthritis.[42] They estimated a cost-effectiveness ratio of $18,300 per QALY gained, although for high-risk patients this was much higher, at $28,100. The cost of TKA and post-operative quality of life both affected the level of cost-effectiveness achieved, but no other patient- or procedure-related factors such as revision rates were important to this outcome.

In the U.K., Dakin *et al*. analyzed data from a large, randomized trial of different knee prostheses measuring both costs and quality of life.[27] They estimated an average cost-effectiveness ratio of £5,623 per QALY gained, using conservative assumptions about the extent of changes in costs and quality of life due to TKA. This ratio is well below £20,000 per QALY gained, which is a threshold defined by NICE below which pharmaceutical and other interventions are, without further qualification, accepted for funding. Moreover, although patients' age, gender and baseline severity, as measured by ASA (American Society of Anesthesiologists) grade and OKS score, impacted on cost-effectiveness, there are very few eligible patients for whom the cost per QALY gained exceeds the NICE threshold. Although TKA costs more for patients who had worse pre-operative health states, the greater QALY gains that they achieved meant that it was more cost-effective than for patients with only moderate symptoms. This study also examined the impact of different assumptions about factors that affect cost-effectiveness. This included the length of stay in hospital following the procedure, confirming that shorter hospital stays would improve cost-effectiveness.

In 2016, Pennington *et al*. compared the relative cost-effectiveness of different implants, using data from the U.K. National Joint Registry.[48] In identifying the most cost-effective option, they found that the main determinant was differences between the implants in the post-operative quality of life that they generate for patients. For the range of implants covered, factors such as their cost and revision rates were not so important – improving patients' quality of life was found to be key. Moreover, the quality of life differences between the implants were relatively small, further emphasizing the importance of this as a determinant of cost-effectiveness. What may appear to be small changes in quality of life at a single point of time can translate into large changes in QALYs if the improvement is sustained over a long period of time. This study covered TKAs implanted between August 2008 and July 2012, since then, new implants have been introduced which may affect the conclusions.

The evidence suggesting that TKA is highly cost-effective in terms of improvements to patients' quality of life applies to all relevant age groups.

Additional benefits may be applicable to TKA patients whose ability to work is affected by knee problems. TKA will enable such individuals to continue working, which is beneficial to society. These are known as indirect costs, by contrast to the direct costs of health care that arise from either TKA or its alternatives. Ruiz *et al.* estimated the total additional direct costs of TKA over the lifetime of a patient in the U.S. to be on average $20,635 in 2009 dollars, offset by a reduction in lifetime indirect costs of $39,565.[58] TKA therefore generates an average societal savings of $18,930 per patient. Most of these savings directly benefit patients by increasing their employment potential and earnings, but there is a wider benefit to society of increased production and reduced disability payments.

1.6 Barriers to Referral for Treatment

National professional associations for orthopaedic surgeons and the policy bodies of national health systems emphasize that the decision to refer a patient for TKA should only depend on individual clinical judgements that a patient will benefit from treatment. In particular, decisions should not be made using "scoring tools" that identify which patients are eligible for referral. In the U.K., for example, NICE has issued quality guidelines that instruct health professionals, health care providers and health care commissioners not to use such scoring systems.[10] These guidelines also attempt to drive consistency in equity of care provided across the NHS in the U.K.

Sometimes, other eligibility criteria are used that are equally arbitrary and are opposed by national bodies. These include a requirement that patients lose weight or stop smoking before they can be referred for TKA; that patients must be experiencing extreme pain or disability; and that patients must be under a specified age. None of these are regarded as justifiable if they do not adversely affect the likelihood of a patient benefiting from surgery. The NICE guidelines state if there are to be referral thresholds, these should not be based on such criteria, or scoring tools, but on discussions between patient representatives, referring clinicians and surgeons.

In the U.S., global payment models reward hospitals that show decreased complications and readmissions following TKA. These payment models could potentially create an adverse incentive to screen patients and forgo surgery on individuals that have a higher risk of a complication or readmission. The unintended consequences of these policies in the aforementioned major TKA markets, which are aimed at minimizing short-term costs with approaches to rationing, may lead to problems in the access to care for many patients who would otherwise benefit from this procedure. Potentially, such approaches could lead to increased overall health care direct and indirect costs in the longer term.

2 THE ATTUNE KNEE SYSTEM

2.1 Improving the Performance of Total Knee Arthroplasty

In an effort to improve the performance of contemporary TKA, DePuy Synthes Companies designed the ATTUNE Knee System with university researchers and a team of 35 experienced total knee surgeons from around the world. The team set about studying surgical workflow, implant sizing, kinematics, patellar tracking, ligament balancing and instrumentation issues in-depth, and new concepts were developed and tested in laboratories around the world. This collaboration led to over 30 peer reviewed publications, more than 60 patents and to the development of new methods to address clinical problems through implant and instrument design and manufacturing.

The ATTUNE Knee is a highly versatile implant system with options for bearing design, kinematics, patellar design and ligament balancing techniques. The instrument system incorporates the use of low weight composite materials designed to allow precise bone preparation, implant balancing and implant insertion. Primary ATTUNE Knee implants have been implanted since 2011, with wide availability since 2013, and are used in countries around the world.

The evidence strategy for the ATTUNE Knee represents the largest clinical program in DePuy Synthes' history and has been designed to extensively focus on measuring the extent to which the ATTUNE Knee is meeting the unmet needs of TKA patients and other key stakeholders.

Additional information about the ongoing in vivo studies is available online (see Appendix Table 1).

Factors that can influence TKA outcomes include patient demographics, implant design and the instruments that help surgeons implant total knee devices with greater precision. Standard surgical instruments and tools used to insert total knee implants have proven more than adequate to perform high quality TKAs in most surgeons' hands. However, there is variability in surgeon experience and skills in performing this complex operation. Surgical efficiency can lower aggregate costs, improve outcomes by reducing complications, and improve operating room productivity. One study conducted at Duke University in the U.S. showed that a surgical team dedicated to total

joint replacement improved the performance of those procedures, improved on time starts, and increased the number of cases by 29%.[14] Attempts to improve performance through professional education and training are ongoing to ensure consistency in surgical process. More training may be useful, potentially focusing on surgeons who perform fewer cases than the academics who typically publish.

If the performance of a higher quality knee reconstruction led to shorter surgery time, shorter length of stay in hospital, reduced utilization of skilled nursing facilities, reduced time of recovery, higher patient satisfaction, fewer complications and revisions, and lower overall costs of care, it would be a significant improvement to the current standard of care, which would benefit all stakeholders.

2.2 Total Knee Arthroplasty Outcomes Using the ATTUNE Knee

National total joint registries offer the opportunity to track implant-specific performance by means of patient reported outcomes, reoperations, and revisions. Sweden, New Zealand, Australia and the United Kingdom are some of the countries that have national registries. Per the 2016 published report from the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man (NJR),[3] the three-year cumulative percent revision rate for over 4,000 patients receiving the ATTUNE Knee was 1.39% (NJR Table 3.28), which compares favorably to the class of cemented implants, which had a 1.50% cumulative percentage probability of revision (NJR Table 3.24). ATTUNE Knee survivorship data is also available in the 2016 published report from the National Joint Replacement Registry from Australia (AOANJRR).[5] Per the 2016 AOANJRR, in which 4,831 ATTUNE Knees are being tracked, the ATTUNE Knee estimated cumulative percent revision was 0.5% (ATTUNE Cruciate Retaining), 0.4% (ATTUNE Posterior Stabilized) at one year.[6] This compares favorably to the overall class of cemented total knee arthroplasty (TKA) at one year, which has an estimated cumulative percent revision of 1.0% (Tables KT9 and KT22).[5]

While the science behind implant design has improved, the evidence of improvement lies in patient perception and function. Performance measures such as pain relief and improved function are issues patients can relate to their knee through the various measurement tools previously described. With these tools, knee function and pain can be assessed pre- and post-operatively. Furthermore, improvements can be tracked to compare outcomes between different hospitals, surgeons, and implants.

As described on the next page, a number of independent single-center studies and company-sponsored multi-center studies of the ATTUNE Knee have reported an improvement in patient outcomes compared with other knee implants. A prospective multi-center study by Hamilton *et al*. compared 926 patients receiving an ATTUNE Knee with a similar group of 845 patients who received knee implants of other designs.[31] Knee function and patient satisfaction scores were collected using four PROMs: KOOS, OKS, PKIP, and EQ-5D. Figure 1 shows that at one-year post-operative, the ATTUNE Knee patients had statistically better scores in most of these.

Figure 1. Patient reported outcome measures including condition specific (KOOS, PKIP, OKS) and generic (EQ5D) comparing the ATTUNE Knee and other knee systems, p-values less than 0.01 are highlighted and considered statistically significant.[31]

KOOS	Scale	Timing		Unadjusted Mean ± SD, (Change from Pre-op Baseline)					(Covariate Adjusted) p-value for Means
			N	Leading Knee Brands		N	ATTUNE Knee		
Activities of Daily Living	0-100	Min. 1yr.	751	85.1 ± 15.7	(35.0 ± 20.0)	746	88.1 ± 13.5	(38.4 ± 19.2)	<0.0001
		Min. 2yr.	674	87.6 ± 14.9	(37.0 ± 20.6)	363	90.0 ± 13.5	(37.3 ± 19.0)	0.0945
Pain	0-100	Min. 1yr.	752	84.6 ± 16.9	(38.6 ± 20.5)	746	87.2 ± 14.6	(42.8 ± 19.4)	0.0001
		Min. 2yr.	674	87.6 ± 15.6	(41.1 ± 20.7)	362	89.4 ± 14.5	(42.9 ± 19.0)	0.1599
Symptoms	0-100	Min. 1yr.	752	78.5 ± 16.9	(30.4 ± 22.5)	746	80.9 ± 14.6	(33.6 ± 21.2)	0.0016
		Min. 2yr.	674	82.5 ± 15.5	(33.8 ± 21.8)	363	84.1 ± 14.9	(35.6 ± 20.6)	0.1552
Function in Sport/ Recreation	0-100	Min. 1yr.	744	55.5 ± 30.4	(37.1 ± 31.1)	727	59.9 ± 28.2	(42.3 ± 29.7)	0.0013
		Min. 2yr.	655	61.2 ± 29.3	(42.9 ± 31.5)	349	63.8 ± 28.4	(45.1 ± 28.1)	0.2081
Quality of Life	0-100	Min. 1yr.	750	70.0 ± 23.3	(45.0 ± 25.8)	746	73.2 ± 21.9	(48.7 ± 25.6)	0.0034
		Min. 2yr.	674	74.9 ± 22.9	(49.7 ± 26.3)	363	78.3 ± 21.2	(52.2 ± 24.8)	0.0694

PKIP	Scale	Timing		Unadjusted Mean ± SD, (Change from Pre-op Baseline)					(Covariate Adjusted) p-value for Means
			N	Leading Knee Brands		N	ATTUNE Knee		
Overall	0-100	Min. 1yr.	746	71.3 ± 19.1	(43.6 ± 21.9)	729	74.4 ± 18.0	(45.7 ± 21.5)	0.0032

OKS	Scale	Timing		Unadjusted Mean ± SD, (Change from Pre-op Baseline)					(Covariate Adjusted) p-value for Means
			N	Leading Knee Brands		N	ATTUNE Knee		
Overall Score	0-48	Min. 1yr.	750	40.2 ± 7.4	(17.1 ± 8.8)	742	41.4 ± 6.4	(18.4 ± 8.6)	0.0002
		Min. 2yr.	672	41.4 ± 6.8	(18.1 ± 9.1)	362	42.3 ± 6.4	(18.0 ± 8.9)	0.2033

EQ5D-3L	Scale	Timing		Unadjusted Mean ± SD, (Change from Pre-op Baseline)					(Covariate Adjusted) p-value for Means
			N	Leading Knee Brands		N	ATTUNE Knee		
Overall Score	-1-1	Min. 1yr.	746	0.8 ± 0.2	(0.3 ± 0.3)	746	0.9 ± 0.2	(0.3 ± 0.3)	0.0109
		Min. 2yr.	672	0.9 ± 0.2	(0.3 ± 0.3)	362	0.9 ± 0.2	(0.3 ± 0.3)	0.7594

Another presentation combined data from the Hamilton, *et al.* study with an additional study on ATTUNE TKAs, cumulatively totalling 2,370 ATTUNE Knees and 845 knees from other leading knee systems performed by surgeons from around the world. This analysis assessed the outcomes of early "learning curve" defined as the first 10 ATTUNE Knee cases, compared to subsequent procedures. Average operating time improved after the first 10 cases. Additionally, when the first 10 ATTUNE TKAs by an individual surgeon (learning curve cases) were compared to later ATTUNE TKA cases, there was no impact on the rate of intra-operative complications, nor was there an impact on PROMs. These results may be useful evidence for institutions when considering adoption of a new product.[21]

Patellofemoral complications are one of the problems encountered in TKA patients. Some patients may hear noise as a grinding or clunking sound when moving their knee from extension to flexion. This situation is caused by the entrapment of soft tissue between the components and can be associated with pain and impair certain activities. Symptoms usually begin within 12 months of surgery and have been reported in up to 18% of patients after TKA.[26] Patellofemoral complications have been a cause of revision surgery in approximately 6% to 11.6%[5,28,51] of revisions. Furthermore, patellofemoral complications, especially crepitus and clunk, are more common in posterior stabilized (PS) implants.

Four independent studies[32,43,53,62] have demonstrated fewer patellofemoral complications and one biplanar fluoroscopy study[15] demonstrated improved patellofemoral biomechanics in the ATTUNE Knee, compared to other knee systems, primarily the well-performing SIGMA® Knee. This data suggests that certain design features, including the modified trochlear groove and corresponding patellar articulation, may lead to fewer reoperations for patellar symptoms in ATTUNE Knee patients compared to primarily SIGMA Knee patients.

1) In a prospective study by Toomey *et al.,*[62] patellofemoral symptoms were specifically evaluated by patients and investigators. At one and two years, the cumulative incidence of symptomatic crepitus in patients with ATTUNE PS Knee implants was significantly less than that of the non-ATTUNE Knees, primarily the SIGMA PS Knee design, (0.78% versus 2.53% at one year, and 1.21% versus 3.14% at two years). Furthermore, the risk of patellar symptoms increased fourfold for patients achieving more than 110 degrees of flexion with non-ATTUNE Knee systems, while there was no increased risk in the ATTUNE Knee patients with over 110 degrees of knee flexion.[2]

2) Martin *et al.*[43] reported a single institution study that compared the incidence of crepitus for subjects implanted with the ATTUNE PS Total Knee (N=728) and subjects implanted the SIGMA PS Total Knee (N=1165). The results showed significantly less symptomatic patellofemoral crepitus at both minimum one and minimum two years post-operatively for the ATTUNE Knee versus the SIGMA Knee design (0.14 versus 2.7%, $p<0.001$ at minimum one year and 0.33% versus 2.3%, $p<0.001$ at minimum two years).

3) Ranawat *et al*.[53] compared 100 each of the ATTUNE PS Knee with the SIGMA PS Knee. While not statistically significant, the incidence of symptomatic crepitus at two years was 1.0% for the ATTUNE Knee cohort compared to 4.1% for the SIGMA Knee cohort. Their results also demonstrated a statistically significant reduction in anterior knee pain at two years post-operative (12.5% for the ATTUNE Knee cohort versus 25.8% for the SIGMA Knee cohort, $p =0.02$).

4) Another study by Indelli *et al*.[32] also compared 100 patients each with the ATTUNE Fixed Bearing Knee and the SIGMA Fixed Bearing PS Knee. The ATTUNE Knee group had significantly less anterior knee pain (2% versus 9%), higher flexion (123 degrees versus 115 degrees, $p=0.009$) and more patients with over 130 degrees of flexion (37% versus 16%, $p=0.0008$). Two patients in the SIGMA Knee group required surgery for patellar clunk and there were no revisions in the ATTUNE Knee cohort. The ATTUNE Knee patients experienced a statistically significant ($p=0.007$) reduction in the incidence of symptomatic crepitus (1%) compared to the SIGMA Knee patients (5%).

The ATTUNE Knee was designed to improve the patellofemoral articulation. The trochlear design of the PS implant has a reduced thickness of the anterior implant flange, and an altered box configuration that was specifically designed to maintain patellar contact through deep flexion and avoid entrapment of soft tissue as the patellar implant slides over the box. The native patella has a dome whose apex is closer to the medial edge of the bone and, in a similar fashion, the ATTUNE Knee patellar implants restore the dome to a medial position on the patella. The patellar implant is available in a medialized dome or medialized anatomic configuration. While each is designed to restore the dome of the patella to the original position on the patella, the anatomic version has facets which can increase the contact area of the patellar implant on the femoral component throughout the range of motion. In addition to the above clinical studies which demonstrated fewer patellofemoral complications, a comparative, kinematic study in the U.S. of both patellar component designs showed that study subjects with medialized anatomic geometry achieved greater patellar flexion (the angular orientation of the patella relative to

the femur) than those with the medialized dome during lunge activity, and demonstrated patellofemoral kinematics closer to that of the native knee.[15] The anatomic patellar design also has more polyethylene proximally which may prevent ingrowth of the fibrous tissue meniscus that eventually encircles most domed implants.

Recovery from TKA is a process that takes time. Most patients will experience improvement in knee function for up to 12 months following surgery; however, the most rapid phase of this recovery is in the first six weeks, when about 80% of recovery has occurred. This acute recovery phase is mainly related to the soft tissue healing and remodelling that occurs following the procedure. Recovery rates vary between patients but, in general, TKA patients will continue to have startup stiffness, discomfort, difficulty sleeping through the night, and weakness going up and down stairs for six to 12 weeks. Efforts to enhance early recovery from TKA have included pre-operative exercises, less invasive surgical approaches, aggressive physical therapy pathways, pain management protocols and educational efforts to help prepare patients for the recovery phase of their treatment. While some of these have been shown to reduce length of hospital stay and made the recovery more tolerable for many patients, surgical pathways and implant design may also contribute to the speed of recovery.

While length of stay, rehabilitation time, and return of function are multifactorial, implant design and surgical technique may be contributing factors. The ATTUNE Knee was designed to allow surgeons to provide stability and anatomical reconstruction of the arthritic knee. With 14 primary femoral sizes, 10 tibial sizes, and one millimeter increments in polyethylene thickness, the options to size and balance the knee have been enhanced with the ATTUNE Knee from other available systems. Improving component stability was one way the designing surgeons felt they could impact function with activities such as climbing and descending stairs. Another effect of this component stability may be enhanced post-operative recovery. While patient reported outcomes up to two years have favored the ATTUNE Knee versus other leading knee systems, some early recovery data also lends support. Specifically, a U.S. claims database study[29] compared 1,178 ATTUNE Knee patients to 5,707 Stryker Triathlon® knee patients implanted in 38 hospital systems that used both products.

The results showed a significant difference in the length of hospital stay and use of extended care facilities. The adjusted mean length of stay (LOS) for ATTUNE Knee patients in this dataset was 0.19 days shorter than for the Triathlon® patients (2.94 vs. 3.13; p<0.001). The mean adjusted proportion of ATTUNE Knee patients in this dataset who were discharged to a skilled nursing facility (SNF) was 24.3%, compared to 34.3% of the Triathlon® patients. The adjusted odds of ATTUNE Knee patients in this dataset being discharged to a SNF were 39% lower than for the Triathlon® patients (Odds Ratio= 0.61; 95% Confidence Interval: 0.50-0.75; p<.001).

Sensitivity analyses in this study indicated that these effects could not be explained by patient factors including age, insurance or marital status.

A study from Germany on the early (six month) clinical results with 55 prospective ATTUNE Knee patients showed significant improvement in range of motion (112 degrees pre-op to 123 degrees post-op; p<.001) and improved coronal stability throughout the range of motion compared to pre-operative status.[50] The stability tests were carried out in a standardized fashion at zero, 30, and 90 degrees of flexion. The study authors felt that the improved kinematics observed in these patients were a result of the femoral component design and the ability to fine-tune the knee balance with one millimeter increments in polyethylene thickness. An in-vivo fluoroscopic analysis (video x-rays which allow researchers to study the relative motion of the components during activities) of the ATTUNE Knee gradually changing radius (ATTUNE GRADIUS™ Curve) compared to the SIGMA Knee multi-radius design showed improved kinematic function and femoral roll-back with the ATTUNE Knee.[49] Both of these studies, which focus on stability, are consistent with experimental data performed by finite element analysis and previous experimental laboratory research.[24]

2.3 Economic Evaluation of the ATTUNE Knee

Although a full cost and benefit profile for the ATTUNE Knee does not currently exist, there is emerging evidence that evaluates the economic implications of the ATTUNE Knee System.

In a claims database evaluation of data from 2013-2014 of the ATTUNE Knee System versus the Triathlon® knee system, within a sample of U.S. hospitals and surgeons, the patients in the dataset who received the ATTUNE Knee had a shorter length of stay; the length of stay for the ATTUNE Knee patients was statistically significantly lower than for Triathlon® patients, by an average 0.19 days adjusted for case-mix.[29] These results may be meaningful in systems that are interested in reducing length of stay and post-acute care. The ATTUNE Knee System could be part of the care pathway that is aligned with the goals of the healthcare system. Although small expressed in per patient terms, this may be important where there is a larger volume of patients, and, in the U.K. in particular, lower length of stay has been found to reduce cost sufficiently to improve the cost-effectiveness ratio.[27] The same study found that the adjusted odds of ATTUNE Knee patients in the dataset being discharged to a skilled nursing facility were 39% lower than for the Triathlon® patients. Because such facilities are comparatively very expensive, this may also improve cost-effectiveness. Further research in this area would be beneficial.

Although revision rates and secondary procedures have not been shown to impact on cost-effectiveness, the lower reported patellofemoral complications[32,43,53,62] that often lead to reoperations, and the low revision rates for the ATTUNE Knee reported in National Joint Registries[5,9,11] suggests a source of reduction in overall costs.

Additionally, some studies indicate that there is evidence of improved health related quality of life, as measured by validated PROMs questionnaires, using the ATTUNE Knee. For example, the study by Hamilton *et al.*[31] showed that ATTUNE Knee patients had consistently improved one- year scores on a broad range of PROMs compared with those patients who had other knee products, although not all differences were statistically significant. These improvements appear to be modest, which is to be expected as TKAs in general have been shown to have a positive effect on patients' quality of life.[60] However, as the cost-effectiveness modelling evidence described earlier shows, even a small improvement significantly raises cost-effectiveness favorability when translated into gains in Quality Adjusted Life Years.

These benefits have been observed in real world settings, where many variables that effect LOS and other outcomes that impact the value to payors and other stakeholders.

CONCLUSIONS

Advancements in the provision of TKA have reduced the burden on patients with osteoarthritis of the knee and technological advancements have led to improved outcomes over time. The ATTUNE Knee has been available for a number of years in a large number of countries and was designed to improve patient outcomes through advancements in implant design and surgical workflow. The current data reviewed in this paper has demonstrated improved outcomes compared to other leading knee systems. Based on registry data collected over time in multiple countries, the ATTUNE Knee performs well in terms of implant survivorship to three years; registry data will continue to be reviewed. For the patient, this may mean enhanced recovery from the surgical procedure (leading to earlier discharge, and reduced follow-up requirements in some cases), an earlier and higher return of knee function, and fewer reoperations from procedure related complications such as patellofemoral crepitation. The improvements in function documented thus far include improved pain level, activities of daily living, function in sports and recreation, and quality of life after one year. For hospital systems receiving bundled payments, decreased length of stay and fewer transfers to extended care facilities can reduce the cost of episodic care. These financial savings could also benefit hospitals under the Healthcare Resource Group (HRG)/Diagnosis Related Group (DRG) reimbursement systems. Earlier discharge could assist with capacity constraints, particularly where there are extensive waiting lists for a wide variety of procedures. Finally, for society more generally, the costs associated with total knee arthroplasty may be lowered, which could allow for more total knee patients to be treated or scarce resources used to generate benefits in other areas. Based on available data, the ATTUNE Knee appears to be advancing outcomes for patients and creating value for clinicians, providers and payors in a challenging and dynamic healthcare environment. The DePuy Synthes evidence program will continue to monitor the clinical and economic performance of the ATTUNE Knee as more data and longer term follow-up data becomes available.

Appendix Table 1: Summary of studies on the ATTUNE Knee with additional information available on Study Registration Sites

Study registration number	Type of Study	Functional Outcomes	Fixation	Survivorship	Safety	Health Economics
NCT01497730	C	1		X	X	
NCT01746524	C	1		X	X	
NCT01754363	C	X		X	X	X
NCT02339610	C	X		1	X	
NCT02251535	IIS	1				
NCT02358434	IIS	1				
NCT02323386	IIS	1				
NCT02204748 NCT02613338	IIS	1				
NCT02532933	IIS	1				
UMIN000020380	IIS	1				
NCT02177227	IIS	1				X
NCT02256098	IIS		1			
NCT02103504	IIS		1			
NCT02791477	Indep	1				

Legend
- NCT#: Study is registered on www.clinicaltrials.gov
- UMIN: Study is registered on UMIN-Clinical Trials Registry, www.upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000023536
- 1= primary objective
- C=Company Initiated Study
- IIS= Investigator Initiated Study funded by DePuy Synthes
- Indep= Independent study not funded by DePuy Synthes

ACKNOWLEDGEMENTS AND DISCLOSURES

This white paper was commissioned by DePuy Synthes Companies, and the lead authors received compensation for their time associated with the development of the document. Additional consultation on content and editing was provided by: Kim Dwyer PhD, Vanessa Danielson MSc and Bronwyn Do Rego MSc of DePuy Synthes Companies.

*David Fisher, M.D. is a paid consultant for DePuy Synthes Companies and is member of the ATTUNE Knee surgeon design team.

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Table KT7 : Primary Total Knee Replacement by Reason for Revision

Reason for Revision	Number	Percent
Loosening/Lysis	4990	28.1
Infection	3985	22.5
Patellofemoral Pain	2059	11.6
Pain	1535	8.7
Instability	1194	6.7
Patella Erosion	772	4.4
Arthrofibrosis	611	3.4
Fracture	486	2.7
Malalignment	403	2.3
Wear Tibial Insert	290	1.6
Metal Related Pathology	286	1.6
Incorrect Sizing	222	1.3
Other	897	5.1
Total	17730	100.0

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Extracted from Table KT9 Cumulative Percent Revision of Primary Total Knee Replacement with Cemented Fixation

Femoral Component	Tibial Component	N Revised	N Total	1 Yr	3 Yrs	5 Yrs	7 Yrs	10 Yrs	15 Yrs
Attune CR	Attune	17	3199	0.5 (0.3, 0.9)					
Attune PS	Attune	7	1632	0.4 (0.2, 0.9)					
Genesis II CR	Genesis II	421	13019	0.9 (0.8, 1.1)	2.4 (2.2, 2.7)	3.1 (2.8, 3.5)	4.0 (3.6, 4.4)	4.3 (3.9, 4.7)	5.6 (4.7, 6.7)
Genesis II PS	Genesis II	518	14812	1.2 (1.1, 1.4)	2.8 (2.6, 3.1)	3.7 (3.4, 4.1)	4.3 (3.9, 4.7)	5.0 (4.5, 5.5)	
Journey Oxinium	Journey	220	3032	1.4 (1.0, 1.9)	4.5 (3.8, 5.3)	6.4 (5.5, 7.4)	8.8 (7.6, 10.0)		
Nexgen CR Flex	Nexgen	254	16286	0.7 (0.6, 0.8)	1.5 (1.3, 1.7)	2.0 (1.8, 2.3)	2.3 (2.0, 2.6)	2.7 (2.2, 3.2)	
Nexgen LPS Flex	Nexgen	838	27014	0.9 (0.8, 1.0)	2.3 (2.1, 2.5)	3.2 (3.0, 3.4)	3.9 (3.6, 4.2)	5.0 (4.7, 5.5)	
PFC Sigma CR	PFC Sigma	277	11461	0.8 (0.7, 1.0)	1.9 (1.6, 2.2)	2.4 (2.1, 2.7)	2.9 (2.5, 3.3)	3.4 (3.0, 3.9)	
PFC Sigma PS	PFC Sigma	241	7167	1.2 (1.0, 1.5)	2.6 (2.2, 3.0)	3.2 (2.7, 3.6)	3.5 (3.1, 4.0)	4.5 (3.9, 5.3)	
Triathlon CR	Triathlon	497	25632	0.8 (0.7, 0.9)	2.1 (1.9, 2.3)	2.6 (2.4, 2.8)	3.0 (2.7, 3.4)	3.8 (3.2, 4.5)	
Triathlon PS	Triathlon	185	5886	1.5 (1.2, 1.8)	3.2 (2.7, 3.7)	4.0 (3.4, 4.6)	4.6 (3.9, 5.3)		
Vanguard CR	Maxim	133	6778	0.6 (0.4, 0.8)	2.2 (1.8, 2.7)	2.8 (2.4, 3.4)	3.3 (2.7, 4.0)		
Vanguard PS	Maxim	166	3500	1.9 (1.5, 2.4)	4.6 (3.9, 5.4)	5.7 (4.9, 6.7)	6.8 (5.7,8.0)		

Table KT22 Cumulative Percent Revision of Primary Total Knee Replacement by Fixation (Primary Diagnosis OA)

Fixation	N Revised	N Total	1 Yr	3 Yrs	5 Yrs	7 Yrs	10 Yrs	15 Yrs
Cemented	8439	258789	1.0 (0.9, 1.0)	2.6 (2.5, 2.6)	3.4 (3.4, 3.5)	4.2 (4.1, 4.3)	5.1 (5.0, 5.3)	7.3 (6.9, 7.7)
Cementless	4612	103903	1.2 (1.1, 1.3)	3.2 (3.1, 3.3)	4.3 (4.2, 4.4)	5.0 (4.9, 5.2)	6.1 (5.9, 6.3)	8.1 (7.7, 8.6)
Hybrid	3964	119262	0.9 (0.9, 1.0)	2.5 (2.4, 2.6)	3.3 (3.2, 3.5)	3.9 (3.8, 4.1)	4.8 (4.7, 5.0)	6.6 (6.2, 7.0)
Total	17015	481954						

Note: Excluding cementless Genesis Oxiniu and Profix femoral prostheses

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