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WHITE PAPER

CIRCLES FOR ROBOTIC-ASSISTED TOTAL KNEE ARTHROPLASTY

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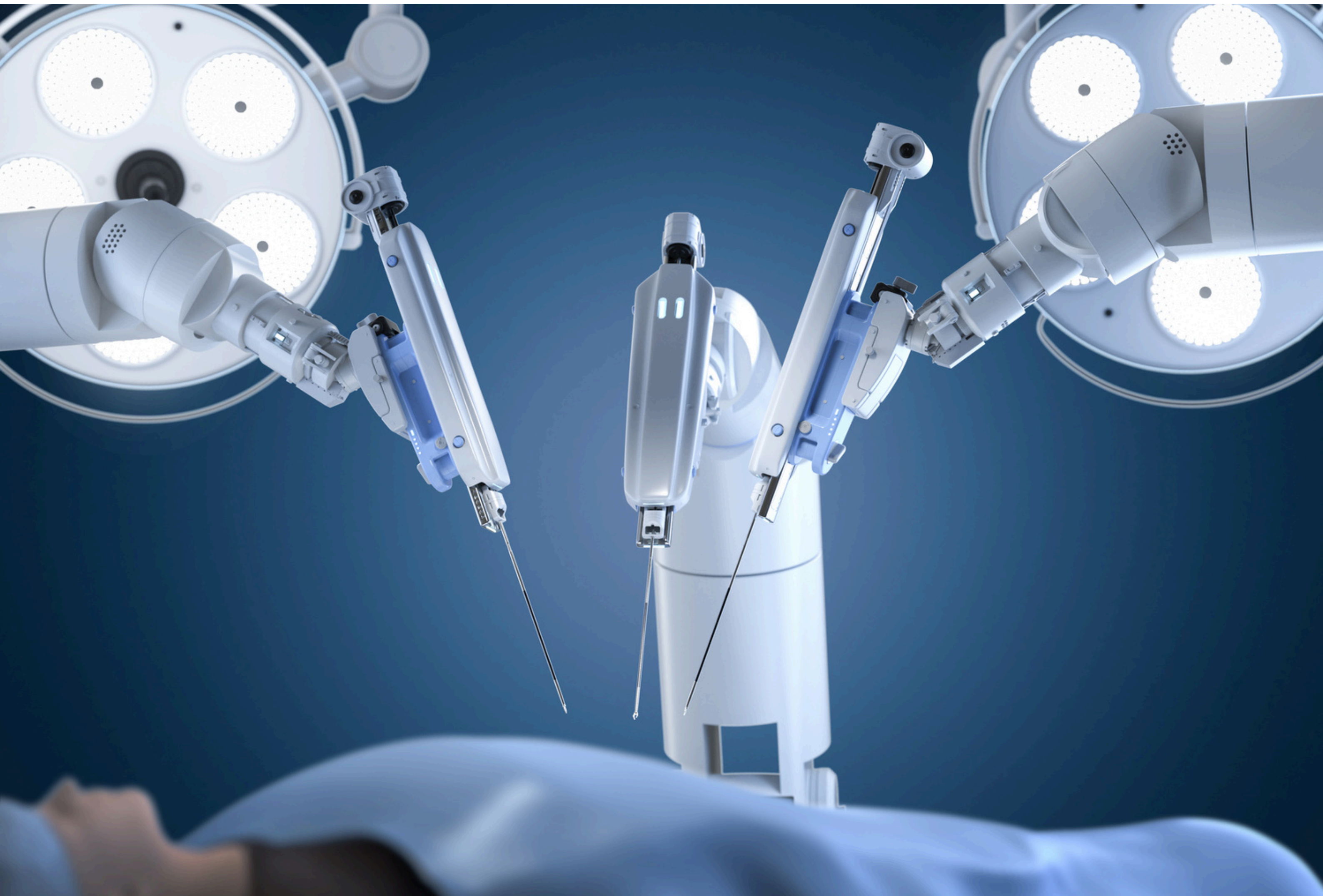

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EXECUTIVE SUMMARY

Total Knee Arthroplasty (TKA) remains a cornerstone intervention for end-stage knee osteoarthritis, with a growing volume of procedures performed annually. The advent of robotic assistance (RA-TKA) has introduced enhanced precision and accuracy in implant placement, aiming to improve patient satisfaction and long-term implant survivorship. However, despite these technical advancements, the orthopedic community faces persistent clinical challenges and ongoing debates.

These include the lack of comprehensive long-term outcome data, the significant initial costs and learning curve associated with robotic systems, and the unresolved question of which alignment strategy — Kinematic Alignment (KA) or Mechanical Alignment (MA) — yields superior patient- perceived benefits. Furthermore, inconsistencies in reported clinical outcomes between RA-TKA and conventional methods highlight a critical disconnect between objective radiographic improvements and subjective patient experience.

Traditional "big data" Real-World Evidence (RWE) often falls short in addressing these complex issues due to inherent limitations in data integrity, verifiability, completeness, and clinical relevance. RegenMed's Circles platform presents a novel and robust framework designed to overcome these shortcomings. By emphasizing direct data sourcing, transparent collection within a closed platform, longitudinal case tracking, and inherent adherence to Good Clinical Practice (GCP), Circles generates high-fidelity RWE that is analogous in rigor to traditional clinical trials.

This unique approach positions Circles as a powerful tool to resolve critical clinical questions in RA-TKA. It can facilitate robust comparative effectiveness studies of different alignment strategies and robotic platforms, enable long-term tracking of implant performance and patient satisfaction, and provide crucial data for comprehensive cost-effectiveness analyses and surgeon learning curve assessments. By providing definitive, trustworthy, and clinically meaningful evidence, Circles can inform the development of evidence-based clinical guidelines, guide responsible technology adoption, and ultimately lead to optimized patient outcomes in robotic-assisted TKA.

Overview of TKA and the Advent of Robotic Assistance

Total Knee Arthroplasty (TKA) is a globally recognized and highly successful surgical intervention, widely considered the gold standard for treating end-stage knee osteoarthritis. Its prevalence continues to rise significantly, with over 600,000 procedures performed annually in the United States alone, a number projected to increase by a substantial 673% by 2030. [1] This high procedural volume underscores the critical role TKA plays in alleviating pain, restoring function, and improving the overall quality of life for a vast patient population.

Despite the established efficacy and widespread success of TKA, a notable proportion of patients, estimated between 20% and 25%, continue to report postoperative dissatisfaction. [2] This dissatisfaction is frequently attributed to the failure of conventional TKA methods to precisely replicate the knee's complex natural kinematics, leading to a sensation of an "unnatural" or "unforgotten" joint. This persistent challenge highlights a crucial gap between objective surgical success and subjective patient-perceived outcomes, signaling a continued need for advancements in surgical techniques and a deeper understanding of individual patient biomechanics.

In response to these challenges and the relentless pursuit of enhanced precision and improved patient satisfaction, Robotic-Assisted TKA (RA-TKA) has emerged as a significant innovation in orthopedic surgery. Robotic technology has garnered increasing attention and popularity due to its potential to augment the accuracy and precision of component implantation.[1] The overarching goal of integrating robotic assistance into TKA is to improve patient satisfaction by achieving more precise surgical execution, which is hypothesized to optimize implant survivorship and enhance functional outcomes.

These advanced systems achieve their precision through sophisticated imaging capabilities and real-time intraoperative feedback mechanisms. This guidance enables surgeons to make more accurate bone cuts, achieve optimal limb alignment, and ensure balanced soft tissue tension around the knee joint. [4] Robotic systems employed in TKA vary in their level of autonomy, encompassing passive computer-assisted navigation systems that provide guidance, active robots that autonomously perform resections, and semi-active systems where the surgeon maintains control while the robot provides surveillance and live feedback to limit deviations from the preoperative surgical plan. [1]

Real-World Evidence in Clinical Decision-Making

Traditionally, Randomized Controlled Trials (RCTs) have been considered the pinnacle of evidence generation in medicine, providing robust data on the efficacyand safety of interventions due to their rigorous control over confounding variables and inherent ability to minimize bias.

However, RCTs often operate under strict inclusionand exclusion criteriaand in highly controlled environments, which can limit the generalizability of their findings to the diverse patient populations and varied clinical practices encountered in routine healthcare settings.

In this context, Real-World Evidence (RWE), derived from data collected during routine clinical practice, has gained increasing recognition as a crucial complement to traditional trial data. RWE provides invaluable insights into how treatments and technologies performin real-world scenarios, reflecting actual patient populations, clinical variability, and long-term outcomes outside the confines of a controlled study. This broader perspective is essential for understanding treatment effectiveness, safety profiles, and patient outcomes in a more representative context.

The ongoing debates surrounding the true clinical benefits of RA-TKA, particularly concerning its long-term efficacy, overall cost-effectiveness, and the comparative advantages of different alignment strategies (such as kinematic versus mechanical alignment), underscore a critical need for high-quality RWE. Such evidence is indispensable for complementing traditional trial data, informing widespread clinicaladoption, and guidingthe continuous evolutionof surgical standards and best practices in orthopedic surgery.[5]

Circles’ Approach to RWE

The Circles platform is a novel and robust solution specifically engineered to generate high-quality, verifiable, and clinically relevant RWE. This platform fundamentally distinguishes itself from conventional "big data" approaches by systematically addressing their inherent shortcomings, which include issues related to data integrity, verifiability, completeness, and direct clinical relevance.

Circles' unique methodology emphasizes direct data sourcing from primary providers, such as physicians, their patients, and laboratories, thereby ensuring the authenticity and traceability of information. Furthermore, it promotestransparent data collection and aggregation withina closed technical platform, and employs a structured, longitudinal, case-based approach to data organization.

This meticulous design means that the datasets generated through Circles are explicitly analogous to those produced by traditional clinical trials in terms of their rigor, control, and trustworthiness. This approach offers a powerful new tool for evidence generation in complex medical fields like orthopedic surgery, promising to deliver more reliable and actionable insights from real-world clinical practice.

CURRENT CLINICAL LANDSCAPE OF RA-TKA

Principles and Objectives of RA-TKA

The fundamental objective of Robotic-Assisted Total Knee Arthroplasty (RA-TKA) is to achieve superior precision and accuracy in implant positioning and limb alignment when compared to conventional manual surgical techniques.[1] This heightened accuracy is considered a critical prognostic factor, directly influencing the long-term survivorship of the implant, overall patient satisfaction, and the ultimate clinical outcomes of the procedure.[1] Robotic systems are designed to minimize deviations from the meticulously planned surgical trajectory through the use of advanced imaging and real-time intraoperative feedback.

RA-TKA integrates with various philosophical approaches to knee alignment, each with distinct objectives. Traditionally, **Mechanical Alignment (MA)** has been the prevailing philosophy. MA aims to achieve a neutral mechanical axis (defined as 0° Hip-Knee-Ankle (HKA) angle) in all patients, typically by making bone cuts perpendicular to the mechanical axis of the femur and tibia.[9] While historically associated with higher implant survivorship, this standardized approach may not always perfectly replicate the individual patient's unique, pre-arthritic knee kinematics [10], potentially contributing to patient dissatisfaction.

In contrast, **Kinematic Alignment (KA)** represents a more customized and patient-specific technique. KA seeks to restore the patient's unique pre-arthritic limb alignment, joint lines, and rotational axes. [9] This "ligament sparing" approach aims to reproduce the native knee motion, with proponents suggesting it leads to a more natural-feeling knee and improved bending and functional outcomes. [9] KA often involves detailed preoperative planning, utilizing advanced imaging such as CT scans to generate precise 3D images of the patient's unique knee anatomy, enabling the surgeon to design a personalized plan tailored to the individual. [9]

Robotic assistance can be specifically integrated with the Kinematic Alignment philosophy. This combination aids the surgeon in making the precise bone cuts requiredto reproduce the patient's normal anatomy, thereby achieving highly personalized implant placement. This integration is hypothesized to further improve patient satisfaction by delivering a knee that feels more natural and functions more akin to its pre-arthritic state. [13]

Reported Benefits of RA-TKA

The adoption of Robotic-Assisted TKA has been driven by several reportedadvantages over conventional manual techniques:

- **Improved Implant Positioning and Alignment:** Studies consistently demonstrate that RA- TKA leads to more accurate component alignment and significantly lower rates of radiographic outliers (i.e., implants positioned outside the desired alignment range) compared to conventional manual methods. [1] For example, one study reported a dramatic reduction in radiographic outliers from 76% in conventional TKA to 16% with RA-TKA. [1] This enhanced precision in implant placement is a key technical advantage.

- **Early Functional Recovery and Pain Reduction:** Patients undergoing RA-TKA have shown improvements in early functional outcomes, including a reduction in postoperative painlevels and a decreased need for opioidanalgesics. [1] Patients frequently report experiencing less stiffness and achieving greater knee flexion in the early postoperative period, contributing to a smoother recovery process. [16]

- **Higher Patient Satisfaction:** A notable benefit reported in the literature is higher patient satisfaction rates with robotic surgery. One published study indicated that 94% of patients who underwent robotic-assisted total knee arthroplasty reported being very satisfied or satisfied, comparedto 82% in the traditional manual instruments group. The robotic-assisted group consistently achieved better average scores across various satisfaction questions. [3] Patients commonly perceive benefits such as more accurate implant placement (56.2% of patients), better overall results (49%), and faster recovery times (32.1%). [3]

- **Reduced Complications and Mid-term Revision Rates:** The enhanced precision afforded by robotic assistance may contribute to a reduction in the risks of iatrogenic soft tissue injuries during surgery, potentially leading to less blood loss and postoperative drainage.[1] Furthermore, a meta-analysis has indicated lower revision rates and improved mid-term survivorship with RA-TKA when compared to conventional techniques. [7]

Key Clinical Issues and Debatesin RA-TKA

Despite the compelling technical advantages and reportedearly benefits of RA-TKA, several significant clinical issues and ongoing debates warrant further investigation and clarification.

Long-term Outcomesand Implant Longevity

Despite promising early and mid-term results, a substantial gap persists in the availability of comprehensive long-term outcome data, extending over decades, to definitively substantiate the true clinical benefits and durability of RA-TKA. [1] Implantlongevity is consistently highlighted as a very important outcome from the patient's perspective. [17] The long-term performance of robotic- assisted implants, including wear patterns, rates of aseptic loosening, and sustained functional outcomes over the lifespan of the implant, remains largely unproven.

This situation creates a "wait-and-see" scenario for clinicians, policymakers, and patients, where the perceived benefits and initial technical precision might not fully translate into proven, enduring advantages over the decades-long lifespan of the implant. This evidence gap is a major hurdle for widespread, confident adoption and for establishing definitive long-term clinical guidelines for RA-TKA.

CURRENT CLINICAL LANDSCAPE OF RA-TKA

Cost-Effectiveness and Financial Implications

Robotic-assisted arthroplasty involves substantial high initial capital costs for the acquisition and maintenance of the technology. [7] Furthermore, the integration of advanced technologies, particularly when pursuing philosophies like kinematic alignment, can add to both the financial burden and the operative time.[6] Given the rising utilization of robotic systemsand their associated financial implications [4], there is a pressing need for a comprehensive assessment to determine whether these significant investments are justified by clinically meaningful and superior advantages for the patient.

The considerable investment required for RA-TKA, encompassing high upfront costs for equipment and potentially longer operative times [3], places its overall value proposition under intense scrutiny. In a healthcare landscape increasingly focused on efficiency and cost- effectiveness, without clear, consistent, and clinically important evidence of superior long-term outcomes that patients can genuinely perceive (as suggested by meta-analyses [6]), the higher cost becomes a significant barrier.

This situation necessitates rigorous health economic evaluations, alongside clinical outcome studies, to definitively determine the true cost-effectiveness of RA-TKA and ensure that the additional investment translates into tangible, justifiable benefits for patients and healthcare systems.

Surgeon Learning Curve

The adoption of robotic-assisted arthroplasty is associated with a potentially steep learning curve for surgeons.[7] Surgeon experience has been identified as a key predictor influencing outcome variability in RA-TKA, suggesting that proficiency with the technology directly impacts results. [4] The inherent precision of robotic systems [1] is a significant advantage, but its consistent realization in clinical practice is directly linked to the surgeon's proficiency and experience with the technology. [4]

A "steep learning curve" implies that the reported benefits of RA-TKA might not be uniformly achievable across all surgeons, particularly during the initial phases of adoption. This introduces variability in outcomes and potentially higher complication rates for less experienced robotic surgeons. Understanding and quantifying this learning curve is crucial for developing effective training programs, establishing credentialing standards, and ensuring that the benefits of RA-TKA are consistently delivered across the surgical community, mitigating risks during the adoption phase.

CURRENT CLINICAL LANDSCAPE OF RA-TKA

Inconsistent Clinical Outcomes and Meta-analysis Findings

While some studies report modest improvements in specific clinical outcomes, such as Knee Society Scores (KSS) and Visual Analog Scale (VAS) pain scores with RA-TKA, the results show considerable variability across different patient subgroups and specific robotic systems used. [4]

Several meta-analyses of Randomized Controlled Trials (RCTs) have indicated that despite achieving superior post-operative anatomical and mechanical alignment, the clinicaland functional outcomes (e.g., Oxford Knee Score (OKS), Hospital for Special Surgery (HSS) score, Western Ontario and McMaster University Osteoarthritis Index (WOMAC), and range of motion (ROM)) and complication rates are often statistically similar between robotic and conventional TKA. [4]

One meta-analysis specifically found no clinically important benefit favoring kinematic over mechanical alignment in TKA based on the available RCTs. [6] The evidence reveals a critical disconnect: while RA-TKA demonstrably achieves superior radiographic alignment, this statistically significant improvement in component positioning does not consistently translate into clinically important improvements in patient-reported outcomes (PROMs) or functional scores. [6]

This "statistical significance versus clinical importance" divide is a central point of debate. It suggests that while robotic systems provide unparalleled technical precision, the clinical relevance of that precision for the averagepatient's experience (e.g., pain, function, satisfaction) is still under question, especially when weighed against the added cost and complexity. This highlights the need for RWE that focuses on patient-perceived benefits and long-term functional outcomes, rather than solely on radiographic measures.

Debate on Kinematic vs. Mechanical Alignment

There is an ongoing and significant debate within the orthopedic community regarding the superiority of kinematic alignment (KA) versus mechanical alignment (MA) in TKA. [6] Some meta- analyses and randomized controlled trials suggest that KA can reduce the need for ligament releases, improve functional outcomes, and does not increase the complication rate when compared to MA. [2]

However, other high-quality RCTs and meta-analyses have not consistently reproduced these benefits, showing no clinically important improvements in PROMs or range of motion for KA over MA. [5]
The clinical relevance of observed differences in gait analysis parameters, such as knee adduction, extension, and external rotation moments, with KA still requires further evaluation. [5] It is posited that advanced technologies like robotic-assisted TKA and compartmental pressure sensors may play a crucial role in improving our understanding of the optimal alignment strategy and implant position. [5]

CURRENT CLINICAL LANDSCAPE OF RA-TKA

The fundamental clinical question of which alignment strategy — Kinematic (KA) or Mechanical (MA) — is truly superiorfor TKA remains unresolved. [5] While KA offersa theoretically appealing approach by aiming to restore native knee kinematics [9], the robust, high-quality RCT evidence demonstrating its consistent clinical superiority over MA is still lacking. [5] This means that despite advancements in robotic precision that can execute either strategy with high accuracy, the ideal target for that precision — whether a standardized "straight" mechanical axis or a "personalized" kinematic one — is still a subject of active research and debate.

High-quality RWE, particularly when combined with robotic assistance, is essential to gather sufficient data on diverse patient populations and long-term outcomes for both approaches to inform best practices and ultimately resolve this critical debate.

Appendix A provides a summary of the reported benefits and challenges of RA-TKA.

THE ADVANTAGES OF CIRCLES FOR RA-TKA

Fundamental Characteristics and Advantages

Circles are distinguished by a set of fundamental characteristics that collectively establish it as a robust framework for generating high-quality RWE. These attributes directly address the limitations commonly associated with traditional "big data" approaches.

Data Integrity and Verifiability

The Circles platform is designed to ensure paramount data integrity. A cornerstone of its approach is direct data sourcing: information is collected verifiably and directly from primary origins, including physicians, their patients, and laboratories. This direct sourcing contrasts sharply with the often-unidentified and untraceable sources of conventional "big data" RWE.

To further guarantee authenticity and reliability, each Datapoint within a Circle Dataset is time-stamped and immune to data manipulation or "AI hallucination." Furthermore, any Circle Dataset is created within a closed, integrated technical platform, ensuring that the methods of data collection and aggregation are fully transparent and auditable. This allows for traceability to original sources, their entry date, and mechanism. For complex and high-stakes medical procedures like Total Knee Arthroplasty, where the outcomes profoundly impact a patient's quality of life and long-term mobility, the trustworthiness of the underlying data is paramount.

Circles' almostforensic approach to data integrityelevates the resulting RWE to a level of reliability and credibility that can genuinelyinform and influenceclinical practice, research directions, and even regulatory considerations for advanced surgicaltechniques like RA-TKA. It builds a foundation of trust that is often absent in other RWE sources.

Completeness and Longitudinal Tracking

A defining feature of each Circle Dataset is its composition of "well-correlated, longitudinal Cases". This means that every Datapoint within a dataset is specifically relatable to an individual patient's journey, ensuring a comprehensive and interconnected view of their clinical course. This design facilitates the capture and integration of all relevant clinical data, spanning from the initial patient enrollment, through variousclinical diagnoses and interventions, and critically, throughthe completion of long-term patient-reported and/or clinical outcomes surveys. This continuous, integrated record is essential for understanding the long-term effects and progression of conditions and treatments, such as those following TKA.

A pervasive limitation of many RWE initiatives and traditional "big data" analyses is their inability to provide a complete, unbroken, and longitudinal view of a patient's journey. Such datasets frequently suffer from data gaps, missing follow-upinformation, and a general lack of meaningful long-term outcomes. For a procedure like TKA, where implant longevity, sustained functional improvement, and long-term patientsatisfaction are crucialmetrics, this "snapshot" limitation is a critical deficiency.

Circles explicitly focuson creating well-correlated, longitudinal Cases that integrate data across the entire patient continuum — from initial enrollment through long-term follow-up surveys. This capability is indispensable for accurately assessing the true, durable impact of surgical techniques like RA-TKA and for comparing the long-term efficacy of different alignment strategies.

THE ADVANTAGES OF CIRCLES FOR RA-TKA

Clinical Relevance through Specific Observational Protocols (OPs)

Each Circle Dataset is highly focused and contains only primary demographic, clinical, and outcomes data directly pertaining to a specific Observational Protocol (OP)". This OP is prospectively defined by a single anatomical region, pathology, treatment, protocol, and standardized outcomesassessment.
The Circles platform also associated other Attributes to each OP, such as medical codes (GPT, ICD, SNOMED, HCPCS, etc.).

This extensive OP definition ensures that the collected data is highly targeted, clinically relevant, and coherent for addressing a particular clinical question, avoiding the broad and often diluted relevance of general "bigdata." It also means that all data collected against a specific OP is closely correlated withinany Circle Dataset, maintaining the integrityand coherence of the information and ensuring its direct applicability to the defined clinical protocol.

Clinical relevance is an absolute prerequisite for any RWE to be truly valuable and actionable in informing clinical practice. Traditional "big data" RWE often collects information from a wide variety of clinical settings and contexts, which are frequently undisclosed, thereby limiting its overall clinical utility and making it difficult to draw actionable conclusions. Circles' innovative and highly structured approach addresses these weaknesses. A Circle Dataset is not merely a collection of disparate data points but rather targeted, interpretable evidence directly applicable to specific clinical scenarios in RA-TKA, such as comparing alignment techniques or evaluating the performance of new robotic systems. This focus ensures that insights are directly translatable into clinical decision-making.

Robust Reporting Capabilities

Circles offer robust and flexible reporting capabilities. Any OP Question can be queried against any outcomes assessment, allowing for the generation and comparison of many dozens of expected and unexpected correlations.

Adherence to Good Clinical Practice (GCP)

A significant impediment to the broader acceptance and utilization of "big data" RWE is the unknown or often poor adherence to Good Clinical Practice (GCP), including a lack of documented IRB involvement or proper informed patient consents. In contrast, the patented technical platform underpinning Circles inherently help enforce GCP, without interrupting normal clinical flow.

THE ADVANTAGES OF CIRCLES FOR RA-TKA

Unambiguous Ownership and Equitable Financial Benefit

Data ownership within the Circles ecosystem is unambiguously established in favor of the Circle Sponsor (if any), Investigators, and RegenMed. This clear ownership structure resolves common disputes encountered with data derived from various "big data" sources (e.g., EMR systems, registries, insurance claims), where ownership can often be contentious. Furthermore, Circles can return up to 85% of the resulting license value directly to Circle Members, providing a substantial financial incentive for participation. Beyond direct income, these datasets can represent significant and increasing balance sheet equity for Circle Members.

Lower Cost and Minimal Burden

Circles are designed not only to generate verifiable, high-quality datasets but also to do so at a significantly lower cost than alternative approaches. This cost-efficiency is a critical advantage for expanding the scope of RWE generation. Moreover, it is complemented by a comprehensive suite of RegenMed services, many provided at no additional cost, which are specifically tailored to ensure that busy clinicians and patients incur minimal time and resourceburdens during their data contribution.

The generation of high-quality, protocol-driven RWE was previously only feasible for large, well-funded academic institutions or pharmaceutical companies. Moreover, those datasets remained partially or wholly inaccessible. In contract, Circles enables even smaller provider groups to generate clinically and statistically significant RWE for any medical condition or treatment protocol, ***and*** to make it available to all healthcare professionals and patients.

This has the potential to democratize high-quality evidence generation, leading to a broader, more diverse, and rapidly accumulating evidence base for complex procedures like RA-TKA, addressing granular questions about different robotic systems, alignment techniques, and patient demographics that might otherwise remain unexplored and/or locked away due to resource constraints.

Distinction from Traditional "Big Data" RWE

The Circles platform fundamentally differentiates itself from traditional "big data" Real-World Evidence by addressing the pervasive limitations that often compromise the latter's utility for rigorous clinical research. Conventional "big data" RWE is typically derived from multiple, often unidentified and unidentifiable sources such as Electronic Medical Records (EMRs), society registries, hospital records, and insurance claims. This fragmented sourcing often leads to poor data integrity, where information is manipulated by various "cleansing" and undisclosed algorithms that cannot be reversed. Consequently, it is usually impossible to trace datapoints back to their original sources, or to ascertain their date or mechanism of entry.

Furthermore, traditional "big data" solutions typically have significant gaps, which substantially reduce their clinical relevance, and they rarely contain meaningful longitudinal outcomes data. The data is collected from a wide variety of clinical settings and contexts, which are often undisclosed. Even when disclosed, their multiple contexts limit the usefulness of the data, as such datasets can be selective, often omitting crucial comorbidities, social determinants of health, and adjunct therapies. Moreover, the circumstances under which "big data" was collected, or by whom, are often unknown and unknowable, making it generally impossible to determine whether an Institutional Review Board (IRB) was involved, informed patient consents were collected, or Good ClinicalPractice (GCP) certificates or training exist. Data ownership is also frequently in dispute.

In stark contrast, Circles' foundational design principles — including its direct, verifiable data sourcing, the guarantee of time-stamped and unmanipulated data, transparent collection and aggregation methods within a closed platform, and a sharp focus on specific Observational Protocols — directly address and systematically overcome these inherent limitations. This rigorous approach consistently provides a demonstrably higher quality of RWE. Instead of disparate, often incomplete data points, Circles focuses on building structured, longitudinal "Cases" that provide a holistic and continuous patient journey perspective, ensuring a more comprehensive and reliable evidence base.

Analogy to Traditional Clinical Trials

A pivotal characteristic of the Circles platform, which significantly bolsters the credibility and utility of its generated RWE, is its explicit analogy to traditional clinical trials. The structured nature of Circles datasets and their underlying processes are designed to mirror the rigor and control typically associated with randomized controlled studies.

THE ADVANTAGES OF CIRCLES FOR RA-TKA

This analogy is rooted in several key design elements. Circles mandates the structured collection of data against predefined "Specific Observational Protocols" (OPs), ensuring that data collection is highly targeted and relevant to specific clinical questions. The data collected within these OPs is closely correlated within longitudinal cases, providing a comprehensive and continuous patient journey. Furthermore, the platform's inherent enforcement of Good Clinical Practice (GCP) principles ensures ethical and compliant data collection, a hallmark of high-quality clinical trials.

This unique approach provides a level of rigor, control, and trustworthiness in RWE that is often lackingin broader, less structured RWE initiatives. By adhering to principles that resemble clinical trial design, Circles data becomes more comparable to the evidence generated from gold-standard controlled studies, making it highly valuable for informing clinical guidelines, regulatory submissions, and the responsible adoption of advanced medical technologies like robotic-assisted TKA.

Appendix B provides a summarytable comparing the advantages of Circle Datasetsover "big data" RWE.

LEVERAGING CIRCLES FOR CLINICAL ISSUES IN RA-TKA

The unique designand capabilities of the "Circles" platform offer a compelling solutionfor addressing the key clinical issues and debates currently surrounding RA-TKA.

Enhancing Data Quality and Verifiability for RA-TKA Outcomes

Problem: Current research on RA-TKA, particularly studies that rely on broad"big data" or less controlled methodologies, often presents mixed or inconclusive results regarding the true clinical benefits. [4] This ambiguity stems, in part, from inherent issues with data integrity, verifiability, and transparency in traditional RWE sources. The inability to trace datapoints to original sources and the potential for undisclosed data manipulation in large, aggregated datasets significantly hinder the ability to conduct robust and trustworthy analyses.

Circles Solution: The Circles platform directly addresses these challenges through its core design principles. Its commitment to direct data sourcing from primary origins (physicians, patients, laboratories), coupled with the strict adherence to time-stamping and the absolute prohibition of data manipulation or AI "hallucination," ensures unparalleled data integrity for RA-TKA outcomes. Furthermore, the transparent nature of data collection and aggregation within a closed platform provides complete auditability and traceability, which is crucial for building a stronger, more credible evidence base for robotic surgery.

Longitudinal Outcome Tracking for Implant Survivorship and Patient Satisfaction

Problem: A major limitation in the current body of research on RA-TKA is the scarcity of high- quality, long-term outcome data. [1] This deficiency makes it challenging to definitively substantiate the true clinical benefits of robotic assistance over extended periods, particularly concerning crucial aspects like implant longevity, the incidence of late complications, and sustained patient satisfaction. Traditional "big data" solutions are often fragmented and typically lack the comprehensive, longitudinal outcomes data necessary for such long-term assessments, frequently suffering from data gaps over extended follow-up periods.

Circles Solution: Circle Datasets are grounded in well-correlated, longitudinal Cases, enabling the comprehensive capture and integration of clinical data from patient enrollment, through clinical diagnoses and interventions and, critically, to long-term outcomes capture. Circles are thus an ideal tool for tracking TKA patients over extended post-operative periods, such as the 24-month follow-up noted in the NCT06709703 clinical trial [13]. The integrated and longitudinal Circle Datasets move well beyond mere outcome reporting to proactive clinical intelligence.

Moreover, Investigators have complete flexibility in using, or designing their own, outcomes assessments. For example, by employing PROMs like the Forgotten Joint Score and Joint Perception Question [13], Circles can identify subtle trends in implant wear, loosening, or the emergence of late-onset complications that might not be apparent in shorter-term studies.[1] This continuous, real-time monitoring capability can provide early warnings of declining patient satisfaction or functional issues, enabling clinicians to intervene promptly or to refine surgical protocols and post-operative care strategies.

This shifts the focus from reactive problem-solving to a proactive, iterative process of continuous improvement in RA-TKA techniques and implant designs, directly informed by real-world, long-term patient experience and outcomes.

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Investigating Alignment Strategies

Problem: A significant and ongoing debate in TKA revolves around the comparative superiority of Kinematic Alignment (KA) versus Mechanical Alignment (MA). [5] While proponents of KA suggest benefits such as reduced ligament releases and improved functional outcomes, a pivotal meta-analysis of randomized controlled trials (RCTs) found no clinically important improvements in PROMsor range of motion (ROM) for KA, despite the added costs and potential risks associated with its implementation, especially when combined with advanced technologies. [6] This highlights a critical need for well-designed, robust studies to definitively resolve this clinical debate.

Circles Solution: Through Circles, physician-investigators can define and execute "fit-for- purpose" Observational Protocols. An OP can be quickly designed and implemented to rigorously compare outcomes between various alignment strategies, such as robotic-assisted KA versus robotic-assisted MA, or even to benchmark against conventional KA or MA techniques.

This meta-analysis [6] delivers a strong cautionary note, explicitly advising against the widespread adoption of Kinematic Alignment (particularly when combined with advanced technologies like robotics) until its advantages are unequivocally demonstrated in *well-designed RCTs*. This creates a significant dilemma for the orthopedic field: how to responsibly evaluate and potentially integrate innovative techniques without incurring prohibitive costsor delaying patient access to potentially superior methods. Circles help address that dilemma in a cost and clinically efficient manner.

Assessing Cost-Effectiveness and Surgeon Learning Curves

Problem: Significant barriers to the widespread adoption of RA-TKA include its high initial capital costs, the potential for increased operative time, and the acknowledged steeplearning curve for surgeons. [4] Traditional "big data" RWE often lacks the granularity and structured collection mechanisms required to capture detailed cost data comprehensively or to accurately track surgeon-specific performance metrics over time, making robust cost-effectiveness analyses challenging.

Circles Solution: The flexibility of Observational Protocol design and outcomes **Scoring Groups** enable Circles easily to analyze value-based care from several perspectives. Moreover, the inherent collaboration and "always-on" dataset accessibility makes Circles efficient educational and training platforms for RA-TKA. The high initial costs associated with acquiring robotic systems and the potentially steep learning curve for surgeons [4] represent significant barriers to their widespread and equitable adoption.
Circles can materially help overcome those barriers.

Capturing PROMs and Complications with High Fidelity

Problem: Patient satisfaction and functional outcomes are paramount metrics for success in TKA. However, accurately capturing these inherently subjective measures and reliably linking them to specific surgical techniques (like robotic assistance or KA) can be particularly challenging within broad, less structured "big data" sets. [2] Moreover, the systematic and detailed tracking of both intra-operative and post-operative complications is essential for a complete safety profile, but this can be inconsistent across disparate data sources. [13]

Circles Solution: The Circles platform is explicitly designed to integrate standard or custom outcomes measures into complete clinical Cases. The platform also enables the capture of specific intra-operative complications (e.g., need for ligamentous release, tibial or femoral recut, unplanned ligament injury, neurovascular damage, intra-operative fracture) [13] and post-operative issues (e.g., deep vein thrombosis, pulmonary embolism, acute renal failure, systemic complications) [16], ensuring a comprehensive and high-fidelity safety profile for RA-TKA procedures.

While objective measures like radiographic alignment and technical precision are important indicators of surgical success, the ultimate measure of TKA effectiveness lies in the patient's actual experience, functional improvement, and overall satisfaction. [1]

CONCLUSION

The landscape of Total Knee Arthroplasty is continually evolving, with robotic assistance representing a significant technological advancement aimed at enhancing surgical precision and patient outcomes. While Robotic-Assisted TKA (RA-TKA) demonstrates clear advantages in achieving superior implant alignment and reducing radiographic outliers, the current evidence presents an inconsistent picturegarding its consistent superiority in clinically meaningful patient- reported outcomes and long-term survivability. Critical debates persist, particularly concerning the optimal alignment strategy (kinematic versus mechanical) and the overall cost-effectiveness of these advanced systems.

RegenMed's Circles address these pressing clinical issues and evidence gaps. Their emphasis on direct data sourcing, time-stamped and unmanipulated data, comprehensive longitudinal case tracking, and inherent adherence to specific, clinically relevant Observational Protocols fundamentally distinguish them from traditional "big data" Real-World Evidence. By providing verifiable, high-fidelity data that is analogous in rigor to traditional clinical trials, Circles can generate the robust, clinically meaningful evidence necessary to resolve current debates, such as the true patient benefit of kinematic alignment when performed robotically.

Critically, Circles are cost and clinically efficient. Moreover, they provide Circle Members with unambiguous ownership – and the abilityto monetize – the real-world evidence they generate in their everyday practices.

APPENDIX A: TABLE OF REPORTED BENEFITS AND CHALLENGES OF RA-TKA

Category	Reported Benefits of RA- TKA	Challenges & Debates in RA-TKA
Precision & Alignment	Enhanced Precision and Accuracy in Implant Placement (1)	Inconsistent or No Significant Superiority in Overall Clinical/Functional Outcomes (e.g., PROMs, ROM) compared to Conventional TKA, despite radiographic precision (6)
	Improved Component Alignment and Reduced Radiographic Outliers (1)	Ongoing Debate Regarding Clinical Significance of Alignment Precision (especially KA) (6)
Complications & Revision	Potential for Reduced Complications (e.g., iatrogenic soft tissue injuries, systemic complications) (1)	Higher Risk of Conversion to Open Surgery (4)
	Lower Mid-Term Revision Rates (7)	
Patient Experience	Improved Early Functional Recovery (1)	Lack of Definitive Long-Term Outcome Data (1)
	Reduced Postoperative Pain and Opioid Use (4)	

APPENDIX A: TABLE OF REPORTED BENEFITS AND CHALLENGES OF RA-TKA

Category	Reported Benefits of RA- TKA	Challenges & Debates in RA-TKA
	Higher Patient Satisfaction Rates (3)	
	Personalized Treatment Planning (9)	
Operational & Economic		High Initial Costs of Robotic Systems (4)
		Increased Operative Time (variable, sometimes comparable) (1)
		Potentially Steep Surgeon Learning Curve (4)

APPENDIX B:
TABLE OF COMPARISON OF CIRCLES VS. "BIG DATA" RWE

QUALITY CRITERION	BIG DATA RWE	CIRCLES
Data Integrity, Verifiability	Poor: Derived from multiple, often unidentified/unidentifiable sources; manipulated by undisclosed algorithms; usually impossible to trace datapoints to original sources.	Strong: Sourced directly/verifiably from primary sources (physicians, patients, labs); each datapoint time-stamped, not subject to manipulation/AI "hallucination"; transparent collection/aggregation within closed platform.
Completeness	Poor: Typically has gaps, significantly reducing clinical relevance; rarely contains meaningful longitudinal outcomes data.	Strong: Comprised of well-correlated, longitudinal Cases; all datapoints relatable to a Case; captures/integrates relevant clinical data from enrollment through long-term outcomes.
Clinical Relevance	Poor: Collected from a wide variety of undisclosed clinical settings/contexts; selective, often omitting comorbidities, social determinants of health, adjunct therapies.	Strong: Each dataset relates to a specific Observational Protocol (OP) defined by single anatomical region, pathology, treatment, protocol, standardized outcomes; closely correlated data; analogous to traditional clinical trial.

APPENDIX B:
TABLE OF COMPARISON OF CIRCLES VS. "BIG DATA" RWE

QUALITY CRITERION	BIG DATA RWE	CIRCLES
Good Clinical Practice (GCP)	Unknown and Unknowable; Usually Poor: Impossible to know circumstances/collectors; generally impossible to determine IRB involvement, informed consents, or GCP certificates.	Strong: Patented technical platform inherently helps enforce GCP; many Circles explicitly provide for collection of GCP certificates, practitioner credentials, IRB/MEC support.
Ownership	Often in Dispute: Derives from EMR, registries, hospital records, insurance claims, with increasing claims of ownership from sources.	Unambiguous: Data exclusively collected/aggregated/correla te d within a closed platform; ownership unambiguously established in favor of sponsor, Physicians-Owned Circles Members, and/or RegenMed.
Cost and Burden	High: Expensive vendor payments, data manipulation algorithms, large margins; substantial time/resource burden on physicians/patients creating primary data.	Low: Designed to generate verifiable high-quality data at much lower cost than traditional trials; supported by services ensuring minimal burden on clinicians/patients.

APPENDIX B: TABLE OF COMPARISON OF CIRCLES VS. "BIG DATA" RWE

QUALITY CRITERION	BIG DATA RWE	CIRCLES
Financial Benefit	Inequitable: Sources (physicians, patients) receive nothing of the $70 billion market value.	Equitable: Physicians-Owned Circles return up to 85% of licensing value to POC Members; datasets represent significant/increasing balance sheet equity.
Reporting Capabilities	Limited, Extra Charges: Constrained by dataset limitations; most vendors impose separate charges for various reports.	Robust, Included: Any Circles Question can be queried against any outcomes assessment, allowing many dozens of specific reports; no additional charge for POC Members.

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