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CIRCLES FOR PEDIATRIC MUSCULOSKELETAL CARE

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EXECUTIVE SUMMARY

Pediatric musculoskeletal (MSK) conditions represent a diverse and significant health challenge, encompassing a wide spectrum from common injuries and developmental abnormalities to complex chronic diseases and rare genetic disorders. The unique developmental physiology of children necessitates specialized diagnostic and therapeutic approaches, yet traditional clinical research methodologies, such as randomized controlled trials (RCTs), often face ethical and practical limitations in this vulnerable population. Consequently, substantial evidence gaps persist regarding long-term outcomes, treatment effectiveness in real-world settings, and the holistic burden on children and their families.

Real-World Evidence (RWE), derived from the analysis of routinely collected Real-World Data (RWD), offers a transformative paradigm for addressing these critical issues. RWE provides broader patient representation, captures long-term outcomes, and can inform regulatory decisions more efficiently than traditional trials.

The Circles platform is well positioned to overcome many of the inherent limitations of RWD. By minimizing administrative burden for clinicians, emphasizing patient engagement, fostering cross-institutional collaboration, and implementing a sustainable financial model, Circles can generate high-quality, validatable RWE. This report details the key clinical issues in pediatric MSK, elucidates the role of RWE, and demonstrates how the Circles methodology can significantly enhance diagnostic accuracy, optimize treatment strategies, improve patient quality of life, and inform robust regulatory and clinical guidelines for this distinct patient population.

Pediatric musculoskeletal conditions are among the most common reasons children and adolescents seek medical attention, particularly during periods of rapid growth or high physical activity. The landscape of these conditions is remarkably diverse, ranging from acute injuries to chronic and complex disorders, each presenting unique challenges in diagnosis, treatment, and long-term management.

Prevalence and Diversity of Musculoskeletal Issues in Children

Children experience a wide array of musculoskeletal issues. Common forms of pain include joint pain, often caused by inflammation, stiffness, overuse, injuries, or chronic conditions like juvenile rheumatoid arthritis. Muscle pain can result from overuse during exercise, infections, autoimmune diseases, or certain medications. Bone pain is most frequently associated with broken bones and surgical procedures, while tendon and ligament pain typically stems from sprains and strains. Headaches, often linked to tight muscles or inflammation, are also a common type of musculoskeletal pain in children.[2]

Beyond general pain, specific structural and developmental conditions are notable. Scoliosis, a curvature of the spine, affects approximately 3% of children and adolescents and often becomes apparent during puberty growth spurts. Severe curves can lead to pain and difficulty breathing. Congenital deformities like clubfoot, where the foot is turned inward, are present in about 1 in 1,000 births and can impede walking if untreated. Developmental dysplasia of the hip (DDH), another common condition affecting about 1 in 1,000 births, involves a shallow hip socket leading to instability. Slipped capital femoral epiphysis (SCFE), a hip condition occurring in early adolescence, affects about 0.5 in 1,000 children and can cause pain and limping.[3]

Genetic disorders also contribute to pediatric musculoskeletal morbidity, with muscular dystrophy being a prominent example. Duchenne muscular dystrophy (DMD), the most common childhood form, is characterized by progressive muscle weakness. Inflammatory and infectious conditions are also significant, including juvenile idiopathic arthritis (JIA), an autoimmune disease affecting about 1 in 1,000 children, and osteomyelitis (bone infection), which affects 13 in 100,000 children. Septic arthritis, a joint infection, is another critical concern. Furthermore, musculoskeletal tumors, such as osteosarcoma, Ewing sarcoma (bone cancers), and rhabdomyosarcoma (muscle cancer), represent serious neoplastic conditions in children.[3] Muscle strains and overuse injuries alone account for over 23% of pediatric musculoskeletal pain, particularly in active adolescents.[4]

Developmental Considerations in Pediatric Diagnosis and Treatment

A fundamental principle in pediatric care acknowledges that children are physiologically distinct from adults. Their developing bodies, including growth plates and evolving musculoskeletal systems, necessitate a different set of differential diagnoses, examination techniques, and treatment considerations.[3]

For instance, scoliosis typically manifests during puberty, while congenital conditions like clubfoot and DDH are present at birth.[3] The peak incidence of bone infections occurs between ages 5 and 10 years, and joint infections are most frequent during the first 5 years of life.[6] This inherent developmental variability means that a standardized, adult-centric approach to musculoskeletal diagnosis in children is inherently inadequate. The child's specific developmental stage profoundly influences not only the types of conditions encountered but also their clinical presentation, the urgency of intervention (e.g., the critical need for rapid diagnosis in septic arthritis), and the appropriate diagnostic modalities.

This complexity underscores the challenge in achieving early and accurate diagnosis, demanding specialized pediatric expertise and tailored diagnostic algorithms that account for growth and development.

The Imperative for Robust Evidence in Pediatric Care

Early diagnosis and timely intervention are paramount to prevent complications, mitigate pain, and ensure proper physical development. For instance, untreated chronic conditions like JIA can lead to permanent joint damage, abnormal growth, long-term disability, and active disease persisting into adulthood.[7] The long-term trajectory of many pediatric MSK conditions, coupled with the ethical and practical challenges of conducting **traditional randomized controlled trials (RCTs**) in children, highlights the critical need for alternative, robust evidence generation methodologies.

The broad and prevalent spectrum of conditions, from common injuries to rare genetic diseases and cancers, suggests that pediatric musculoskeletal issues are not merely transient discomforts but represent a substantial, often chronic, burden. This burden significantly impacts children's physical development, their overall quality of life, and the healthcare system, with consequences that can extend well into their adult lives. The diverse and sometimes subtle presentations of these conditions can lead to delayed diagnosis and intervention, exacerbating long-term challenges and contributing to what can be described as a "hidden burden."

KEY CLINICAL ISSUES IN PEDIATRIC MUSCULOSKELETAL CONDITIONS

Addressing pediatric musculoskeletal conditions presents a unique set of clinical challenges, primarily stemming from diagnostic complexities, gaps in understanding long-term treatment efficacy, and the profound holistic impact on children and their families.

Diagnostic Complexities and Challenges

Pediatric musculoskeletal symptoms can be non-specific, including aching, stiffness, fatigue, and swelling.[2] Differentiating benign conditions like "growing pains" from serious underlying pathologies is a significant challenge. Clinicians must be vigilant for "red flags" such as persistent night pain, deep bone pain, fever, systemic symptoms (e.g., anorexia, weight loss, malaise), delayed or regressed motor milestones, and unexplained weakness or bony lumps.[5]

It is crucial to note that limb pain can be a presenting feature in 43% of children with leukemia, and joint pain in 11%, underscoring the necessity to consider systemic diseases.[5] Even common occurrences like falls can be misleading, potentially masking underlying arthritis or even non-accidental injury.[5] Younger children, in particular, may not verbalize pain, requiring clinicians to observe for signs like stiffness, swelling, limping, or changes in function.[5]

The diagnostic process is further complicated by the delayed appearance of objective signs; for example, changes in osteomyelitis may not be visible on X-rays for one to two weeks after infection onset.[6] Conditions like septic arthritis demand urgent diagnosis due to the risk of permanent joint damage, yet inflammatory markers (such as complete blood count and Creactive protein) may be late signs in young children.[5] The differential diagnosis for acute bone pain is broad, encompassing trauma, leukemia, malignant bone tumors (e.g., Ewing sarcoma or osteogenic sarcoma), and sickle cell crisis.[6] While clinical history and physical examination are primary for conditions like muscle strains, imaging is often crucial for assessing the extent and prognosis of injury, and blood tests or gait analysis can aid in identifying underlying systemic or functional causes.[1]

The confluence of overlapping symptoms, the presence of misleading signs, and the nonspecific nature of early indicators (especially in young children who cannot verbalize pain) significantly increase the risk of misdiagnosis or delayed diagnosis. The critical time-sensitive nature of conditions like septic arthritis, coupled with delayed objective diagnostic indicators for others, means that clinical suspicion, comprehensive history-taking, and astute physical examination, often extending beyond initial imaging, are paramount. This diagnostic complexity highlights a critical need for more robust, real-time data to improve pattern recognition and decision support for clinicians.

Treatment Efficacy and Long-Term Management Gaps

Treatment approaches for pediatric musculoskeletal conditions are highly variable, depending on the specific condition and its severity. Available options include physical therapy (aimed at improving strength, flexibility, mobility, and aiding rehabilitation), medications (such as anti-inflammatory drugs or pain relievers), bracing or orthotic devices (e.g., for scoliosis), and lifestyle modifications.

For scoliosis, bracing primarily aims to prevent curve progression rather than to cure the condition, with surgical options like spinal fusion or vertebral body tethering reserved for more severe cases.[8] The Schroth Method, a specialized physical therapy, focuses on threedimensional spinal de-rotation and stabilization.[9] Juvenile idiopathic arthritis management involves a range of pharmacological agents, from nonsteroidal anti-inflammatory drugs (NSAIDs) to biologic disease-modifying anti-rheumatic drugs (bDMARDs), with early initiation of methotrexate and bDMARDs recommended for certain risk factors.[7] Surgical intervention for musculoskeletal infections is primarily focused on evacuating purulent material and removing necrotic bone.[6]

Many pediatric musculoskeletal conditions are chronic or progressive. Muscle strains, for instance, evolve through acute, subacute, and chronic phases, carrying a risk of re-injury and potential complications like compartment syndrome.[4] Juvenile idiopathic arthritis, if inadequately treated, can lead to permanent joint damage and active disease persisting into adulthood.[7] Scoliosis curves can worsen significantly during growth spurts.[8] Genetic conditions like muscular dystrophy are characterized by progressive muscle weakness.[3] Understanding and effectively managing these long-term trajectories are critical for optimal patient outcomes.

Pain is a central issue, requiring systematic assessment using scales like the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS).[4] Musculoskeletal conditions can significantly limit a child's ability to participate in normal daily activities, sports, and overall physical development. Functional assessment is therefore essential to guide treatment decisions and evaluate readiness to return to activities.[4]

While pharmacological treatments for conditions like JIA have detailed cost and outcome data [7] , there appears to be a relative deficit in comprehensive, long-term real-world evidence for non-pharmacological interventions in pediatric musculoskeletal conditions. This includes therapies such as bracing and physical therapy. This gap makes it challenging to establish fully evidence-based care pathways that effectively integrate all treatment modalities.

Holistic Impact on Children and Families

Beyond physical symptoms, pediatric musculoskeletal conditions impose a significant psychosocial burden. Chronic headaches, for example, can lead to sleep disturbances and difficulties with concentration.[2] Chronic illnesses like JIA affect the entire family, causing emotional distress and economic strain.[7] Caregivers often face challenges such as job resignation, absenteeism, and reduced productivity due to their caregiving responsibilities.[7]

The management of pediatric musculoskeletal conditions can incur substantial costs. For JIA, medication, particularly expensive biologic therapies, constitutes the largest direct cost.[7]

Indirect costs, including lost caregiver working hours, travel expenses for appointments, and accommodation during hospitalizations, also contribute significantly to the overall economic burden on families.[7] The impact of chronic pediatric musculoskeletal conditions extends far beyond immediate clinical symptoms. They impose a profound and often unquantified burden on children's long-term physical development, psychosocial well-being, and family economic stability.

The "cost of illness" encompasses not only direct medical expenses but also reduced quality of life, potential educational disruption, social isolation, and significant caregiver strain. Traditional clinical trials often focus on narrow efficacy endpoints, but real-world evidence is uniquely positioned to capture these broader, holistic impacts, providing a more complete and realistic picture of the true disease burden and the comprehensive value of interventions, especially for conditions with long trajectories that extend into adulthood.

Table 1 summarizes key common pediatric MSK conditions and associated clinical challenges.

REAL-WORLD EVIDENCE: A PARADIGM SHIFT IN HEALTHCARE DATA

The evolving landscape of healthcare data has paved the way for Real-World Evidence to play an increasingly pivotal role in understanding disease, evaluating medical products, and informing clinical practice.

Defining Real-World Data and Real-World Evidence

As defined by the FDA, **Real-World Data** (RWD) encompasses information relating to patient health status and/or the delivery of healthcare that is routinely collected from a variety of sources.[11] **Real-World Evidence** (RWE), in turn, is the clinical evidence regarding a medical product's use and potential benefits or risks, derived from the analysis of RWD.[11] The **21st Century Cures Act** specifically defines RWE as evidence derived from "data regarding the usage, or potential benefits or risks, of a drug derived from sources other than randomized clinical trials".[12]

Distinction from Randomized Controlled Trials (RCTs) and Complementary Role

Randomized Controlled Trials (RCTs) have long been considered the "gold standard" for clinical research. They are meticulously designed to eliminate bias, providing clear, impartial results on the efficacy of medical interventions in highly controlled settings.[15] However, RCTs face critiques regarding the generalizability of their findings to the broader population. They often exclude diverse patient populations, including children, the elderly, and pregnant or breastfeeding women, typically for safety reasons.[15] Furthermore, the controlled environment of RCTs frequently fails to mirror real-world clinical practice, where patient behaviors and environmental factors vary significantly.[15]

RWE studies, often designed as "pragmatic trials," aim to evaluate the effectiveness of interventions in routine clinical practice.[12] RWE thus complements RCTs by providing insights into how medical products and interventions perform in heterogeneous, real-world patient cohorts.[15] The ethical and practical limitations of conducting extensive RCTs in pediatric populations create significant evidence gaps regarding drug and device safety, efficacy, and optimal treatment strategies.

RWE, by capturing data from routine clinical practice across broad and diverse patient populations, becomes not merely a complementary tool but an essential methodology for generating evidence specific to children. This addresses the critical unmet need created by RCT limitations, particularly for rare conditions or the assessment of long-term outcomes in a growing and developing population.

Key Sources of RWE

The increasing availability of RWD stems from various sources:

- **Electronic Health Records (EHRs):** A rapidly expanding source, with 99% of hospitals and 90% of office-based doctors in the US now utilizing EHR systems.[12] EHRs provide rich clinical data for retrospective, observational analyses of treatments and outcomes.[14]
- **Medical Claims Data:** Routinely collected administrative data used for retrospective, longitudinal, and cross-sectional analyses of healthcare resource utilization and costs.[14]
- **Product or Disease Registries:** Structured databases that collect information on specific patient populations or medical products, often used for post-market surveillance or to track long-term outcomes.[11] An example is the cVAD registry used for pediatric Impella RP evaluation.[17]
- **Digital Health Technologies:** Including wearable devices and smartphones, which generate billions of user-specific data points daily, though much remains unanalyzed.[12]

- **Patient-Generated Data:** Including information from social media.[12]
- **Other sources** include open data policies (e.g., Open FDA) and academic data sharing initiatives. [12]

Advantages of RWE in Pediatric Populations

RWE offers several compelling advantages, particularly for pediatric populations:

- **Broader Patient Representation:** RWE can encompass a diverse patient population, including individuals often excluded from traditional clinical trials, providing a more comprehensive understanding of how interventions perform in the real world.[15] This is vital for pediatric populations, where specific age groups, rare conditions, or complex comorbidities might be underrepresented in RCTs.
- **Long-term Data:** RWE enables the assessment of long-term safety and effectiveness, which is critical for pediatric conditions where disease progression and the impact of interventions manifest over extended periods of growth and development.[16]
- **Cost-effectiveness:** Generating RWE is generally less resource-intensive than conducting traditional clinical trials.[16]
- **Faster Decision-making:** RWE provides continuous monitoring of product safety and effectiveness, allowing for timely identification of adverse events and enabling swift regulatory responses.[16]
- **Enhanced Safety Surveillance:** RWE has a long history of use by regulatory bodies like the FDA for post-market safety monitoring of approved drugs and devices.[13] It can also inform regulatory decisions regarding new indications, populations, dosing information, or for meeting post-approval study requirements.[11]

By systematically capturing data from a wider, more representative pediatric population (encompassing diverse demographics, disease severities, and care settings), RWE can uncover variations in treatment effectiveness and safety that might be overlooked in controlled trials.

This capability allows for a deeper understanding of how interventions perform across the full spectrum of real-world pediatric contexts, thereby fostering more personalized and equitable care. It can identify disparities in outcomes, inform the development of tailored treatment protocols, and ensure that evidence-based guidelines are applicable to all pediatric patients, not just a select, homogenous subgroup.

Limitations and Methodological Considerations in RWE Generation

Despite its advantages, RWE generation has inherent limitations:

- **Data Quality:** RWE relies on existing healthcare data, which can vary significantly in quality, completeness, and consistency, potentially leading to biases and inaccuracies in analyses. The maxim "data in, data out" is highly relevant.[16]
- **Data Availability and Accessibility:** Challenges exist in accessing and linking disparate data sources across different healthcare systems or platforms.[16]
- **Confounding Factors:** Patient outcomes can be influenced by numerous unmeasured or inadequately controlled variables in real-world settings.[16]
- **Selection Bias:** Certain patient groups may be over- or under-represented in RWD sources, leading to skewed results.[16]
- **Lack of Randomization:** Unlike controlled clinical trials, RWE studies typically lack randomization, making it more difficult to establish direct causality and infer cause-andeffect relationships.[16]
- **Complex Outcomes:** For orthopedic devices, outcomes related to mobility and pain improvement can be complex and subjective to measure accurately in RWE.[16]
- **Restricted Patient Diversity:** Despite RWE's general advantage in representation, specific pediatric subgroups might still be underrepresented in certain RWD sources.[16]
- **Heterogeneity in Devices/Practices:** The diverse landscape of medical devices and variable clinical practices require unique considerations when applying RWE.[16]
- **Regulatory Challenges:** While the FDA is increasingly accepting RWE, specific guidance and acceptance criteria for different regulatory decisions are still evolving.[11]

Table 2 summarizes the advantages and limitations of RWE in pediatric healthcare.

While RWE offers significant promise, its utility is dependent on the quality and structure of the underlying data. The patented Circles platform represents a structured and innovative approach to generating high-quality, validatable RWE, particularly well-suited for the complexities of pediatric musculoskeletal care.

Overview of the Circles Methodology and Technical Platform

Circles are designed to capture RWD and develop RWE in a minimally burdensome and cost-efficient manner. **The Observational Protocol** (OP) underlying each Circle is prospectively designed to address a particular RWE objective, with the goal of generating demonstrable clinical, scientific, and financial value – e.g., research funding – for all participating members. The platform encompasses the physician-facing inCytes™ and patient-facing Benchmarc™ modules, and associated processes ensuring clinical efficiency as well as seamless collaboration within and across institutional and even national borders.

Mechanism of Data Collection, Aggregation, and Validation

A Circle represents the coherent integration within a closed system of (i) clinically significant diagnosis and associated treatment data, (ii) pertaining to a specific and statistically significant patient cohort, (iii) well correlated to the long-term outcomes of that cohort. Each Circle focuses on a specific anatomical region, pathology, treatment protocol, and outcomes assessment, ensuring focused and relevant **Circles Datasets**. The model typically involves a **Principal Investigator** collaborating with any number of physician- and/or scientist **Investigators**.

Circles inherently foster **collaboration** among Investigators treating similar patient cohorts, whether within or across institutional and even national borders. For pediatric orthopedics, where patient cohorts for specific rare conditions are small at any single institution, aggregating data across multiple physician practices through Circles becomes a powerful mechanism for achieving statistical significance and generalizability.

Circles thus operate as a continuous cycle of improvement, moving from (i) the clinical/scientific hypothesis reflected in an OP, (ii) collaborative data generation, (iii) ongoing analysis and learning, to (iv) new and refined standards of care. The core objective is to produce "validatable real-world evidence," defined as high-quality, longitudinal datasets suitable for clinical decision-making, regulatory submissions, value-based care, medical innovation, health equity, and research. Because **Circles Datasets** are generated within a controlled, closed system, they are **unambiguously owned**, and free of error and artifacts.

Circles thus address the inherent limitations of traditional RWE generation. For pediatric musculoskeletal care, where data can be sparse, patient populations heterogeneous, and longterm follow-up crucial, this structured, high-fidelity data capture is critical for building trustworthy evidence that can truly inform complex clinical and regulatory decisions. The emphasis on "long-term outcomes" is particularly valuable for chronic pediatric conditions that evolve over many years.

Specific Benefits of Circles for Pediatric Research

Circles offer several important advantages for pediatric research:

- **Minimizing Administrative Burden:** This is particularly valuable in pediatric settings where healthcare providers are often time-constrained and data entry can be a significant additional task.
- **Emphasis on Patient Engagement and Long-term Compliance:** Circles prioritize patient (or caregiver) engagement, ensuring comprehension of medical conditions and treatment paths, and fostering long-term compliance.
- **Inherent Collaboration Support:** This collaborative model is highly beneficial for studying rare pediatric conditions or for aggregating sufficiently large patient cohorts that are geographically dispersed.
- **Key Opinion Leader (KOL) and Investigator Recruitment:** Specific processes within Circles support the identification, onboarding, and active involvement of clinical and scientific experts, along with additional Circle Members.
- **Select Use Cases:**

Clinical Decision Making: Capture long-term outcomes, developing and confirming standards of care, coordinating care pathways across multiple healthcare professionals, supporting remote patient therapies and monitoring, and integrating evidence-based medicine into treatment protocols.

Education and Training: Augment residency/fellowship programs, CME courses, and medical practice educational materials.

Legal/Regulatory Compliance: Support evidence generation for novel, compassionate use, right-to-try, and experimental treatment protocols, confirms adverse event tracking, and provides data for expert medical opinions.

Funding: given the high-quality and unambiguous ownership of Circles Datasets, they represent valuable assets, which can drive funding from a variety of sponsors and donors for research and other mission-critical objectives.

Enhancing Diagnostic Accuracy and Early Intervention

- **Atypical Presentations Of Serious Conditions**

Circles can systematically collect comprehensive RWD, including detailed clinical histories, physical examination findings, and results from various diagnostic tests (e.g., imaging like Xrays/MRIs, blood tests for inflammatory markers, gait analysis) across large, diverse pediatric cohorts.

By correlating these granular RWD points with confirmed diagnoses and long-term patient outcomes, Circles can facilitate the identification of subtle "red flags" or atypical presentations of serious conditions (e.g., leukemia presenting as limb pain[5]) that might be overlooked or misdiagnosed in routine clinical practice, especially given the diagnostic complexities in children.[5]

- **Rare MSK Diseases**

Pediatric musculoskeletal conditions often present with non-specific symptoms, and rare but serious conditions (like leukemia or bone tumors [5]) can mimic more benign ones. By aggregating high-fidelity data from numerous collaborating physicians, Circles can identify subtle, underlying patterns in symptom presentation, laboratory results (e.g., the significance of late inflammatory markers in septic arthritis [5]), or imaging progression (e.g., early signs of osteomyelitis [6]) that lead to earlier and more accurate diagnoses for conditions that are individually rare but collectively represent a significant diagnostic challenge.

This is particularly valuable for conditions where delayed diagnosis can lead to permanent damage, such as septic arthritis, where "time is joint".[5] This capability allows for the development of advanced diagnostic support tools, potentially leveraging artificial intelligence and machine learning, based on real-world patient trajectories. Circles can thus significantly improve the speed and accuracy of diagnosis, especially for conditions with critical time windows for effective intervention, ultimately leading to better patient outcomes.

- **Longitudinal Datasets**

The inherent longitudinal data capture capability of Circles [18] allows for continuous tracking of the natural history of pediatric musculoskeletal conditions, such as scoliosis [3], JIA [3], and muscular dystrophies [3], from their onset through various developmental stages. This continuous, real-world data stream can reveal how symptoms evolve over time, how conditions respond to initial and subsequent interventions, and help identify crucial prognostic factors across a heterogeneous patient population, reflecting the diversity often excluded from traditional RCTs.[15]

Optimizing Treatment Strategies and Outcomes

- **Multi-Year Capture**

A foundational element of each Circle is well-correlated long-term outcomes capture. This is uniquely suited for pediatric musculoskeletal care, where the full impact of interventions (e.g., bracing for scoliosis [8]; biologic therapies for JIA [7]) often unfolds over many years. This includes assessing the real-world effectiveness and safety profiles of pharmacological treatments (e.g., biologics for JIA [7]), various surgical procedures (e.g., spinal fusion, vertebral body tethering for scoliosis [8]), and medical devices (e.g., cryoablation probes).

- **Where RCTs Are Lacking or Impractical**

Circles inherently foster collaboration among physician-investigators treating similar patient cohorts, whether within or across institutional and even national borders. For pediatric orthopedics, where patient cohorts for specific rare conditions are small at any single institution, aggregating data across multiple physician practices through Circles becomes a powerful mechanism for achieving statistical significance and generalizability.

Given the ethical and practical limitations of conducting extensive RCTs in children, many treatments used in pediatric populations lack robust evidence and are sometimes used "offlabel".[15] A successful RWE project highlighted the use of EHR data to expand the labeling of a cryoablation probe for adolescents. Circles capture data from "routine clinical practice" [12] and are designed to support novel, compassionate use, right-to-try, experimental and similar treatment protocols".

Circles can thus systematically collect high-quality RWD on treatments currently used in pediatric musculoskeletal care that lack strong RCT evidence, including specific drugs, medical devices, and surgical techniques. This capability can generate the necessary RWE to expand indications, refine dosing regimens, or validate the safety and effectiveness of interventions in specific pediatric subgroups. Such evidence can accelerate regulatory approvals and facilitate broader access to appropriate and evidence-based care for children.

- **Single Or Combined Therapies**

By capturing granular data on individual patient characteristics, treatment adherence, and varied outcomes, Circles can help identify which interventions or combinations of therapies are most effective for specific patient profiles (e.g., based on age, disease severity, or genetic factors). This data-driven approach supports the development and refinement of standards of care and the coordination of care pathways across multiple healthcare professionals involved in a child's treatment, leading to more tailored and effective management.

Many pediatric musculoskeletal conditions, particularly scoliosis and sports injuries, heavily rely on non-pharmacological interventions like bracing and physical therapy. While their clinical importance is widely recognized, robust, long-term RWE on their effectiveness, patient adherence, and impact on functional outcomes in diverse real-world settings is often less available or less rigorously quantified compared to pharmacological therapies. Circles, with their emphasis on patient engagement and long-term outcomes capture, are well positioned to collect this type of data.

By systematically collecting data on adherence to bracing, the frequency and intensity of physical therapy sessions, and correlating these with objective functional assessments (e.g., range of motion, return-to-play criteria [4]) and patient-reported quality of life, Circles can provide compelling RWE on the true impact and cost-effectiveness of conservative management and rehabilitation. This evidence can inform and strengthen clinical guidelines, support the justification for reimbursement of these therapies, and empower clinicians to make more evidence-based decisions about non-surgical care options.

Improving Patient Quality of Life and Reducing Burden

- **Patient And Caregiver User Experience**

Circles' patient-facing Benchmarc™ platform [18] provides a direct mechanism for the systematic collection of patient-generated data and patient-reported outcomes. This includes subjective measures like pain levels (using scales such as VAS/NRS [4]), objective functional capacity (e.g., Childhood Health Assessment Questionnaire (CHAQ) and Pediatric Quality of Life Inventory (PedsQL) for JIA [7]), and overall quality of life. This moves beyond purely clinical metrics to capture the holistic lived experience of the child and their family, providing a more patient-centered view of treatment success.

- **Value-Based Care and Health Economics And Outcomes Research**

Circles can also systematically collect detailed data on the indirect costs associated with pediatric musculoskeletal conditions, such as caregiver work absences, travel expenses for medical appointments, and the need for specialized assistance or mobility devices, as demonstrated in the JIA cost study.[7] The detailed JIA study clearly illustrates the significant direct (medication, specialist visits) and indirect (caregiver lost work hours, transportation, accommodation) costs of a chronic pediatric musculoskeletal condition.

By quantifying the full economic burden of pediatric musculoskeletal conditions on both healthcare systems and affected families, Circles can provide crucial data for comprehensive health economic evaluations. This evidence can support the development of value-based care models, inform policy decisions regarding resource allocation, and strengthen advocacy efforts for better support systems for families. This moves the assessment of interventions beyond just clinical efficacy to demonstrate their holistic value, encompassing economic and social well-being.

Informing Regulatory Decisions and Clinical Guidelines

Regulatory bodies like the FDA are increasingly committed to leveraging RWE to inform decisions regarding new indications for approved drugs, expanding populations, refining dosing information, and fulfilling post-approval study requirements.[11] The validatable RWE generated through Circles meets the quality and rigor necessary to support these regulatory submissions.

Examples include the RWE evaluation of Impella RP in pediatric patients using the cVAD registry [17] and the UCSF-Stanford Pediatric Device Consortium's use of EHR data mining to expand cryoablation probe labeling for adolescents. The continuous cycle of improvement inherent in the Circles methodology, coupled with its ability to develop, improve, and confirm standards of care, facilitates the direct translation of robust RWE insights into updated and more effective clinical guidelines for pediatric musculoskeletal conditions.

Table 3 summarizes some of the ways Circles can be used in pediatric MSK care.

Illustrative Observational Protocols in Pediatric MSK Care

Circles Datasets hold real potential to advance understanding and management across various pediatric musculoskeletal conditions.

- **Juvenile Idiopathic Arthritis (JIA): Outcomes, Costs, and Treatment Patterns**

A non-Circles RWE study conducted in Spain assessed the direct healthcare, indirect resource utilization, and associated costs of moderate-to-severe JIA in children.[7] The study revealed that JIA imposes significant costs on both the Spanish healthcare system and affected families, primarily driven by expensive biologic therapies. Despite the high cost, these treatments were effective in maintaining inactive disease/low disease activity and a good quality of life.[7] Crucially, the study also highlighted substantial indirect costs, such as lost caregiver working hours and travel expenses, which directly impact families.[7] A Circle focused on JIA could build upon this by continuously tracking long-term outcomes, real-world adherence to biologic therapies, and the evolving impact on family quality of life across diverse geographical and socioeconomic settings. This would provide more granular and generalizable data on real-world treatment effectiveness, safety, and comprehensive cost-benefit ratios, informing value-based care models.

- **Scoliosis Management: Bracing Efficacy and Surgical Outcomes**

Scoliosis treatment is highly dependent on curve size and the child's remaining growth potential.

Bracing is a common non-surgical intervention aimed at preventing curve progression, while surgical options like spinal fusion, vertebral body tethering, and expanding rods are available for more severe cases.[8] The Schroth Method, a specialized physical therapy, aims to improve posture, strength, and breathing.[9]

Circles could provide crucial RWE by tracking long-term curve progression, patient adherence to bracing regimens (potentially via smart brace data or patient-reported usage, and functional outcomes (e.g., mobility, pain levels, respiratory function) for various treatment approaches (conservative versus surgical). This would offer valuable and proprietary real-world data on the optimal timing and type of intervention, particularly for non-surgical methods where robust, long-term evidence is often less available.[8]

- **Congenital Deformities and Rare Conditions**

Common congenital deformities include clubfoot and developmental dysplasia of the hip (DDH).[3] Genetic conditions like muscular dystrophies (e.g., Duchenne Muscular Dystrophy, DMD) are progressive, leading to muscle weakness.[3] Case studies highlight conditions such as Charcot-Marie-Tooth disease, Spinal Muscular Atrophy, and Myotonic Dystrophy, all presenting with muscle weakness or developmental delays.[21] For rare pediatric musculoskeletal conditions, patient cohorts are typically small and geographically dispersed, making traditional research methods like RCTs extremely challenging or impossible.

Circles' inherent collaborative structure and its ability to aggregate high-quality data from multiple clinical sites, potentially across different countries, directly address this limitation.[18] This enables the creation of statistically significant patient cohorts for conditions that would otherwise be too rare to study effectively. This capability is crucial for generating robust RWE on natural history, the effectiveness of emerging treatments, and long-term outcomes for these underserved patient populations, thereby accelerating drug development and the formulation of clinical guidelines.

- **Sports Injuries and Overuse Syndromes: Prevention and Rehabilitation**

Muscle strains and overuse injuries constitute a significant portion (>23%) of pediatric musculoskeletal pain, particularly prevalent in adolescents actively involved in sports.[4] Contributing factors include rapid muscle contractions, inadequate warm-up, and fatigue from repetitive use.[4] Functional assessment is a key part of evaluation, guiding treatment and readiness for return to physical activities.[4]

A Circle focused on pediatric sports injuries could systematically track injury incidence, identify specific risk factors (e.g., training load, environmental conditions, nutrition [4]), evaluate the effectiveness of different rehabilitation protocols, and monitor long-term recurrence rates in young athletes. This RWE could inform the development of evidencebased prevention programs, optimize rehabilitation strategies, and establish safer return-tosport guidelines.

For pediatric orthopedic devices and surgical innovations, where conducting large-scale RCTs is often impractical, ethically complex, or even impossible, Circles can serve as a robust and validated platform for collecting RWE. This allows for essential post-market surveillance, the assessment of long-term durability, and the evaluation of complex functional outcomes in routine clinical use. By providing high-quality, validated RWE, Circles can significantly accelerate the regulatory approval process for pediatric indications of new technologies and ensure that these innovations are safely and effectively integrated into real-world clinical practice, ultimately benefiting young patients.

CONCLUSION

Real-World Evidence offers unparalleled opportunities to address the complex diagnostic dilemmas, optimize treatment strategies, and alleviate the holistic burden associated with pediatric musculoskeletal conditions. By leveraging data from routine clinical practice, RWE moves beyond the limitations of traditional clinical trials, providing a more comprehensive and representative understanding of disease progression and intervention effectiveness in diverse pediatric populations.

With their structured, collaborative, patient-engaged, and financially sustainable approach, Circles are well positioned to generate high-quality, validatable RWE. Circles Datasets can bridge critical evidence gaps in pediatric musculoskeletal care, accelerating the translation of insights into improved clinical practice and robust regulatory decisions.

To fully realize the transformative potential of Circles in pediatric musculoskeletal health, several approaches are recommended. Circles support all of them.

- **Fostering Multi-Stakeholder Collaboration:** Stronger partnerships are essential among clinicians, academic researchers, the pharmaceutical and medical device industries (as potential sponsors of Private or White Label Circles), healthcare payers, and regulatory bodies.

- **Developing Standardized Data Collection and Interoperability:** Continued efforts are needed to establish common data models and ensure interoperability across different RWD sources and RWE platforms. This will maximize the utility and generalizability of data collected through various Circles and other healthcare systems, enabling broader analyses and more robust conclusions.

- **Integrating RWE into Clinical Decision Support:** Practical tools and guidelines must be developed that translate RWE insights into actionable, real-time guidance for clinicians at the point of care. This will directly improve diagnostic accuracy and treatment optimization for pediatric musculoskeletal conditions.

- **Informing Pediatric-Specific Regulatory Pathways:** Regulatory agencies, payers and providers should continue to refine and expand clear guidelines for the acceptance and use of RWE in pediatric drug and device approvals. This acknowledges the unique challenges and ethical considerations inherent in this patient population and facilitates the timely introduction of safe and effective therapies.

- **Prioritizing Patient and Family Engagement:** It is imperative to build upon Circles' inherent emphasis on patient and caregiver engagement.[18] This ensures that research questions, outcome measures, and treatment strategies are truly patient-centered and reflect the lived experiences and priorities of children and their families, leading to more relevant and impactful evidence.

TABLE 1:
PEDIATRIC MSK CONDITIONS, CLINICAL CHALLENGES

Condition	Key Clinical Issue/Challenge
Juvenile Idiopathic Arthritis (JIA)	Diagnostic delay/misdiagnosis, progressive nature/long-term disability, high treatment costs/burden on families, functional limitations, persistent active disease into adulthood
Scoliosis	Diagnostic delay (apparent during puberty), progressive nature (worsens with growth), variable treatment response (bracing vs. surgery), lack of long-term evidence for non-pharmacological therapies
Clubfoot / Developmental Dysplasia of the Hip (DDH)	Congenital deformity, need for early intervention, potential for walking problems/pain if untreated
Muscular Dystrophy	Progressive muscle weakness, increasing trouble with movement, difficulty breathing, frequent falls, changes in posture and gait
Osteomyelitis / Septic Arthritis	Diagnostic delay (late radiographic signs, late inflammatory markers in young children), need for urgent intervention ("time is joint" for septic arthritis), high fever, severe pain, difficulty using affected area
Muscle Strains / Overuse Injuries	Risk of re-injury, potential for complications (compartment syndrome), need for functional assessment and return-to-play criteria, prevalence in active adolescents
General Pediatric MSK Pain	Non-specific symptoms, differentiating benign vs. serious conditions, "red flags" (night pain, bone pain, systemic symptoms), difficulty verbalizing pain in younger children, psychosocial burden (sleep,

TABLE 2:
LIMITATIONS OF BIG DATA RWE IN PEDIATRIC HEALTHCARE

Category	Advantages of RWE	Limitations of "Big Data RWE
Patient Representation	Broader patient base, includes individuals often excluded from RCTs (e.g., children, elderly, diverse demographics)	Potential for selection bias (over/under-representation of groups)
Data Scope & Duration	Captures long-term outcomes and disease progression over extended periods; reflects real-world patient behaviors and environments	Data availability and accessibility issues across disparate sources; complex outcomes (e.g., mobility, pain) can be subjective to measure
Resource Intensity	Generally more cost-effective than traditional RCTs	Data quality can vary significantly, leading to inaccuracies; reliance on existing data
Regulatory Impact	Faster insights for safety surveillance; supports regulatory decisions for new indications, populations, dosing, and postapproval requirements	Lack of randomization makes causality difficult to establish; evolving regulatory guidance and acceptance criteria
Methodological Rigor	Provides evidence on effectiveness in routine clinical practice (pragmatic trials)	Confounding factors not always adequately controlled; heterogeneity in devices/practices requires unique considerations

TABLE 3:
SELECT CIRCLES USE CASES IN PEDIATRIC MSK CARE

Key Clinical Issue	How Circles Help	Specific Mechanism/Feature of Circles
Diagnostic Delay for Rare/Complex Conditions	Enables pattern recognition for early and accurate diagnosis; identifies atypical presentations	Multi-site collaboration; structured data validation (free of error and artifacts); comprehensive RWD capture (clinical history, imaging, labs)
Gaps in Long-Term Efficacy of Non-Pharmacological Therapies	Provides longitudinal effectiveness data on adherence and functional outcomes for conservative management	Long-term outcomes capture; patient-facing Benchmarc™ for adherence tracking; correlation with objective functional assessments
Unmeasured Patient/Family Burden (Psychosocial & Economic)	Captures comprehensive patient-reported outcomes (PROs) and detailed indirect costs; quantifies true "cost of illness"	Patient-facing Benchmarc™ for PROs; structured data collection on caregiver impact, travel, and resource utilization
Limited Evidence for Pediatric-Specific Interventions (Drugs/Devices)	Generates robust evidence for new indications, offlabel uses, and post-market surveillance in pediatric populations	Validatable RWE for regulatory submissions; multi-site collaboration for rare cohorts; support for novel/experimental protocols
Optimizing Personalized Treatment Pathways	Informs tailored care plans and coordinated pathways based on real-world effectiveness across diverse patient profiles	Granular data on individual characteristics and varied outcomes; development/confirmation of standards of care; multiprofessional care coordination

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1. Circles inherently foster **collaboration** among physician-investigators treating similar patient cohorts, whether within or across institutional and even national borders. For pediatric orthopedics, where patient cohorts for specific rare conditions are small at any single institution, aggregating data across multiple physician practices through Circles becomes a powerful mechanism for achieving statistical significance and generalizability.
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