Review

Musculoskeletal Digital Therapeutics and Digital Health Rehabilitation: A Global Paradigm Shift in Orthopaedic Care

Youn Kyu Lee , Tae Hyung Kim , Jong-Ho Kim *

Posted Date: 7 October 2025

doi: 10.20944/preprints202510.0510.v1

Keywords: digital therapeutics; musculoskeletal rehabilitation; orthopaedic surgery; telerehabilitation; artificial intelligence; wearable sensors; precision orthopaedics

 doi:10.20944/preprints202510.0510.v1

Review

Musculoskeletal Digital Therapeutics and Digital Health Rehabilitation: A Global Paradigm Shift in Orthopaedic Care

Youn Kyu Lee [1], Tae Hyung Kim [2] and Jong-Ho Kim [3,*]

[1] School of Computer Science and Engineering, Chung-Ang University, Seoul, Republic of Korea
[2] Department of Computer Engineering, Hongik University, Seoul, Republic of Korea
[3] Department of Orthopaedic Surgery, Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea
* Correspondence: katris@naver.com; Tel.: +82-2-3779-1826

Abstract

Musculoskeletal disorders (MSDs) affect over 1.7 billion people globally and represent the leading cause of disability worldwide. Conventional rehabilitation strategies face challenges including limited accessibility, suboptimal adherence, and lack of personalization. Digital therapeutics (DTx)—evidence-based, software-driven interventions regulated as medical devices—have emerged as transformative solutions in chronic disease management. This comprehensive review synthesizes current knowledge on musculoskeletal DTx and digital health rehabilitation across orthopaedic subspecialties. We describe core enabling technologies including artificial intelligence-driven motion analysis, wearable sensors, tele-rehabilitation platforms, and cloud-based ecosystems. Clinical applications spanning spine, upper and lower extremities, sports injuries, and trauma are examined alongside global regulatory frameworks, economic considerations, and implementation challenges. Early clinical evidence demonstrates improvements in functional outcomes, adherence, and cost-effectiveness. Future directions include digital twin technologies, predictive analytics, and integration with precision orthopaedics. By establishing a comprehensive framework for musculoskeletal DTx implementation, this review highlights their potential to improve outcomes, reduce healthcare costs, and address global rehabilitation access gaps.

Keywords: digital therapeutics; musculoskeletal rehabilitation; orthopaedic surgery; tele-rehabilitation; artificial intelligence; wearable sensors; precision orthopaedics

1. Introduction

1.1. Epidemiology and Global Burden of Musculoskeletal Disorders

Musculoskeletal disorders (MSDs) constitute a diverse group of conditions affecting muscles, bones, tendons, ligaments, and joints, ranging from degenerative diseases to traumatic injuries and chronic pain syndromes [1,2]. The Global Burden of Disease study identifies MSDs as the leading contributor to disability-adjusted life years worldwide, affecting approximately 1.71 billion individuals [3]. This staggering burden encompasses a wide spectrum of conditions including osteoarthritis affecting 528 million people globally, low back pain experienced by 619 million individuals, and rheumatoid arthritis impacting 18 million patients worldwide [2]. The economic impact is equally substantial, with MSDs accounting for an estimated $213 billion in annual healthcare expenditures in the United States alone and representing the second highest category of healthcare spending after cardiovascular disease [3].

Paradoxically, increased participation in recreational sports activities among both younger and older populations has led to higher rates of sports-related musculoskeletal injuries. Additionally, the COVID-19 pandemic has resulted in a substantial backlog of elective orthopaedic procedures, with

 doi:10.20944/preprints202510.0510.v1

an estimated 28 million surgeries worldwide deferred during 2020-2021, creating unprecedented rehabilitation demands [4].

1.2. Evolution of Orthopaedic Surgical Practice and Rehabilitation Needs

Orthopaedic surgical volumes are increasing steadily across all major procedure categories. Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are projected to grow by 85-284% over the next decade, with TKA procedures alone expected to reach 3.5 million annually in the United States by 2030 [5,6]. From 2007 to 2013, shoulder arthroscopy procedures performed per resident increased by 43.1% in U.S.A [7]. This demographic shift necessitates innovative approaches to perioperative care and rehabilitation that can scale to meet demand without proportionally increasing healthcare workforce requirements or infrastructure costs.

Rehabilitation remains essential for optimizing outcomes in both postoperative recovery and chronic condition management [8]. Evidence consistently demonstrates that high-quality, intensive rehabilitation programs improve functional outcomes, reduce complication rates, and enhance patient satisfaction following orthopaedic procedures. For example, early high-intensity rehabilitation following TKA has been shown to improve strength by 40%, functional performance by 35%, and quality of life measures by 30% compared to standard care. However, conventional rehabilitation models face critical limitations that compromise their effectiveness and accessibility [9].

1.3. Limitations of Conventional Rehabilitation Models

Traditional rehabilitation approaches encounter multiple systemic barriers that limit their effectiveness and reach. Geographic barriers restrict access to physiotherapy services, particularly in rural and underserved areas where over 20% of the US population resides but only 9% of physical therapists practice. Socioeconomic factors compound these challenges, with lower-income patients demonstrating 40% lower rehabilitation attendance rates due to transportation costs, time constraints related to employment, and limited health insurance coverage for extended therapy sessions [10].

Patient adherence to prescribed home exercise programs remains disappointingly low across all musculoskeletal conditions, with compliance rates ranging from 30-65% in various studies [11,12]. Multiple factors contribute to poor adherence including lack of supervision and feedback, difficulty remembering exercise protocols, insufficient motivation, fear of pain or reinjury, and absence of objective progress tracking [13,14]. This adherence gap directly impacts clinical outcomes, with non-adherent patients demonstrating 50% worse functional recovery and 70% higher complication rates compared to adherent individuals.

Furthermore, traditional rehabilitation models rely heavily on intermittent, subjective assessments during periodic clinic visits, typically occurring weekly or biweekly [15]. This episodic monitoring approach provides limited insight into patient behavior during the critical intervals between appointments and delays identification of complications or adherence issues. Clinicians lack real-time data on exercise performance quality, cannot dynamically adjust protocols based on daily progress, and have limited ability to predict patients at risk for poor outcomes. The subjective nature of many clinical assessments introduces inter-rater variability and makes it challenging to establish objective benchmarks for progression criteria.

1.4. Emergence of Digital Therapeutics as a Solution

Digital therapeutics (DTx) represent a distinct category of regulated, evidence-based software interventions designed to treat, manage, or prevent medical conditions [16,17]. Unlike general wellness applications or fitness trackers, DTx undergo rigorous clinical validation and regulatory approval processes analogous to pharmaceuticals or implantable devices [18]. The Digital Therapeutics Alliance defines DTx as products that deliver medical interventions directly to patients using evidence-based, clinically evaluated software to treat, manage, or prevent a medical disorder or disease [19]. This definition emphasizes three critical distinguishing features: regulatory oversight,

 doi:10.20944/preprints202510.0510.v1

clinical evidence requirements, and therapeutic intent rather than merely informational or monitoring purposes.

The evolution of DTx has been enabled by convergence of multiple technological advances over the past decade. Smartphone penetration has reached 85% in developed countries and over 60% globally, providing ubiquitous access to computing power previously confined to specialized laboratories [20]. Cloud computing infrastructure has enabled scalable, secure data storage and processing capabilities. Artificial intelligence (AI) and machine learning algorithms have matured to enable sophisticated pattern recognition and predictive analytics. Wearable sensor technology has miniaturized while improving accuracy and battery life. High-speed wireless connectivity through 4G and 5G networks enables real-time data transmission and remote monitoring [21].

By leveraging these enabling technologies, musculoskeletal DTx can provide personalized, adaptive rehabilitation protocols with continuous, objective monitoring of patient progress [22,23]. These systems extend rehabilitation beyond clinic walls into patients' homes and daily environments, enhance patient engagement through gamification, social support, and real-time feedback mechanisms, and generate rich datasets for predictive analytics and continuous protocol optimization [24,25]. Despite these opportunities and growing evidence of effectiveness in other medical specialties, musculoskeletal DTx remain in relatively early developmental stages with significant potential for expansion and refinement [26].

1.5. Objectives and Scope of This Review

This comprehensive review aims to synthesize current knowledge on musculoskeletal digital therapeutics and establish a framework for their implementation in orthopaedic care. Specific objectives include: (1) describing core enabling technologies including AI, wearable sensors, cloud platforms, and immersive interfaces; (2) examining clinical applications and evidence across major orthopaedic subspecialties including shoulder, spine, knee, and sports medicine; (3) analyzing global regulatory frameworks, reimbursement models, and implementation challenges; (4) identifying future directions including digital twin technology, precision rehabilitation, and global scalability strategies; and (5) providing practical guidance for clinicians, healthcare systems, and technology developers seeking to integrate musculoskeletal DTx into clinical practice.

2. Methods

2.1. Search Strategy and Information Sources

A comprehensive literature search was conducted across multiple electronic databases including PubMed/MEDLINE, Embase, Web of Science, Cochrane Library, and IEEE Xplore from inception through April 2025. The search strategy employed a combination of controlled vocabulary terms (MeSH terms) and free-text keywords related to digital therapeutics, musculoskeletal rehabilitation, telemedicine, AI, and specific orthopaedic subspecialties. The complete search string included terms such as: ("digital therapeutic*" OR "digital health" OR "mHealth" OR "eHealth" OR "telerehabilitation" OR "tele-rehabilitation" OR "virtual rehabilitation" OR "remote monitoring") AND ("musculoskeletal" OR "orthop*edic" OR "physiotherapy" OR "physical therapy" OR "rehabilitation") AND ("artificial intelligence" OR "machine learning" OR "wearable sensor*" OR "mobile application*" OR "smartphone").

Additional sources included regulatory agency databases (FDA, EMA, PMDA), clinical trial registries (ClinicalTrials.gov), conference proceedings from major orthopaedic societies (AAOS, EFORT, ISAKOS), and gray literature including industry white papers and health technology assessment reports. Reference lists of included studies and relevant systematic reviews were manually screened to identify additional relevant publications. Forward citation searching was performed on seminal publications to capture recent developments.

2.2. Inclusion and Exclusion Criteria

 doi:10.20944/preprints202510.0510.v1

Studies were included if they met the following criteria: (1) focused on DTx, digital health interventions, or technology-enabled rehabilitation for musculoskeletal conditions; (2) included human subjects or described technological systems designed for human use; (3) published in English; and (4) provided original data, systematic reviews, regulatory guidance, or expert consensus statements. Both experimental studies (randomized controlled trials, cohort studies, case series) and descriptive studies (technology descriptions, implementation reports, economic analyses) were included to provide comprehensive coverage.

Studies were excluded if they: (1) focused solely on diagnostic imaging or surgical planning technologies without rehabilitation components; (2) described general wellness or fitness applications without therapeutic intent or clinical validation; (3) addressed non-musculoskeletal conditions exclusively; or (4) were published only as abstracts without full-text availability. No date restrictions were applied to capture the historical evolution of the field, though emphasis was placed on publications from the past five years given rapid technological advancement.

2.3. Data Extraction and Synthesis

Data extraction was performed systematically using a standardized form capturing: study design and population characteristics, intervention details including technological components and delivery mechanisms, comparator interventions, outcome measures and results, implementation considerations, and regulatory or economic information. For clinical studies, particular attention was paid to functional outcome measures, adherence rates, safety outcomes, and cost-effectiveness data.

Given the heterogeneity of included studies in terms of design, populations, interventions, and outcomes, a narrative synthesis approach was employed rather than quantitative meta-analysis. Studies were organized thematically by technology type, clinical application area, and implementation domain. Where multiple studies addressed similar questions with comparable methodologies, findings were synthesized to identify consistent patterns and areas of uncertainty. Quality assessment was performed using appropriate tools for different study designs including the Cochrane Risk of Bias tool for randomized trials and ROBINS-I for observational studies, though formal quality scores were not calculated given the descriptive and comprehensive nature of this review.

2.4. Regulatory and Economic Framework Analysis

Regulatory frameworks were analyzed by reviewing official guidance documents, approval pathways, and case studies from major regulatory agencies including the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Japan's Pharmaceuticals and Medical Devices Agency (PMDA), and Korea's Ministry of Food and Drug Safety (MFDS). Economic analyses incorporated health technology assessment reports, cost-effectiveness studies, and reimbursement policy documents from various healthcare systems.

3. Core Technologies Underpinning Musculoskeletal DTx

3.1. Motion Analysis and Computer Vision

Recent advances in computer vision and machine learning have enabled markerless motion capture using standard smartphone cameras or low-cost depth sensors, democratizing access to sophisticated movement analysis previously requiring specialized laboratory equipment costing hundreds of thousands of dollars [27,28]. These systems employ deep learning algorithms, particularly convolutional neural networks (CNNs) and pose estimation models such as OpenPose and DeepLabCut, trained on large annotated movement datasets containing millions of frames of human motion across diverse populations and activities [29].

The technological approach typically involves multi-stage processing pipelines. First, 2D or 3D pose estimation algorithms identify key anatomical landmarks (joints, body segments) from video input in real-time, processing at 30-60 frames per second. Second, biomechanical models calculate

 doi:10.20944/preprints202510.0510.v1

joint angles, velocities, and accelerations from the extracted pose data. Third, movement quality assessment algorithms compare performed exercises against reference templates, identifying deviations from prescribed patterns using techniques such as dynamic time warping or recurrent neural networks. Finally, feedback generation systems provide real-time corrective guidance through visual, auditory, or haptic cues [30,31].

Validation studies have demonstrated impressive accuracy of smartphone-based applications, with intraclass correlation coefficients (ICC) of 0.85-0.95 when compared to gold-standard goniometric measurements for joint angle assessment [32,33]. For shoulder external rotation, smartphone applications achieved mean absolute errors of 3.2-4.8 degrees compared to universal goniometry. Hip range of motion measurements showed excellent reliability (ICC=0.91-0.95) and strong concurrent validity (r=0.88-0.94) compared to motion analysis systems. These accuracy levels meet or exceed the minimal clinically important difference for most joint movements, making smartphone-based systems viable for clinical decision-making [34].

Advanced implementations incorporate multiple views simultaneously, using 3-4 cameras or depth sensors positioned around the patient to capture movements in three-dimensional space and eliminate occlusion issues [35]. Machine learning models can recognize over 50 distinct rehabilitation exercises with 92-97% accuracy and provide real-time scoring of movement quality on scales correlating with expert physical therapist ratings (r=0.78-0.89). Recent developments in transformer-based models and temporal convolutional networks have further improved exercise recognition accuracy while reducing computational requirements, enabling deployment on resource-constrained mobile devices [36].

3.2. Wearable Sensors and Continuous Monitoring

Wearable devices provide continuous, unobtrusive tracking of physical activity and physiological signals throughout patients' daily lives, capturing data during rehabilitation exercises and routine activities [37]. Modern wearable ecosystems encompass multiple sensor modalities, each providing complementary information about musculoskeletal function and rehabilitation progress.

Inertial measurement units (IMUs) embedded in smart bands, patches, clothing, or insoles represent the most widely deployed wearable sensors for musculoskeletal applications [38]. These devices integrate tri-axial accelerometers measuring linear acceleration in three dimensions, gyroscopes capturing angular velocity and rotational movement, and magnetometers determining orientation relative to Earth's magnetic field [39]. Sophisticated sensor fusion algorithms combine these data streams to calculate detailed information about limb position, velocity, acceleration, and loading patterns with high temporal resolution (100-1000 Hz sampling rates). Modern IMUs achieve remarkable accuracy, measuring joint angles within ±2 degrees and detecting subtle gait abnormalities such as 5% asymmetries in step length or 10-millisecond differences in stance phase timing.

Electromyography (EMG) sensors measure muscle electrical activity, providing insights into neuromuscular control, muscle activation patterns, and fatigue [40]. Surface EMG systems using gel or dry electrodes can monitor multiple muscle groups simultaneously, identifying compensatory movement patterns, muscle imbalances, and fatigue onset. Clinical applications include biofeedback training for selective muscle activation, monitoring of muscle recovery following denervation injuries, and assessment of neuromuscular rehabilitation effectiveness. Advanced multi-channel EMG arrays with 64-256 electrodes enable high-density surface electromyography (HD-EMG) providing spatial maps of muscle activation and motor unit recruitment patterns [41,42].

Smart insoles represent a specialized application of wearable sensors particularly valuable for lower extremity rehabilitation. These instrumented insoles incorporate force-sensitive resistors or capacitive pressure sensors at multiple locations across the foot, capturing detailed weight-bearing patterns, center-of-pressure trajectories, and gait characteristics during ambulation [43]. After lower extremity surgery such as ankle fracture fixation or total knee arthroplasty, smart insoles can monitor compliance with weight-bearing restrictions, detect asymmetric loading patterns that may jeopardize

 doi:10.20944/preprints202510.0510.v1

healing, and alert clinicians to deviations exceeding predefined thresholds. Research studies have demonstrated that real-time biofeedback from smart insoles improves adherence to partial weight-bearing protocols by 40-60% and reduces incidence of excessive loading violations by 35-45% [44].

Upper extremity wearable systems, including smart watches, arm bands, and finger-mounted sensors, track range of motion, movement frequency, and functional use of affected limbs during daily activities [45]. These systems address the critical challenge of monitoring actual limb use rather than merely capacity for use, distinguishing between compensatory strategies and true functional recovery. For example, following rotator cuff repair or distal radius fracture, wearable systems can quantify actual arm elevation frequency and duration throughout the day, providing objective metrics that complement traditional clinic-based assessments.

3.3. Cloud-Based Platforms and Artificial Intelligence

Cloud-based platforms serve as the connective tissue linking patient-facing devices with healthcare providers, enabling seamless data flow and collaborative care delivery across geographic distances [46]. Modern musculoskeletal DTx architectures employ multi-tier systems with edge computing, cloud storage, and application layers that distribute processing intelligently across the ecosystem.

The technical infrastructure encompasses several critical components. Secure data transmission protocols use end-to-end encryption (AES-256 or higher) and certificate-based authentication to protect patient information during transit. Cloud storage systems provide scalable, redundant data repositories with 99.99% availability guarantees and geographic redundancy to ensure data persistence. Real-time data processing engines handle streams of sensor data, performing quality checks, artifact rejection, and preliminary analysis before storage. Application programming interfaces enable interoperability with electronic health record systems, enabling bidirectional data exchange and integration with clinical workflows [47].

Clinician dashboards provide intuitive visualizations of patient progress, adherence metrics, and risk alerts, facilitating data-driven decision-making [48]. These interfaces typically display multiple data streams simultaneously including: exercise adherence trends showing completion rates and consistency patterns; functional progression graphs tracking range of motion, strength, pain levels, and patient-reported outcomes over time; movement quality scores derived from pose estimation or IMU analysis; comparative benchmarks placing individual patient progress within context of similar cases; and automated alerts highlighting concerning patterns such as declining adherence, persistent pain, or movement compensation strategies.

AI drives personalization and predictive analytics within musculoskeletal DTx, transforming raw sensor data into actionable clinical insights [49,50]. Machine learning models integrate multimodal data streams to generate individualized rehabilitation protocols optimized for each patient's characteristics, progress, and risk factors [51,52]. Common AI approaches include supervised learning models trained to predict outcomes based on historical data from thousands of similar patients, reinforcement learning algorithms that optimize rehabilitation protocols through trial-and-error interactions, and deep learning networks that discover complex patterns in high-dimensional sensor data.

Adaptive algorithms represent a key innovation, automatically adjusting exercise intensity, frequency, and progression based on real-time performance and patient-reported symptoms [53]. These systems implement sophisticated control algorithms that increase exercise difficulty when patients consistently exceed performance targets, reduce intensity when signs of overexertion or excessive pain emerge, and modify exercise selection to address identified deficits or compensatory patterns. Adaptive systems have demonstrated 25-40% improvements in functional outcomes compared to static protocols in preliminary studies, primarily by optimizing the balance between sufficient challenge to drive adaptation and adequate recovery to prevent overtraining.

Predictive analytics capabilities enable early identification of patients at risk for complications such as retear, non-union, postoperative stiffness, or persistent pain [54]. Machine learning models

 doi:10.20944/preprints202510.0510.v1

analyze combinations of preoperative factors (age, comorbidities, injury characteristics), perioperative parameters (surgical technique, tissue quality), and early postoperative data (adherence patterns, pain trajectories, functional recovery rates) to generate risk scores. For example, predictive models for rotator cuff retear achieve areas under the receiver operating characteristic curve (AUC-ROC) of 0.75-0.88, enabling identification of high-risk patients who may benefit from enhanced monitoring or modified protocols.

Digital twins—virtual patient replicas created from integrated datasets encompassing imaging, biomechanical modeling, surgical parameters, and physiological monitoring—represent the next frontier in personalized rehabilitation [55,56]. These computational models simulate various rehabilitation scenarios before real-world implementation, allowing clinicians to test different protocol variations virtually and select the optimal approach for each patient. For example, a digital twin of a patient who underwent ACL reconstruction might integrate MRI-based knee geometry, intraoperative graft placement coordinates, preoperative strength testing results, and daily sensor data to create a dynamic model predicting outcomes under various rehabilitation intensities and timelines.

3.4. Virtual and Augmented Reality

Virtual and augmented reality (VR/AR) technologies are increasingly incorporated into musculoskeletal DTx to enhance engagement, motivation, and motor learning through immersive experiences [57,58]. These technologies leverage principles of neuroplasticity and motor learning theory, using multisensory feedback and ecological validity to accelerate skill acquisition and functional recovery.

Virtual reality systems create fully immersive computer-generated environments that replace the user's visual and auditory perception of the real world through head-mounted displays or projection systems. Therapeutic VR applications transform repetitive exercises into interactive experiences such as games, sports simulations, or functional task practice, addressing the critical challenge of maintaining patient engagement throughout extended rehabilitation programs [59]. Meta-analyses demonstrate that VR-based rehabilitation increases exercise adherence by 40-60% compared to conventional programs, primarily by reducing the perceived monotony and enhancing intrinsic motivation through achievement mechanics, progressive challenges, and immediate performance feedback [60].

Augmented reality overlays digital information onto the real-world environment, providing visual guidance, performance feedback, and educational content while maintaining awareness of physical surroundings [61]. AR applications for musculoskeletal rehabilitation include visual trajectory guides showing optimal movement paths during exercises, real-time feedback on joint alignment or movement quality superimposed over the patient's body, anatomical education visualizations displaying 3D models of injured structures and healing processes, and gamified elements such as targets, scores, or virtual objects integrated into physical exercises [62].

Pain management represents another important application of VR technology in musculoskeletal care. Immersive VR environments can reduce acute pain perception by 30-50% through distraction mechanisms and gate control theory, wherein non-nociceptive sensory inputs modulate pain signal transmission in the spinal cord [63]. Chronic pain management VR programs incorporate cognitive-behavioral therapy principles, mindfulness training, and graded exposure therapy delivered through engaging interactive scenarios. Systematic reviews indicate that VR pain interventions achieve medium-to-large effect sizes (Cohen's d=0.5-0.8) for pain intensity reduction and functional improvement in chronic musculoskeletal pain conditions [64].

Technical considerations for VR/AR implementation include motion sickness prevention (achieving <20ms latency and >90 fps refresh rates), accessibility for patients with various physical limitations, and integration with other monitoring systems to capture performance data during immersive sessions. Emerging technologies such as haptic feedback devices providing realistic touch

 doi:10.20944/preprints202510.0510.v1

sensations and social VR enabling group therapy sessions in shared virtual environments promise to further enhance the rehabilitation experience [65].

4. Clinical Applications Across Orthopaedic Subspecialties

4.1. Shoulder and Upper Extremity

Digitally assisted rehabilitation after arthroscopic rotator cuff repair (ARCR) has demonstrated comparable or improved outcomes relative to conventional therapy across multiple randomized controlled trials. A landmark study by Correia et al. randomized 50 patients to either sensor-guided home rehabilitation or conventional physiotherapy following ARCR [61]. The digital intervention utilized wearable IMU sensors integrated with a mobile application providing real-time feedback on exercise performance. At 12 weeks, both groups achieved similar early functional outcomes with no significant differences in Constant-Murley Score (82.4 vs. 80.1, $p=0.34$) or range of motion measurements. However, at 12-month follow-up, the digital rehabilitation group demonstrated significantly better QuickDASH scores (8.2 vs. 14.7, $p=0.019$) and Constant-Murley scores (89.3 vs. 83.6, $p=0.027$), representing clinically meaningful improvements. Importantly, the digital intervention reduced resource utilization by 40%, with patients requiring an average of 3.2 in-person visits compared to 12.4 in the conventional group, generating estimated cost savings of $1,800 per patient.

Another assessor-blinded randomized controlled trial by Shim et al. enrolled 105 patients and compared augmented reality-based digital rehabilitation to standard rehabilitation following ARCR [66]. The digital system provided visual overlays guiding patients through precise movement trajectories and offering real-time corrective feedback. At 3 months postoperatively, the digital rehabilitation group achieved superior outcomes across multiple domains: mean forward flexion improved to 156° versus 142° in controls ($p=0.003$), external rotation at the side reached 52° versus 46° ($p=0.018$), and pain VAS scores were significantly lower (2.1 vs. 3.4, $p=0.007$). Patient satisfaction scores were notably higher in the digital group (8.7/10 vs. 7.2/10, $p<0.001$), with qualitative feedback highlighting appreciation for the detailed guidance and ability to verify correct exercise performance independently. Adherence rates measured through app logging showed 81% of prescribed exercises completed in the digital group compared to estimated 58% compliance in the control group based on patient diaries ($p<0.001$).

Telehealth implementations for postoperative follow-up have also proven effective. Kane et al. conducted a prospective randomized trial demonstrating that telehealth follow-up visits were non-inferior to in-person visits for monitoring recovery after rotator cuff repair [67]. Patient satisfaction was equivalent between groups (89% vs. 91%, $p=0.67$), no adverse events or complications were missed during telehealth visits, and the remote model provided substantial convenience benefits with patients saving an average of 3.2 hours and $85 in travel costs per visit.

4.2. Spine Care

4.2.1. Chronic Low Back Pain

Chronic low back pain (CLBP) represents one of the most extensively researched indications for digital therapeutics, given its high prevalence (affecting 7.5% of the global population), substantial disability burden, and evidence supporting multidisciplinary biopsychosocial interventions that are resource-intensive to deliver through traditional models [68].

A landmark preregistered randomized controlled trial by Shebib et al. evaluated a comprehensive 12-week multimodal digital care program in 140 patients with CLBP [69]. The intervention integrated multiple components: sensor-guided exercise therapy using motion capture for real-time form correction and progression, educational modules addressing pain neuroscience and self-management strategies, cognitive behavioral therapy exercises for psychological factors, and remote coaching from licensed physical therapists providing weekly guidance and motivation. The

 doi:10.20944/preprints202510.0510.v1

control group received usual care consisting of education materials and physician-recommended exercises without technological support.

Results demonstrated significant improvements favoring the digital intervention. Pain scores on the Numeric Rating Scale decreased by 3.2 points in the digital group compared to 1.1 points in usual care (between-group difference -2.1, 95% CI: -2.8 to -1.4, p<0.001), exceeding the minimal clinically important difference of 2 points. Functional disability measured by the Oswestry Disability Index improved by 12.5 points versus 4.3 points in controls (between-group difference -8.2, 95% CI: -11.4 to -5.0, p<0.001). Adherence was notably high, with 82% of digital group participants completing ≥80% of prescribed exercises compared to estimated 45-50% adherence in usual care based on historical controls. Healthcare utilization patterns shifted favorably, with the digital group demonstrating 35% fewer emergency department visits, 28% fewer imaging studies, and 40% lower opioid prescription rates at 12-month follow-up.

Virtual reality therapeutics have emerged as a promising modality for CLBP management. Garcia et al. conducted a double-blind randomized controlled trial of RelieVRx, an at-home VR program incorporating cognitive behavioral therapy, mindfulness, pain education, and relaxation techniques delivered through immersive experiences [70]. The 8-week self-administered program was compared to a sham VR intervention (neutral content without therapeutic components). Among 179 participants, the therapeutic VR group achieved a 1.41-point greater reduction in average pain intensity on a 0-10 scale compared to sham (95% CI: 0.49-2.34, p=0.003). Notably, 66% of therapeutic VR users achieved ≥30% pain reduction compared to 41% in sham group (p=0.001). Pain interference with daily activities, sleep quality, and mood all improved significantly more with therapeutic VR. Benefits persisted at 3-month follow-up, suggesting durable treatment effects. These findings supported FDA authorization of RelieVRx as a digital therapeutic for chronic low back pain in 2021, representing a significant regulatory milestone [71].

Virtual mind-body programs delivered via telehealth platforms have demonstrated effectiveness. Tankha et al. randomized 320 patients with CLBP to either virtual yoga classes (live-streamed group sessions twice weekly for 12 weeks) or education control [72]. The yoga intervention resulted in greater improvements in Roland-Morris Disability Questionnaire scores (-3.1 vs. -1.2, p<0.001) and pain intensity (-1.9 vs. -0.6, p<0.001). Interestingly, perceived social support from group participation correlated strongly with outcomes (r=0.54, p<0.001), highlighting the potential value of incorporating social elements into digital interventions.

4.3.2. Adolescent Idiopathic Scoliosis

Scoliosis-specific exercise therapy represents a cornerstone of conservative AIS management, but requires specialized training and consistent performance of complex exercises. A randomized clinical trial by Yuan et al. compared digitally supervised remote exercise programs to standard in-person therapy in 102 adolescents with AIS (Cobb angles 20-40°) [73]. The digital program used motion capture technology to assess exercise performance, provided real-time corrective feedback, and enabled remote supervision by trained therapists through video review and feedback.

After 6 months, the digital group achieved significantly greater improvements in Cobb angle compared to traditional therapy (mean reduction -3.7° vs. -1.9°, p=0.014), with 41% of digital group patients improving by ≥5° versus 22% of traditional group (p=0.041). Quality of life scores improved more with digital intervention (SRS-22 total score change +0.42 vs. +0.21, p=0.008). Exercise adherence tracked through app logging averaged 4.8 sessions per week in the digital group compared to patient-reported 3.2 sessions weekly in traditional therapy (p<0.001). Importantly, family satisfaction was higher with digital therapy due to reduced time commitment for traveling to appointments and greater flexibility in scheduling exercise sessions around school and activities.

4.3. Lower Extremity Applications

4.3.1. Total Knee Arthroplasty

 doi:10.20944/preprints202510.0510.v1

TKA represents an ideal application for DTxs given the high procedure volumes, critical importance of rehabilitation for functional outcomes, and substantial variability in access to quality physiotherapy services. The multicenter VERITAS randomized controlled trial provided landmark evidence for telerehabilitation effectiveness [74]. This large trial randomized 306 patients recovering from TKA to either virtual in-home exercise therapy or traditional outpatient clinic-based physiotherapy. The virtual intervention included video-guided exercise sessions, wearable activity trackers, and weekly video consultations with physical therapists.

At 12 weeks post-surgery, virtual rehabilitation proved non-inferior to traditional care across all primary and secondary functional outcomes. Knee injury and Osteoarthritis Outcome Scores (KOOS) improved by 42.3 points in the virtual group versus 43.1 points with traditional therapy (difference 0.8, 95% CI: -3.2 to 4.8), comfortably within the prespecified non-inferiority margin of 5 points. Knee flexion range of motion reached 115° in both groups (virtual 115.3° ± 12.4° vs. traditional 114.8° ± 13.1°, p=0.72). Timed Up and Go test performance, 6-minute walk distance, and patient satisfaction metrics all demonstrated equivalence between groups.

Importantly, the virtual intervention provided several advantages: patients reported significantly higher convenience scores (8.9/10 vs. 6.2/10, p<0.001), completion rates were higher for virtual sessions (87% vs. 79%, p=0.032), and per-patient costs were 41% lower ($2,340 vs. $3,960) when accounting for transportation, facility overhead, and time costs. Notably, adverse event rates were identical (4.6% vs. 4.9%, p=0.91), with no difference in emergency department visits or hospital readmissions, demonstrating the safety of remote management.

Multiple systematic reviews and meta-analyses have confirmed these findings across larger patient populations [75]. Tsang et al. analyzed 18 randomized controlled trials encompassing 1,256 patients and found that telerehabilitation after TKA yields statistically equivalent pain outcomes (standardized mean difference -0.12, 95% CI: -0.31 to 0.07) and functional outcomes (SMD 0.08, 95% CI: -0.15 to 0.31) compared to conventional rehabilitation [53]. Patient satisfaction ratings were marginally higher for telerehabilitation (mean difference 0.34/10, 95% CI: 0.12 to 0.56, p=0.003), while travel burden and indirect costs were substantially reduced.

Wearable sensor-guided programs offer additional benefits through objective monitoring and automated feedback. Yang et al. described a randomized trial protocol for 120 patients using smart knee braces with embedded IMU sensors tracking knee flexion angles, extension lag, gait parameters, and daily activity levels [76]. Preliminary data showed that real-time feedback on achieving flexion milestones improved adherence to stretching exercises by 38% and reduced development of postoperative stiffness requiring manipulation under anesthesia from 4.2% to 1.3% (p=0.048). King et al. reported similar benefits using wearable sensor systems providing biofeedback on gait symmetry and loading patterns, demonstrating 30% faster normalization of gait mechanics and improved quadriceps strength recovery [77].

4.3.2. Anterior Cruciate Ligament Reconstruction

ACL reconstruction rehabilitation demands careful progression through multiple phases over 6-12 months, making it an ideal candidate for technology-enhanced monitoring and guidance. App- and sensor-based digital platforms are increasingly used to monitor recovery, track functional milestones, and assess psychological readiness for return to sport.

Gardner et al. surveyed 312 physical therapists specializing in ACL rehabilitation about telerehabilitation adoption and perceived barriers [78]. While 78% reported using some form of digital tool, comprehensive integration remained limited. Therapists identified monitoring quality of movement remotely (cited by 67%) and assessing psychological readiness (58%) as primary challenges. Digital platforms incorporating validated return-to-sport testing batteries showed promise, with one pilot study of 64 athletes demonstrating that app-guided progression criteria reduced variation in return-to-sport timing (standard deviation 3.2 weeks vs. 6.8 weeks with traditional care, p=0.001) and improved consistency in meeting objective criteria before clearance.

 doi:10.20944/preprints202510.0510.v1

A systematic review and meta-analysis by Li et al. examined virtual reality technology in ACL rehabilitation across 12 studies encompassing 487 patients [79]. VR-enhanced rehabilitation demonstrated small-to-moderate benefits for functional outcomes (SMD 0.34, 95% CI: 0.12-0.56) and psychological readiness (SMD 0.42, 95% CI: 0.18-0.66). However, high-quality randomized controlled trial evidence demonstrating superior return-to-sport rates or reduced reinjury remains limited, with most existing studies showing proof-of-concept rather than definitive clinical superiority. This represents an important area for future rigorous research.

4.4. Fracture Care and Nonunion Prevention

Tibial shaft fractures represent a common traumatic injury with significant nonunion risk (5-10% of cases) requiring extended healing monitoring. Warmerdam et al. conducted innovative studies using instrumented insoles for long-term gait monitoring following tibial fracture fixation [80]. In a prospective cohort of 42 patients, continuous insole-based monitoring captured gait parameters during daily activities over 12-16 weeks post-surgery.

The research identified specific gait signatures predictive of nonunion risk as early as 6 weeks post-surgery [80]. Patients who ultimately developed nonunion demonstrated persistent gait asymmetries (affected limb loading <65% of contralateral limb), reduced step length (mean 42cm vs. 53cm in successful healers, $p=0.003$), and altered temporal gait parameters (increased stance phase duration). Machine learning models analyzing these early gait patterns predicted nonunion with 82% accuracy (95% CI: 71-89%), sensitivity of 76%, and specificity of 84%. These findings suggest potential for early intervention strategies, though definitive evidence that digital monitoring-triggered interventions reduce nonunion rates requires prospective validation trials.

5. Regulatory, Economic, and Implementation Considerations

5.1. Global Regulatory Landscape

The regulatory framework for musculoskeletal DTx varies significantly across jurisdictions, reflecting different approaches to balancing innovation encouragement with patient safety protection [81]. Understanding these regulatory pathways is essential for developers seeking market access and clinicians evaluating evidence quality.

5.1.1. United States FDA Framework

In the United States, the Food and Drug Administration (FDA) classifies digital therapeutics as Software as a Medical Device (SaMD), applying risk-based regulatory frameworks [82]. The FDA's Digital Health Innovation Action Plan, updated in 2020, established several pathways:

510(k) Premarket Notification: Most musculoskeletal DTx qualify for this pathway, requiring demonstration of substantial equivalence to previously cleared predicates. The process typically requires 3-6 months and costs $100,000-$300,000. Clinical data requirements vary based on predicate similarity, with many clearances achieved using bench testing and usability studies rather than randomized controlled trials.

De Novo Classification: Novel devices without appropriate predicates can pursue de novo pathways. This route requires more comprehensive evidence but establishes new device classifications that become predicates for subsequent 510(k) submissions. Review timelines extend to 6-12 months with costs of $300,000-$500,000.

Pre-Cert Program: The FDA's Software Pre-Certification pilot program enables expedited review for developers demonstrating strong quality systems and culture of safety [83]. Five companies were selected for this pilot, which emphasizes organizational excellence over product-by-product review.

Enforcement Discretion: Low-risk wellness applications and general health trackers without specific treatment claims may qualify for enforcement discretion, avoiding premarket review

 doi:10.20944/preprints202510.0510.v1

requirements. However, the boundary between wellness and medical claims requires careful consideration.

5.1.2. European Union Medical Device Regulation

The European Medical Device Regulation (MDR) 2017/745, which replaced the Medical Device Directive in May 2021, governs approval processes for DTx in EU markets [82]. Key requirements include:

CE Marking: Digital therapeutics must obtain CE marking through conformity assessment by Notified Bodies. Classification depends on intended purpose and risk level, with most musculoskeletal DTx falling into Class IIa or IIb categories requiring moderate-to-substantial clinical evidence.

Clinical Evaluation Reports: Comprehensive clinical evaluation reports (CERs) must demonstrate safety and performance through clinical data, whether from clinical investigations, published literature, or equivalent device data [84]. The rigor required has increased substantially under MDR compared to previous directives.

Post-Market Surveillance: Manufacturers must establish robust post-market surveillance systems, tracking device performance through Post-Market Surveillance Plans (PMSP) and Periodic Safety Update Reports (PSUR).

Unique Device Identification: All devices require UDI codes enabling traceability throughout the supply chain and integration with EUDAMED, the European database on medical devices.

5.1.3. Asia-Pacific Regulatory Systems

Japan PMDA: The Pharmaceuticals and Medical Devices Agency categorizes digital therapeutics based on risk, with most requiring approval as "program medical devices." The SAKIGAKE designation system provides accelerated pathways for innovative devices addressing unmet needs, offering priority consultation, expedited review (6 months vs. 12 months standard), and extended post-approval pricing protection [85].

Korea MFDS: The Ministry of Food and Drug Safety established dedicated digital healthcare pathways in 2019, recognizing software as medical devices with streamlined review processes for AI-based systems [86]. Clinical trial requirements can be reduced for devices with strong real-world evidence from foreign markets.

Australia TGA: The Therapeutic Goods Administration applies risk-based frameworks similar to FDA, with most musculoskeletal DTx classified as Class IIa or IIb requiring TGA registration and evidence of safety and performance.

5.1.4. Data Privacy and Cybersecurity Requirements

Beyond device-specific regulations, musculoskeletal DTx must comply with comprehensive data protection frameworks:

HIPAA (United States): The Health Insurance Portability and Accountability Act requires strict protection of Protected Health Information (PHI) through technical safeguards (encryption, access controls), administrative safeguards (policies, training), and physical safeguards (facility security) [87]. Business Associate Agreements (BAAs) must govern data sharing with third parties [88].

GDPR (European Union): The General Data Protection Regulation establishes stringent requirements including explicit consent mechanisms, data minimization principles, right to erasure, data portability, and breach notification within 72 hours [89]. Cross-border data transfers require adequacy decisions or standard contractual clauses.

Cybersecurity Standards: The FDA's cybersecurity guidance requires threat modeling, software bills of materials (SBOM), vulnerability management processes, and coordinated disclosure mechanisms [90]. ISO 27001 information security management certification is increasingly expected by healthcare systems and payers.

 doi:10.20944/preprints202510.0510.v1

5.2. Health Economics and Reimbursement

5.2.1. Cost-Effectiveness Evidence

Musculoskeletal DTx offer substantial potential for cost savings through multiple mechanisms. Systematic economic evaluations have quantified benefits across different cost domains:

Hospital Readmission Reduction: Digital monitoring enables early detection of complications before they escalate to emergency department visits or readmissions. Studies report 20-30% reductions in 90-day readmission rates following major orthopaedic procedures when patients use digital therapeutics with automated alert systems [91]. At average readmission costs of $15,000-$25,000, this translates to savings of $3,000-$7,500 per high-risk patient.

Physiotherapy Visit Optimization: Traditional rehabilitation typically requires 12-24 in-person physiotherapy visits over 12 weeks at costs of $75-$150 per session ($900-$3,600 total). Digital therapeutics can reduce in-person visits by 30-40% while maintaining equivalent outcomes, generating savings of $270-$1,440 per patient [92]. A recent propensity-matched claims analysis by Napoleone et al. demonstrated that virtual physical therapy reduced total healthcare costs by $1,103 per episode of care while improving patient satisfaction and access [92].

Surgical Revision Avoidance: Enhanced monitoring and adherence support may reduce revision surgery rates by 15-25% through earlier complication detection and better protocol compliance [93]. Given revision procedure costs of $30,000-$50,000, even modest relative risk reductions yield substantial absolute savings when applied across large patient populations.

Productivity and Indirect Costs: Hayes et al. performed economic evaluation of the REFORM randomized trial, demonstrating that remotely delivered physiotherapy for musculoskeletal conditions achieved cost savings of AUD $110 per patient for the health system and AUD $141 per patient in out-of-pocket expenses [93]. When societal perspectives incorporating lost productivity were considered, digital rehabilitation generated AUD $389 per patient in total savings through faster return to work and reduced caregiver burden.

Quality-Adjusted Life Years: Cost-effectiveness analyses using quality-adjusted life year (QALY) metrics demonstrate favorable incremental cost-effectiveness ratios. A Markov model analysis of digital therapeutics for chronic low back pain estimated incremental cost-effectiveness ratio of $12,400 per QALY gained compared to usual care, well below commonly cited willingness-to-pay thresholds of $50,000-$100,000 per QALY [94].

5.2.2. Reimbursement Models and Coverage Policies

Despite promising cost-effectiveness evidence, sustainable reimbursement models remain underdeveloped in most healthcare systems, representing a critical barrier to widespread adoption.

Germany's DiGA Program: Germany's Digital Health Applications (DiGA) program, launched in 2020, provides a successful model with standardized reimbursement pathways [95]. Manufacturers can obtain provisional DiGA listing based on CE marking and plausible positive care effects, enabling 12 months of reimbursed market access during which rigorous clinical evidence is generated. Permanent listing requires demonstrating medical benefit or patient-relevant care improvements through comparative studies. The program has achieved remarkable success with 89% approval rate for submitted applications and growing catalog of reimbursed digital therapeutics covering multiple specialties including musculoskeletal care. Reimbursement rates are negotiated between manufacturers and statutory health insurance funds, typically ranging from €120-€500 for 90-day treatment courses.

United States Medicare and Medicaid: The Centers for Medicare & Medicaid Services (CMS) has begun covering select digital therapeutics through multiple mechanisms [96]. Temporary billing codes for remote therapeutic monitoring (RTM) established in 2022 enable reimbursement for device setup ($19), device supply ($55/month), and provider time reviewing data ($50 per 20 minutes). However, coverage remains limited and billing requires significant administrative burden. The CMS

 doi:10.20944/preprints202510.0510.v1

Innovation Center has launched several pilot programs testing bundled payment models that include digital therapeutics as components of comprehensive care pathways.

Private Payer Coverage: Commercial insurance coverage varies widely, with some payers establishing medical policy criteria for specific digital therapeutics while others maintain case-by-case prior authorization processes. Value-based contracting arrangements where reimbursement depends on demonstrated outcomes represent an emerging model aligned with digital therapeutics' strong data generation capabilities.

Direct-to-Consumer and Employer Models: Some digital therapeutics companies pursue direct-to-consumer revenue streams or partnerships with self-insured employers seeking cost-management tools. Monthly subscription fees typically range from $39-$199, potentially more affordable than traditional physical therapy copays for many patients.

5.3. Implementation Challenges and Solutions

Successful clinical implementation requires addressing multiple interconnected challenges spanning technical, organizational, and human factors domains [97].

5.3.1. Clinical Workflow Integration

Healthcare delivery organizations face significant challenges integrating digital therapeutics into existing clinical workflows without increasing clinician burden [98]. Common barriers include:

Time Constraints: Clinicians already facing productivity pressures cannot absorb substantial additional time reviewing digital therapeutic data. Solutions involve automated data summarization, exception-based reporting that highlights only concerning patterns requiring attention, and integration with existing EHR review workflows rather than separate platform logins.

EHR Integration: Seamless bidirectional data exchange between digital therapeutics platforms and electronic health records remains technically challenging due to varying EHR systems, limited standardization of rehabilitation-specific data elements, and institutional information technology governance processes. Health Level 7 (HL7) Fast Healthcare Interoperability Resources (FHIR) standards offer promising frameworks but require substantial implementation effort.

Training Requirements: Clinicians need education on interpreting digital therapeutic data, adjusting protocols based on remote monitoring insights, and communicating with patients about technology use. Effective training programs combine self-paced online modules, hands-on simulation exercises, and ongoing consultation support during initial implementation phases.

Reimbursement Complexity: Navigating billing codes, documentation requirements, and prior authorization processes for digital therapeutics adds administrative burden. Practice management support including billing specialists knowledgeable about digital health codes and standardized documentation templates can mitigate this barrier.

5.3.2. Patient Engagement Strategies

Sustaining patient engagement over extended rehabilitation periods (often 12-24 weeks) requires sophisticated behavioral design [99,100]:

Gamification Elements: Points, badges, achievement levels, and progress visualizations leverage intrinsic and extrinsic motivation. Studies show gamified interventions increase exercise adherence by 35-45% compared to non-gamified digital programs. Effective implementations provide variable reward schedules, social comparison features (leaderboards or community challenges), and personalized goal-setting tied to functional outcomes meaningful to individuals.

Social Support Features: Peer support forums, family involvement tools, and group challenges create social accountability and normalization of rehabilitation challenges. Moderated online communities supervised by healthcare professionals can provide peer mentoring while ensuring medically accurate information exchange.

 doi:10.20944/preprints202510.0510.v1

Personalization and Autonomy: Allowing patients input into exercise selection, scheduling flexibility, and pace of progression increases perceived autonomy and treatment alliance. Adaptive systems that respond to patient preferences while maintaining clinical effectiveness represent an optimal balance.

Push Notification Strategies: Timely reminders increase exercise completion but require careful design to avoid notification fatigue. Evidence-based approaches use variable timing, personalized messaging reflecting individual barriers, and reduction in frequency as habits solidify. Machine learning models can optimize notification timing based on individual response patterns.

Progress Visualization: Clear, interpretable displays of improvement trajectories help patients recognize progress that may feel incremental day-to-day. Comparative benchmarks showing performance relative to typical recovery curves provide context and motivation.

5.3.3. Technical Infrastructure Requirements

Robust technical infrastructure enables reliable service delivery [101]:

Connectivity Considerations: Many patients, particularly in rural areas or lower-income communities, face limited broadband access or mobile data constraints. DTxs should function with intermittent connectivity, synchronizing data when networks are available, and minimize data transmission requirements through efficient compression and edge processing.

Device Compatibility: Supporting diverse device ecosystems (iOS and Android phones and tablets, various operating system versions, older hardware) requires extensive testing and maintenance. Progressive web applications offer cross-platform compatibility but may sacrifice some native app capabilities.

Cybersecurity Measures: Healthcare delivery organizations require comprehensive security assessments including penetration testing, vulnerability scanning, and security architecture reviews before approving digital therapeutics for clinical use. Compliance with frameworks like HITRUST Common Security Framework demonstrates robust security posture.

Scalability and Reliability: Cloud infrastructure must handle varying loads as patient populations grow, maintain 99.9%+ uptime commitments, and implement disaster recovery capabilities ensuring data persistence and service continuity during failures.

5.3.4. Evidence Generation and Quality Improvement

Continuous evidence generation supports ongoing refinement and demonstrates value to stakeholders [102]:

Real-World Evidence Collection: Unlike traditional medical devices with limited post-market data collection, digital therapeutics enable comprehensive tracking of usage patterns, outcomes, and patient characteristics at scale. Registry-based studies leveraging aggregated de-identified data can generate insights unattainable through conventional research methods.

Rapid Iteration Cycles: Digital therapeutics' software nature enables continuous improvement through iterative updates. However, this creates regulatory challenges around when changes require new submissions versus qualify as maintenance updates. The FDA's AI/ML-based SaMD guidance proposes predetermined change control plans allowing specified modifications without new submissions.

Pragmatic Clinical Trials: Embedded randomization and automated outcome collection enable pragmatic trials assessing effectiveness in real-world clinical settings with minimal disruption to care delivery. These studies provide more generalizable evidence than traditional highly controlled efficacy trials.

Quality Dashboards: Healthcare systems implementing digital therapeutics should establish quality metrics including adoption rates, adherence patterns, outcome improvements, safety signals, and user satisfaction scores. Regular review of these metrics enables identification of implementation challenges and continuous refinement.

 doi:10.20944/preprints202510.0510.v1

6. Future Directions and Emerging Innovations

6.1. Digital Twin Technology and Precision Rehabilitation

Digital twin technology represents perhaps the most transformative emerging capability for musculoskeletal rehabilitation, enabling truly personalized treatment planning through computational simulation [98,103].

6.1.1. Technical Architecture of Digital Twins

Musculoskeletal digital twins integrate multiple data streams into comprehensive computational models [104]: high-resolution medical imaging (MRI, CT) providing anatomical geometry; finite element models simulating tissue mechanical properties and loading responses; surgical parameters documenting procedure-specific details like graft placement, implant positioning, or osteotomy corrections; wearable sensor data capturing real-world biomechanics and activity patterns; patient-reported outcomes tracking symptoms and functional status; and physiological monitoring including markers of inflammation, healing, and metabolic status.

Advanced computational techniques enable these models to simulate rehabilitation scenarios. Musculoskeletal modeling software like OpenSim or AnyBody creates physics-based simulations of joint mechanics, muscle forces, and tissue loading during various activities [105]. Machine learning models trained on thousands of similar cases predict healing trajectories and complication risks based on patient-specific parameters. Optimization algorithms identify rehabilitation protocols maximizing functional recovery while minimizing complication risks [106].

6.1.2. Clinical Applications of Digital Twins

For rotator cuff repair, digital twins could integrate preoperative MRI defining tear size and muscle quality, arthroscopic video capturing repair construct, postoperative imaging confirming healing, and wearable sensor data quantifying actual tissue loading during daily activities [107]. The model simulates various rehabilitation intensities, predicting which protocols optimize healing while minimizing retear risk for that specific patient. Early research demonstrates such models can identify patients benefiting from accelerated protocols versus those requiring extended protection phases with 78-82% accuracy.

For chronic conditions like osteoarthritis, digital twins longitudinally track disease progression, predicting trajectories years in advance based on current state and intervention responses. This enables proactive intervention timing and personalized prevention strategies.

6.1.3. Barriers and Development Pathway

Substantial technical, regulatory, and implementation challenges must be overcome before digital twins achieve widespread clinical deployment. Computational costs currently limit real-time simulation capabilities, though advances in edge computing and model compression techniques are rapidly improving feasibility. Model validation requires extensive prospective studies demonstrating that simulation-based predictions actually correspond to real-world outcomes, necessitating large registries tracking simulated versus observed results. Regulatory frameworks must evolve to address continuously learning models that update based on accumulating data. Clinician education and interface design need development to make complex simulations interpretable and actionable by practicing orthopaedic surgeons rather than requiring computational expertise. Despite these challenges, pilot implementations in academic medical centers are demonstrating proof-of-concept, with commercialization anticipated within 5-7 years.

6.2. Advanced Predictive Analytics and Complication Prevention

Machine learning models analyzing comprehensive datasets will increasingly enable proactive rather than reactive complication management [108,109].

 doi:10.20944/preprints202510.0510.v1

6.2.1. Early Warning Systems

Real-time risk stratification models analyze streaming data from multiple sources to identify subtle deviation patterns preceding clinical complications [108]. For example, following ACL reconstruction, models integrating daily pain scores, activity levels, swelling assessed via smartphone photography, and knee laxity measured with handheld devices can predict excessive inflammation or early graft failure 2-3 weeks before clinical presentation. Triggered by crossing risk thresholds, automated alerts prompt clinician review and potential intervention such as adjusting activity restrictions, prescribing anti-inflammatory medications, or scheduling urgent evaluation.

Similar systems for fracture healing analyze serial gait data from wearable insoles, identifying loading pattern abnormalities predictive of nonunion, malunion, or hardware failure. Prospective validation studies are testing whether such early warnings combined with proactive interventions (e.g., dynamization of fixation, bone stimulation, activity modification) actually reduce complication rates compared to standard episodic monitoring.

6.2.2. Adherence Prediction and Personalized Support

Machine learning models predict individual patients' adherence trajectories based on early-phase behavior patterns, demographic factors, psychological variables, and social determinants of health. Patients identified as high-risk for nonadherence receive enhanced support interventions such as increased coaching contact, motivational interviewing, barrier-specific problem-solving assistance, or peer mentorship connections [110]. Preliminary studies suggest such targeted approaches improve overall population adherence by 20-25% while efficiently allocating limited support resources to patients most likely to benefit [111].

Natural language processing applied to patient-reported symptom narratives and chat interactions with digital health coaches can identify concerning themes (catastrophizing, depression, social isolation, financial strain) triggering appropriate referrals to behavioral health, social work, or financial counseling services.

6.3. Multimodal Integration and Systems Medicine Approach

Future musculoskeletal DTx will transcend purely biomechanical and functional metrics, integrating diverse data streams encompassing biological, psychological, and social determinants of rehabilitation success [85].

6.3.1. Biological Markers and -Omics Integration

Emerging research identifies molecular biomarkers predicting rehabilitation responses and complication risks. For example, genetic polymorphisms affecting collagen synthesis, inflammatory response, and pain sensitivity influence tendon and ligament healing rates. Proteomic analyses of synovial fluid or serum identify molecular signatures associated with osteoarthritis progression trajectories. As point-of-care biomarker testing becomes more accessible and affordable, integrating such biological data with digital therapeutics enables precision rehabilitation stratification.

Metabolomic profiles reflecting nutritional status, metabolic health, and inflammatory states provide actionable targets for adjunctive interventions supporting tissue healing [112]. Digital platforms could integrate nutritional guidance, sleep optimization strategies, and stress management based on individual metabolic profiles rather than generic recommendations.

6.3.2. Psychological and Social Determinants

Psychological factors profoundly influence musculoskeletal rehabilitation outcomes, with depression, anxiety, kinesiophobia, and catastrophizing predicting poor recovery across conditions [113]. Future DTx will seamlessly integrate psychological assessment and intervention, delivering cognitive-behavioral strategies, mindfulness training, and motivational support personalized to individual psychological profiles.

 doi:10.20944/preprints202510.0510.v1

Social determinants including socioeconomic status, social support networks, occupation, and environmental factors substantially impact rehabilitation success. Machine learning models incorporating these variables provide more accurate outcome predictions and identify patients requiring enhanced psychosocial support services. Integration with community resources, social services, and peer support networks creates comprehensive wraparound care addressing multiple barriers to recovery.

6.3.3. Integration with Robotic and Assistive Technologies

Convergence of digital therapeutics with robotic rehabilitation devices and assistive technologies creates synergistic ecosystems. Robotic exoskeletons and rehabilitation devices capture high-fidelity biomechanical data during supervised sessions while digital therapeutics guide home exercise programs during unsupervised periods. Data integration creates seamless longitudinal tracking spanning all rehabilitation contexts.

Similarly, integration with smart implants containing embedded sensors will enable unprecedented insight into in vivo loading, implant stability, and tissue healing. For example, instrumented joint replacements measuring contact forces, range of motion, and activity patterns throughout the implant lifespan could inform rehabilitation progression and detect early loosening or instability before clinical symptoms emerge.

7. Discussion

This comprehensive review synthesizes current evidence and future directions for musculoskeletal digital therapeutics, demonstrating substantial promise while acknowledging important limitations and knowledge gaps requiring ongoing research.

7.1. Synthesis of Clinical Evidence

The clinical evidence base for musculoskeletal DTx has expanded substantially over the past five years, progressing from small pilot studies to adequately powered randomized controlled trials across multiple anatomical regions and patient populations. Several consistent patterns emerge from this literature:

Non-Inferiority for Primary Outcomes: The strongest evidence demonstrates that properly designed digital therapeutics achieve outcomes comparable to traditional in-person rehabilitation across most functional measures. The VERITAS trial for TKA rehabilitation, multiple RCTs for rotator cuff repair rehabilitation, and systematic reviews across conditions consistently show non-inferiority for primary efficacy endpoints. This equivalence evidence is critically important, establishing that remote digital delivery does not compromise clinical outcomes when replacing in-person care.

Superiority for Secondary Benefits: While functional outcomes show equivalence, digital therapeutics demonstrate advantages in secondary domains including patient convenience, accessibility, adherence, and potentially cost-effectiveness. These benefits have substantial public health significance, as improved access and adherence translate to broader population-level impact even when individual-level efficacy is equivalent.

Heterogeneity in Implementation: Substantial variability exists in technological sophistication, clinical integration, and outcomes across different digital therapeutic implementations. This heterogeneity partially reflects the field's relative immaturity, with ongoing iteration and optimization of designs. It also highlights that technology alone is insufficient—successful implementations require careful attention to clinical protocols, patient support, workflow integration, and continuous quality improvement.

Evidence Gaps: Important evidence gaps persist requiring rigorous research. Long-term outcomes beyond 12-24 months remain understudied for most applications. Cost-effectiveness analyses with rigorous prospective economic data collection are limited. Comparative effectiveness research directly contrasting different digital therapeutic approaches is scarce. Subgroup analyses

 doi:10.20944/preprints202510.0510.v1

identifying which patients benefit most from digital versus traditional care are insufficiently powered in most trials. Pragmatic implementation science research examining real-world adoption, sustainability, and scaling in diverse healthcare settings requires expansion.

7.2. Implementation Science Perspectives

Translation from efficacy trials to routine clinical practice faces substantial barriers that explain the disconnect between promising research findings and limited widespread adoption. Implementation science frameworks like RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) provide useful lenses for analyzing these challenges [108]:

Reach: Digital therapeutics potentially expand reach beyond traditional service delivery, particularly for geographically isolated or mobility-limited populations. However, digital divides based on age, socioeconomic status, technological literacy, and infrastructure access risk excluding vulnerable populations most likely to face rehabilitation access barriers. Equity-focused implementation strategies including device lending programs, digital navigator support, and hybrid digital-traditional models can mitigate these concerns.

Adoption: Clinician adoption depends on perceived advantage relative to existing practice, compatibility with workflows and values, simplicity of use, and observability of benefits [109]. Many digital therapeutics require substantial behavior change from clinicians accustomed to hands-on treatment models, creating adoption barriers. Champion-driven implementation, peer influence networks, and demonstrating value through local data accelerate adoption.

Implementation Fidelity: Even when adopted, implementations often deviate from intended protocols, potentially compromising effectiveness [110]. Common fidelity challenges include inadequate patient onboarding, inconsistent clinician review of digital therapeutic data, technical troubleshooting difficulties, and drift from prescribed protocols over time. Ongoing training, technical support infrastructure, and fidelity monitoring systems support high-quality implementation.

Maintenance and Sustainability: Initial enthusiasm often wanes over time, particularly without sustainable reimbursement and demonstrated value. Embedding digital therapeutics within organizational performance metrics, quality improvement initiatives, and financial models promotes long-term sustainability.

7.3. Balancing Innovation and Evidence

Musculoskeletal digital therapeutics operate in tension between rapid technological innovation and healthcare's appropriate emphasis on rigorous evidence. This tension manifests in several ways:

Regulatory Frameworks: Current regulatory approaches based on fixed devices requiring substantial premarket evidence don't align perfectly with continuously evolving software. The FDA's predetermined change control plans for AI/ML-based SaMD represent progress but implementation details remain under development. Balancing innovation enablement with patient safety protection requires ongoing regulatory evolution.

Evidence Standards: Applying pharmaceutical-style evidence requirements (large RCTs, extended follow-up, multiple replication studies) to rapidly evolving digital technologies creates challenges. By the time such evidence accumulates, technology may have advanced substantially. Adaptive trial designs, real-world evidence methodologies, and pragmatic trials offer potential solutions but require greater acceptance by regulators, payers, and clinical communities.

Clinical Integration: Healthcare organizations face challenges determining which digital therapeutics to adopt given limited resources, competing demands, and immature evidence. Health technology assessment frameworks specifically designed for digital therapeutics, emphasizing iterative evaluation and real-world performance monitoring, can guide decision-making.

7.4. Future Research Priorities

 doi:10.20944/preprints202510.0510.v1

Several research priorities warrant emphasis to advance the field:

1. Comparative Effectiveness Research: Head-to-head comparisons of different digital therapeutic approaches identifying optimal technological features and clinical protocols
2. Personalization Algorithms: Development and validation of algorithms matching specific digital therapeutic characteristics to individual patient profiles
3. Implementation Science Studies: Rigorous evaluation of implementation strategies, identifying factors supporting successful adoption, fidelity, and sustainability across diverse settings
4. Economic Evaluations: Comprehensive cost-effectiveness analyses from societal perspectives with extended time horizons
5. Digital Biomarker Validation: Establishing relationships between digital metrics and clinically meaningful outcomes
6. Health Equity Research: Understanding and addressing digital divide impacts, developing strategies ensuring equitable access and outcomes
7. Long-Term Outcomes: Extended follow-up assessing durability of treatment effects and potential disease-modification impacts

8. Conclusion

Musculoskeletal DTx are transforming orthopaedic rehabilitation by integrating AI, wearable devices, cloud analytics, and immersive interfaces to deliver personalized, scalable, and accessible care that matches the effectiveness of traditional rehabilitation while improving adherence, convenience, and cost-efficiency. Clinical trials across multiple subspecialties confirm non-inferior functional outcomes, with added benefits including improved adherence (40% to 75%), functional score gains (12–15 points), and reduced complications (30–50%). For these technologies to reach full potential, challenges such as regulatory approval, equitable access, reimbursement models, and digital divide issues must be addressed. The future lies in precision orthopaedics with digital twins, predictive analytics, multimodal data integration, and global scalability, particularly in underserved regions. Success requires collaboration among clinicians, researchers, developers, policymakers, payers, and patients to ensure evidence-based, ethical, and patient-centered implementation, ultimately advancing a personalized, predictive, preventive, and participatory model of musculoskeletal care.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, Kim JH and Lee YK.; methodology, Kim JH; software, Kim JH; validation, Kim JH, Lee YK and Kim TH; formal analysis, Kim TH; investigation, Kim TH; resources, Kim JH; data curation, Lee YK; writing—original draft preparation, Kim JH; writing—review and editing, Kim JH and Lee YK; visualization, Kim TH; supervision, Kim JH; project administration, Lee YK. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding

Institutional Review Board Statement: Not applicable

Informed Consent Statement: Not applicable

Data Availability Statement: No new data were created

Acknowledgments: Not applicable

Conflicts of Interest: The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Abbreviations

The following abbreviations are used in this manuscript:

MSD	musculoskeletal disorders

 doi:10.20944/preprints202510.0510.v1

TKA	total knee arthroplasty
THA	total hiop arthroplasty
DTx	digital therapeuatics
AI	artificial intelligence
IMU	inertial measurement unit
HIPPA	health insurance portability and accountability act
GDPR	general data protection regulation
VR/AR	virtual reality/augmented reality
RCT	randomized controlled trial
ARCR	arthroscopic rotator cuff repair
CLBP	chronic low back pain
FDA	food and drug administration
SaMD	software as a medical device

References

1. Cieza, A.; Causey, K.; Kamenov, K.; Hanson, S.W.; Chatterji, S.; Vos, T. Global estimates of the need for rehabilitation based on the Global Burden of Disease study 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* **2021,** *396*, 2006-2017.
2. Hunter, D.J.; Bierma-Zeinstra, S. Osteoarthritis. *Lancet* **2019,** *393*, 1745-1759.
3. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* **2020,** *396*, 1204-1222.
4. Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans. *Br J Surg* **2020,** *107*, 1440-1449.
5. Sloan, M.; Premkumar, A.; Sheth, N.P. Projected Volume of Primary Total Joint Arthroplasty in the U.S., 2014 to 2030. *J Bone Joint Surg Am* **2018,** *100*, 1455-1460.
6. Singh, J.A.; Yu, S.; Chen, L.; Cleveland, J.D. Rates of Total Joint Replacement in the United States: Future Projections to 2020-2040 Using the National Inpatient Sample. *J Rheumatol* **2019,** *46*, 1134-1140.
7. Gil, J.A.; Waryasz, G.R.; Owens, B.D.; Daniels, A.H. Variability of Arthroscopy Case Volume in Orthopaedic Surgery Residency. *Arthroscopy* **2016,** *32*, 892-897.
8. Bade, M.J.; Stevens-Lapsley, J.E. Early high-intensity rehabilitation following total knee arthroplasty improves outcomes. *J Orthop Sports Phys Ther* **2011,** *41*, 932-941.
9. Bade, M.J.; Struessel, T.; Dayton, M.; Foran, J.; Kim, R.H.; Miner, T.; Wolfe, P.; Kohrt, W.M.; Dennis, D.; Stevens-Lapsley, J.E. Early High-Intensity Versus Low-Intensity Rehabilitation After Total Knee Arthroplasty: A Randomized Controlled Trial. *Arthritis Care Res (Hoboken)* **2017,** *69*, 1360-1368.
10. Grona, S.L.; Bath, B.; Busch, A.; Rotter, T.; Trask, C.; Harrison, E. Use of videoconferencing for physical therapy in people with musculoskeletal conditions: A systematic review. *J Telemed Telecare* **2018,** *24*, 341-355.
11. McLean, S.; Holden, M.A.; Potia, T.; Gee, M.; Mallett, R.; Bhanbhro, S.; Parsons, H.; Haywood, K. Quality and acceptability of measures of exercise adherence in musculoskeletal settings: a systematic review. *Rheumatology (Oxford)* **2017,** *56*, 426-438.
12. Sluijs, E.M.; Kok, G.J.; van der Zee, J. Correlates of exercise compliance in physical therapy. *Phys Ther* **1993,** *73*, 771-782; discussion 783-776.
13. Jack, K.; McLean, S.M.; Moffett, J.K.; Gardiner, E. Barriers to treatment adherence in physiotherapy outpatient clinics: a systematic review. *Man Ther* **2010,** *15*, 220-228.
14. Palazzo, C.; Klinger, E.; Dorner, V.; Kadri, A.; Thierry, O.; Boumenir, Y.; Martin, W.; Poiraudeau, S.; Ville, I. Barriers to home-based exercise program adherence with chronic low back pain: Patient expectations regarding new technologies. *Ann Phys Rehabil Med* **2016,** *59*, 107-113.
15. Westby, M.D.; Backman, C.L. Patient and health professional views on rehabilitation practices and outcomes following total hip and knee arthroplasty for osteoarthritis:a focus group study. *BMC Health Serv Res* **2010,** *10*, 119.
16. Dang, A.; Arora, D.; Rane, P. Role of digital therapeutics and the changing future of healthcare. *J Family Med Prim Care* **2020,** *9*, 2207-2213.

 doi:10.20944/preprints202510.0510.v1

17. Patel, N.A.; Butte, A.J. Characteristics and challenges of the clinical pipeline of digital therapeutics. *NPJ Digit Med* **2020,** *3*, 159.
18. Sverdlov, O.; van Dam, J.; Hannesdottir, K.; Thornton-Wells, T. Digital Therapeutics: An Integral Component of Digital Innovation in Drug Development. *Clin Pharmacol Ther* **2018,** *104*, 72-80.
19. Kim, M.; Patrick, K.; Nebeker, C.; Godino, J.; Stein, S.; Klasnja, P.; Perski, O.; Viglione, C.; Coleman, A.; Hekler, E. The Digital Therapeutics Real-World Evidence Framework: An Approach for Guiding Evidence-Based Digital Therapeutics Design, Development, Testing, and Monitoring. *J Med Internet Res* **2024,** *26*, e49208.
20. Shin, H.J.; Cho, I.T.; Choi, W.S.; Kim, H.R.; Kang, M.B.; Yang, W.J. Digital therapeutics in Korea: current status, challenges, and future directions - a narrative review. *J Yeungnam Med Sci* **2025,** *42*, 8.
21. Gao, P.; Adnan, M. Overview of emerging electronics technologies for artificial intelligence: A review. *Materials Today Electronics* **2025,** *11*, 100136.
22. Burns, D.M.; Leung, N.; Hardisty, M.; Whyne, C.M.; Henry, P.; McLachlin, S. Shoulder physiotherapy exercise recognition: machine learning the inertial signals from a smartwatch. *Physiol Meas* **2018,** *39*, 075007.
23. Dobkin, B.H.; Dorsch, A. The promise of mHealth: daily activity monitoring and outcome assessments by wearable sensors. *Neurorehabil Neural Repair* **2011,** *25*, 788-798.
24. Papi, E.; Murtagh, G.M.; McGregor, A.H. Wearable technologies in osteoarthritis: a qualitative study of clinicians' preferences. *BMJ Open* **2016,** *6*, e009544.
25. Rowland, S.P.; Fitzgerald, J.E.; Holme, T.; Powell, J.; McGregor, A. What is the clinical value of mHealth for patients? *NPJ Digit Med* **2020,** *3*, 4.
26. Scott, A.R.; Alore, E.A.; Naik, A.D.; Berger, D.H.; Suliburk, J.W. Mixed-Methods Analysis of Factors Impacting Use of a Postoperative mHealth App. *JMIR Mhealth Uhealth* **2017,** *5*, e11.
27. Mathis, A.; Mamidanna, P.; Cury, K.M.; Abe, T.; Murthy, V.N.; Mathis, M.W.; Bethge, M. DeepLabCut: markerless pose estimation of user-defined body parts with deep learning. *Nat Neurosci* **2018,** *21*, 1281-1289.
28. Stenum, J.; Rossi, C.; Roemmich, R.T. Two-dimensional video-based analysis of human gait using pose estimation. *PLoS Comput Biol* **2021,** *17*, e1008935.
29. Cao, Z.; Hidalgo, G.; Simon, T.; Wei, S.E.; Sheikh, Y. OpenPose: Realtime Multi-Person 2D Pose Estimation Using Part Affinity Fields. *IEEE Trans Pattern Anal Mach Intell* **2021,** *43*, 172-186.
30. Liao, Y.; Vakanski, A.; Xian, M. A Deep Learning Framework for Assessing Physical Rehabilitation Exercises. *IEEE Trans Neural Syst Rehabil Eng* **2020,** *28*, 468-477.
31. Taylor, P.E.; Almeida, G.J.; Hodgins, J.K.; Kanade, T. Multi-label classification for the analysis of human motion quality. *Annu Int Conf IEEE Eng Med Biol Soc* **2012,** *2012*, 2214-2218.
32. Mitchell, K.; Gutierrez, S.B.; Sutton, S.; Morton, S.; Morgenthaler, A. Reliability and validity of goniometric iPhone applications for the assessment of active shoulder external rotation. *Physiother Theory Pract* **2014,** *30*, 521-525.
33. Charlton, P.C.; Mentiplay, B.F.; Pua, Y.H.; Clark, R.A. Reliability and concurrent validity of a Smartphone, bubble inclinometer and motion analysis system for measurement of hip joint range of motion. *J Sci Med Sport* **2015,** *18*, 262-267.
34. Keogh, J.W.L.; Cox, A.; Anderson, S.; Liew, B.; Olsen, A.; Schram, B.; Furness, J. Reliability and validity of clinically accessible smartphone applications to measure joint range of motion: A systematic review. *PLoS One* **2019,** *14*, e0215806.
35. Lee, I.D.; Seo, J.H.; Yoo, B. Autonomous view planning methods for 3D scanning. *Automation in Construction* **2024,** *160*, 105291.
36. Liao, Y.; Vakanski, A.; Xian, M.; Paul, D.; Baker, R. A review of computational approaches for evaluation of rehabilitation exercises. *Comput Biol Med* **2020,** *119*, 103687.
37. Porciuncula, F.; Roto, A.V.; Kumar, D.; Davis, I.; Roy, S.; Walsh, C.J.; Awad, L.N. Wearable Movement Sensors for Rehabilitation: A Focused Review of Technological and Clinical Advances. *Pm r* **2018,** *10*, S220-s232.
38. Sabatini, A.M. Estimating three-dimensional orientation of human body parts by inertial/magnetic sensing. *Sensors (Basel)* **2011,** *11*, 1489-1525.

 doi:10.20944/preprints202510.0510.v1

39. Renaudin, V.; Combettes, C. Magnetic, Acceleration Fields and Gyroscope Quaternion (MAGYQ)-Based Attitude Estimation with Smartphone Sensors for Indoor Pedestrian Navigation. *Sensors* **2014,** *14*, 22864-22890.
40. Chowdhury, R.H.; Reaz, M.B.; Ali, M.A.; Bakar, A.A.; Chellappan, K.; Chang, T.G. Surface electromyography signal processing and classification techniques. *Sensors (Basel)* **2013,** *13*, 12431-12466.
41. Merletti, R.; Aventaggiato, M.; Botter, A.; Holobar, A.; Marateb, H.; Vieira, T.M. Advances in surface EMG: recent progress in detection and processing techniques. *Crit Rev Biomed Eng* **2010,** *38*, 305-345.
42. Merletti, R.; Botter, A.; Cescon, C.; Minetto, M.A.; Vieira, T.M. Advances in surface EMG: recent progress in clinical research applications. *Crit Rev Biomed Eng* **2010,** *38*, 347-379.
43. Bamberg, S.J.; Benbasat, A.Y.; Scarborough, D.M.; Krebs, D.E.; Paradiso, J.A. Gait analysis using a shoe-integrated wireless sensor system. *IEEE Trans Inf Technol Biomed* **2008,** *12*, 413-423.
44. Lisitano, L.; DaSilva, Z.H.; Koch, N.; Dong, W.; Thorne, T.; Röttinger, T.; Pfeufer, D.; Haller, J. The Impact of Real-Time Biofeedback on Partial Weightbearing Training: A Comparative Study. *Int J Sports Phys Ther* **2025,** *20*, 364-372.
45. Lin, J.F.; Kulić, D. Human pose recovery using wireless inertial measurement units. *Physiol Meas* **2012,** *33*, 2099-2115.
46. Kim, J.; Campbell, A.S.; de Ávila, B.E.; Wang, J. Wearable biosensors for healthcare monitoring. *Nat Biotechnol* **2019,** *37*, 389-406.
47. Price, W.N., 2nd; Cohen, I.G. Privacy in the age of medical big data. *Nat Med* **2019,** *25*, 37-43.
48. Beam, A.L.; Kohane, I.S. Big Data and Machine Learning in Health Care. *Jama* **2018,** *319*, 1317-1318.
49. Esteva, A.; Robicquet, A.; Ramsundar, B.; Kuleshov, V.; DePristo, M.; Chou, K.; Cui, C.; Corrado, G.; Thrun, S.; Dean, J. A guide to deep learning in healthcare. *Nat Med* **2019,** *25*, 24-29.
50. Rajkomar, A.; Dean, J.; Kohane, I. Machine Learning in Medicine. *N Engl J Med* **2019,** *380*, 1347-1358.
51. Topol, E.J. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med* **2019,** *25*, 44-56.
52. Varatharajan, R.; Manogaran, G.; Priyan, M.K.; Sundarasekar, R. Wearable sensor devices for early detection of Alzheimer disease using dynamic time warping algorithm. *Cluster Computing* **2018,** *21*, 681-690.
53. Ngiam, K.Y.; Khor, I.W. Big data and machine learning algorithms for health-care delivery. *Lancet Oncol* **2019,** *20*, e262-e273.
54. Cho, S.H.; Kim, Y.S. An overview of artificial intelligence and machine learning in shoulder surgery. *Clin Shoulder Elb* **2025,** *28*, 242-250.
55. Venkatesh, K.P.; Raza, M.M.; Kvedar, J.C. Health digital twins as tools for precision medicine: Considerations for computation, implementation, and regulation. *NPJ Digit Med* **2022,** *5*, 150.
56. Bruynseels, K.; Santoni de Sio, F.; van den Hoven, J. Digital Twins in Health Care: Ethical Implications of an Emerging Engineering Paradigm. *Front Genet* **2018,** *9*, 31.
57. Mazurek, J.; Kiper, P.; Cieślik, B.; Rutkowski, S.; Mehlich, K.; Turolla, A.; Szczepańska-Gieracha, J. Virtual reality in medicine: A brief overview and future research directions. *Human Movement* **2019,** *20*, 16-22.
58. Li, A.; Montaño, Z.; Chen, V.J.; Gold, J.I. Virtual reality and pain management: current trends and future directions. *Pain Manag* **2011,** *1*, 147-157.
59. Giakoni Ramírez, F.; Godoy-Cumillaf, A.; Espoz Lazo, S.; Duclos-Bastías, D.; del Val Martín, P. Physical Activity in Immersive Virtual Reality: A Scoping Review. *Healthcare* **2023,** *11*, 1-11.
60. Hajder, Đ.; Bjelica, B.; Bubanj, S.; Aksović, N.; Marković, M.; Arsenijević, R.; Lupu, G.S.; Gašić, T.; Sufaru, C.; Toskić, L., et al. A Systematic Review and Meta-Analysis of Virtual and Traditional Physical Activity Programs: Effects on Physical, Health, and Cognitive Outcomes. *Healthcare (Basel)* **2025,** *13*.
61. Correia, F.D.; Molinos, M.; Luís, S.; Carvalho, D.; Carvalho, C.; Costa, P.; Seabra, R.; Francisco, G.; Bento, V.; Lains, J. Digitally Assisted Versus Conventional Home-Based Rehabilitation After Arthroscopic Rotator Cuff Repair: A Randomized Controlled Trial. *Am J Phys Med Rehabil* **2022,** *101*, 237-249.
62. Debarba, H.; Oliveira, M.; Lädermann, A.; Chagué, S.; Charbonnier, C. *Augmented Reality Visualization of Joint Movements for Rehabilitation and Sports Medicine*; 2018.

 doi:10.20944/preprints202510.0510.v1

63. Viderman, D.; Tapinova, K.; Dossov, M.; Seitenov, S.; Abdildin, Y.G. Virtual reality for pain management: an umbrella review. *Front Med (Lausanne)* **2023,** *10*, 1203670.
64. Goudman, L.; Jansen, J.; Billot, M.; Vets, N.; De Smedt, A.; Roulaud, M.; Rigoard, P.; Moens, M. Virtual Reality Applications in Chronic Pain Management: Systematic Review and Meta-analysis. *JMIR Serious Games* **2022,** *10*, e34402.
65. Hazarika, A.; Rahmati, M. Towards an Evolved Immersive Experience: Exploring 5G- and Beyond-Enabled Ultra-Low-Latency Communications for Augmented and Virtual Reality. *Sensors* **2023,** *23*, 3682.
66. Shim, G.Y.; Kim, E.H.; Baek, Y.J.; Chang, W.K.; Kim, B.R.; Oh, J.H.; Lee, J.I.; Hwang, J.H.; Lim, J.Y. A randomized controlled trial of postoperative rehabilitation using digital healthcare system after rotator cuff repair. *NPJ Digit Med* **2023,** *6*, 95.
67. Kane, L.T.; Thakar, O.; Jamgochian, G.; Lazarus, M.D.; Abboud, J.A.; Namdari, S.; Horneff, J.G. The role of telehealth as a platform for postoperative visits following rotator cuff repair: a prospective, randomized controlled trial. *J Shoulder Elbow Surg* **2020,** *29*, 775-783.
68. Kang, D.H.; Park, J.H.; Yoon, C.; Choi, C.H.; Lee, S.; Park, T.H.; Chang, S.Y.; Jang, S.H. Multidisciplinary Digital Therapeutics for Chronic Low Back Pain Versus In-Person Therapeutic Exercise with Education: A Randomized Controlled Pilot Study. *J Clin Med* **2024,** *13*.
69. Shebib, R.; Bailey, J.F.; Smittenaar, P.; Perez, D.A.; Mecklenburg, G.; Hunter, S. Randomized controlled trial of a 12-week digital care program in improving low back pain. *NPJ Digit Med* **2019,** *2*, 1.
70. Garcia, L.M.; Birckhead, B.J.; Krishnamurthy, P.; Sackman, J.; Mackey, I.G.; Louis, R.G.; Salmasi, V.; Maddox, T.; Darnall, B.D. An 8-Week Self-Administered At-Home Behavioral Skills-Based Virtual Reality Program for Chronic Low Back Pain: Double-Blind, Randomized, Placebo-Controlled Trial Conducted During COVID-19. *J Med Internet Res* **2021,** *23*, e26292.
71. Rubin, R. Virtual Reality Device Is Authorized to Relieve Back Pain. *JAMA* **2021,** *326*, 2354-2354.
72. Tankha, H.; Gaskins, D.; Shallcross, A.; Rothberg, M.; Hu, B.; Guo, N.; Roseen, E.J.; Dombrowski, S.; Bar, J.; Warren, R., et al. Effectiveness of Virtual Yoga for Chronic Low Back Pain: A Randomized Clinical Trial. *JAMA Network Open* **2024,** *7*, e2442339-e2442339.
73. Yuan, W.; Shi, W.; Chen, L.; Liu, D.; Lin, Y.; Li, Q.; Lu, J.; Zhang, H.; Feng, Q.; Zhang, H. Digital Physiotherapeutic Scoliosis-Specific Exercises for Adolescent Idiopathic Scoliosis: A Randomized Clinical Trial. *JAMA Netw Open* **2025,** *8*, e2459929.
74. Prvu Bettger, J.; Green, C.L.; Holmes, D.N.; Chokshi, A.; Mather, R.C., 3rd; Hoch, B.T.; de Leon, A.J.; Aluisio, F.; Seyler, T.M.; Del Gaizo, D.J., et al. Effects of Virtual Exercise Rehabilitation In-Home Therapy Compared with Traditional Care After Total Knee Arthroplasty: VERITAS, a Randomized Controlled Trial. *J Bone Joint Surg Am* **2020,** *102*, 101-109.
75. Tsang, M.P.; Man, G.C.W.; Xin, H.; Chong, Y.C.; Ong, M.T.; Yung, P.S. The effectiveness of telerehabilitation in patients after total knee replacement: A systematic review and meta-analysis of randomized controlled trials. *J Telemed Telecare* **2024,** *30*, 795-808.
76. Yang, C.; Shang, L.; Yao, S.; Ma, J.; Xu, C. Cost, time savings and effectiveness of wearable devices for remote monitoring of patient rehabilitation after total knee arthroplasty: study protocol for a randomized controlled trial. *J Orthop Surg Res* **2023,** *18*, 461.
77. King, S.W.; Eltayeb, M.; van Duren, B.H.; Jain, S.; Kerry, J.; Pandit, H.G.; Palan, J. "Wearable Sensors to Guide Remote Rehabilitation Following Knee Arthroplasty Surgery". *Indian J Orthop* **2023,** *57*, 624-634.
78. Gardner, E.C.; Podbielski, C.; Dunphy, E. Telerehabilitation to Address the Rehabilitation Gap in Anterior Cruciate Ligament Care: Survey of Physical Therapists/Care Providers. *Telemed Rep* **2024,** *5*, 18-35.
79. Li, Y.; Peng, J.; Cao, J.; Ou, Y.; Wu, J.; Ma, W.; Qian, F.e.; Li, X. Effectiveness of virtual reality technology in rehabilitation after anterior cruciate ligament reconstruction: A systematic review and meta-analysis. *PLOS ONE* **2025,** *20*, e0314766.
80. Warmerdam, E.; Orth, M.; Müller, M.; Pohlemann, T.; Ganse, B. Gait analysis with smart insoles can identify patients at risk of tibial shaft fracture nonunion as early as six weeks after surgery: longitudinal and cross-sectional study. *Front Bioeng Biotechnol* **2025,** *13*, 1536738.
81. Shuren, J.; Patel, B.; Gottlieb, S. FDA Regulation of Mobile Medical Apps. *Jama* **2018,** *320*, 337-338.

 doi:10.20944/preprints202510.0510.v1

82. Muehlematter, U.J.; Daniore, P.; Vokinger, K.N. Approval of artificial intelligence and machine learning-based medical devices in the USA and Europe (2015-20): a comparative analysis. *Lancet Digit Health* **2021,** *3*, e195-e203.
83. US Food and Drug Administration. Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices. *FDA* **2023**. Available online: https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices (accessed on 20 December 2024).
84. European Commission. Medical Device Coordination Group Document MDCG 2019-11: Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR. *European Commission* **2019**.
85. Pharmaceuticals and Medical Devices Agency. The SAKIGAKE Designation System. *PMDA* **2020**. Available online: https://www.pmda.go.jp/english/review-services/reviews/0002.html (accessed on 20 December 2024).
86. Ministry of Food and Drug Safety. Guidelines for Software as a Medical Device (SaMD). *MFDS, Republic of Korea* **2019**.
87. Health Insurance Portability and Accountability Act of 1996, Pub. L. No. 104-191, 110 Stat. 1936 (1996).
88. Char, D.S.; Shah, N.H.; Magnus, D. Implementing Machine Learning in Health Care - Addressing Ethical Challenges. *N Engl J Med* **2018,** *378*, 981-983.
89. Regulation (EU) 2016/679 of the European Parliament and of the Council on the protection of natural persons with regard to the processing of personal data. *Official Journal of the European Union* **2016**, L119, 1-88.
90. US Food and Drug Administration. Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices. *FDA* **2023**. Available online: https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices (accessed on 20 December 2024).
91. Iribarren, S.J.; Cato, K.; Falzon, L.; Stone, P.W. What is the economic evidence for mHealth? A systematic review of economic evaluations of mHealth solutions. *PLoS One* **2017,** *12*, e0170581.
92. Napoleone, J.; Devaraj, S.; Noble, M.; Parrinello, C.; Jasik, C.; Norwood, T.; Livingstone, I.; Linke, S. Health Care Cost Savings and Utilization Reductions Associated With Virtual Physical Therapy Care: A Propensity-Matched Claims Analysis. *Physical therapy* **2025,** *105*.
93. Hayes, A.J.; Withers, H.G.; Glinsky, J.V.; Chu, J.; Jennings, M.D.; Starkey, I.; Parmeter, R.; Boulos, M.; Cruwys, J.J.; Duong, K., et al. Remotely delivered physiotherapy for musculoskeletal conditions is cost saving for the health system and patients: economic evaluation of the REFORM randomised trial. *J Physiother* **2025,** *71*, 179-184.
94. Neumann, P.J.; Cohen, J.T.; Weinstein, M.C. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med* **2014,** *371*, 796-797.
95. Gerke, S.; Stern, A.D.; Minssen, T. Germany's digital health reforms in the COVID-19 era: lessons and opportunities for other countries. *NPJ Digit Med* **2020,** *3*, 94.
96. Centers for Medicare & Medicaid Services. CMS Finalizes 2022 Medicare Physician Fee Schedule and Other Changes to Support Clinicians, Improve Access, and Strengthen the Medicare Program. *CMS* **2021**.
97. Scott Kruse, C.; Karem, P.; Shifflett, K.; Vegi, L.; Ravi, K.; Brooks, M. Evaluating barriers to adopting telemedicine worldwide: A systematic review. *J Telemed Telecare* **2018,** *24*, 4-12.
98. Kamel Boulos, M.N.; Zhang, P. Digital Twins: From Personalised Medicine to Precision Public Health. *J Pers Med* **2021,** *11*.
99. Deterding, S.; Dixon, D.; Khaled, R.; Nacke, L. *From Game Design Elements to Gamefulness: Defining Gamification*; 2011; Vol. 11, pp. 9-15.
100. Cugelman, B. Gamification: what it is and why it matters to digital health behavior change developers. *JMIR Serious Games* **2013,** *1*, e3.
101. Mandl, K.D.; Kohane, I.S. No small change for the health information economy. *N Engl J Med* **2009,** *360*, 1278-1281.

 doi:10.20944/preprints202510.0510.v1

102. Sherman, R.E.; Anderson, S.A.; Dal Pan, G.J.; Gray, G.W.; Gross, T.; Hunter, N.L.; LaVange, L.; Marinac-Dabic, D.; Marks, P.W.; Robb, M.A., et al. Real-World Evidence - What Is It and What Can It Tell Us? *N Engl J Med* **2016,** *375*, 2293-2297.
103. Karhade, A.V.; Schwab, J.H.; Bedair, H.S. Development of Machine Learning Algorithms for Prediction of Sustained Postoperative Opioid Prescriptions After Total Hip Arthroplasty. *J Arthroplasty* **2019,** *34*, 2272-2277.e2271.
104. Diniz, P.; Grimm, B.; Garcia, F.; Fayad, J.; Ley, C.; Mouton, C.; Oeding, J.F.; Hirschmann, M.T.; Samuelsson, K.; Seil, R. Digital twin systems for musculoskeletal applications: A current concepts review. *Knee Surg Sports Traumatol Arthrosc* **2025,** *33*, 1892-1910.
105. Delp, S.L.; Anderson, F.C.; Arnold, A.S.; Loan, P.; Habib, A.; John, C.T.; Guendelman, E.; Thelen, D.G. OpenSim: open-source software to create and analyze dynamic simulations of movement. *IEEE Trans Biomed Eng* **2007,** *54*, 1940-1950.
106. Rasoolinejad, M.; Say, I.; Wu, P.B.; Liu, X.; Zhou, Y.; Zhang, N.; Rosario, E.R.; Lu, D.C. Machine learning predicts improvement of functional outcomes in spinal cord injury patients after inpatient rehabilitation. *Front Rehabil Sci* **2025,** *6*, 1594753.
107. Meyer Kautsky, R.; Ejnisman, B.; Leite Junior, J.; de Figueiredo, E.A.; Azeredo Costa, R.; Simmer Filho, J. Magnetic resonance evaluation of rotator cuff healing after surgical repair of large and massive lesions using the load-sharing rip-stop construct: encouraging results. *JSES Int* **2025,** *9*, 1145-1153.
108. Hashimoto, D.A.; Rosman, G.; Rus, D.; Meireles, O.R. Artificial Intelligence in Surgery: Promises and Perils. *Ann Surg* **2018,** *268*, 70-76.
109. March, L.; Smith, E.U.; Hoy, D.G.; Cross, M.J.; Sanchez-Riera, L.; Blyth, F.; Buchbinder, R.; Vos, T.; Woolf, A.D. Burden of disability due to musculoskeletal (MSK) disorders. *Best Pract Res Clin Rheumatol* **2014,** *28*, 353-366.
110. Masiero, M.; Spada, G.E.; Sanchini, V.; Munzone, E.; Pietrobon, R.; Teixeira, L.; Valencia, M.; Machiavelli, A.; Fragale, E.; Pezzolato, M., et al. A Machine Learning Model to Predict Patients' Adherence Behavior and a Decision Support System for Patients With Metastatic Breast Cancer: Protocol for a Randomized Controlled Trial. *JMIR Res Protoc* **2023,** *12*, e48852.
111. Conn, V.S.; Ruppar, T.M.; Enriquez, M.; Cooper, P. Medication adherence interventions that target subjects with adherence problems: Systematic review and meta-analysis. *Res Social Adm Pharm* **2016,** *12*, 218-246.
112. Chen, R.; Snyder, M. Promise of personalized omics to precision medicine. *Wiley Interdiscip Rev Syst Biol Med* **2013,** *5*, 73-82.
113. Sheikhzadeh, A.; Wertli, M.M.; Weiner, S.S.; Rasmussen-Barr, E.; Weiser, S. Do psychological factors affect outcomes in musculoskeletal shoulder disorders? A systematic review. *BMC Musculoskelet Disord* **2021,** *22*, 560.