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Standard Guide for Clinical Outcomes for Clinical Trials and/or Clinical Registries for Knee Reconstructive Surgery[1]

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1. Scope

1.1 This guide is intended as a resource for individuals and organizations when designing clinical trials and/or clinical registries and addresses the selection of patient-reported outcomes, safety outcomes, imaging outcomes and other topics related to knee reconstructive surgery (KRS) including: *(1)* knee replacement systems, *(2)* anterior cruciate ligament reconstruction, *(3)* knee meniscus implants or tissue engineered medical products (TEMPs), *(4)* articular cartilage implants or TEMPS, *(5)* peri-articular knee osteotomies, *(6)* peri-articular knee fractures (including distal femur, patella, and proximal tibia fractures), or other knee surgeries.

1.2 In this guide, methods to measure the efficacy, effectiveness, and safety of KRS devices through standardizing clinical outcome measures are provided for designing, reviewing, and accepting human clinical trial protocols.

1.3 This guide is intended to provide consistency in study design, review, regulatory approval, and health insurance coverage approval for knee reconstructive surgery to the health care market.

1.4 For the purpose of this guide, KRS pertains to any device or TEMP that is intended to replace, resurface, reconstruct, and/or provide fixation of the knee joint, in part or in total, as a treatment for joint disease, trauma, or dysfunction, where long-term improvement in function and pain relief without major adverse events are the desired outcomes.

1.5 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.6 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

F561 Practice for Retrieval and Analysis of Medical Devices, and Associated Tissues and Fluids

F2809 Terminology Relating to Medical and Surgical Materials and Devices (Withdrawn 2019)[3]

F2979 Guide for Characterization of Wear from the Articulating Surfaces in Retrieved Metal-on-Metal and other Hard-on-Hard Hip Prostheses

2.2 *ISO Standards:*[4]

ISO 12891-1 Retrieval and analysis of surgical implants – Part1: Retrieval and handling

ISO 12891-2:2014 Retrieval and analysis of surgical implants – Part 2: Analysis of retrieved surgical implants

3. Terminology

3.1 *Definitions:*

3.1.1 *level of evidence, n*—strength of clinical evidence for evidence-based medicine (**1**).[5]

3.1.2 *safety, n*—the condition of being protected from or unlikely to cause risk or injury.

3.2 *Acronyms:*

3.2.1 *AAHKS*—American Association of Hip and Knee Surgeons

3.2.2 *AAOS*—American Academy of Orthopaedic Surgeons

3.2.3 *ACL*—anterior cruciate ligament

3.2.4 *AJRR*—American Joint Replacement Registry

3.2.5 *ASA*—American Society of Anesthesiologists

[1] This guide is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.39 on Human Clinical Trials.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] The last approved version of this historical standard is referenced on www.astm.org.

[4] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.

[5] The boldface numbers in parentheses refer to the list of references at the end of this standard.

3.2.6 *CAT*—Computer Adaptive Testing

3.2.7 *CDRH*—Center for Devices and Radiologic Health

3.2.8 *CMS*—Centers for Medicare & Medicaid Services

3.2.9 *EQ-5D*—European Quality of Life – 5 Domains

3.2.10 *FDA*—Food and Drug Administration

3.2.11 *HRQL*—Health-related quality of life

3.2.12 *ICD*—International Classification of Diseases

3.2.13 *IKDC*—International Knee Documentation Committee

3.2.14 *KOOS*—Knee injury and Osteoarthritis Outcome Score

3.2.15 *KOOS JR*—Knee injury and Osteoarthritis Outcome Score Joint Replacement

3.2.16 *KRS*—Knee Reconstructive Surgery

3.2.17 *KSS*—Knee Society Score

3.2.18 *LEAS*—Lower Extremity Activity Scale

3.2.19 *MCID*—Minimum clinically important difference

3.2.20 *MDC*—Minimum detectable change

3.2.21 *MOON*—Multicenter Orthopaedic Outcomes Network

3.2.22 *MRI*—Magnetic Resonance Imaging

3.2.23 *NPRS*—Numeric Pain Rating Scale

3.2.24 *OKS*—Oxford Knee Score

3.2.25 *PRO*—Patient-reported outcome

3.2.26 *PROMIS*—Patient-Reported Outcomes Measurement Information System

3.2.27 *QALY*—Quality Adjusted Life Year

3.2.28 *RSA*—Radiostereometric analysis

3.2.29 *SAE*—Serious adverse event

3.2.30 *SD*—Standard deviation

3.2.31 *SEM*—Standard error of the mean

3.2.32 *SF-6D*—Short Form (6 dimensions)

3.2.33 *SF-12*—Short Form (12 questions)

3.2.34 *SF-36*—Short Form (36 questions)

3.2.35 *TEMP*—Tissue Engineered Medical Products (ASTM Subcommittee F04.40)

3.2.36 *TKA*—Total Knee Arthroplasty

3.2.37 *UKA*—Unicompartmental Knee Arthroplasty

3.2.38 *VAS*—Visual Analog Scale

3.2.39 *VR-6D*—Veterans Rand (6 dimensions)

3.2.40 *VR-12*—Veterans Rand (12 questions)

3.2.41 *VR-36*—Veterans Rand (36 questions)

3.2.42 *WOMAC*—Western Ontario and McMaster Universities Osteoarthritis Index

3.2.43 *WOMET*—Western Ontario Meniscal Evaluation Tool

4. Summary of Guide

4.1 It is the intent of this guide to provide an overview of appropriate outcomes that are to be addressed in human clinical trials of knee reconstructive surgery (KRS). Depending on the requirements of the clinical trial, the outcomes to be addressed include knee-specific patient-reported outcomes, health-related quality-of-life patient-reported outcomes, activity level scales, pain relief (i.e., VAS, NPRS), and adverse events collection and reporting.

4.2 Because of the broad range of indications for KRS, patient comorbidities, and functional/activity levels, it is impossible to identify or specify a single instrument score that measures the "success" of KRS. Instead, a clinically significant improvement (minimum clinically important difference [MCID]) in a joint-specific, disease-specific, or quality-of-life instrument should be used as a measure of clinical "success" (**2**). Clinical success measured with patient-reported outcomes may be defined through clinical improvement in terms of MCIDs and/or achieving a clinical success threshold value defined and justified in the study protocol or literature. The MCID can be calculated using consensus methods (also known as Delphi method), anchor-based methods, and distribution methods. Consensus methods use clinical and domain experts to define the MCID (**3**). Anchor-based approaches compare the change in the patient-reported outcome (PRO) score to some other measure of change, considered an anchor or external criterion, to determine whether or not a magnitude of change is significant. The anchor may consist of a clinical measure or a Global Assessment Rating in which the patients rate themselves to some extent as ''better,'' ''unchanged,'' or ''worse.'' Distribution-based approaches compare the change in PRO scores to some measure of variability such as the standard error of the mean (SEM), the standard deviation (SD), the effect size, or the minimum detectable change (MDC) (**4**). Although there is no consensus as to the superior method to determine the MCID, it is recommended that the MCID be based primarily on relevant patient-based and clinical anchors. Distribution-based methods should be used to support the estimates from anchor-based approaches and can be used in situations where anchor-based estimates are unavailable (**5**). Whenever possible, investigators should use validated scores with established MCID values.

4.3 The application of this guide does not guarantee clinical success of a finished product but will help to ensure consistency and adequacy of the data collected based on the clinical trial protocol.

4.4 The insurance coverage criteria for medical treatments include: *(1)* that a net health outcome is achieved, *(2)* the clinical trial results are applicable (generalizable) to the patient population, and *(3)* the clinical trial results are applicable (generalizable) to medical providers. Therefore, subgroup analyses based on patient characteristics (age, sex) and provider characteristics (academic medical center practice vs. community orthopaedic practice setting, high vs. low surgical volume centers, urban vs. rural geographic practice locations)

should be included. Financial disclosures of clinical investigators should be provided based on Code of Federal Regulations Title 21 Part 54 "Financial Disclosure by Clinical Investigators."[6]

4.5 This guide does not suggest that all patient-reported outcome instruments be used for each KRS. However, inclusion of an outcome measure from each section will provide a thorough description of the benefits of KRS, including knee function, pain relief, health-related quality of life including a health utility measure with the ability to calculate Quality Adjusted Life Years (QALYs) (**6**), and mobility/activity level.

5. Significance and Use

5.1 Approximately 650,000 primary total knee arthroplasties (TKAs) and 50,000 revision TKAs are performed in the United States annually (**7, 8**). There are between 100,000 and 200,000 anterior cruciate ligament knee injuries per year in the United States (**9**).

6. Use (Outcome Measures)

6.1 *Patient-Reported Outcomes (PROs):*

6.1.1 Patient-reported outcomes (PROs) are vital to understanding the value patients receive from health care. Value can be defined as the change in quality of life and function divided by the total cost of care. Improvement in quality of life is most commonly measured by Quality Adjusted Life Years (QALYs) (**6**). QALYs are required for cost-effectiveness analyses and comparative effectiveness analyses used in coverage decisions. Standardization of PRO measures is necessary to compare outcomes of procedures (**10**). Standardizing PRO measures for implant and outcome registries will make comparative effectiveness data available to the clinical and regulatory communities.

6.1.2 *PRO Measure Selection*—PRO measure selection shall be pragmatic. High-respondent burden (too many questions) will result in poor rates of patient completion. High licensing fees make it difficult for not-for-profit registries to license the measure. Selection of PRO measures should be based on whether they serve as primary or secondary outcomes in clinical trials, as different PRO measures have strengths and weaknesses.

6.1.3 *Knee-Specific or Disease-Specific Outcome Instruments (*Table 1*):*

6.1.3.1 *Knee Osteoarthritis/Arthroplasty*—The knee-specific PRO recommendation measure consensus for total knee arthroplasty (TKA) or unicompartmental knee arthroplasty (UKA) from the American Academy of Orthopaedic Surgeons (AAOS), the American Association of Hip and Knee Surgeons (AAHKS), and the American Joint Replacement Registry (AJRR) is the Knee injury and Osteoarthritis Outcome Score JR (KOOS JR) (**11**). The KOOS JR has been validated for total knee replacement surgery (**12**). The AJRR will present national bench marking data for the KOOS JR. The most frequently used PROs for knee replacement surgery are the Oxford Knee Score (OKS) (**13**) and Knee injury and Osteoarthritis Outcome Score (KOOS) (**14**). The OKS is used in the New Zealand Joint Registry (**15**) and the National Joint Registry of England, Wales, and Northern Ireland (**16**). In

[6] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=54

TABLE 1 Recommended Patient Reported Outcome Measures for Knee Reconstructive Surgery

	Health-Related Quality of Life	Knee or Disease Specific	Activity Level	Pain
Knee Arthroplasty	PROMIS Global Health Veterans Rand 12 EQ-5D Veterans Rand-36 SF-12 SF-36	KOOS JR KOOS OKS KSS WOMAC PROMIS Physical Function	LEAS	NPRS VAS, Likert
ACL Reconstruction	PROMIS Global Health Veterans Rand 12 EQ-5D	KOOS IKDC Lysholm	Marx Tegner	NPRS, VAS, Likert
Meniscus Repair/ Reconstruction	PROMIS Global Health Veterans Rand 12 EQ-5D	KOOS WOMET	Marx Tegner	NPRS, VAS, Likert
Articular Cartilage Reconstruction	PROMIS Global Health Veterans Rand 12 EQ-5D	KOOS	Marx Tegner	NPRS, VAS, Likert
Peri-Articular Osteotomies	PROMIS Global Health Veterans Rand 12 EQ-5D	KOOS KOOS JR OKS KSS WOMAC	LEAS Marx	NPRS, VAS, Likert
Peri-Articular Fractures	PROMIS Global Health Veterans Rand 12 EQ-5D	KOOS KOOS JR OKS KSS WOMAC	LEAS Marx	NPRS, VAS, Likert