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Standard Guide for Characterization and Assessment of Tissue Engineered Medical Products (TEMPs) for Knee Meniscus Surgical Repair and/or Reconstruction[1]

This standard is issued under the fixed designation F3223; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This guide is intended as a resource for individuals and organizations involved in the production, delivery, and regulation of tissue engineered medical products (TEMPs) and other tissues intended for use in the surgical repair, replacement, and/or reconstruction of the knee meniscus.

1.2 *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 and health practices and determine the applicability of regulatory limitations prior to use.*

1.3 *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]

D570 Test Method for Water Absorption of Plastics

F1635 Test Method for ***in vitro*** Degradation Testing of Hydrolytically Degradable Polymer Resins and Fabricated Forms for Surgical Implants

F2150 Guide for Characterization and Testing of Biomaterial Scaffolds Used in Tissue-Engineered Medical Products

F2210 Guide for Processing Cells, Tissues, and Organs for Use in Tissue Engineered Medical Products (Withdrawn 2015)[3]

F2211 Classification for Tissue Engineered Medical Products (TEMPs)

F2212 Guide for Characterization of Type I Collagen as Starting Material for Surgical Implants and Substrates for Tissue Engineered Medical Products (TEMPs)

F2312 Terminology Relating to Tissue Engineered Medical Products

F2386 Guide for Preservation of Tissue Engineered Medical Products (TEMPs) (Withdrawn 2013)[3]

F2739 Guide for Quantifying Cell Viability within Biomaterial Scaffolds

2.2 *ISO Standards:*[4]

ISO 10993-1 Biological evaluation of medical devices

ISO 13022:2012 Medical products containing viable human cells—Application of risk management and requirements for processing practices

ISO 18362:2016 Manufacture of cell-based health care products—Control of microbial risks during processing

2.3 *Code of Federal Regulations*[5]

CFR 610.12 General Biological Products Standards—Sterility

CFR 820 Current Good Manufacturing Practice for Quality System Regulation

CFR 1270 Current Good Manufacturing Practice for Human Tissue Intended for Transplantation

CFR 1271 Current Good Manufacturing Practice for Human Cells, Tissues, and Cellular and Tissue-Based Products

3. Terminology

3.1 Unless provided otherwise in 3.2, terminology shall be in conformance with Terminology F2312.

3.2 *Definitions of Terms Specific to This Standard:*

3.2.1 *ECM, n*—extracellular matrix.

[1] This test method is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.44 on Assessment for TEMPs.

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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 International Organization for Standardization (ISO), ISO Central Secretariat, BIBC II, Chemin de Blandonnet 8, CP 401, 1214 Vernier, Geneva, Switzerland, http://www.iso.org.

[5] Available from U.S. Government Printing Office, Superintendent of Documents, 732 N. Capitol St., NW, Washington, DC 20401-0001, http://www.access.gpo.gov.

3.2.2 *osteoarthritis (OA), n*—a disease of the entire joint involving the cartilage, joint lining, ligaments, and underlying bone.

3.2.3 *product, n*—TEMPs, and other tissues or devices used in the surgical repair, replacement, augmentation and/or reconstruction of the knee meniscus.

3.2.4 *surgical reconstruction, n*—surgical procedure to promote healing of replacement meniscus structure.

3.2.5 *surgical repair, n*—surgical procedure to promote healing of native meniscus structure.

4. Summary of Guide

4.1 It is the intent of this guide to provide a compendium of information that may be related to the functional characteristics of TEMPs, and other tissues or devices used in the surgical repair, replacement, augmentation and/or reconstruction of the knee meniscus. TEMPs may be composed of biological products (for example, cells, organs, tissues (both human and xenograft), derivatives, and processed biologics), biomaterials (for example, substrates and scaffolds composed of polymers, extra-cellular matrices or collagen), and biomolecules (for example, recombinant proteins, alginates, and hyaluronates) (see Terminology F2312). Examples of TEMPs are listed in Classification F2211.

4.2 The reader is referred to other documents that may provide specific information that can be applied in the processing and manufacture (Guide F2210, ISO 18362: 2016), characterization and testing (Guide F2150; ISO 10993-1) and the preservation, storage, transport, recovery, post-preservation processing, quality assurance, and process control (Guide F2386-04, ISO 13022:2012) of TEMPs. Section 2lists referenced standards and particularly relevant Code of Federal Regulations (CFR).

4.3 The application of this guide does not guarantee clinical success of a finished product but will help to ensure consistency in the properties, testing, and characterization of a given TEMP or device developed for the purpose of enhancing surgical repair, replacement, augmentation and/or reconstruction of the knee meniscus.

4.4 This guide does not suggest that all the listed tests be conducted. The decision regarding applicability or suitability of any particular test method remains the responsibility of the supplier, user, or regulator of the material based on applicable regulations, characterizations, and preclinical/clinical testing.

5. Significance and Use

5.1 Injuries to the knee meniscus are one of the most common orthopaedic problems. Meniscus injures include acute tears (such as occur in sports injuries), chronic degenerative tears, extrusion/subluxation, and/or degenerative dysfunction that occurs as part of the knee aging process or as a result of multiple meniscus surgeries. Knee arthroscopy for partial excision of the knee meniscus (partial meniscectomy) is the most commonly performed orthopaedic procedure.

5.2 Complete or near complete excision of the meniscus in a young individual is associated with an early increased risk of knee osteoarthritis due to the loss of the meniscus chondroprotective effects. Lateral meniscal injuries tend to be more severe than medial injuries. Meniscus repair, augmentation, transplantation, and/or reconstruction is recommended in individuals to restore the chondroprotective effect of the meniscus, relieve pain, and prevent degenerative knee osteoarthritis. The potential of TEMPs to enhance the outcome of the surgical meniscus repair and/or reconstruction has been recognized.

5.3 The knee joint and temporomandibular joint (TMJ) are examples of joints with meniscal structures.

5.4 TEMPS may be used with the intent of enhancing the surgical outcome by improving the biological repair at the site of implantation, by providing mechanical function at a defect site, or by a combination of these mechanisms.

5.5 Improving surgical outcome may include improving function relative to the pre-operative condition, shortening the recovery time after surgery, relieving pain, enabling return to normal daily activities, encouraging tissue growth into the defect site, restoring the mechanical function of the meniscus, delaying the progression of osteoarthritis, or any combination thereof.

6. Cells

6.1 *Cell Types*—Cell-seeded products may be used. The cell population may be allogenic or autologous. Cell type should be defined in order to provide accurate and comprehensive materials and methods descriptions so that studies can be repeated, the mechanisms of action can be understood and clinical feasibility and regulatory aspects can be ascertained. Suggested cell populations include: (a) meniscal fibrochondrocytes, (b) mesenchymal stem cells (MSCs)/induced pluripotent stem cells (iPSCs)/embryonic stem cells (ESCs), or (c) synoviocytes. Cells may be allogeneic or autologous. Allogeneic cells should be isolated, prepared, and stored at a cell/tissue bank. These cells may have undergone substantial proliferation prior to being seeded into the TEMPs product, and the cell phenotype should be characterized and compared to a population of freshly isolated or early passage cells. It is intended that the cells in the cell/tissue bank should have significant similarities to the fresh or early passage cells, in particular for properties that are critical for formation and function of the TEMPs, such as production of types I and II collagen and sulfated glycosaminoglycans (sGAGs). Autologous cells may be isolated and re-implanted during the same surgical procedure, or undergo proliferation prior to re-implantation. However, like the allogeneic cells, the autologous cells should be managed to undergo minimal changes during manipulation.

6.2 *Cell Performance Requirements*—Cell lines should be established, maintained, and supplied in line with existing recommendations (**1**, **2**, **3**, **4**, **5**).[6]. In formation of the TEMPs in vitro, the cells will be combined with biomaterials, and must be able to attach to the biomaterial and/or extracellular matrix (ECM) of the TEMPs. For some TEMPs, the cells should be able to proliferate and secrete a functional ECM in vitro. When

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

implanted, the cells may be required to synthesize an ECM *in vivo*, function in biologic repair, or resorb, but the implanted cells and biomaterials should not induce immune or inflammatory responses that prevent meniscus repair. Both allogeneic and autologous cells that undergo expansion and proliferation in vitro should be characterized for their differentiation capacity into a fibrochondrogeneic phenotype (producing type I and II collagen and sGAGs).

7. Attachment and Incorporation

7.1 *Attachment in vivo*—The product should provide or be adaptable to clinically applicable anchoring or fixation methods to enable attachment to the extent needed to enable function. Fixation methods include anchoring via sutures, specifically designed meniscus fixation devices, anchors, screws, and bone blocks to enable attachment to the meniscal remnant, capsule, and/or bone. The products should be capable of retaining sutures, fixation devices, or anchors in a manner that is appropriate for the surgical procedure. Once implanted and fixed, the product should be retained in place for the time required for it to complete its functional requirements and maintain or at least restore the ability of the structure to withstand physiological hoop stresses and provide chondroprotection.

8. Sterilization

8.1 The product shall be provided sterile to the clinical field. Acellular products may be sterilized after manufacture by a number of different techniques, some examples of which are: ethylene oxide, gamma irradiation, or plasma irradiation. If the product is cellular, the product may be maintained aseptic during manufacture using a closed culture system.

9. Packaging

9.1 The product shall be packaged so that it can be stored and transported to the clinical site, while remaining sterile/aseptic and functional.

10. Biochemical Composition and Tests

10.1 *Extracellular Matrix Composition*—The native meniscus is a fibrocartilaginous matrix composed primarily of collagen, proteoglycans, cells, adhesion glycoproteins (<1%), and elastin (<1%). It is recognized that TEMPs may produce ECM that differs in content and distribution relative to the native tissue, but nonetheless the produced ECM should function similarly to the native meniscal tissue. Regardless, produced collagen, glycosaminoglycans and cells within TEMPs should be quantified with time *in vivo* or in culture. The extracellular matrix of TEMPs is often a collagen-based hydrated material also containing proteoglyans, elastin, and other proteins and glycoproteins. These components can be quantified, and usually their amounts are expressed per wet weight or dry weight. Composition assessments can be relatively simple (for example, protein content), or can be highly specific (quantitation of a specific molecule). In all measurements of TEMP composition, comparison to native meniscus tissue composition is necessary.

10.2 *Collagen (by types)*—The meniscus is primarily composed of collagen (~22% of the wet weight), with type I, II, III, V and VI all reported in meniscal tissue. However type I collagen is the most abundant type accounting for over 90% of collagen in the meniscus, with type II being the second most abundant. Type I collagen is primarily organized into circumferential fibers within the peripheral zone of the meniscus and helps the meniscus resist hoop stresses. Type II collagen is primarily found in the more highly compressed inner, white zone. Total collagen content of the TEMPs can be determined by papain digestion of the tissue constructs. Collagen content can be measured using a hydroxyproline assay with trans-4-hydroxyproline standards (**6**, **7**, **8**). However, this assay does not distinguish between types of collagen. Immunohistochemical staining can be utilized to identify the specific collagen types, such as types I, II, III, V, and VI. The orientation and arrangement of collagen fibrils within the TEMP is also important for functional tissue. Therefore, picrosirius red staining may be used to assess collagen alignment and organization throughout the TEMPs. The reader is referred to Guide F2212 for the characterization of Type I collagen as a starting material for TEMPs.

10.3 *Proteoglycans/Glycosaminoglycans*—Proteoglycans are the second major component of the meniscus (~0.8% of the wet weight); however, they are found primarily in the inner, white zone of the meniscus and are approximately eightfold less common than that found in articular cartilage. The most common large sulfated glycosaminoglycans found in the meniscus are chondroitin-6-sulfate, chondroitin-4-sulfate, dermatan sulfate, and keratin sulfate. The most common large proteoglycan is aggrecan, with decorin and biglycan being the most common small proteoglycans. Total glycosaminoglycan content of the TEMPs can be determined by papain digestion of the tissue constructs overnight at 65°C. Total sulfated glycosaminoglycan content can be determined using a 1, 9-dimethylmethylene blue (DMMB) assay and reported normalized to wet or dry weight of the tissue (**9**). The assay should be performed at a pH of 1.5 to avoid interference with polyanions such as hydroxyproline or RNA (**10**). Bovine trachea chondroitin-4-sulfate type A standards are included to allow calculation of the sGAG content and absorbance should be read within 5 min of DMMB addition at 525 nm. Individual types of glycosaminoglycan can be determined using immunohistochemistry or specific gene expression assays; however, are not often needed. The proteoglycan profile can be more extensively characterized by extraction of the proteoglycans from the TEMPs, proteolytic degradation, and chromatography or electrophoresis to characterize the sGAG composition in comparison to native meniscus tissue (**11**).

10.4 *DNA*—The amount of DNA in meniscal products that contain live cells should be quantified with time in culture or with time *in vivo* to determine cellular content or proliferation. DNA can be quantified by simple colorimetric biochemical assays such as PicoGreen or Hoechst DNA and normalized to wet weight or dry weight of the product (**12**).

10.5 *Water Content*—The meniscus is ~72% water. The percent water content of TEMPs can be determined by measuring the wet weight of the constructs followed by lyophilization and measurement of the dry weight. Techniques as described in Test Method D570 can also be used.

10.6 *Metabolic Activity*—Metabolic activity of TEMPs that contain live cells can be assessed by reference to techniques outlined in Guide F2739. Tests include an assessment of mitochondrial dehydrogenase activity, which is a measure of cell proliferation or viability using the BioVision Quick Cell Proliferation Assay Kit, which measures the cleavage of 2-(4-Iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium monosodium salt (WST-1) (**13**). Metabolic activity of cells within TEMPs can also be determined throughout in vitro culture using colorimetric assays such as AlamarBlue or MTT. It is important that proper controls are always run with these assays to account for variability due to color. Further these assays should be used to measure metabolic activity and are only a baseline of viability. Live-dead assays or DNA quantification should be performed for more accurate analysis of viability prior to implantation.

10.7 *Growth Factors*—Growth factors have been applied to TEMPs to enhance proliferation, migration, matrix production, and phenotype maintenance or differentiation, the most common of which include transforming growth factor beta-1 and beta-3 (TGF-β1 and TGF-β3), basic fibroblast growth factor (b-FGF), platelet derived growth factor (PDGF)-AB, insulin-like growth factor (IGF)-1), epidermal growth factor (EGF), and hepatocyte growth factor (HGF). The concentration of growth factor used can have significant effects on desired cellular responses and cytotoxicity, thus dose/concentration should always be reported. Growth factors that are secreted from TEMPs can be detected by Western blot and quantified using enzyme linked immunosorbent assays (ELISAs) specific for the growth factors of interest.

11. Mechanical Properties and Tests

11.1 The high load environment of the knee joint combined with its exposure to millions of loading cycles per year places importance on assessing the response of products for meniscal augmentation, repair, or replacement to physiologically relevant loads. In designing such tests, it should be recognized that the force magnitudes experienced by a product inserted into a meniscal defect will be dependent on the intended compartment for implantation, the location within the compartment where the product is positioned, and its method of fixation to the host tissue. As such, the mechanical tests conducted on the product should be dictated by their intended function within the joint and the expected duration for which that function must be maintained.

11.2 A broad range of tissue mechanical properties for the normal ‘uninjured’ human meniscus have been reported in literature. The effect of property variation on mechanical function of the meniscus as a structure is as yet unclear; thus there are no current guidelines as to the range of properties that products intended for meniscal repair must exhibit in order to mechanically function in the joint. Nonetheless, to enable a full characterization of the material and structural properties of a product intended for meniscal repair, augmentation, or replacement, mechanical tests should enable the following features to be quantified: (i) material properties in tension and compression, (ii) creep/viscoelastic behavior, (iii) fixation strength and stiffness, (iv) wear and frictional characteristics, (v) functional performance of the structure within the joint, and (vi) an ability to withstand physiological hoop stresses.

11.3 Tests should be conducted on the terminally sterilized (or aseptic) product, and should capture the time zero properties as well as the change in those properties with time. The change of properties with time can be captured either by mechanically testing samples after *in vivo* implantation, or after artificial ageing. In the case of degradable products, mechanical tests should capture the change in mechanical properties as a function of rate of degradation. In the case of non-degradable materials mechanical tests should capture the characteristics of the construct to handle both static and cyclic, fatigue-type loads.

11.4 *Tensile Properties*—In defining the test setup, the following should be reported: method of gripping the specimens ends, specimen geometry, method of measuring cross-sectional area and displacement, loading rates and/or displacement rates used, environmental conditions, and, in the case of an anisotropic product specimen, orientation (circumferential, radial, or axial). Examples of tensile test methodology using dumbbell-shaped meniscal tissue explants are available in (**14** and **15**). An example of tensile test methodology as applied to strips of scaffolds for meniscal repair are available in (**16**). Depending on the test employed, the following results can be reported: stress-strain plot, modulus, yield and failure stress, and yield and failure strain, and degree of anisotropy. The meniscus has an anisotropic and inhomogeneous collagenous structure, which results in anisotropic and inhomogeneous properties (**17**); a comparison to those properties should be made.

11.5 *Compressive Properties*—In defining the test setup, the following should be reported: specimen orientation (circumferential, radial, or axial), boundary conditions (confined or unconfined), loading platen configuration, specimen geometry, method of measuring displacement, loading rates and/or displacement rates used, and environmental conditions. Examples of compression tests on the native meniscus using indentation testing techniques are found in (**14, 18, 19,** and **20**). Examples of compression tests on the native meniscus using confined compression techniques are found in (**15**). Examples of compression tests on the native meniscus using unconfined compression techniques are found in (**21** and **22**). Depending on the test employed, the following results can be reported: stress-strain plot, modulus, permeability, maximum stress, and maximum strain. Depending on the product and its intended function, permeability, aggregate modulus, and dynamic modulus should be reported.

11.6 *Viscoelastic Characteristics*—The viscoelastic characteristics of the material should be reported through an analysis of the creep, stress-relaxation, or dynamic response of the scaffold or implant. Such testing can be conducted using indenters (**23**), under confined compression conditions (**24**). In describing the test setup, the following should be reported: specimen orientation (circumferential, radial, or axial), boundary conditions for the specimen (confined or unconfined),

specimen geometry, method of measuring displacement, loading rates and loading profile or displacement rates and profile used, number of cycles, and environmental conditions.

11.7 In the case of degradable scaffolds, the rate of change of tensile and compressive properties at different stages of degradation should be reported. This requirement can be achieved by simulating a degradative environment in the laboratory, or by assessing the mechanical properties of the TEMP after a period of *in vivo* implantation in an appropriately selected animal model.

11.8 *Wear*—An analysis of the wear characteristics of a TEMP can be made through modified simulator tests where unidirectional (**25**), or multidirectional forces (**26, 27**) are applied across the product. Outputs will include an analysis of the deformation, damage, and wear debris (size and morphology). An assessment of biological reactivity to that debris in a subsequent *in vivo* synovial joint model should be conducted. Assessment of wear can also be conducted through an analysis of TEMP response in a large animal (sheep, goat) model. Outputs will include changes in mechanical properties, changes in shape, and analysis of reactivity of the joint synovium, articular cartilage and underlying bone, to any particulate debris. The frictional characteristics of the scaffold, at time zero and as a function of time after implantation (**28**), and as a function of sliding velocity (**26**, **29**) should be assessed

11.9 *Models for Assessing Function*—The particular model that is chosen to assess function will be dictated by the intended function of the product. For example, in a product intended to distribute forces across the tibial plateau, cadaveric models can be used; where the distribution of joint contact force, before and after implantation of the product is measured, or the effect of product implantation on joint kinematics is quantified (**26, 30, 31, 32, 33**). Data should be compared to the un-implanted condition that best represents the intended clinical defect that will be treated by the product. Interpretation of the data will rely on the rate of degradation (if expected to occur) of the product. For quickly degrading products, data generated from this model may be less useful than those from products that degrade slowly. Function can also be assessed using computational finite element (FE) models. Such models can be used to mimic the time-varying characteristics of the scaffold and to mimic the effect of patient-to-patient variability on contact mechanics (**34, 35, 36**). Models can be either elastic or biphasic and a more simplified representation of the compartment that is targeted for the scaffold and the size and location of the defect that is being considered. The data generated can include analysis of the stress state of the product (circumferential, radial, or axial stresses/strains) which can be used to assess the ability of the product to withstand physiological loads. Joint contact stresses can also be computed. Comparison of the data output from the computational models to either literature or to physical experiments is a requisite for the use of data from this approach.

11.10 *Fixation Strength and Stiffness*—Fixation strength and stiffness: Fixation strength and stiffness test configuration and interpretation of data will be dependent on the method of fixation. For example, the pull-out strength of sutures should be compared to the expected *in vivo* forces and failure strength of the TEMP. The strength of the interface between the native tissue and the product should be quantified from *in vivo* animal model explants.

12. Biologic Tests and Evaluations

12.1 Animal models typically used for such studies include the canine, goat, sheep and pig models (**37, 38, 39**). The choice of the control depends on many factors, but comparison to an untreated partial meniscectomy that mirrors the (critical) size and location of the treated defect is ideal.

12.2 *Chondroprotective Evaluation—In vivo* evaluation of the product's chondroprotective abilities should include measures of articular cartilage degeneration as quantified using gross inspection (e.g. visual assessment of the extent and location of India ink staining), histological grading and scoring (**40, 41**), and/or quantitative MRI assessment (e.g. T2 or T1rho mapping), (**42**).

12.3 *Ability to Integrate with the Host Tissue*—While integrative capacity can be assessed using histological and mechanical tests of explants from *in vivo* animal models, the integrative capacity of a product for meniscal repair can also be assessed using in vitro tissue culture models (**43, 44**). The in vitro tests may be conducted under static loading conditions, or with simulated physiological loading to better mimic the loading conditions to which the TEMPS may be exposed *in vivo*. Outcomes should include an analysis of interfacial strength as computed using push-out tests and histological and biochemical assessments of the content of the TEMP-meniscal junction.

12.4 *Histological Characterization of the Product*—The knee meniscus primary histologic structure is composed of circumferentially-oriented type I collagen fibers to resist the hoop stresses, radial-oriented type I collagen "tie" fibers, inner-zone proteoglycan to resist compressive loads, and meniscofibrochondrocytes distributed throughout the ECM over a spectrum of phenotypes based on location. Histological evaluation should be sufficient to characterize the three-dimensional structure of the meniscus and the product under investigation, cell density and morphology, and should specifically address vascularity due to the unique and critical arrangement of the meniscal blood supply (**40, 41, 42**).

13. Degradation Properties and Tests

13.1 Dependent on the substrate material and processing, many of the aforementioned chemical, physical, mechanical, or biological properties may change while the scaffold is degrading either *in vivo* or in cell culture conditions. A thorough characterization should be made of any property changes expected to occur under actual service conditions or expected conditions of use. Additionally, TEMPs degradation profiles may be affected by sterilization. Consequently, it is recommended that potentially affected properties be reevaluated for design compliance after sterilization/aseptic processing.

13.2 Such degradation profiling can be conducted under specific controlled in vitro or *in vivo* conditions that model the

intended application. When a material's degradation is primarily hydrolytic in nature, physiological conditions may be modeled in vitro at 37oC under controlled pH conditions as described in Test Method F1635.

14. Patient Reported Outcomes

14.1 Patient-reported outcomes (PROs) are vital to understanding the value patients receive from healthcare. 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) (**45**). QALYs are required for cost-effectiveness analyses and comparative effectiveness analyses used in insurance coverage decisions. Standardization of PRO measures is necessary to compare outcomes of procedures (**46**). Standardizing PRO measures for implant and outcome registries will make comparative effectiveness data available to the clinical and regulatory communities.

14.2 *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.

14.3 *Knee-Specific or Meniscus-Specific Outcome Instruments*—The knee-specific PRO measure most frequently used is the Knee injury and Osteoarthritis Outcome Score (KOOS) (**47**). The KOOS has been used as a PRO for anterior cruciate ligament reconstruction and is not limited by ceiling effects in high-functioning athletes. The Western Ontario Meniscal Evaluation Tool was developed specifically for the knee meniscus (**48**). Other PRO instruments developed for knee osteoarthritis are unlikely to have the sensitivity needed to evaluate meniscus outcomes.

14.4 *Knee-Specific Patient Subjective Outcome Measure*—The International Knee Documentation Committee (IKDC) Subjective knee evaluation form is used to detect improvement or deterioration in symptoms, function, and activities due to knee impairment (**49**). Although it was originally designed for ligament disruption, the IKDC instrument has been showed to provide a good overall measure of knee-related disability in patients who have undergone a meniscus procedure with demonstrating reliability, validity, and responsiveness (**50**). The minimum clinically important difference has been reported to be 11.5 to 20.5 (range 6-28 months) (**51**).

14.5 *General Health-Related Quality of Life (HRQL) Outcome Instruments*—Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), and 12-Item Short-Form Health Survey (SF-12) from the Health Institute, New England Medical Center; Boston, MA, are frequently used as HRQL outcomes instruments (**52, 53**). The Veterans Rand 36 (VR-36) and VR-12 are equivalent to the SF-36 and SF-12, respectively, and are public domain instruments (**54, 55, 56**). The Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health instrument may be used to assess health-related quality of life (**57**).

14.6 *Activity Level Scales*—The Marx Knee Activity Scale (**58**) is a validated knee activity scale for athletes. Historically, the Tegner scale was used as a knee activity scale for athletes (**59**).

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