Experts Achieve Consensus on a Majority of Statements Regarding Ethics, Transparency, Regulation, and Best Practices for the Use of Orthobiologics

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Purpose: To establish consensus statements via a modified Delphi process about ethics, transparency, regulation, and best practices for the use of orthobiologics in clinical practice for musculoskeletal pathology. **Methods:** A consensus process on the regulation of orthobiologics at the provider level was conducted using a modified Delphi technique. Twenty orthopaedic surgeons, sports medicine physicians, or basic scientists participated. Each participant was a Biologic Association member organization representative and asked to participate because of their active interest in the field of orthobiologics. Levels of consensus were delineated according to the number of votes for each statement: no consensus, <80%; consensus, 80% to 89%; strong consensus, 90% to 99%; unanimous, 100%. **Results:** The 26 consensus statements on orthobiologics resulted in 14 achieving unanimous consensus, 8 achieving strong consensus, 3 achieving consensus, and 1 did not achieve consensus. Overall, 85% of the statements reached either a unanimous or strong consensus. Of the statements regarding communication and transparency, 9 reached unanimous consensus, including information to convey and helpful tools to describe current orthobiologics, persistent misinformation, use of the word "stem cells," "off-label" use, and problems with the present regulatory environment. Five statements discussing the regulation of novel orthobiologics achieved unanimous consensus. These statements highlighted research regulation, safety, and suggested improvements to regulatory issues. The statement that did not achieve any consensus was on the regulatory processes that should be in place by an institution providing novel orthobiologic treatments. No statement reached a unanimous

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Received September 30, 2024; accepted January 27, 2025.

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0749-8063/241583/$36.00

https://doi.org/10.1016/j.arthro.2025.01.062

agreement on cost or ethical considerations. **Conclusions:** This study successfully identified key consensus statements emphasizing the importance of ethics, transparency, and regulation in the use of orthobiologics, with 85% of statements reaching unanimous or strong consensus. These findings underscore the need for standardized communication, improved regulatory frameworks, and enhanced safety measures while highlighting persistent challenges in addressing cost and ethical considerations. **Level of Evidence:** Level V, expert opinion.

Musculoskeletal pathology remains a significant cause of pain and disability for millions worldwide.[1] In the last 2 decades, orthobiologics, a biologic substance to treat musculoskeletal pathologies, have emerged to treat a variety of these conditions and augment healing.[2,3] Orthobiologics broadly define various approaches such as growth factors, autogenic- and allogenic-derived blood products, and cell therapies. They are used both as nonsurgical treatment measures to modify symptoms and in combination with surgical procedures to support healing for bone, cartilage, tendon, ligament, and muscular injuries.[3] Common orthobiologic treatments for orthopaedic injuries include bone marrow aspirate concentrate (BMAC), platelet-rich plasma (PRP), and microfragmented adipose tissue (MFAT), for which there are currently more than 1,000 clinical trials for BMAC and PRP listed on ClinicalTrials.gov.[4-7]

With an increase in the number of clinical trials and use of orthobiologics in orthopaedics and sports medicine, there is concern for a lack of homogeneity in how these products are described to patients, the use of advertisements, the introduction of novel therapies, and cost.[8-10] A 2021 study found 1,480 businesses marketing purported stem cell therapies online, of which 689 businesses advertised stem cell therapies to treat orthopaedic conditions and 339 businesses offered stem cells for sports injuries.[11] Of businesses marketing stem cell interventions online, it was found that some interventions were noncompliant with governmental regulations.[9] These bad actors have resulted in concern for patient safety. Although patient safety is of utmost importance, there exists concern that more stringent federal regulations around these products to curb the negative impacts of bad actors will lead to slower introduction of novel therapies. This is evident from the United States versus Regenerative Sciences, 2012 case in which members of the orthopaedics and sports medicine communities sought to challenge the Food and Drug Administration's (FDA) control over orthobiologics.[12]

A positional statement by the American Medical Society for Sports Medicine (AMSSM) set guidelines for orthobiologics use in sports medicine practice, including (1) the need for informed consent (risks, benefits, alternatives), (2) out-of-pocket costs, (3) conflicts of interest, and (4) a thorough discussion of the current literature.[13] Several other societies also have previously developed national and international expert consensuses on a variety of topics using a modified Delphi method.[8,14,15] The modified Delphi method uses multiple rounds to encompass expert opinions on a topic, ultimately leading to defined consensus statements. Orthobiologics are biologic procedures that are regulated by the FDA and as part of orthopaedic medical and surgical practice but do not require premarket authorization in the form of a Biologic License Application.[16] Common orthobiologics, like BMAC and PRP, are legally "allowed" to be used in medical practice because they fall under the 510(k) medical device pathway, meaning they are equivalent to current medical devices on the market.[17] However, orthopaedic and sports medicine applications of these treatments, such as meniscus repair, have not been approved and thus are considered off-label uses.[17] Thus, it falls on the expertise of the medical providers to develop statements for best practices. As a result, the Biologic Association, an international consortium of orthopaedic and sports medicine professional societies, established an initiative to create specific consensus statements surrounding the use of orthobiologics at the provider level.

The Biologic Association's purpose is to create a collaboration to speak upon the musculoskeletal biologics environment with a unified voice. The organization aims to advocate for the responsible use of biologics, lead standards development, and report on the safety and efficacy of orthobiologics. Biologic Association members are orthopaedic surgeons with fellowship training in sports medicine, orthopaedic primary care physicians, and basic scientists whose work emphasizes orthopaedics and regenerative medicine. Each member has a significant interest in the field of biologics and regenerative medicine, indicated by research efforts (www.thebiologicassociation.com).

The purpose of this study was to establish consensus statements via a modified Delphi process about ethics, transparency, regulation, and best practices for the use of orthobiologics in clinical practice for musculoskeletal pathology. Our hypothesis was that there would be a consensus on the majority of statements on ethics, transparency, regulation, and best practices for the use of orthobiologics.

Methods

Consensus Working Group

Twenty-four orthopaedic surgeons, sports medicine physicians, and basic scientists were invited to participate in these expert statements on orthobiologics, with

20 participating in each round and 4 declining. Of the 20 who participated, there were 13 orthopaedic surgeons, 4 sports medicine physicians, and 3 basic scientists from 3 countries. Each participant was a Biologic Association member organization representative and was invited on the basis of their current interest, experience, and expertise in orthobiologics. Biologic Association member organization representatives are experts in the field of biologics, whom their peers have selected to represent their organization within the Biologic Association, on the basis of their significant contribution to the field of biologics research. By holding this position, they have demonstrated significant experience in research and/or administration of orthobiologics. Together, the 20 participants have published 750+ journal articles on orthobiologics. Many participants have held or currently hold leadership positions in the field of regenerative medicine, such as Chair of the AMSSM's Regenerative Medicine Task Force. All participants were instructed to complete the questionnaires based on their belief as to the best answer, refraining from personal bias. A liaison (S.A.M.) provided the primary point of contact and distribution of questionnaires to ensure consistency throughout the process. On the basis of responses from previous rounds, the liaison also formulated each subsequent round of questionnaires. The liaison did not submit answers to questionnaires or participate in voting to decrease the potential for bias in data analysis and/or literature review.

Modified Delphi Consensus Method

The initial set of questionnaires was created by the 4 members of a steering committee via email correspondence (B.J.C., R.M.F., S.A.R., S.A.S.). To establish the questions, expert opinions of contentious topics and a review of the current literature identified areas in need of discussion. The literature review was conducted to search for current positional and consensus statements focusing on ethical and regulatory issues at the provider level for current and novel orthobiologic treatments. A positional statement and narrative review highlighted issues with communication, transparency, and ethical and regulatory considerations that lacked worldwide consensus from experts.[13,17] In addition, a review of cost-effectiveness studies for common orthobiologics exposed a need for more research and consensus by experts while more studies are conducted.[18-21] A modified Delphi method was used to create expert statements, similar to previously established methods.[8,14,15] The participants completed 2 rounds of questionnaires and then a final vote over a 3-month period, with all responses being anonymous. Any questions that reached 80% agreement over the 2 rounds were elevated to a final vote. Between rounds, the questionnaires evolved from open-ended responses to structured statements with the ability to rate their agreement on a Likert scale and space for additional comments. The final vote had all 20 participants rate their agreement with the expert statements on a Likert scale, either "strongly agree," "agree," "neither agree nor disagree," "disagree," or "strongly disagree."[22] All responses were collected anonymously via Google Forms.

Final Voting

When the final votes for the consensus round were completed, the level of agreement was represented as a percentage rounded to the nearest whole number. Levels of consensus were delineated according to the number of votes for each statement: no consensus, <80%; consensus, 80% to 89%; strong consensus, 90% to 99%; unanimous, 100%.[15,23-25]

Results

Overall Consensus

The 26 consensus statements on orthobiologics resulted in 14 achieving unanimous consensus, 8 achieving strong consensus, 3 achieving consensus, and 1 not achieving consensus. Detailed results of final consensus round responses can be found in Figure 1.

Communication and Transparency

Ninety-three percent of the statements on communication and transparency reached either a unanimous consensus (60%) or a strong consensus (33%). These statements discussed helpful tools to describe current orthobiologics, persistent misinformation, use of the word "stem cells," "off-label" use, and problems with the present regulatory environment. The statements are shown in Table 1.

Introduction of New Orthobiologics—Regulatory Aspects

Most statements on communication and transparency (62.5%) reached unanimous consensus. These statements highlighted research regulation, safety, and suggested improvements to regulatory issues. The statement that did not achieve any consensus was on the regulatory processes that should be in place by an institution providing novel orthobiologic treatments. The statements are shown in Table 2.

Ethical Considerations

The 2 statements regarding ethical considerations of orthobiologics both achieved strong consensus. The statements are shown in Table 3.

Costs

The 1 statement regarding the cost of orthobiologics reached a consensus. The statement can be found in Table 4.

Discussion

The most important finding was that 96% of the statements reached some degree of consensus and 85% reached unanimous or strong consensus. Overall, among Biologic Association member organization representatives, there is a strong agreement regarding key points that should be included when discussing orthobiologics with patients. However, there is still a gap in the standardization of regulatory procedures for novel orthobiologics, along with best practice recommendations at the provider level. The statements that reached unanimous consensus pertained to describing orthobiologic treatments to patients and the role of regulatory authorities. The only statement that did not achieve consensus debated institutional regulations for monitoring novel treatments.

Various issues exist when orthobiologic therapies are presented to patients. Many studies have shown misleading direct-to-consumer marketing that highlights exaggerated benefits and selling regenerative options over standard-of-care treatments,[26-28] including the field of orthobiologics.[29] One study found that some patients seeking orthobiologic therapy believed they could repair/regenerate tissue, suggesting these marketing efforts are disseminating misinformation to the public, as there is little to no evidence to support these claims.[30] A study by Petersen et al.[31] demonstrated that there are patients who are knowledgeable about the potential benefits and risks, having conducted research themselves. The Biologic Association agreed that misinformation promising a cure or regeneration without sufficient evidence and sensationalism of the current literature is leading to unrealistic patient expectations.

The regenerative ability of current orthobiologic treatments should be highlighted. This idea likely arises from many direct-to-consumer marketing efforts that describe these interventions as "stem cell" therapies.[11,32] The most basic definition of a "stem cell" includes the ability to self-renew and is multipotent, meaning it can differentiate into various tissue types.[33] The steering committee used this definition to generate the first round of questions. However, the term "stem cells" was not defined for all respondents, which may impact three statements. It is probable that some members of the public understand this basic definition to mean these cells can generate new tissue or repair damaged tissue, leading to the idea that orthobiologics have regenerative capabilities. Although the Biologic Association unanimously agreed that the term "stem cells" may be part of the discussion with patients for educational purposes, the respondents also highlighted that the term "stem cells" should not be used to describe current orthobiologic treatments. In addition, the present study suggests that the issue of regeneration should be addressed with patients, and potential regenerative characteristics should be in line with current available evidence, which is controversial. These statements reached a unanimous consensus and are likely a result of the current literature demonstrating few if any, mesenchymal stem cells being present in BMAC and PRP and insufficient evidence to show they function in a regenerative capacity.[34-36] In other terms, although "stem cells" may be present in orthobiologics on the basis of the basic aforementioned definition, the Biologic Association concludes there is insufficient evidence to show these "stem cells" use their multipotency to generate new tissue. Instead, physicians

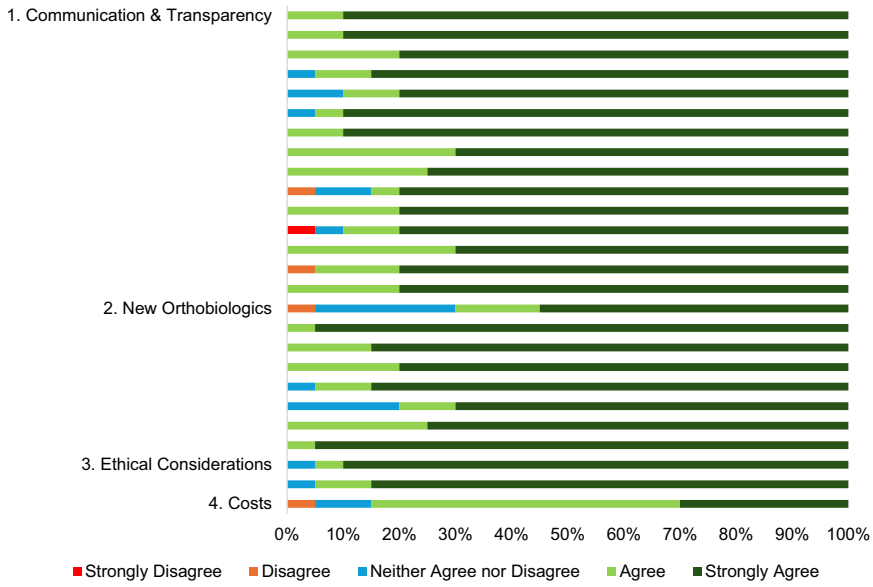

Fig 1. Stacked bar chart representing the percentage of each type of response (strongly disagree, disagree, neither agree nor disagree, agree, and strongly agree) for every question in the final questionnaire.

Table 1. Communication and Transparency

Questions (Q) and Answers (A)	Agreement	Consensus
Q: When discussing an orthobiologic treatment with a patient, what information should be included?	100%	Unanimous
A: When discussing an orthobiologic treatment with a patient, the physician and the patient should have a thorough discussion of the product type, presumed mechanism of action, and possible risks and benefits, including evidence-based expected outcomes and common adverse effects. Due to common misconceptions, it is critical to emphasize the treatment is intended to modify symptoms and there is no evidence for regenerative properties. Finally, FDA label status, costs, and the immediate postprocedure instructions should be provided by the physician or a trained physician extension.		
Q: What are some problems you see when orthobiologics are described to patients?	100%	Unanimous
A: Current problems that exist when orthobiologics are described to patients include a promise to cure the disease or regenerate tissues without sufficient evidence and sensationalism of the current literature that leads to unrealistic patient expectations. The use of the word "stem cells" can also lead to misconceptions without a thorough explanation. When orthobiologics are described to patients, any promise of a cure, regeneration, and unsubstantiated claims should be avoided, unless there is strong clinical evidence for a particular diagnosis or indication.		
Q: What tools, if any, should be used to describe orthobiologics to a patient?	100%	Unanimous
A: Scientific literature, models, imaging, handouts, brochures, websites, and educational videos are all helpful tools when describing orthobiologics to patients.		
Q: Do you believe that informed consent should be obtained for orthobiologic treatments?	95%	Strong consensus
A: Informed consent should be obtained for all orthobiologic treatments. Informed consent should preferably be obtained with a signed written paper/electronic form. However, verbal agreement which is well-documented in the clinic or operative note may also be acceptable in some jurisdictions. The consent should include the pertinent information as described in statement number 1 of this consensus.		
Q: What common misconceptions of orthobiologics should be addressed when communicating with a patient (if any)?	90%	Strong consensus
A: The concept that orthobiologics are regenerative is controversial and as such, possible regenerative attributes should only be described in a manner that is supported by the available evidence for the limited specific indication. The term "stem cells" should be addressed as to what they are and what they are not and their role in orthobiologic treatment.		
Q: What role does the medical community play in ensuring that orthobiologics are described appropriately to patients?	95%	Strong consensus
A: The medical community has the role of providing objective and transparent information through their description of orthobiologics to patients. Moreover, the medical community should be tracking outcomes of these treatments as well as publishing peer-reviewed data in order to create treatment and best practice guidelines.		
Q: When describing a cell-based therapy to a patient, what information should be included in that description?	100%	Unanimous
A: With cell-based therapy, similar to any orthobiologic treatment, the physician and the patient should have a thorough discussion as described in statement 1. Specifically, for cell-based therapy, the source of cells and how the cells will be handled after harvesting should be provided.		
Q: What are your thoughts on the use of the word "stem cells" given current available evidence?	100%	Unanimous
A: The term "stem cells" may be part of a discussion with patients. However, it should not be used to describe current orthobiologic treatments and certainly should not be a selling point. It should be made clear that currently used cell therapy formulations contain few if any true "stem cells" by any formal cellular, molecular, or functional criteria.		
Q: What should be included in the discussion regarding off-label use of orthobiologics and who should have the discussion with the patient?	100%	Unanimous
A: The discussion with patients regarding off-label-use of orthobiologics should be carried out by the physician or trained physician extension. The discussion includes the meaning of off-label, describe the off-label use, the goal of the off-label use, risks, and costs.		
Q: How should an orthobiologic, which is part of a research study, be presented to a patient?	85%	Consensus
A: An orthobiologic treatment, which is part of a research study, should be presented to the patient as an investigational product with potential benefits according to the scientific literature following the guidelines of the IRB or similar entity. Any orthobiologic being evaluated in a formal clinical trial, such as a trial registered on ClinicalTrials.gov, should be provided to the patient at no cost to the patient.		
Q: What should be included in the discussion with the patient regarding out-of-pocket cost of orthobiologics and who should have this discussion with the patient?	100%	Unanimous
A: The physician should have the discussion with the patient regarding out-of-pocket cost of orthobiologics, including why insurance does not cover it. The administrative staff may enter into more detail surrounding cost and payment.		

(continued)

Table 1. Continued

Questions (Q) and Answers (A)	Agreement	Consensus
Q: How should potential conflicts of interest be discussed?	90%	Strong consensus
A: Any potential conflicts of interest should be discussed and documented upfront with patients. These conflicts may be found within informed consents, standard disclosures, or via conversation. Discussions about conflict of interest should be documented in the medical record.		
Q: What is most important to discuss in order to synchronize patient expectations with current available evidence and physician experience?	100%	Unanimous
A: A thorough explanation of the current scientific evidence between the patient and physician is most important to synchronize patient expectations with current evidence. Physician experience with orthobiologics should be presented with the appropriate weight based on experience and collection of registry data.		
Q: How should advertisement of an orthobiologic treatment by a health care provider and/or institution be handled or monitored?	95%	Strong consensus
A: Advertisement of orthobiologics should be limited to on-label uses and monitored by regulatory agencies such as the Federal Trade Commission or similar entity. Depending on the local regulatory environment, third parties within the institution may monitor the advertisements or promotional materials.		
Q: How would you rate the current regulatory environment for orthobiologics?	100%	Unanimous
A: The importance of FDA or equivalent authority regulations are valuable and promote responsible clinical research and clinical use of orthobiologics. However, the current regulations are sometimes unclear and vague in many instances and there is concern that not all adhere to these rules. Improved communication between the regulatory authority and providers specializing in orthobiologics may bridge this gap in the future.		

FDA, Food and Drug Administration; IRB, institutional review board.

should focus on better evidence for the symptom-modifying effects of orthobiologics.[3,37,38]

With nearly 25% of sports medicine physicians using advertisements to market the use of orthobiologics, it is essential that these advertisements are monitored by the Federal Trade Commission or a similar entity.[39] We suggest any marketing of orthobiologic treatments be limited to on-label uses and that monitoring by third parties within the providers' institution may be useful.

To improve transparency and consistency, without clear regulations at the provider level, there have been many different efforts by the orthopaedic community to standardize how orthobiologics are being reported in the literature and presented to patients. A group of 34 international experts agreed on the communication tool DOSES (Donor, Origin tissue, Separation method, Exhibited cell characteristics associated with behavior, Site of delivery) to standardize the reporting of cell therapies,[8] after highlighting the clear lack of comprehensive reporting of PRP preparation protocols.[40] The tool is designed to improve transparency and scientific progress by better reporting how cell therapies are described in scientific publications.[8] As mentioned, another positional statement by the AMSSM set guidelines for implementing orthobiologic therapies into sports medicine practice, including (1) the need for informed consent (risks, benefits, alternatives), (2) out-of-pocket costs, (3) conflicts of interest, and (4) a thorough discussion of the current literature.[13] In this consensus statement, the consensus working group agreed that informed consent should be obtained for all orthobiologic treatments. Although in agreement with the positional paper from the AMSSM, the consensus working group agreed that the discussion with patients regarding orthobiologics should also include (1) product type, (2) mechanism of action, (3) emphasis on symptom modification over regeneration, (4) FDA label-status, and (5) immediate postprocedure instructions. It is hoped that this statement will bring more clarity to the provider level of expectations and best practices for those providing orthobiologic therapies. In addition, there is a lack of guidance surrounding how conflicts of interest should be presented to patients. In this study, a strong consensus was reached that it is appropriate for conflicts of interest to be disclosed via informed consent, standard disclosures, or conversations. The discussion should be documented in the medical records.

Current orthobiologics like BMAC, PRP, and MFAT are regulated under the FDA through the 361 pathway as they meet the criteria for "minimally manipulated" tissue.[16,41] Other countries have approved orthobiologic therapies with different regulations, which is a detailed discussion beyond the scope of this paper.[17] Moreover, as the field of orthobiologics is growing rapidly,[2,3] governmental agencies do not possess the bandwidth to monitor the exponential growth of novel therapies in great depth due to funding, staffing shortages, and insufficient expert knowledge.[42,43] It is, therefore, essential that highly regarded experts in the field continue to have conversations and set standards so that progress can be made in novel orthobiologics

Table 2. Introduction of New Orthobiologics——Regulatory Aspects

Questions (Q) and Answers (A)	Agreement	Consensus
Q: What regulatory processes and checkpoints should be set in place by an institution providing novel orthobiologic treatments?	70%	No consensus
A: An institutional multidisciplinary committee should review and approve new orthobiologic treatments, considering clinical safety, clinical outcomes evidence, regulatory status, ethical considerations, and costs. Outcomes and adverse effects should be monitored and reported back to the committee to maintain approval status at a timeline set by the committee.		
Q: What regulatory processes and checkpoints should be set in place by an institution researching novel orthobiologic treatments?	100%	Unanimous
A: Standard IRB regulatory processes should be adhered to by an institution researching novel orthobiologic treatments.		
Q: What differences in such processes are expected between various health care facilities (hospital-based, independent private practice, etc.)?	100%	Unanimous
A: Ideally there should be no differences between various health care facilities, and all should adhere to the highest ethical standards. While based upon resources the setting may change, direct physician involvement should be maintained.		
Q: How should orthobiologic treatment safety be defined, and who is responsible for the ascertainment of a product safety profile within their institution?	100%	Unanimous
A: Orthobiologic treatment safety should be defined by prior available evidence and predicted risk of adverse effects. Providers should establish formal mechanisms to report adverse events and track such events internally to allow review by institutional leadership.		
Q: Who should monitor the outcomes and adverse effects of a novel orthobiologic treatment (at the institutional and health care provider level)?	95%	Strong consensus
A: Outcomes and adverse effects of a novel orthobiologic treatment should be monitored by the provider and medical staff. An independent safety and quality monitoring staff may assist to optimize the monitoring process.		
Q: If there are concerns about a product's safety after administration to humans, who should be informed and how should this be addressed at the health care provider level?	80%	Consensus
A: Safety issues with current orthobiologics treatment techniques are rare. The provider should report any concerns in a written format to the hospital/practice leadership. Further notifications should then be sent to the appropriate local and national regulatory bodies and relevant professional societies, to the manufacturer, FDA, and IRB.		
Q: What regulatory changes would you recommend to improve the approval process for orthobiologic treatments?	100%	Unanimous
A: Efforts should be made by the FDA, manufacturers, and the professional authoritative societies and regulatory bodies for more unified and comprehensive registries for evaluation of clinical outcomes and adverse effects. Efforts should be made to allow appropriate regulation which is not prohibitive for the advancement of novel therapies, but also highly vigilant to ensure safe and ethical patient care.		
Q: In your view, what are the critical regulatory issues that need to be addressed in the next 5 years in order to promote best practices to evaluate new technologies in the orthobiologics field?	100%	Unanimous
A: In the next 5 years we believe the following regulatory issues should be addressed to optimize best practices using new technologies in the orthobiologics field: a. Provider-level best practice recommendation b. Standardization of definitions, procedures, compositions, and doses c. Building robust data registries d. Allowing fast-track and streamline testing and approval processes of novel therapies. Special considerations should be made for products with prior international experience and approval by accepted international regulatory agencies e. Establishing training standards for orthobiologics education, research, and practice		

FDA, Food and Drug Administration; IRB, institutional review board.

research. The consensus working group in this study reached a unanimous consensus that institutions researching novel orthobiologics should adhere to standard institutional regulatory board processes, and there should ultimately be no differences between various facilities. In this study, the Biologic Association also unanimously agreed to ensure the safety profile of novel orthobiologics and support the idea that providers should establish formal mechanisms to report adverse events and extensive oversight by institutional leadership. The only statement that did not reach a consensus recommended an institutional multidisciplinary committee approve and continuously monitor novel orthobiologics introduced at their institution. The lack of consensus on this statement points to a need for further conversation between clinicians and other

Table 3. Ethical Considerations

Questions (Q) and Answers (A)	Agreement	Consensus
Q: What ethical concerns do you think are most pressing in the field of orthobiologics?	95%	Strong consensus
A: Significant ethical concerns include inaccurate marketing accompanied by unproven claims suggesting regenerative and structure-modifying properties with the promise of curing the disease. Further potential ethical concerns include high costs and the provider's conflicts of interest.		
Q: How do you suggest practitioners navigate the ethical dilemmas associated with off-label use or experimental orthobiologic therapies?	95%	Strong consensus
A: To navigate the ethical dilemmas associated with off-label use or experimental orthobiologic therapies an honest, open, and transparent discussion should occur. The discussion should be guided by regulations as set forth by the FDA (or equivalent entity), by evidence-based medicine guidelines, and by position papers by authoritative professional agencies and organizations.		

FDA, Food and Drug Administration.

professionals involved with orthobiologics care. Some respondents commented on wanting more clarity as to whether the multidisciplinary committee was for routine use, which they disagreed with the statement. Another though the use of "institution" precludes the private practice setting. Future conversations are needed to address the complexity of different protocols for various practice settings.

The cost of common orthobiologics varies widely depending on location, market, and procedure, as evident by a consensus for this statement. Further, there was a strong consensus that ethical concerns of these orthobiologic treatments include the high costs. The large range is likely due to a lack of agreement on reimbursement and the out-of-pocket costs of the procedures.[18,19] This highlights a need for further research into the cost-effectiveness of these treatments so that there is more continuity in cost and insurance companies may consider orthobiologics to become a covered benefit. For all treatments, but BMAC and MFAT in particular, there is a serious lack of cost-effectiveness studies. Bendich et al. showed PRP is cost-effective for knee osteoarthritis when it costs less than $1,192.[20] A study by Samuelson et al.[44] concluded there was no difference in cost-effectiveness between a series of 3 PRP or hyaluronic acid injections for knee osteoarthritis. With these treatments being used for a variety of procedures, there is a clear need for more randomized controlled trials in order to conduct these cost-effectiveness studies. We may speculate that the controversy or lack of high-quality evidence in support of orthobiologics' efficacy and cost-effectiveness might be the reasons why most insurance companies do not cover these treatments.

Limitations

For one, consensus statements are Level V evidence because they represent expert opinion, which opens them up to bias in the selection and allocation of participants.[45,46] Nonetheless, we looked to include physicians and scientists with an active interest and expertise in the area, as evident by their academic accomplishments on the topic. In addition, the topics included may be a potential source of bias, as there was no standardized process for creating them. The topics were selected and agreed upon by the group leaders. Moreover, the participant selection process was not broadly advertised, and the steering committee and the Biologic Association organization member representatives were chosen on the basis of their roles as leaders and representatives of their organization, which may introduce some bias. Finally, the respondents could not see other participants' responses and could not discuss potential conflicts or reconsider their positions through discussion.

Table 4. Costs

Questions (Q) and Answers (A)	Agreement	Consensus
Q: What do you believe should be the appropriate out-of-pocket cost for common orthobiologics (Please specify PRP, BMAC, etc.)?	85%	Consensus
A: The appropriate out-of-pocket cost for PRP/BMAC/MFAT/SVF injections may vary according to several factors including location, market, and the specific procedure involved. In general, at this time, we find common out-of-pocket costs to be as follows: a. PRP (1 injection): range between $100 and $2,000 b. PRP (3 injections series): range between $250 and $4,500 c. BMAC: range between $1,000 and $5,000 d. MFAT/SVF: range between $1,000 and $5,000		

BMAC, bone marrow aspirate concentrate; MFAT, microfragmented adipose tissue; PRP, platelet-rich plasma; SVF, stromal vascular fraction.

Conclusions

This study successfully identified key consensus statements emphasizing the importance of ethics, transparency, and regulation in the use of orthobiologics, with 85% of statements reaching unanimous or strong consensus. These findings underscore the need for standardized communication, improved regulatory frameworks, and enhanced safety measures while highlighting persistent challenges in addressing cost and ethical considerations.

Disclosures

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: A.A. reports board or committee member, Andrews Research and Education Foundation; and IP royalties; paid consultant; paid presenter or speaker; research support from Arthrex. A.B. reports board or committee member, American Orthopaedic Society for Sports Medicine; paid consultant for and royalties from Arthrex; and publishing royalties, financial or material support from SLACK Incorporated and Springer. D.B. reports board or committee member, Arthroscopy Association of North America and Interventional Orthobiologics Foundation; editorial or governing board, *Biologic Orthopedics Journal*; paid consultant for CONMED Linvatec; and stock or stock options from Trice Medical. J.C. reports royalties from Springer; consulting/advisory/other remuneration from 2nd.MD and Carelon Specialty Health; and ownership or partnership in Musculoskeletal Ultrasound Consultants, LLC. B.C. reports research support from Aesculap/B. Braun; editorial or governing board, *American Journal of Sports Medicine* and the *Journal of the American Academy of Orthopedic Surgeons*; IP royalties, paid consultant, and research support from Arthrex; stock or stock options from Bandgrip and Ossio; IP royalties, publishing royalties, financial or material support from Elsevier Publishing; other financial or material support from JRF Ortho; and research support from the National Institutes of Health (National Institute of Arthritis and Musculoskeletal and Skin Diseases and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development). L.D. reports paid presenter or speaker, Arthrex; board or committee member, ESSKA, Italian Mesenchymal Stem Cell Group, and ON Foundation; research support from Fidia and IGEA S.p.A; and paid consultant, Lipogems International SpA. A.D. reports immediate past president of the Interventional Orthobiologics Foundation; instructor for OrthoSono MSK Ultrasound and IOF Labs; education support from Arthrex; research support, consulting fees, and board member, Jointtech Labs; board member, DataBiologics; consulting fees, Sonex Health, Apex Biologix, and Reparel; and hospitality payments from Pacira Pharmaceuticals and Zimmer Biomet Holdings. R.F. reports board or committee member, AAOS, American Orthopaedic Society for Sports Medicine, Arthroscopy Association of North America, and International Cartilage Restoration Society; paid presenter or speaker, Arthrex; publishing royalties, financial or material support from Elsevier; and editorial or governing board, *Orthopedics Today*. R.G. reports editorial board, *Arthroscopy*. E.K. reports editorial or governing board, *American Journal of Sport Medicine*, *BMC Musculoskeletal Disorders*, *International Orthopaedics Research*, *Joints*, and *Journal of Experimental Orthopedics*; support from CartiHeal; paid consultant and stock or stock options from CartiHeal (Israel); paid presenter or speaker, Fidia (Italy); research support from Fidia Farmaceutici; Paid consultant for Fidia Farmaceutici Spa, Geistlich Biosurgery, and Terra Quantum; board or committee member, International Cartilage Repair Society and SIAGASCOT; paid consultant and research support from Mastelli; and paid presenter or speaker; research support from Zimmer. K.M. reports co-founder and MAB of Tendonova. C.M. reports Co-Chair of the C. Wayne McIlwraith Translational Medicine Institute Board; President of the Interventional Orthobiologics Foundation; and Chair of the Scientific Advisory Board of eQcell, Canada. L.M. reports editorial or governing board, *Orthopedics Today*; employee, US Orthopedic Partners; and IP royalties; paid consultant; paid presenter or speaker; stock or stock options from Zimmer. N.N. reports editorial or governing board, *American Journal of Sports Medicine*, *Journal of Experimental Orthopaedics*, *Journal of ISAKOS*, *Journal of Orthopaedic Science*, and Sage (Cartilage); paid consultant; research support, Cell Source; board or committee member, International Cartilage Repair Society and International Society of Arthroscopy, Knee Surgery, and Orthopaedic Sports Medicine; and research support from Two Cells Ltd. S.N. reports paid consultant for ACI Clinical; IP royalties; stock or stock options from Aevumed and HealthExl; board or committee member, American Shoulder and Elbow Surgeons and Philadelphia Orthopaedic Society; research support from Arthrex and DePuy, A Johnson & Johnson Company; IP royalties; paid consultant; and paid presenter or speaker for Biederman Motech; stock or stock options from CLEU Diagnostics, Complete Surgical Nutrition, Coracoid Solutions, and Parvizi Surgical Innovations; IP royalties; paid consultant; paid presenter or speaker, and research support from Enovis, Smith & Nephew, Stryker; editorial or governing board of the *Journal of Bone and Joint Surgery — American* and *Shoulder & Elbow*; IP royalties; stock or stock options from MediFlix and SurgiWipe: research support from Roche and Zimmer; publishing royalties, financial or material support from Saunders/Mosby-Elsevier and SLACK Incorporated; paid consultant, Synthes; IP

royalties from Tigon; and publishing royalties, financial or material support from Wolters Kluwer Health - Lippincott Williams & Wilkins. N.S.N. reports board or committee member, American Medical Society for Sports Medicine; and publishing royalties, financial or material support from Wolters Kluwer Health - Lippincott Williams & Wilkins. S.R. reports consulting with Novartis Pharmaceuticals Corporation and Advance Medical; research support from Virginia Toulmin Foundation, Orthopaedic Research & Education Foundation, Arthritis Foundation, Angiocrine Biosciences, Weill Cornell Clinical & Translational Science Center; National Institutes of Health; and stock options from Jannu Therapeutics and Overture Medical. J.T. reports IP royalties; paid consultant; paid presenter or speaker from Arthrex; board or committee member, Arthroscopy Association of North America; editorial or governing board, publishing royalties, financial or material support from *Journal of Shoulder and Elbow Surgery*; and editorial or governing board, *Orthopedics Today*. All other authors (S.M., E.H., A.Y., C.F., R.C., D.G., S.S.) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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