Delphi Panel Survey

Use of Bone Marrow Concentrate to Treat Pain and Musculoskeletal Disorders: An Academic Delphi Investigation

Christopher J. Centeno, MD[1,2], Mairin A. Jerome, MD[1], Sarah M. Pastoriza, DO[1], Shane Shapiro, MD[3], Ken Mautner, MD[4], Gerard A. Malanga, MD[5], Michael J. DePalma, MD [6], R. Amadeus Mason, MD[4], Ian Stemper, MS[2], and Ehren Dodson, PhD[2]

From: [1]Centeno-Schultz Clinic, Broomfeld, CO; [2]Regenexx, LLC, Des Moines, IA; [3]Department of Orthopedic Surgery, Mayo Clinic, Jacksonville, FL; [4]Department of Orthopaedics, Emory University, Brookhaven, GA; [5]NJ Regenerative Institute, Cedar Knolls, NJ; [6]Virginia iSpine Physicians, Richmond, VA

Address Correspondence: Ehren Dodson, PhD 403 Summit Blvd Suite 201, Broomfield, CO 80021 Email: edodson@regenexx.com

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: CJC is a shareholder and CMO of Regenexx, LLC, and president and owner of the Centeno-Schultz Clinic. MJD had received research support from Discgenics; Vivex; Mesolbast; Samumed; Avanos; Vertiflex; SPR. DSMB: Anges; Intralink Spine. Advisory Board: Spine BioPharma; Vivex; Avanos. GAM: Editor of the following textbooks: Musculoskeletal Physical Examination: An Evidence-Based Approach (Elsevier); Atlas of Ultrasound-Guided Musculoskeletal Injections (McGraw-Hill); Regenerative Treatments in Sports Medicine (Demos). Consultant/instructor: Lipogems. Medical Advisory Board/stockholder: Biorestorative Technologies; TendoNova. Founder/Principal: DataBiologics. SMP, MAJ, SS, KM, RAM, IS, and ED declare no conflicts of interest.

Manuscript received: 02-26-2020
Revised manuscript received: 08-11-2020
Accepted for publication: 10-13-2020

Free full manuscript: www.painphysicianjournal.com

Background: Acute and degenerative musculoskeletal disorders are among the most common etiologies of disability worldwide. Recently, there has been interest in the field of regenerative medicine to bridge the gap between conservative and surgical management of these conditions. Autologous bone marrow concentrate is one type of injectate that has increased in popularity over the last few decades. Though there is promising evidence supporting its efficacy, standard of care practice guidelines to govern the appropriate use and implementation of such technology are currently lacking.

Objectives: The aim of this article is to report findings from a survey administered using the Delphi technique to a group of physicians using bone marrow concentrate in practice to determine best practice consensus regarding optimization of patient safety and education.

Study Design: Delphi panel technique.

Setting: The study was first announced at a national meeting and continued remotely across the United States via 4 rounds of online surveys.

Methods: An initial panel of 30 expert members was convened and a 5-member steering committee was established. Four rounds of consensus questionnaires totaling 11 unique questions were distributed. Ten questions included a 5-point Likert scale from "Strongly Agree" to "Strongly Disagree," and one question had a selection of 5 options regarding minimum level of evidence required. The anonymized aggregate results of each round were shared with the group prior to voting in the subsequent round in accordance with the Delphi process. Consensus was defined as 80% agreement of the statements indicating either "Strongly Agree" or "Agree" for the 10 questions with the Likert Scale and 80% agreement among 2 of 5 choices in the question regarding levels of evidence.

Results: Three invited participants were excluded by the second round of questions due to lack of response in a timely manner, leaving 27 physicians queried. Nine of the 11 questions met criteria for > 80% consensus. Areas of agreement included importance of a treatment registry, candidacy grading, expanded informed consent, scientific accuracy in advertising, institutional review board approval for novel uses, performance of procedures by only licensed physicians or mid-level providers with direct physician oversight, use of image guidance for injections, data submission for publication in peer reviewed literature, and a minimum requirement of case-series level of evidence for use of bone marrow concentrate in musculoskeletal medicine. The 2 areas that did not meet criteria for consensus included online publishing of individual clinic data and standards around cell counting for dosing.

Limitations: The Delphi panel of experts was convened on a voluntary basis rather than a nomination process. Our panel of experts were all physicians who use bone marrow concentrate in practice, therefore it is possible that a different panel of experts within other disciplines would reach different conclusions.

Conclusions: There is significant consensus among a panel of physicians performing bone marrow concentrate injections regarding best practice guidelines for musculoskeletal conditions.

Key words: Bone marrow concentrate, musculoskeletal, BMC, BMAC, injections, orthopedic, orthobiologic, Delphi method, regenerative medicine, bone marrow aspirate

Pain Physician 2021: 24:263-273

Degenerative musculoskeletal conditions are a leading cause of disability and poor quality of life worldwide (1). In the United States, absenteeism from work due to the burden of osteoarthritis (OA) leads to an annual cost of $10.3 billion and results in more days of work lost than other disease processes (2). With a clear need for more treatment options for degenerative musculoskeletal conditions, orthobiologics have emerged over the last few decades as a promising treatment modality with the potential to offer greater therapeutic and cost efficacy in a less invasive manner than surgery. Due to the novelty of the technology, however, the clinical application of orthobiologics has been plagued with inconsistencies and lack of standardized protocols, which has led to variability in outcomes (3). This has also contributed to a lack of consensus regarding efficacy, optimal methods of treatment delivery, standards within the field for patient education, registry data, and level of evidence required for use.

Regenerative medicine has traditionally referred to the utilization of substances that can promote healing and encourage a healthier local environment, while decreasing chronic inflammation (4). Bone marrow concentrate (BMC) is a commonly used autologous regenerative medicine therapy. Bone marrow harvesting is one of the oldest medical procedures, with evidence dating back more than 7000 years (5). The first attempts to obtain bone marrow samples for diagnostic purposes were performed in the early 1900s by Pianese in Italy and Wolff in Germany (6). Bone marrow aspirations performed for musculoskeletal applications were first described in 1989 as a method to improve osteogenic potential of bone grafts in pediatric patients (7). Bone marrow aspirate (BMA) is harvested via inserting a trocar through the bony cortex and withdrawing bone marrow stroma via a syringe. BMC is then created by density gradient centrifugation of BMA (8). The buffy coat isolated from BMC has a number of cells, including mesenchymal and hematopoietic stem cells, myelopoietic and erythropoietic cells, mature leukocytes, platelets, and megakaryocytes (9). The posterior superior iliac crest is the most common site of BMA harvest because it is safe, easy to access, and yields a higher number of mesenchymal stromal cells when compared to other sites (10-12). The mechanism of action of BMC is not yet fully understood but is theorized to include paracrine signaling (13,14), tissue differentiation (15), exosome release (16), mitochondrial transfer (17), and alteration of macrophage function to promote anabolism rather than catabolism (18).

BMC has shown promise in treating knee OA (19-21), anterior cruciate ligament (ACL) tears (22,23), rotator cuff pathology (24), osteonecrosis (25-27), and nonunion fractures (28). Though there is much promising early clinical evidence, the rapid rise of regenerative medicine has led to some concerning practices (29). It is important for health care providers to offer such treatments based on the best interests of the patient and the best available scientific evidence, particularly as the current lack of insurance coverage for these procedures introduces out-of-pocket costs for patients. However, it has been documented that there are health care providers who do not practice in a manner consistent with these values (30,31). Therefore, in order to establish consensus among those practicing regenerative medicine, a Delphi panel was convened to further elucidate areas deemed of greatest importance in the use of BMC for musculoskeletal conditions.

The Delphi method facilitates the involvement of professionals from different disciplines to aid in joint problem-solving and decision-making (32-34). The opinions of experts in the field are surveyed through rounds of structured, anonymous questionnaires (35). The advantage of using this method is that it allows for diverse opinions to be elicited without scrutiny, thereby creating a lens through which to examine particular topics and seek a group consensus among experts (34-36). The Delphi technique was selected for this project in order to have an organized method of correlating viewpoints on 11 different categories within the utilization of BMC for musculoskeletal use. The primary aim of this paper is to drive toward consensus on BMC for musculoskeletal use in order to establish guidelines around, and therefore, optimize patient protection.

Methods

Participant Selection

Physicians practicing regenerative musculoskeletal medicine were informed of the Delphi panel by a generalized announcement at The Orthobiologic Institute meeting in Chicago, IL, that took place on June 7 – 8, 2019 (37). Participants responded via email agreeing to participate. To be selected for the panel, the physicians needed to meet the following criteria:

1. Actively use BMC in his/her medical practice.
2. Have an American Board of Medical Specialties (ABMS) recognized board certification in a medical specialty with musculoskeletal expertise, such

as orthopedic surgery, interventional pain management, interventional musculoskeletal radiology, physical medicine and rehabilitation, or family medicine with a sports medicine Certificate of Added Qualification (CAQ).
3. Have an academic appointment, be published in the field of regenerative musculoskeletal care, or have committee or other appointments in major medical societies that intersect with regenerative musculoskeletal care.

A steering committee of 5 participants was chosen by the first author (CJC) based on their willingness to contribute additional time to the panel administration.

Question Generation

Nine initial questions were determined by the first author (CJC) in the first query with a tenth question used for open-ended responses to guide formation of questions in subsequent rounds. Based on the feedback from the panel and the steering committee, a total of 11 final questions were generated with 9 being minimally edited from the original round. These questions were distributed starting in round 2. The 11 final categories surveyed are as follows:

1. Registry data collection
2. Collection and online reporting of patient outcomes for each medical practice performing BMC procedures for patient review
3. Grading of patient candidacy and communication of those grades to prospective patients
4. Informed patient consent with inclusion of BMC as an investigational therapy at present
5. Submission of data from novel uses of BMC for peer-reviewed publication
6. Accurate, factual advertising to the general public that is grounded in known basic and clinical science
7. Institutional Review Board (IRB) approval prior to use of BMC for novel application in humans
8. Restriction of therapeutic delivery of BMC for musculoskeletal use by a licensed physician or nurse practitioner/physician assistant with direct on-site physician supervision
9. Use of direct visualization or image guidance for BMC delivery to specifically targeted structures
10. Quantification of cell dosing via total nucleated cell count (TNCC) or cell differential
11. Minimum level of evidence required to perform BMC procedures for musculoskeletal indications

Survey Technique

The Delphi technique was carried out with 4 rounds of questioning delivered electronically via Survey Monkey. Participants were provided up to 4 reminders to complete the survey. Those who failed to respond at that point were dropped from the panel to ensure that the panel participants had an uninterrupted series of questionnaires. After the close of the survey, the anonymized aggregate results of each round were shared with the group prior to voting in the next round in accordance to the Delphi process prior to opening of the subsequent survey.

A 5-point Likert scale from "Strongly Agree" to "Strongly Disagree" was used for 10 questions. One question regarding minimum desirable level of evidence prior to performing BMC procedures had 5 options for answers: case reports, case series, comparison trials against traditional therapies, controlled trials, and multiple randomized placebo-controlled trials.

Survey Analysis

Consensus was determined by 80% agreement of the statements indicating either "Strongly Agree" or "Agree," as defined by Putnam and Bruininks (35) and an 80% consensus cluster of 2 of the 5 answer choices for the level of evidence question. Means and standard deviations were calculated for each question to measure the dispersion for the mean, which estimates consensus criterion as described by Rogers and Lopez as mean ± 1.64 (38). A decrease in standard deviation and increase in mean towards consensus on a 5-point Likert scale is considered closer to achieving consensus (39). The means were calculated with "5" being "Strongly Agree" and "1" being "Strongly Disagree." Therefore, each response was numbered with means and standard deviations calculated from that numeric score.

Results

Of the initial 30 invited participants, 2 were excluded after the first round and one was excluded after the second round due to lack of response following the 4 reminders. All responses from these participants were removed from the final data (Fig. 1). Two panel members had their data included but decided not to be named in the final publication.

Participants Demographics

The participants represented a variety of medical specialties, including anesthesia, family medicine, orthopedic surgery, physical medicine and rehabilitation

(PM&R), and radiology. Fellowship training was also diverse and included interventional pain, interventional sports and spine, primary care sports medicine, orthopedic surgery-based sports medicine, musculoskeletal radiology, interventional radiology, and spine surgery subspecialties. Eighty-five percent of the respondents were fellowship-trained. The mean number of years in practice was 20.3 (+ 9.1), with 26 men and one woman. The mean percentage of practice devoted to MSK-related issues was 91.3% (+ 20.5). Sixty-five percent of respondents work in private practice, 46% work in academics, 11% do both, and 65.4% are engaged with the teaching of residents and/or fellows. The average number of cases performed for each physician was 487.4 (+ 460). Twenty-three of the 27 final participants have been published in areas relevant to the field of regenerative medicine research (Table 1).

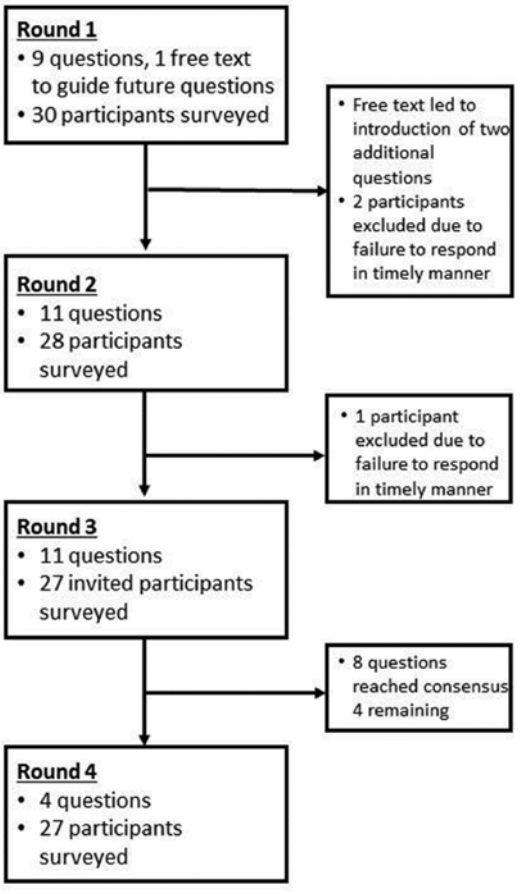

Fig. 1. *Flow chart of questions and participants inclusion.*

Survey Results

Round 1 consisted of 9 questions with the tenth question requesting open-ended responses to use as feedback for the addition of relevant questions in subsequent surveys. The free text responses led to the addition of questions related to cell counting and use of image guidance in the remaining rounds. Four total rounds were completed. The fourth round included only those questions that had not previously achieved an 80% consensus. Table 1 outlines questions asked with responses for each round (Table 2).

Of the 11 questions, 9 reached a minimum of 80% consensus. Topics reaching consensus included the use of candidacy grades, expanded informed consent for pa-

Table 1. *Participants demographics.*

	n = 27
Gender - Men:Women (% male)	26:1 (96%)
Mean age years (SD)*	51.7 (+ 8.7)
Mean number of years in practice (SD)*	20.3 (+9.1)
Published in the field of regenerative medicine (%)	23/27 (85%)
Mean # of BMC procedures performed (SD)†	487.4 (+460)
Practice setting*	
Private Practice	65.4%
University	46.2%
Both Private and Academic	11.5%
Teach Residents and/or Fellows	65.4%
% of Practice Devoted to MSK (mean, SD)	91.3% (+ 20.5)
Specialty Representation	
Anesthesia pain (%)	2/27 (7)
Family Medicine total	7/27 (26)
- Family Medicine Sports	- 6/27 (22)
- Family Med anti-aging, regenerative medicine	- 1/27 (4)
Physical Medicine & Rehabilitation (PM&R) total	12/27 (44)
- PM&R	- 2/27 (7)
- PM&R Sports	- 5/27 (19)
- PM&R Spine	- 2/27 (7)
- PM&R Pain	- 1/27 (4)
- PM&R Interventional Orthopedics	- 1/27 (4)
- PM&R Interventional Pain and Sports	- 1/27 (4)
Surgical Orthopedics overall	4/27 (15)
- Surgical Orthopedics Sports	- 3/27 (11)
- Surgical Orthopedics Spine	- 1/27 (4)
Musculoskeletal Radiology:	2/27 (7)
Fellowship trained: (%)	23/27 (85)

MSK, musculoskeletal. SD, standard deviation. *Data available for only 26 of 27 respondents. †Data available for only 25/27 respondents.

Table 2. *Questions and responses by Delphi round.*

Prompt	Response	Round 1	Round 2	Round 3	Round 4
It is desirable that patients who receive BONE MARROW CONCENTRATE for an orthopedic indication should be entered into a formal treatment registry that uses validated outcome tools and collects complications data at set time points.	Strongly Agree	51.6%	66.7%	51.9%	
	Agree	29.0%	25.9%	40.7%	
	Neither agree nor disagree	12.9%	3.7%	3.7%	
	Disagree	6.5%	3.7%	3.7%	
	Strongly disagree	0%	0%	0%	
The medical group using BONE MARROW CONCENTRATE to treat an orthopedic indication should publish results transparently online for patients and regulators to review.	Strongly Agree	25.8%	25.9%	18.5%	18.5%
	Agree	6.5%	25.9%	48.1%	44.4%
	Neither agree nor disagree	45.2%	37.0%	22.2%	25.9%
	Disagree	19.4%	11.1%	11.1%	11.1%
	Strongly disagree	3.2%	0%	0%	0%
Each patient receiving BONE MARROW CONCENTRATE for an orthopedic indication should be provided a documented candidacy grade based on the best available medical evidence (if available).	Strongly Agree	32.3%	29.6%	25.9%	22.2%
	Agree	35.5%	40.7%	51.9%	59.3%
	Neither agree nor disagree	19.4%	18.5%	14.8%	7.4%
	Disagree	12.9%	11.1%	7.4%	11.1%
	Strongly disagree	0%	0%	0%	0%
Informed consent should include simple language that the use of the BONE MARROW CONCENTRATE for an orthopedic indication is not standard of care and is investigational and as such, it may pose unknown risks.	Strongly Agree	41.9%	55.6%	59.3%	29.6%
	Agree	25.8%	22.2%	18.5%	51.9%
	Neither agree nor disagree	16.1%	11.1%	14.8%	7.4%
	Disagree	12.9%	7.4%	7.4%	11.1%
	Strongly disagree	3.2%	3.7%	0%	0%
If the BONE MARROW CONCENTRATE is used in a medical indication where a controlled trial doesn't yet exist, then the data generated by that use should be submitted for publication in the peer-reviewed literature by the individual or group using that orthobiologic.	Strongly Agree	22.6%	25.9%	37.0%	
	Agree	38.7%	51.9%	48.1%	
	Neither agree nor disagree	32.3%	14.8%	11.1%	
	Disagree	6.5%	3.7%	3.7%	
	Strongly disagree	0%	3.7%	0%	
Any advertising to the general public about BONE MARROW CONCENTRATE for an orthopedic indication must be grounded in the basic science or known clinical science.	Strongly Agree	74.2%	81.5%	88.9%	
	Agree	22.6%	18.5%	7.4%	
	Neither agree nor disagree	0%	0%	3.7%	
	Disagree	3.2%	0%	0%	
	Strongly disagree	0%	0%	0%	
If BONE MARROW CONCENTRATE is used for an indication where animal models show promise, but this is a first in human use, an institutional review board should review and approve.	Strongly Agree	45.2%	51.9%	37.0%	
	Agree	25.8%	14.8%	44.4%	
	Neither agree nor disagree	12.9%	18.5%	14.8%	
	Disagree	6.5%	14.8%	3.7%	
	Strongly disagree	9.7%	0%	0%	
Prior to the establishment of level 1 evidence for that medical indication, BONE MARROW CONCENTRATE for an orthopedic indication should only be used by licensed physicians or a by a physician-supervised mid-level and not in office settings where direct physician supervision is absent.	Strongly Agree	77.4%	81.5%	88.9%	
	Agree	12.9%	11.1%	7.4%	
	Neither agree nor disagree	0%	0%	3.7%	
	Disagree	0%	7.4%	0%	
	Strongly disagree	9.7%	0%	0%	
Image guidance or direct visualization should be used to deliver BMC to the target joint or tissue (i.e. ultrasound imaging, fluoroscopy, or arthroscopy/open surgery as appropriate).	Strongly Agree		85.2%	74.1%	
	Agree		11.1%	25.9%	
	Neither agree nor disagree		3.7%	0%	
	Disagree		0%	0%	
	Strongly disagree		0%	0%	

Table 2. *Questions and responses by Delphi round (continued).*

Prompt	Response	Round 1	Round 2	Round 3	Round 4
Cell dosing characteristics such as Total Nucleated Cells or Cell Differential should be used for each patient treatment.	Strongly Agree		14.8%	14.8%	18.5%
	Agree		40.7%	37.0%	44.4%
	Neither agree nor disagree		25.9%	29.6%	22.2%
	Disagree		18.5%	14.8%	14.8%
	Strongly disagree		0%	3.7%	0%
What level of evidence must be required before using BONE MARROW CONCENTRATE for an orthopedic indication?	Case reports	0%	11.1%	7.4%	
	Case series	45.2%	33.3%	40.7%	
	Comparison trials against traditional therapies	45.2%	51.9%	44.4%	
	Controlled trial	3.2%	3.7%	7.4%	
	Multiple randomized controlled placebo trials	6.5%	0%	0%	

tients, scientific accuracy in advertising, IRB approval for novel uses, performance of procedures by only licensed physicians or mid-levels with direct physician oversight, use of image guidance for procedures, importance of data submission for publication in peer reviewed literature, and a minimum requirement of case-series level of evidence for BMC in musculoskeletal use. Topics reflecting initial variation that later reached consensus in rounds 3 or 4 after discussion included submission for publication, IRB approval, candidacy grading, and patient consent. The 2 areas that did not meet criteria for consensus included online publishing of individual clinic data and standards around cell counting for dosing. It should be noted that consensus of 80% for both the candidacy and consent categories was reached in the final round without iteration (Table 3).

For the 10 Likert Scale questions, there was a trend towards an increase in means with decreasing standard deviation in the questions reaching consensus, further confirming agreement. For questions not reaching consensus, the mean stayed relatively consistent across the rounds and the standard deviations either did not change or decreased (Table 4). Levels of evidence gravitated towards comparison trials and case series with 90.4% consensus in Round 1, 85.2% consensus in Round 2, and 85.1% consensus in Round 3. Case reports became a more acceptable level of evidence in Round 2, and in Round 3, more controlled trials were favored than in prior rounds. Round 1 was the only round in which some experts deemed that multiple randomized controlled placebo trials were necessary (Table 2).

Discussion

Twenty-seven physicians actively using BMC for musculoskeletal use found consensus in 9 out of 11 categories queried. This consensus was reached via 4 rounds of surveys with results distributed between queries to allow for discussion and agreement-building, per the Delphi technique.

Registry data reached 80% consensus in the first 3 rounds and was among the most highly agreed upon categories. The history of orthopedic patient registries dates back to 1975, with the first such registry developed by Dr. Bauer in Sweden for nationwide data collection on total knee arthroplasty. The first in the United States for joint prosthesis was developed at the Mayo Clinic in 1969 (40). Although registry data is noted to be less satisfactory, prospective clinical studies are challenging in musculoskeletal medicine due to the considerable time needed to obtain and disseminate the results which precludes effectiveness of early failures and successes (41). The organizers of an orthopedic joint replacement registry note the solution to this is web-based registries (42). Registry data helps create overall improvement in the field. The purpose of a registry is to collect institutional, regional, or national data in order to analyze and draw statistically significant conclusions regarding patient information that led to optimal versus poor outcomes (43). Therefore, use of registry data to track outcomes and data is recommended as standard of care for the use of BMC procedures.

Importance of guided injections was added in the second round based on the freestyle questions from the first round and reached strong consensus in round 2. This was one of the most strongly agreed upon topics, with almost all participants selecting "strongly agree." Image-guided procedures have been shown to be most accurate, such as in one trial demonstrating

Table 3. *Categories reaching 80% consensus for Strongly Agree and Agree per round.*

Category	Round 1	Round 2	Round 3	Round 4
Registry	X+	X+	X+	
Publish Results	-	-	-	-
Candidacy	-	-	-	X+
Consent	-	-	-	X+
Peer-reviewed	-	-	X+	
Advertising	X+	X*	X*	
IRB-Approval	-	-	X+	
Physician required	X+	X*	X*	
Image guidance		X*	X+	
Dosing		-	-	-
Level of Evidence	X%	X%	X%	

X*: Met at Strongly Agree
X+: Met at Agree
X%: Combination of "Case Series" and "Comparison trials against traditional therapies"
-: Failed to reach significance
Blank: Questions not asked in that round.
Demonstrating the 11 question areas and when each area reached consensus at either "strongly agree" alone or on both "strongly agree" and "agree" along with which ones failed to reach consensus.

Table 4. *Mean ± standard deviations of responses.*

Category	Round 1	Round 2	Round 3	Round 4
Registry	4.3 + 0.9	4.6 + 0.8	4.4 + 0.7	
Publish Results	3.3 + 1.2	3.7 + 1.0	3.7 + 0.9	3.7 + 0.9
Candidacy	3.9 + 1.0	3.9 + 1.0	4.0 + 0.9	3.9 + 0.9
Consent	3.9 + 1.2	4.2 + 1.1	4.3 + 1.0	4.0 + 0.9
Peer-reviewed	3.8 + 0.9	3.9 + 1.0	4.2 + 0.8	
Advertising	4.7 + 0.7	4.8 + 0.4	4.9 + 0.5	
IRB-approval	3.9 + 1.3	4.0 + 1.2	4.1 + 0.8	
Physician Required	4.5 + 1.2	4.7 + 0.8	4.9 + 0.5	
Image guided		4.8 + 0.5	4.7 + 0.4	
Dosing		3.5 + 1.0	3.4 + 1.1	3.7 + 1.0

Blank: Questions not asked in that round.
Mean of responses ranked 1 – 5 on the Likert Scale for Strongly agree being 5 and Strongly disagree being 1. Standard deviations calculated for each response.

90% accuracy when using ultrasound guidance for glenohumeral joint injections as compared to a 76% rate of accuracy with a blind injection (44).

Consensus agreement that only licensed physicians or mid-levels practitioners with direct physician supervision should be performing BMC procedures reached consensus in the first round with subsequently stronger agreement in the second and third rounds. The difference between bone marrow biopsies and aspirations for musculoskeletal procedures is the multi-site draw that is needed for an adequate cell count (45) versus a simple one-site bone puncture for aspiration and biopsy commonly done in oncologic procedures for diagnostics. The skill level that is required for multi-site draw involves image-guidance with either fluoroscopy or ultrasound, which requires subspecialty training with a fellowship or multiple cadaver skill courses.

Accuracy in advertising to the general public reached consensus after the first round, became stronger in the second round, and maintained strong consensus into the third round. In 1977, the US Supreme Court recognized that health care is both a profession and a business, and therefore must adopt modern business practices in order to survive the current health care climate (Bates v. State bar of Arizona, 1977) (46). In a study by Moser et al (46), advertising and marketing were shown to have a place in the future of medical practice, with the most important aspects being the quality of service provided and reputation of the physician over the price. False and deceptive advertising is grounds for court action as well as license revocation (47), therefore, providing advertising to the general public must be founded on accurate, validated basic science and clinic research.

Consensus regarding submitting peer-reviewed literature from practices that perform BMC-based musculoskeletal procedures was not reached until the third round. This may be due to the heterogeneity among private versus academic practice settings within the panel. However, the ultimate agreement in this area reflects the importance of publishing clinical outcomes data from patient registries for use of BMC in musculoskeletal medicine until level 1 evidence is available.

The importance of IRB approval for novel BMC use in humans reached consensus in the third round. The IRB was formed in the US to protect the rights and welfare of individuals participating in experimental research (48). The general function of the IRB is to "review, monitor, and take action on all proposed research involving human subjects" (48). Therefore, it is reasonable to obtain IRB approval for any use of BMC that is outside the scope of what has been studied in available literature.

Agreement regarding informed consent including investigational use of BMC did not reach consensus until the fourth round. According to legal requirements, physicians must explain the procedure, possible risks and complications, benefits of the procedure, and

available alternatives including the consequences of foregoing treatment (49,50). An issue with informed consent, especially with experimental trials, is the issue of nocebo effects. Indeed, psychological studies suggest that framing and personalizing treatment information, along with emphasizing treatment benefit, might prevent dysfunctional expectations of side effects and decreased decisional conflict (51,52). It is possible the delay in consensus in this particular question had to do with classification of the treatments as investigational, when several studies exist demonstrating efficacy (4,19,20,24,53-55).

Candidacy for BMC did not reach consensus until the fourth round. This could be due to the possible definition of candidacy and perceived inability to accurately stratify patients due to lack of data. Without formal placebo-controlled BMC trials, it is difficult to rigorously determine which patients are good, fair, or poor candidates.

Transparent online publications did not reach consensus in any round. A trend towards transparent publication of outcomes data in other areas of medicine has developed over the last several years, most notably with coronary-artery bypass grafting outcomes to achieve greater health care accountability (56). It is unclear why this topic did not reach 80% consensus for agreement. The overall consensus was between "neither agree nor disagree" and "agree." This may be due to feasibility of online publication and possible restrictions at academic centers of publication of registry data without a formal peer-reviewed publication process.

Agreement regarding standardization of the use of TNCC or cell differential did not reach consensus in this panel after 3 rounds of surveys. The comments provided by the panel members centered around their capabilities to perform such testing. Positive post-procedural outcomes have been shown to be dose-dependent (10) with a minimum dosing of 400 million TNCs for optimal outcomes when treating knee osteoarthritis (54). However, specific BMC dosing studies for other musculoskeletal indications is lacking.

Regarding level of evidence required to perform BMC procedure for musculoskeletal use, as the rounds progressed, fewer physicians felt it imperative to have randomized controlled trials. Ultimately, an 80% consensus was achieved in agreement that either case series or comparison to standard treatment trial was sufficient to provide evidence for use.

Limitations

Though significant consensus was achieved for many of the categories, there are some limitations to this Delphi panel. Our panel of experts were all physicians who use BMC in practice, therefore it is possible that a different panel of experts with different practice methodologies would reach different conclusions. Furthermore, many Delphi panels are constructed through external nomination processes (35,39), however, this panel was convened on a voluntary basis. The respondents represent an experienced group of physicians practicing within the field of regenerative musculoskeletal medicine, however greater gender diversity, a larger number of physicians queried, and an initial screening process to ensure adequate representation would have been ideal. Though the majority of respondents have performed greater than 50 BMC procedures, there was a large range spanning from 35 to 2000 total BMC procedures performed. Furthermore, the topic of IRB approval for novel use of BMC may need to be further clarified since such stringent requirements may limit access to patients for whom a general indication has been established. Finally, the panel commented on the activity of mid-level providers but did not address the topic of alternative health care practitioners administering these treatments, which is of growing concern with the field.

Conclusions

In conclusion, there is much room for improvement within the clinical applications of BMC for musculoskeletal disorders. There is great promise for this treatment modality, but in order to establish a better understanding of outcomes, consistent delivery, ethical communication and care of patients, and patient stratification, standards of care must be established and adhered to. This panel recommends the key points outlined below as starting points from which to more effectively deliver such care.

Key Points

The following are the consensus recommendations of this Delphi panel:

1. Use of a Treatment Registry — It is desirable that patients who receive BMC for a musculoskeletal indication be entered into a formal treatment registry that uses validated outcome tools and collects complications data at set time points.
2. Use of Candidacy Grades — Each patient receiving BMC for a musculoskeletal indication should be provided a documented candidacy grade based on

the best available medical evidence.

3. Expanded Informed Consent — Informed consent should include simple language that the use of the BMC for a musculoskeletal indication is not standard of care, is investigational, and, as such, may pose unknown risks.
4. Publication of Research — If BMC is used for treatment of a medical condition for which a controlled trial does not yet exist, the data generated by that use should be submitted for publication in the peer-reviewed literature by the individual or group implementing the treatment.
5. Advertising — Any advertising to the general public about BMC for a musculoskeletal indication must be consistent with published scientific evidence.
6. Use of an IRB — If BMC is used for an indication where animal models show promise, but have not yet been studied in humans, an institutional review board should review and approve.
7. Use of Mid-levels — Prior to the establishment of level 1 evidence for that medical indication, BMC for a musculoskeletal indication should only be used by licensed physicians or a by a physician-supervised mid-level and not in office settings where direct physician supervision is absent.
8. Imaging Guidance — Image guidance or direct visualization should be used to deliver BMC to the target joint or tissue (i.e., ultrasound imaging, fluoroscopy, or arthroscopy/open surgery, as appropriate).
9. Level of Evidence Required for Clinical Use — At least a case series or comparison trial should exist prior to the use of BMC for a musculoskeletal indication. Meaning, the panel members did not believe that a randomized controlled trial is required before use of BMC.

Contributions

All authors participated in the steering committee and panel or were involved in preparing the manuscript. Contributors participated on the panel and reviewed the manuscript.

Contributors: Sairam Atluri, MD; Tariq M. Awan, DO; Douglas P. Beall, MD; Thomas K. Bond, MD; Joanne Borg-Stein, MD; Robert Bowers, DO, PhD; James P. Bradley, MD; Don Buford, MD; Aaron K. Calodney, MD; Rahul Desai, MD; E. Jeffrey Donner, MD; Jason L. Dragoo, MD; Jonathan Finnoff, DO; Michael D. Freeman, MedDr, PhD; Roger Kruse, MD; Gregory E. Lutz, MD; Grant M. Pagdin, MD; Rowan V. Paul, MD; Christopher J. Rogers, MD; Steven Sampson, DO; Jaspal Ricky Singh, MD; Christopher J. Williams, MD.

References

1. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 386:743-800.
2. Kotlarz H, Gunnarsson CL, Fang H, Rizzo JA. Osteoarthritis and absenteeism costs: Evidence from US national survey data. *J Occup Environ Med* 2010; 52:263-268.
3. Piuzzi NS, Hussain ZB, Chahla J, et al. Variability in the preparation, reporting, and use of bone marrow aspirate concentrate in musculoskeletal disorders: A systematic review of the clinical orthopaedic literature. *J Bone Joint Surg Am* 2018; 100:517-525.
4. Wu PI, Diaz R, Borg-Stein J. Platelet-rich plasma. *Phys Med Rehabil Clin N Am* 2016; 27:825-853.
5. Parapia LA. Trepanning or trephines: A history of bone marrow biopsy. *Br J Haematol* 2007; 139:14-19.
6. Jamshidi K. Swaim WR. Bone marrow biopsy with unaltered architecture: A new biopsy device. *J Lab Clin Med* 1971; 77:335-342.
7. Wientroub S, Goodwin D, Khermosh O, Salama R. The clinical use of autologous marrow to improve osteogenic potential of bone grafts in pediatric orthopedics. *J Pediatr Orthop* 1989; 9:186-190.
8. Schafer r, DeBaun MR, Fleck E, et al. Quantitation of progenitor cell populations and growth factors after bone marrow aspirate concentration. *J Transl Med* 2019; 17:115.
9. Malanga GA. Regenerative treatments for orthopedic conditions. *PM R* 2015; 7:S1-S3.
10. Hernigou P, Poignard A, Beaujean F, Rouard H. Percutaneous autologous bone-marrow grafting for nonunions: Influence of the number and concentration of progenitor cells. *J Bone Joint Surg Am* 2005; 87:1430-1437.
11. Hyer CF, Berlet GC, Bussewitz BW, Hankins T, Ziegler HL, Philbin TM. Quantitative assessment of the yield of osteoblastic connective tissue progenitors in bone marrow aspirate from the iliac crest, tibia, and calcaneus. *J Bone Joint Surg Am* 2013; 95:1312-1316.
12. Marx RE, Tursun R. A qualitative and quantitative analysis of autologous human multipotent adult stem cells derived from three anatomic areas by marrow aspiration: Tibia, anterior ilium, and posterior ilium. *Int J Oral Maxillofac Implants* 2013; 28:e290-e294.
13. Ladage D, Brixius K, Steingen C, et al. Mesenchymal stem cells induce endothelial activation via paracine mechanisms. *Endothelium* 2007; 14:53-63.
14. Toh, WS, Lai RC, Zhang B, Lim SK. MSC exosome works through a protein-based mechanism of action. *Biochem Soc Trans* 2018; 46:843-853.
15. Koga H, Muneta T, Nagase T, et al. Comparison of mesenchymal tissues-derived stem cells for in vivo chondrogenesis: Suitable conditions for cell therapy of cartilage defects in rabbit.

Cell Tissue Res 2008; 333:207-215.

16. Lai RC, Yeo RWY, Lim SK. Mesenchymal stem cell exosomes. *Sem Cell Dev Biol* 2015; 40:82-88.
17. Vallabhaneni, KC, Haller H, Dumler I. Vascular smooth muscle cells initiate proliferation of mesenchymal stem cells by mitochondrial transfer via tunneling nanotubes. *Stem Cells Dev* 2012; 21:3104-3113.
18. van Lent PL, van den Berg WB. Mesenchymal stem cell therapy in osteoarthritis: Advanced tissue repair or intervention with smouldering synovial activation? *Arthritis Res Ther* 2013; 15:112.
19. Centeno C, Sheinkop M, Dodson E, et al. A specific protocol of autologous bone marrow concentrate and platelet products versus exercise therapy for symptomatic knee osteoarthritis: A randomized controlled trial with 2 year follow-up. *J Transl Med* 2018; 16:355.
20. Cotter EJ, Wang KC, Yanke AB, Chubinskaya S. Bone marrow aspirate concentrate for cartilage defects of the knee: From bench to bedside evidence. *Cartilage* 2018; 9:161-170.
21. Jayaram P, Ikpeama U, Rothenberg JB, Malanga GA. Bone marrow-derived and adipose-derived mesenchymal stem cell therapy in primary knee osteoarthritis: A narrative review. *PM R* 2019; 11:177-191.
22. Centeno C, Markle, J, Dodson, E, et al. Symptomatic anterior cruciate ligament tears treated with percutaneous injection of autologous bone marrow concentrate and platelet products: A non-controlled registry study. *J Transl Med* 2018; 16:246.
23. Centeno CJ, Pitts J, Al-Sayegh H, Freeman MD. Anterior cruciate ligament tears treated with percutaneous injection of autologous bone marrow nucleated cells: A case series. *J Pain Res* 2015; 8:437-447.
24. Centeno CJ, Al-Sayegh A, Bashir, J, Goodyear S, Freeman MD. A prospective multi-site registry study of a specific protocol of autologous bone marrow concentrate for the treatment of shoulder rotator cuff tears and osteoarthritis. *J Pain Res* 2015; 8:269-276.
25. Hernigou P, Auregan JC, Dubory A, Flouzat-Lachaniette CH, Chevallier N, Rouard H. Subchondral stem cell therapy versus contralateral total knee arthroplasty for osteoarthritis following secondary osteonecrosis of the knee. Int Orthop 2018; 42:2563-2571.
26. Hernigou P, Poignard A, Zilber S, Rouard H. Cell therapy of hip osteonecrosis with autologous bone marrow grafting. *Indian J Orthop* 2009; 43:40-45.
27. Hernigou P, Daltro G, Filippini P, Mukasa MM, Manicom O. Percutaneous implantation of autologous bone marrow osteoprogenitor cells as treatment of bone avascular necrosis related to sickle cell disease. *Open Orthop J* 2008; 2:62-65.
28. Hernigou P, Poignard A, Rouard H. Percutaneous autologous bone-marrow grafting for nonunions. Influence of the number and concentration of progenitor cells. *J Bone Joint Surg Am* 2005; 87:1430-1437.
29. Turner L, Knoepfler P. Selling stem cells in the USA: assessing the direct-to-consumer industry. *Cell Stem Cell* 2016; 19:154-157.
30. ISCCR. ISSCR Applauds FDA, FTC for Holding Deceptive Stem Cell Clinics Accountable. 2018 [cited 2019 Nov 8]; Available from: www.isscr.org/professional-resources/news-publicationsss/isscr-news-articles/article-detail/2018/11/16/isscr-applauds-fda-ftc-for-holding-deceptive-stem-cell-clinics-accountable.
31. ISSCR. *Guidelines for Stem Cell Research and Clinical Translation*. May 12, 2016. www.isscr.org
32. Linstone HT, Turoff M. Delphi: A brief look backward and forward. *Technol Forecast Soc Change* 2011; 78:1712-1719.
33. Putnam JW, Bruininks RH. Future directions of deinstitutionalization and education of children and youth with handicaps: A Delphi investigation. *Except Child* 1986; 53:55-62.
34. Delbecq AL, Van De Ven AH, Gustafson D H. *Group Techniques for Program Planning: A Guide to Nominal Group and Delphi Process*. Green Briar Press, Middleton, WI, 1986.
35. Putnam JW, Spiegel AN, Bruininks RH. Future directions in education and inclusion of students with disabilities: A Delphi investigation. *Except Child* 1995; 61:553-576.
36. Reynolds MC. Delphi technique. In *International Encyclopedia of Education*. Vol 3. Pergamon Press, New York, 1994, pp 1441-1443.
37. The Orthobiologic Institute (TOBI): 10th Annual PRP and Regenerative Medicine Symposium. In TOBI X 2019 Symposium. Chicago, IL. 2019.
38. Rogers MR, Lopez EC. Identifying critical cross-cultural school psychology competencies. *J Sch Psychol* 2002; 40:115-141.
39. von der Gracht HA. Consensus measurement in Delphi studies. *Technol Forecast Soc Change* 2012; 79:1525-1536.
40. Robertsson O. Knee arthroplasty registers. *J Bone Joint Surg Br* 2007; 89:1-4.
41. Maloney WJ. National joint replacement registries: Has the time come? *J Bone Joint Surg Am* 2001; 83:1582-1585.
42. Roder C, El-Kerdi A, Eggli A, Aebi M. A centralized total joint replacement registry using web-based technologies. *J Bone Joint Surg Am* 2004; 86:2077-9; discussion 2079-2080.
43. Malchau H, Garellick G, Berry D, et al. Arthroplasty implant registries over the past five decades: Development, current, and future impact. *J Orthop Res* 2018; 36:2319-2330.
44. Raeissadat SA, Rayegani SM, Langroudi TF, Khoiniha M. Comparing the accuracy and efficacy of ultrasound-guided versus blind injections of steroid in the glenohumeral joint in patients with shoulder adhesive capsulitis. *Clin Rheumatol* 2017; 36:933-940.
45. Friedlis MF, Centeno CJ. Performing a better bone marrow aspiration. *Phys Med Rehabil Clin N Am* 2016; 27:919-939.
46. Moser HR, Stevens R, Loudon D. An empirical analysis of ethical and professional issues in physicians' advertising: A comparative cross-sectional study. *Health Mark Q* 2016; 33:255-273.
47. Peters CR. Ethical issues in professional advertising. *J Fla Med Assoc* 1989; 76:607-608.
48. Bosso JA. The role of the institutional review board in research involving human subjects. *Drug Intell Clin Pharm* 1983; 17:828-834.
49. Kondziolka DS, Pirris SM, Lunsford LD. Improving the informed consent process for surgery. *Neurosurgery* 2006; 58:1184-1189; discussion 1184-1189.
50. Moskop JC. Informed consent in the emergency department. *Emerg Med Clin North Am* 1999; 17:327-340, ix-x.
51. Heisig SR, Shedden-Mora MC, Hidalgo P, Nestoriuc Y. Framing and personalizing informed consent to prevent negative expectations: An experimental pilot study. *Health Psychol* 2015; 34:1033-1037.
52. O'Connor AM, Pennie RA, Dales RE. Framing effects on expectations, decisions, and side effects experienced: The case of influenza immunization. *J Clin Epidemiol* 1996; 49:1271-1276.
53. Hernigou P, Bernaudin F. [Course of bone tissue after bone marrow allograft in adolescents with sickle cell disease]. *Rev Chir Orthop Reparatrice Appar Mot* 1994; 80:138-143.
54. Centeno CJ, Al-Sayegh H, Bashir J, Goodyear S, Freeman, MD. A dose

response analysis of a specific bone marrow concentrate treatment protocol for knee osteoarthritis. *BMC Musculoskelet Disord* 2015; 16:258.

55. Mautner K, Bowers R, Easley K, Fausel Z, Robinson R. Functional outcomes following microfragmented adipose tissue versus bone marrow aspirate concentrate injections for symptomatic knee osteoarthritis. *Stem Cells Transl Med* 2019; 00:1-8.

56. Ferris TG, Torchiana DF. Public release of clinical outcomes data — online CABG report cards. *N Engl J Med* 2010; 363:1593-1595.