Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO): Platelet-Rich Plasma and Mesenchymal Stem Cells

Iain R. Murray, MRCSEd, PhD, Andrew G. Geeslin, MD, Ewan B. Goudie, MRCSEd, Frank A. Petrigliano, MD, and Robert F. LaPrade, MD, PhD

Investigation performed at the Steadman Philippon Research Institute, Vail, Colorado

Background: A comprehensive approach to the evaluation of biologic therapies for musculoskeletal conditions is required to guide appropriate future use. Clinical studies evaluating platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs) are limited by inadequate reporting of scientific details critical to outcome. We developed minimum reporting requirements for clinical studies evaluating PRP and MSCs using Delphi consensus methods.

Methods: The need for consensus on the minimum reporting requirements for studies evaluating biologics was identified at the American Academy of Orthopaedic Surgeons/Orthopaedic Research Society (AAOS/ORS) Biologic Treatments for Orthopaedic Injuries Symposium in 2015 and the American Orthopaedic Society for Sports Medicine (AOSSM) Biologic Treatments for Sports Injuries II Think Tank in 2015. A working group facilitated the development of 2 expert consensus statements for PRP and MSCs using Delphi techniques. Exhaustive lists of items that could be reported on by clinical studies evaluating PRP or MSCs were generated by searching the published literature and protocols. PRP and MSC expert groups, each made up of 24 invited speakers at the AAOS and AOSSM symposia, were surveyed on 3 occasions to establish consensus on the inclusion of each item within minimum reporting guidelines. In addition to rating their agreement, the experts were encouraged to propose further items or modifications. Predefined criteria were used to refine item lists after each survey. Final lists were compiled into checklist statements by the working group.

Results: For PRP, the working group identified 93 experimental information items from the literature. Twenty-three experts (96%) completed 3 rounds of surveys. After 3 rounds, 58 items generated consensus with >75% agreement and <5% disagreement. These items were compiled into a 23-statement checklist. For MSCs, 103 items were identified from the published literature. Twenty-three experts (96%) completed 3 rounds of surveys. After 3 rounds, the 61 items for which consensus was reached were compiled into a 25-statement checklist.

Conclusions: This study has established expert consensus on the minimum reporting requirements for clinical studies evaluating PRP and MSCs.

Clinical Relevance: These checklists provide specifications for the minimum information that should be reported by clinical studies evaluating PRP or MSCs.

Peer Review: This article was reviewed by the Editor-in-Chief and one Deputy Editor, and it underwent blinded review by two or more outside experts. The Deputy Editor reviewed each revision of the article, and it underwent a final review by the Editor-in-Chief prior to publication. Final corrections and clarifications occurred during one or more exchanges between the author(s) and copyeditors.

It is not yet clear whether current and emerging biologic strategies to treat musculoskeletal injuries will provide tangible benefits to patients[1]. Platelet-rich plasma (PRP) is used widely despite a lack of evidence supporting its efficacy. Enthusiasm for mesenchymal stem cell (MSC)-based therapies is reflected by the prodigious number of clinical trials registered at ClinicalTrials.gov to evaluate their use in the treatment of a host of musculoskeletal conditions. Unfortunately, clinical trials evaluating PRP or MSCs that have been published to date have failed to include sufficient experimental detail or to describe

Disclosure: There was no external funding source for this study. On the **Disclosure of Potential Conflicts of Interest** forms, *which are provided with the online version of the article*, one or more of the authors checked "yes" to indicate that the author had other relationships or activities that could be perceived to influence, or have the potential to influence, what was written in this work (http://links.lww.com/JBJS/C890).

even basic attributes of formulations delivered, including platelet and leukocyte concentrations in PRP and basic cell characterization of MSCs, all of which critically influence outcome[1-3]. This precludes interpretation of the exact nature of biologic formulations delivered, prevents comparison between studies, and makes replication by others impossible. The complexity of biologic therapies and the wide array of preparation methods, protocols, and methods of delivery only increase this challenge. Minimum standards of reporting are therefore required to facilitate accurate critical appraisal of emerging clinical studies evaluating PRP and MSCs in orthopaedics[1-4].

Growth factors released by platelets may contribute to tissue regeneration by stimulating progenitors, by dampening local inflammatory responses, and by promoting angiogenesis[5]. As such, there is a good rationale for exploiting platelet-rich concentrates to accelerate healing[6]. Promising preliminary in vitro studies[7,8] and modest regulatory barriers have buoyed popularity, despite a lack of robust clinical evidence supporting efficacy[1,3]. PRP represents a broad spectrum of preparations containing variable levels of platelets, leukocytes, and red cells, with >300 distinct cytokines and growth factors reported to date[9,10]. At present, there are >17 commercially available kits, each yielding PRP with differing compositions and characteristics[11]. Ultimately, the bioavailability of growth factors delivered as PRP depends on individual patient characteristics, platelet concentration, levels of leukocytes and red cells, and the method of activation, among other variables. Accurate and complete reporting of all factors that may influence biologic activity and outcomes is therefore essential if future clinical studies are to identify optimal preparations for individual applications.

MSCs are adult stem cells with the ability to become specialized musculoskeletal cells[12], modulate immune responses, and release trophic cytokines, making them attractive regenerative substrates[13]. The term MSC has been used to describe multiple heterogeneous cell types isolated using different methods from multiple sources including bone marrow[14] and adipose tissue[15], among others[16-18]. These cells have been assigned multiple names, such as multipotent adult progenitor cells[19], marrow isolated multilineage inducible cells[20], and multipotent adult stem cells[21]. Given this heterogeneity, accurate descriptions of the provenance, preparation methods, and characteristics of MSC populations are essential in order to understand the nature of the cells used in clinical studies.

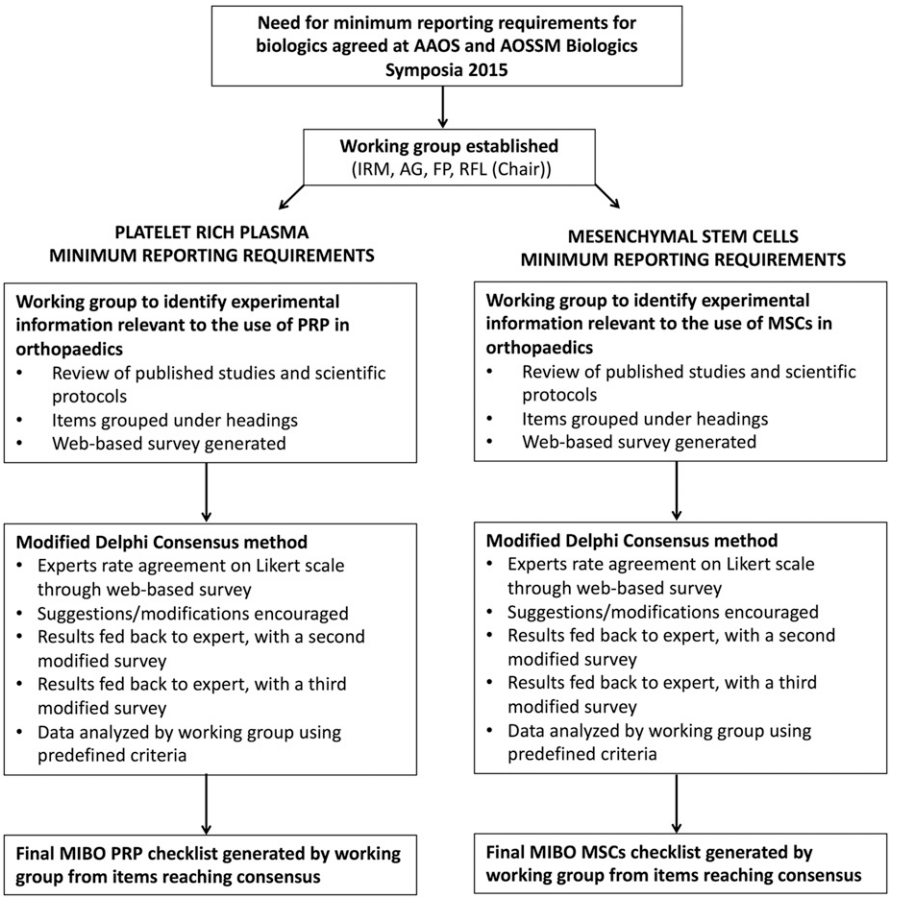

Fig. 1

Summary of methods used to develop minimum reporting requirements for clinical studies evaluating PRP and MSCs. MIBO = minimum information for clinical studies evaluating biologics in orthopaedics.

In response to clear evidence that the reporting of methodology in clinical studies is imperfect, there has been effort to set standards[22,23]. A lack of adequate reporting in randomized controlled trials (RCTs) fueled the development of the original CONSORT (Consolidated Standards of Reporting Trials) statement in 1996[23], which has subsequently been revised and updated[22,24]. Since then, reporting guidelines for observational studies (Strengthening the Reporting of Observational Studies in Epidemiology; STROBE)[25] and meta-analyses (Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRISMA)[26] have become widely recognized. The use of minimum reporting standards has led to improvements in the quality of the reporting of study design in clinical studies[27,28]. While these existing checklists guide the reporting of universal study design features, they do not specify the inclusion of scientific variables that are specific to the study of PRP and MSCs.

To encourage improved reporting standards, our purpose was to develop consensus on the minimum reporting requirements for clinical studies evaluating PRP and MSCs, using modified Delphi techniques. These methods have been used widely in the development of consensus in health research and in advancing clinical practice[29-33].

Materials and Methods

The need for expert consensus on the minimum reporting requirements for studies evaluating biologic therapies was identified at the American Academy of Orthopaedic Surgeons/Orthopaedic Research Society (AAOS/ORS) Biologic Treatments for Orthopaedic Injuries (BTOI) Symposium in 2015[1] and the American Orthopaedic Society for Sports Medicine (AOSSM) Biologic Treatments for Sports Injuries II Think Tank in 2015[3,4,34]. A working group of 4 individuals (R.F.L., I.R.M., A.G.G., and F.A.P.) was made responsible for facilitating the development of consensus using modified Delphi techniques under the leadership of the organizer and co-chair of both symposia (R.F.L.). Given the complexity and diversity of these biologic strategies, and the need for checklists that are both comprehensive and practical, the decision was made to develop distinct checklists for PRP and MSCs. Two independent Delphi studies were therefore performed. Figure 1 provides the details of the process used to develop a checklist of the minimum reporting requirements for studies evaluating PRP and MSCs. First, the working group generated exhaustive lists of items that could be reported by studies evaluating PRP or MSCs for orthopaedic applications. Modified Delphi processes were then performed to establish experts' views on the inclusion of each item within minimum reporting guidelines. Finally, the working group compiled the final information sets into checklists of statements. Institutional review board approval was not required because the study did not involve patient or registry data.

Identification of Experimental Detail Relevant to Clinical Use of PRP or MSCs

The working group prepared 2 lists of potential information items for inclusion within the first round of surveys by searching the clinical and basic-science literature relating to PRP and MSCs. Duplicates were removed, and items were categorized into groups. Online surveys were generated to allow respondents to rate whether items should be included within minimum reporting requirements, with 5 possible responses on a Likert[35] scale: "strongly agree," "agree," "neither agree nor disagree," "disagree," or "strongly disagree." A free-text comments section was included to allow for suggestions of modifications or additional items. Both surveys were piloted by 4 experts for face validity, understandability, and acceptability. Following this, minor modifications were made.

Establishing a Consensus Through the Delphi Process

The Delphi method is an iterative process in which a group of experts is led to achieve consensus on a given topic. A series of surveys are performed, with the results of each round collated and presented back to the group, with each individual's responses remaining anonymous. Participants then reassess their responses in light of the group responses[30,36,37]. The steps of collating and presenting data and the completion of surveys continue until a consensus is achieved.

Delphi methods were used to establish group consensus on the core information set[30]. All experts were invited speakers at the 2015 AAOS/ORS BTOI Symposium and the 2015 AOSSM Biologic Treatments II Think Tank. In addition, allocation to each study group was based on recognized expertise in PRP or MSCs, or both. The PRP study had a total of 24 experts, including 17 (71%) from the Americas, 5 (21%) from Europe, and 2 (8%) from Asia. The MSC study had a total of 24 experts, including 15 (63%) from the Americas, 7 (29%) from Europe, and 2 from (8%) Asia. The experts participated in 3 rounds of surveys between February and May 2016. In the first round, the survey results were analyzed and participants were sent an anonymized summary of the results together with a second survey. In the second round, the surveys contained a reduced number of items, and any additional items suggested in round 1. In the second round, participants were asked to rescore items and provide free-text comments. Questionnaires were reanalyzed and the cycle repeated in the third round. The process was continued until a consensus was reached for all items as defined below, or for a maximum of 3 rounds.

Data Analysis

In round 1 of the survey, items were categorized as "essential" and were retained for round 2 if >70% of the respondents agreed and <20% disagreed. Items not meeting these criteria were discarded or modified according to the responders' suggestions. In round 2, the responses were analyzed with stricter cutoff criteria, retaining items if >70% of respondents agreed on their inclusion and <10% disagreed. Items retained after round 2 were considered in round 3. For consensus, defined a priori, items were included in the final information set if

TABLE I Summary of Results at Completion of Each Survey Round in the Delphi Process to Establish Minimum Reporting Requirements for Studies Evaluating PRP

Delphi Round	No. of Responses	Total No. of Items Included in Survey	Items Reaching Consensus*	No. of New Items or Modifications Suggested
1	23	93	66.6%	15
2	23	75	73.3%	5
3	23	60	96.7%	0

*A consensus was considered to have been reached if >75% of experts agreed that an item should be included within minimum reporting requirements, with <5% of experts disagreeing.

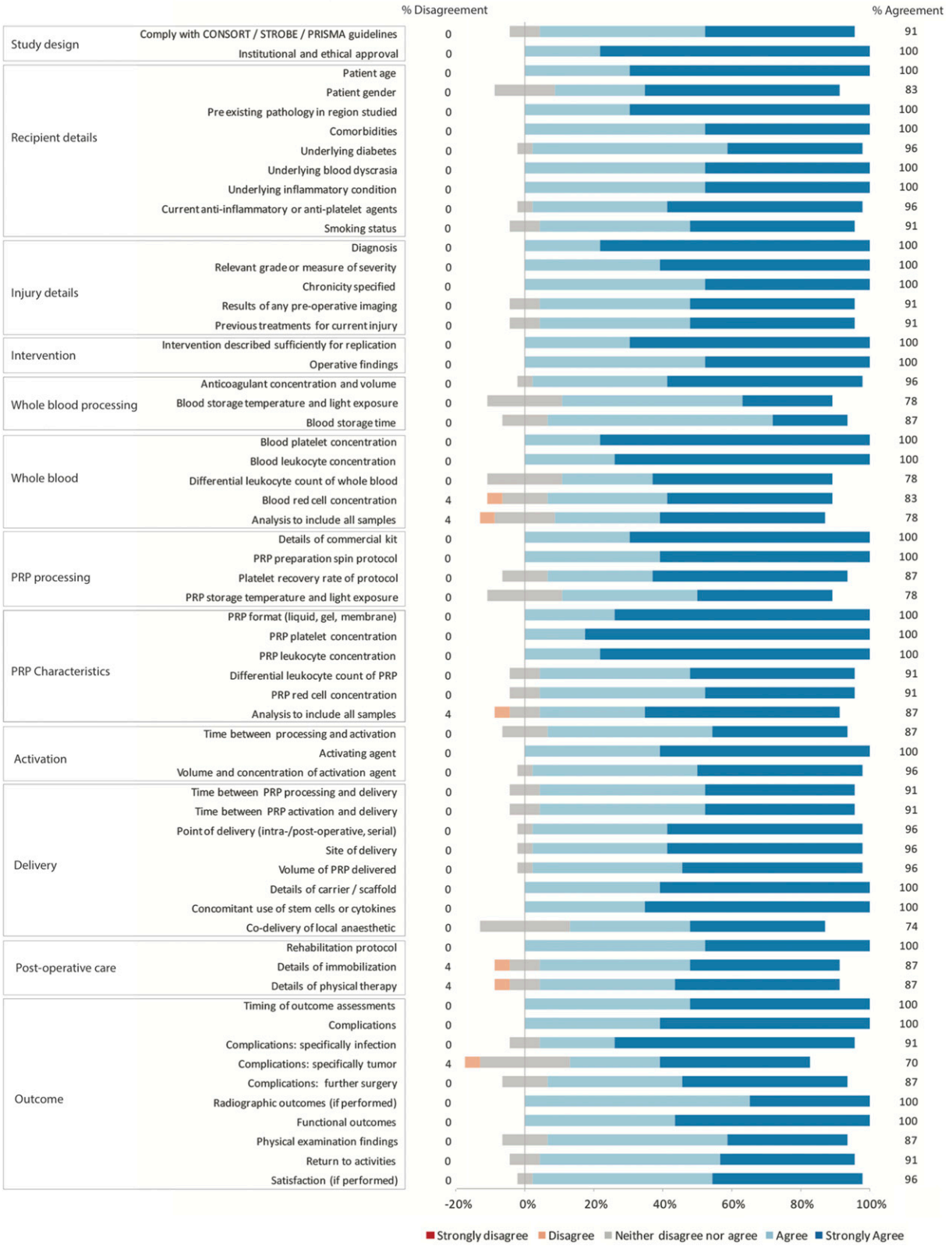

Fig. 2

Results of the final round of the PRP Delphi survey. Respondents were asked to rate whether items should be included within minimum reporting guidelines for clinical studies evaluating PRP.

TABLE II Final Checklist of Minimum Reporting Requirements for Clinical Studies Evaluating PRP That Reached Consensus Through the Delphi Process*

Section or Topic	Item No.	Checklist Item	Reported on Page No.
Study design			
	1	Study conducted in accordance with CONSORT (RCT), STROBE (cohort, case-control, or cross-sectional), or PRISMA (meta-analysis) guidelines	
	2	Relevant institutional and ethical approval	
Recipient details			
	3	Recipient demographics (including age and sex)	
	4	Comorbidities (including underlying diabetes, blood dyscrasia, inflammatory conditions, preexisting joint pathology, and smoking status)	
	5	Current anti-inflammatory or antiplatelet medications	
Injury details			
	6	Diagnosis (including relevant grading system and chronicity)	
	7	Results of any preoperative imaging	
	8	Previous surgical or biologic treatments for current injury	
Intervention			
	9	Intervention described sufficiently to enable replication	
	10	Operative findings	
Whole blood processing	11	Whole blood storage environment (including concentration and volume of anticoagulant, temperature, and light exposure)	
Whole blood characteristics	12	Whole blood platelet, differential leukocyte, and red cell analysis of all samples	
PRP processing			
	13	PRP processing described sufficiently to enable replication (including commercial kit details and spin protocol)	
	14	Platelet recovery rate of protocol	
	15	PRP storage temperature and light exposure	
	16	Time between blood drawing, PRP processing, activation, and delivery	
PRP characteristics			
	17	PRP format (for example: liquid, gel, or membrane)	
	18	PRP platelet, differential leukocyte, and red cell analysis of all samples	
Activation	19	Activation described sufficiently to enable replication (including volume and concentration of activating agent)	
Delivery			
	20	Point of delivery (intraoperative and/or postoperative or serial)	
	21	PRP delivery described sufficiently to enable replication (including volume delivered, concomitant use of stem cells or cytokines, and details of carrier or scaffold)	
Postoperative care	22	Rehabilitation protocol sufficiently described to enable replication (including immobilization and physical therapy)	
Outcome	23	Outcome assessments include functional outcomes and recording of complications (including infection and need for further surgery); if performed, radiographic outcomes, physical examination findings, return to activities, and satisfaction	

*This checklist could be used to guide authors, reviewers, and editors to ensure that submitted manuscripts report sufficient experimental detail to enable results to be evaluated and experiments repeated.

>75% of the respondents were in agreement and <5% disagreed. Agreement among ≥75% of the participants is the most frequently specified determination of a consensus for Delphi studies[38].

Generating Checklist Statements

The final lists of information items generated by each Delphi study were then compiled into checklists of statements by the working group. Care was taken to ensure clarity of wording and to avoid overlap in content within checklists.

Results

PRP

Identification of Relevant Experimental Details

Review of all data sources describing the clinical application of PRP generated 93 items for rating within the first round survey. Items were categorized into 12 groups: study design, recipient details, injury details, intervention, whole blood processing, whole blood characteristics, PRP processing, PRP characteristics, activation, delivery, postoperative care, and outcome.

Establishing Consensus Through the Delphi Process

Twenty-three experts (96%) completed the first round survey within the allotted time. The survey from the 1 expert who responded late was not included within the analysis or subsequent rounds. All 23 remaining experts completed surveys 2 and 3 (a 100% response rate). The results of each survey round are summarized in Table I. The levels of agreement for second round survey items that were not included within the third round survey are summarized in the Appendix. Consensus was reached for 58 (97%) of 60 individual items included within the final survey (Fig. 2).

Compiling Checklist Statements

All 58 items that generated consensus were compiled into 23 checklist statements (Table II). A column heading "Reported on Page No." was included to facilitate both completion of the checklist by investigators and analysis by reviewers and editorial staff.

MSCs

Identification of Relevant Experimental Details

A review of all data sources generated 103 items for rating within the first round survey. Items were categorized into 12 groups: study design, recipient details, injury details, intervention, donor, tissue harvest, processing, cell culture, MSC characteristics, delivery, postoperative care, and outcome.

Establishing Consensus Through the Delphi Process

Twenty-three experts (96%) completed the first round survey within the allotted time frame. The survey from the 1 expert who responded late was not included within the analysis or subsequent rounds. All 23 remaining experts completed surveys 2 and 3 (a 100% response rate). The results of each survey round in the Delphi process are summarized in Table III. The levels of agreement for items in the second round survey that were not included within the third round survey are summarized in the Appendix. Consensus was achieved for 61 items (98%) included within the final survey (Fig. 3).

Compiling Checklist Statements

The working group compiled the 61 final items into 25 checklist statements (Table IV). The potential practical use of the checklist as a required document to accompany submissions to a publisher was considered in the checklist design.

Discussion

The present study established a consensus on the minimum information that must be reported in clinical studies evaluating the use of PRP and MSCs. Each checklist reflects detailed scrutiny of the literature by a working group who then facilitated an iterative consensus process involving the views of 24 experts. It is suggested that these checklists accompany the initial submission of a manuscript to a publisher. By provision of all relevant experimental conditions and characteristics, editors and reviewers can assess the validity of the protocols used. Full disclosure of reagents and analysis methods will enable readers to interpret the results of studies while allowing other investigators to reproduce experimental protocols.

A major conclusion reached through consensus of the PRP experts was the importance of detailing the cellular composition of whole blood and the delivered PRP. It is important to note that consensus was also reached regarding the need to include all experimental samples within reported analyses. The experts cited the marked individual

TABLE III Summary of Results at Completion of Each Survey Round in the Delphi Process to Establish Minimum Reporting Requirements for Studies Evaluating MSCs

Delphi Round	Responses	Total No. of Items Included in Survey	Items Reaching Consensus*	New Items or Modifications Suggested
1	23	103	73.8%	14
2	23	80	77.5%	5
3	23	62	98.4%	1

*A consensus was considered to have been reached if >75% of experts agreed that an item should be included within minimum reporting requirements, with <5% of experts disagreeing.

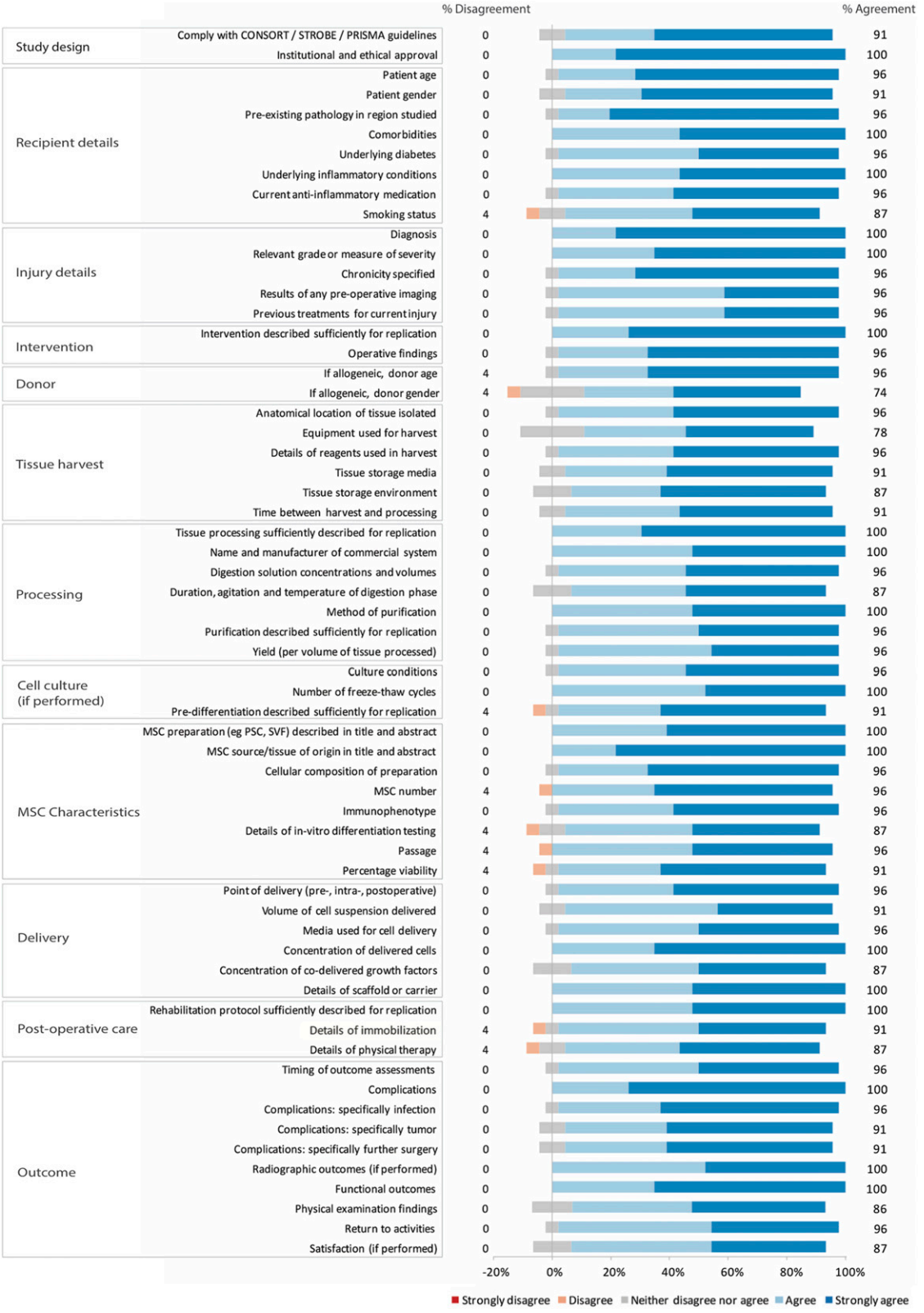

Fig. 3

Results of the final round of the MSC Delphi survey. Respondents were asked to rate whether items should be included within minimum reporting guidelines for clinical studies evaluating MSCs. PSC = perivascular stem cells, and SVF = stromal vascular fraction.

TABLE IV Final Checklist of Minimum Reporting Requirements for Clinical Studies Evaluating MSCs That Reached Consensus Through the Delphi Process*

Section or Topic	Item No.	Checklist Item†	Reported on Page No.
Study design			
	1	Study conducted in accordance with CONSORT (RCT), STROBE (cohort, case-control, or cross-sectional), or PRISMA (meta-analysis) guidelines	
	2	Relevant institutional and ethical approval	
Recipient details			
	3	Recipient demographics (including age and sex)	
	4	Comorbidities (including underlying diabetes, inflammatory conditions, preexisting joint pathology, and smoking status)	
	5	Current anti-inflammatory medications	
Injury details			
	6	Diagnosis (including relevant grading system and chronicity)	
	7	Previous treatments for current injury	
Intervention			
	8	Surgical intervention described sufficiently to enable replication	
	9	Operative findings	
Donors	10	Donor age	
Tissue harvest			
	11	Tissue harvest described sufficiently to enable replication (including anatomical source, equipment, reagents, storage media, and environment)	
	12	Time between tissue harvest and processing	
Processing			
	13	Description of tissue processing that makes replication of the experiment possible (including digestion solution concentrations and volumes, duration, agitation and temperature of digestion phase, and name of commercial system)	
	14	If performed, purification described sufficiently to enable replication (including combination and concentration of antibodies, equipment, and method of confirming purity)	
	15	Yield with respect to volume of tissue processed	
Cell culture			
	16	If performed, cell culture described sufficiently to enable replication (including conditions and number of freeze-thaw cycles)	
	17	If performed, predifferentiation described sufficiently to enable replication	
MSC characteristics			
	18	MSC preparation and source described in title and abstract (e.g., BM-MSC and ADSC)	
	19	Cellular composition and/or heterogeneity	
	20	Immunophenotype and details of in vitro differentiation tested on batch	
	21	Passage and percentage viability	
Delivery			
	22	MSC delivery described sufficiently to enable replication (including point of delivery, volume of suspension, and media used as vehicle)	
	23	If performed, details of codelivered growth factors, scaffolds, or carriers	
Postoperative care	24	Rehabilitation protocol sufficiently described to enable replication (including immobilization and physical therapy)	
Outcome	25	Outcome assessments include functional outcomes and recording of complications (including infection and tumor); if performed, radiographic outcomes, physical examination findings, return to activities, and satisfaction	

*This checklist could be used to guide authors, reviewers, and editors to ensure that submitted manuscripts report sufficient experimental detail to enable results to be evaluated and experiments repeated. †BM-MSC = bone marrow MSC, and ADSC = adipose-derived stem cells.

variation in PRP, for which a clear understanding of the factors influencing such variation was needed, as the reason for this requirement.

The MSC Delphi consensus highlights the importance of reporting a robust characterization of the cells being implanted. Experts cited emerging evidence of MSC heterogeneity, even among populations previously considered homogeneous, as a key rationale for this. In addition to the source and method of isolation, the importance of reporting the culture conditions to which cells are exposed was highlighted by the strong consensus. Laboratory culture may introduce additional risks such as immunogenicity and infection, while investigators have reported an association with genetic instability[39], tumorigenicity[40,41], therapeutic potency[42], and replicative senescence[43] with increasing time in culture. Within this study, there was also a strong consensus with respect to the requirement for reporting the characteristics of delivered MSC preparations, including cellular composition and immunophenotype. Despite this, additional metrics of colony performance, including the traditional colony-forming-unit assay, did not reach the strict levels of agreement required to constitute consensus.

The Delphi working group considered the suggestion from both sets of experts that it would be useful to produce checklists of "desirable" items in addition to the list of essential items developed. Included among such items deemed desirable, but not essential, were details specifically related to particular MSC applications (such as the mandatory reporting of ectopic bone formation for MSCs used in muscle regeneration), or items deemed impractical for reporting in routine use (such as colony-forming-unit assays on each MSC batch delivered). It was ultimately decided that a single, practical list of mandatory items would provide the best possible chance of widespread adoption and compliance with the guidelines. Of necessity, the resultant data set is a compromise between all that would be desirable and useful for comparison and the practicalities of data collection and reporting.

The aim of developing the minimum information for clinical studies evaluating biologics in orthopaedics (MIBO) checklists in the present study was to assist authors in writing reports of clinical studies evaluating PRP or MSCs, editors and peer reviewers in reviewing manuscripts for publication, and readers in critically appraising published articles. The working group deliberately avoided recommending a rigid structure for reporting. Indeed, such strategies have been tried in other settings[44] and have failed in pilot assessments[45]. As such, we recommend that the format of articles should abide by journal style, editorial directions, and author preferences, with authors to include checklist items with clear detail somewhere within the manuscript. We hope that the checklist format, with its subheadings, appeals both to authors submitting reports to journals and to reviewers and editors. It was suggested that details of the checklist be published either in abbreviated form or as an online supplement.

The concept of minimum reporting requirements for clinical studies is not new. The CONSORT[22] and STROBE[25] guidelines outline key features of study design that must be reported by RCTs and observational studies, respectively, but do not specify scientific variables that may critically influence outcome in studies evaluating biologics. The inclusion by consensus of a CONSORT/STROBE/PRISMA checklist completion within both MIBO checklists emphasizes that this checklist should serve to complement these existing study design guidelines, rather than to act as a substitute.

The Delphi methods used in this study are based on the principle that successive rounds of feedback from participants allow each expert to adjust and adapt their responses on the basis of feedback from the group. This method offers a number of advantages over group-based processes, including subject anonymity that can reduce the effects of dominant individuals[46]. As such, online methods are more likely to improve rather than jeopardize the quality of the consensus process[46]. Delphi panels conducted at a distance are as reliable as face-to-face panels[47], with further advantages of reduced cost, increased speed, and greater flexibility for those involved[48]. The Delphi technique is not an inherently scientific process but a method to try to bring expert opinion together and therefore has a number of limitations. It has been reported that the iterative characteristics of the Delphi technique can potentially enable investigators to mold opinions[49]. While the majority of published Delphi studies have used between 15 and 20 respondents[50], studies using 9 to 23 experts have been shown to yield stable, reliable results[51].

In addition to using validated Delphi methods[38,51] to generate expert consensus, the present study has a number of strengths. This study fulfills all methodologic criteria for the reporting of Delphi studies[38], using a number of experts optimal for this technique[51]. Our high response rate across all 3 survey rounds in both Delphi studies demonstrates engagement with the process by all experts. However, we also recognize that this study has some limitations. Although experts were drawn from throughout Europe and Asia, the majority were based in North America. Efforts to establish whether these standards are practical and generalizable to other populations may be merited.

The working group and experts considered the inclusion of minimum or suggested follow-up times within the guidelines. Given the wide range of potential applications for these therapies, a number of experts expressed concern that the inclusion of specified time points for only a fraction of PRP and MSC applications may limit the overall applicability of the guidelines, so follow-up times were omitted on this basis.

The proposed MIBO checklists for PRP and MSCs represent evolving guidelines that will require perpetual reappraisal and, if necessary, modifications. In the future, we plan to revise the material, considering comments, criticisms, experiences, and accumulating new evidence. We therefore invite readers to submit recommendations to the working group through the MIBO web site (www.mibostatement.org), where the MIBO PRP and MSC checklists are available for download. Further studies to establish consensus in minimum reporting standards of other biologic

therapies, such as growth factors and patches, should be explored.

This study used Delphi consensus methods to develop a checklist of minimum reporting guidelines for clinical studies evaluating PRP and MSCs. Adhering to these guidelines will increase experimental transparency and repeatability and promote consistency between laboratories, while encouraging standardization and a wider collaborative effort.

Appendix

eA Figures showing the levels of agreement for the second round PRP and MSC Delphi survey items that were not included within the third round survey are available with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/C894). ■

NOTE: The authors thank all members of the MIBO (Minimum Information for Studies Evaluating Biologics in Orthopaedics) PRP and MSC Expert Groups for their time and participation. The following are members of the MIBO PRP Expert Group: Dr. Adam Anz, Prof. Lars Engebretsen, Dr. Scott Faucett, Dr. Lisa Fortier, Dr. Livia Garbin, Dr. Andrew Geeslin, Dr. Alan Getgood, Dr. Laurie Goodrich, Dr. Andreas Gomoll, Prof. Philippe Hernigou, Dr. Chris Jo, Dr. Jason Koh, Dr. Elizaveta Kon, Dr. Robert LaPrade, Dr. Chris Mendias, Dr. Iain Murray, Dr. Martha Murray, Dr. George Muschler, Prof. Norimasa Nakamura, Dr. Frank Petrigliano, Prof. Pietro Randelli, Dr. Scott Rodeo, Dr. Thomas Vangsness, and Dr. James Wang. The following are members of the MIBO MSC Expert Group: Dr. Adam Anz, Prof. Lars Engebretsen, Dr. Lisa Fortier, Dr. Livia Garbin, Dr. Andrew Geeslin, Dr. Alan Getgood, Dr. Andreas Gomoll, Dr. Laurie Goodrich, Prof. Philippe Hernigou, Dr. Chris Jo, Dr. Jason Koh, Dr. Elizaveta Kon, Prof. Nicola Maffulli, Dr. Robert LaPrade, Dr. Chris Mendias, Dr. Iain Murray, Dr. Martha Murray, Dr. George Muschler, Prof. Norimasa Nakamura, Prof. Bruno Péault, Dr. Frank Petrigliano, Prof. Pietro Randelli, Dr. Scott Rodeo, and Dr. James Wang. The authors also thank Prof. Hamish Simpson for his advice regarding Delphi methods.

Iain R. Murray, MRCSEd, PhD[1]
Andrew G. Geeslin, MD[2]
Ewan B. Goudie, MRCSEd[1]
Frank A. Petrigliano, MD[3]
Robert F. LaPrade, MD, PhD[4]

[1]The University of Edinburgh, Edinburgh, United Kingdom

[2]Western Michigan University School of Medicine, Kalamazoo, Michigan

[3]University of California at Los Angeles, Los Angeles, California

[4]Steadman Philippon Research Institute, Vail, Colorado

E-mail address for R.F. LaPrade: drlaprade@sprivail.org

References

1. LaPrade RF, Dragoo JL, Koh JL, Murray IR, Geeslin AG, Chu CR. AAOS research symposium updates and consensus: biologic treatment of orthopaedic injuries. J Am Acad Orthop Surg. 2016 Jul;24(7):e62-78.

2. Murray IR, LaPrade RF. Platelet-rich plasma: renewed scientific understanding must guide appropriate use. Bone Joint Res. 2016 Mar;5(3):92-4.

3. LaPrade RF, Geeslin AG, Murray IR, Musahl V, Zlotnicki JP, Petrigliano F, Mann BJ. Biologic Treatments for Sports Injuries II Think Tank-current concepts, future research, and barriers to advancement, part 1: biologics overview, ligament injury, tendinopathy. Am J Sports Med. 2016 Dec;44(12):3270-83. Epub 2016 Mar 29.

4. Murray IR, LaPrade RF, Musahl V, Geeslin AG, Zlotnicki JP, Mann BJ, Petrigliano FA. Biologic Treatments for Sports Injuries II Think Tank-current concepts, future research, and barriers to advancement, part 2: rotator cuff. Orthop J Sports Med. 2016 Mar 31;4(3):2325967116636586.

5. Hall MP, Band PA, Meislin RJ, Jazrawi LM, Cardone DA. Platelet-rich plasma: current concepts and application in sports medicine. J Am Acad Orthop Surg. 2009 Oct;17(10):602-8.

6. Kiapour AM, Murray MM. Basic science of anterior cruciate ligament injury and repair. Bone Joint Res. 2014 Feb 04;3(2):20-31.

7. Zaky SH, Ottonello A, Strada P, Cancedda R, Mastrogiacomo M. Platelet lysate favours in vitro expansion of human bone marrow stromal cells for bone and cartilage engineering. J Tissue Eng Regen Med. 2008 Dec;2(8):472-81.

8. Mishra A, Tummala P, King A, Lee B, Kraus M, Tse V, Jacobs CR. Buffered platelet-rich plasma enhances mesenchymal stem cell proliferation and chondrogenic differentiation. Tissue Eng Part C Methods. 2009 Sep;15(3):431-5.

9. Castillo TN, Pouliot MA, Kim HJ, Dragoo JL. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. Am J Sports Med. 2011 Feb;39(2):266-71. Epub 2010 Nov 4.

10. Coppinger JA, Cagney G, Toomey S, Kislinger T, Belton O, McRedmond JP, Cahill DJ, Emili A, Fitzgerald DJ, Maguire PB. Characterization of the proteins released from activated platelets leads to localization of novel platelet proteins in human atherosclerotic lesions. Blood. 2004 Mar 15;103(6):2096-104. Epub 2003 Nov 20.

11. Andia I, Maffulli N. Platelet-rich plasma for managing pain and inflammation in osteoarthritis. Nat Rev Rheumatol. 2013 Dec;9(12):721-30. Epub 2013 Oct 1.

12. Murray IR, Péault B. Q&A: Mesenchymal stem cells - where do they come from and is it important? BMC Biol. 2015 Nov 23;13(1):99.

13. Caplan AI, Correa D. The MSC: an injury drugstore. Cell Stem Cell. 2011 Jul 08;9(1):11-5. Epub 2011 Jul 6.

14. Friedenstein AJ, Piatetzky-Shapiro II, Petrakova KV. Osteogenesis in transplants of bone marrow cells. J Embryol Exp Morphol. 1966 Dec;16(3):381-90.

15. West CC, Hardy WR, Murray IR, James AW, Corselli M, Pang S, Black C, Lobo SE, Sukhija K, Liang P, Lagishetty V, Hay DC, March KL, Ting K, Soo C, Péault B. Prospective purification of perivascular presumptive mesenchymal stem cells from human adipose tissue: process optimization and cell population metrics across a large cohort of diverse demographics. Stem Cell Res Ther. 2016 Mar 30;7:47.

16. Crisan M, Yap S, Casteilla L, Chen CW, Corselli M, Park TS, Andriolo G, Sun B, Zheng B, Zhang L, Norotte C, Teng PN, Traas J, Schugar R, Deasy BM, Badylak S, Buhring HJ, Giacobino JP, Lazzari L, Huard J, Péault B. A perivascular origin for mesenchymal stem cells in multiple human organs. Cell Stem Cell. 2008 Sep 11;3(3):301-13.

17. Toma JG, Akhavan M, Fernandes KJ, Barnabé-Heider F, Sadikot A, Kaplan DR, Miller FD. Isolation of multipotent adult stem cells from the dermis of mammalian skin. Nat Cell Biol. 2001 Sep;3(9):778-84. Epub 2001 Sep 5.

18. Mohal JS, Tailor HD, Khan WS. Sources of adult mesenchymal stem cells and their applicability for musculoskeletal applications. Curr Stem Cell Res Ther. 2012 Mar;7(2):103-9.

19. Jiang Y, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, Reyes M, Lenvik T, Lund T, Blackstad M, Du J, Aldrich S, Lisberg A, Low WC, Largaespada DA, Verfaillie CM. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature. 2002 Jul 04;418(6893):41-9. Epub 2002 Jun 20.

20. D'Ippolito G, Diabira S, Howard GA, Menei P, Roos BA, Schiller PC. Marrow-isolated adult multilineage inducible (MIAMI) cells, a unique population of postnatal young and old human cells with extensive expansion and differentiation potential. J Cell Sci. 2004 Jun 15;117(Pt 14):2971-81. Epub 2004 Jun 1.

21. Beltrami AP, Cesselli D, Bergamin N, Marcon P, Rigo S, Puppato E, D'Aurizio F, Verardo R, Piazza S, Pignatelli A, Poz A, Baccarani U, Damiani D, Fanin R, Mariuzzi L, Finato N, Masolini P, Burelli S, Belluzzi O, Schneider C, Beltrami CA. Multipotent cells can be generated in vitro from several adult human organs (heart, liver, and bone marrow). Blood. 2007 Nov 01;110(9):3438-46. Epub 2007 May 24.

22. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Trials. 2010 Mar 24;11:32.

23. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, Pitkin R, Rennie D, Schulz KF, Simel D, Stroup DF. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. JAMA. 1996 Aug 28;276(8):637-9.

24. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 2001 Apr 14;357(9263):1191-4.

25. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007 Oct 20;370(9596):1453-7.

26. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009 Jul 21;339:b2535.

27. Moher D, Jones A, Lepage L; CONSORT Group (Consolidated Standards for Reporting of Trials). Use of the CONSORT statement and quality of reports of randomized trials: a comparative before-and-after evaluation. JAMA. 2001 Apr 18;285 (15):1992-5.

28. Plint AC, Moher D, Morrison A, Schulz K, Altman DG, Hill C, Gaboury I. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. Med J Aust. 2006 Sep 04;185 (5):263-7.

29. Blazeby JM, Macefield R, Blencowe NS, Jacobs M, McNair AG, Sprangers M, Brookes ST; Research Group of the Core Outcomes and iNformation SEts iN SUrgical Studies-Oesophageal Cancer; Consensus Group of the Core Outcomes and iNformation SEts iN SUrgical Studies-Oesophageal Cancer. Core information set for oesophageal cancer surgery. Br J Surg. 2015 Jul;102(8):936-43. Epub 2015 May 18.

30. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ. 1995 Aug 05;311(7001):376-80.

31. Schmiegelow K, Attarbaschi A, Barzilai S, Escherich G, Frandsen TL, Halsey C, Hough R, Jeha S, Kato M, Liang DC, Mikkelsen TS, Möricke A, Niinimäki R, Piette C, Putti MC, Raetz E, Silverman LB, Skinner R, Tuckuviene R, van der Sluis I, Zapotocka E; Ponte di Legno Toxicity Working Group. Consensus definitions of 14 severe acute toxic effects for childhood lymphoblastic leukaemia treatment: a Delphi consensus. Lancet Oncol. 2016 Jun;17(6):e231-9.

32. Gupta S, Aitken JF, Bartels U, Brierley J, Dolendo M, Friedrich P, Fuentes-Alabi S, Garrido CP, Gatta G, Gospodarowicz M, Gross T, Howard SC, Molyneux E, Moreno F, Pole JD, Pritchard-Jones K, Ramirez O, Ries LA, Rodriguez-Galindo C, Shin HY, Steliarova-Foucher E, Sung L, Supriyadi E, Swaminathan R, Torode J, Vora T, Kutluk T, Frazier AL. Paediatric cancer stage in population-based cancer registries: the Toronto consensus principles and guidelines. Lancet Oncol. 2016 Apr;17(4):e163-72. Epub 2016 Mar 29.

33. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10.

34. Zlotnicki JP, Geeslin AG, Murray IR, Petrigliano FA, LaPrade RF, Mann BJ, Musahl V. Biologic Treatments for Sports Injuries II Think Tank-current concepts, future research, and barriers to advancement, part 3: articular cartilage. Orthop J Sports Med. 2016 Apr 15;4(4):2325967116642433.

35. Likert R. A technique for the measurement of attitudes. Arch Psychol. 1932;140:1-55.

36. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs. 2000 Oct;32(4):1008-15.

37. Fink A, Kosecoff J, Chassin M, Brook RH. Consensus methods: characteristics and guidelines for use. Am J Public Health. 1984 Sep;74(9): 979-83.

38. Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, Wales PW. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol. 2014 Apr;67(4):401-9.

39. Dahl JA, Duggal S, Coulston N, Millar D, Melki J, Shahdadfar A, Brinchmann JE, Collas P. Genetic and epigenetic instability of human bone marrow mesenchymal stem cells expanded in autologous serum or fetal bovine serum. Int J Dev Biol. 2008;52(8):1033-42.

40. Røsland GV, Svendsen A, Torsvik A, Sobala E, McCormack E, Immervoll H, Mysliwietz J, Tonn JC, Goldbrunner R, Lønning PE, Bjerkvig R, Schichor C. Long-term cultures of bone marrow-derived human mesenchymal stem cells frequently undergo spontaneous malignant transformation. Cancer Res. 2009 Jul 01;69(13):5331-9. Epub 2009 Jun 9.

41. Ren Z, Wang J, Zhu W, Guan Y, Zou C, Chen Z, Zhang YA. Spontaneous transformation of adult mesenchymal stem cells from cynomolgus macaques in vitro. Exp Cell Res. 2011 Dec 10;317(20):2950-7. Epub 2011 Sep 22.

42. Muraglia A, Cancedda R, Quarto R. Clonal mesenchymal progenitors from human bone marrow differentiate in vitro according to a hierarchical model. J Cell Sci. 2000 Apr;113(Pt 7):1161-6.

43. Baxter MA, Wynn RF, Jowitt SN, Wraith JE, Fairbairn LJ, Bellantuono I. Study of telomere length reveals rapid aging of human marrow stromal cells following in vitro expansion. Stem Cells. 2004;22(5):675-82.

44. Standards RTG; The Standards of Reporting Trials Group. A proposal for structured reporting of randomized controlled trials. JAMA. 1994 Dec 28;272 (24):1926-31.

45. Rennie D. Reporting randomized controlled trials. An experiment and a call for responses from readers. JAMA. 1995 Apr 05;273(13):1054-5.

46. Greenhalgh T, Wong G, Jagosh J, Greenhalgh J, Manzano A, Westhorp G, Pawson R. Protocol—the RAMESES II study: developing guidance and reporting standards for realist evaluation. BMJ Open. 2015 Aug 03;5(8): e008567.

47. Washington DL, Bernstein SJ, Kahan JP, Leape LL, Kamberg CJ, Shekelle PG. Reliability of clinical guideline development using mail-only versus in-person expert panels. Med Care. 2003 Dec;41(12):1374-81.

48. Holliday C, Robotin M. The Delphi process: a solution for reviewing novel grant applications. Int J Gen Med. 2010 Aug 30;3:225-30.

49. Hsu C, Sandford B. The Delphi technique: making sense of consensus. Pract Assess, Res Eval. 2007;12(10):1-8.

50. Ludwig B. Predicting the future: have you considered using Delphi methodology? J Ext. 1997;35(5):1-4.

51. Akins RB, Tolson H, Cole BR. Stability of response characteristics of a Delphi panel: application of bootstrap data expansion. BMC Med Res Methodol. 2005 Dec 01;5:37.