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# BMAC Guidelines

Guidelines for the Usage of Bone Marrow  
Aspirate Concentrate (BMAC) in  
Musculoskeletal (MSK) Disorders

An Expert Consensus Statement and  
Clinical Practice Recommendation

Prepared by Core Committee Members



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### Disclaimer:

This document is an expert consensus statement and clinical practice recommendation. It is presented as a narrative evidence synthesis and structured expert-consensus process rather than a fully systematic guideline (see Section 1 — Methodology). It does not constitute a substitute for independent clinical judgment and does not represent a formal regulatory standard. The recommendations herein are based on available published evidence and expert consensus at the time of preparation and are due for scheduled review (Section 15). Clinicians are advised to exercise individualized clinical judgment when applying these recommendations. The use of BMAC in musculoskeletal conditions may constitute off-label application in most jurisdictions worldwide, including India, the United States, and the European Union. Informed consent must be obtained from every patient prior to the procedure, with explicit discussion of the off-label nature of the therapy, expected outcomes, and associated risks. The issuing bodies assume no liability for clinical outcomes arising from the application of these guidelines.

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## Section 1

# Methodology

## 1.1 Nature of This Document

This document can be described as an Expert Consensus Statement and Clinical Practice Recommendation, which were developed using narrative evidence synthesis and a multi-reviewer consensus process. It has not been developed by the full systematic guideline development process (SIDIDP), including formal evidence profiling, instrument compliance (AGREE II), and reporting (RIGHT), so the recommendations in this document should be interpreted as such. Conceptually, this revision makes reference to well-established methodological frameworks that are used for evidence appraisal (GRADE, AGREE II, SIGN and RIGHT), and the next edition will aim to incorporate the use of a formal application of one or more of these.

## 1.2 Development Process Literature search:

PubMed/MEDLINE-based search was done for English literature with studies focusing on BMAC use in musculoskeletal applications, and reference lists were hand-searched for additional studies. The terms queried were phrases such as bone marrow aspirate concentrate (BMAC), mesenchymal stromal cells (MSCs), and specific terms related to each individual MSK indication. Randomized controlled trials, prospective and retrospective cohort studies, and systematic reviews/meta-analyses published in peer-reviewed, indexed journals were given priority. Case reports and expert-opinion sources were only used where higher level evidence was not available, and are specifically identified as such in Section 12 (Level IV/Expert Consensus). Evidence appraisal: Body of evidence was appraised based on study design, sample size, comparator arm (if applicable), and consistency of effect across studies. This is a recognised limitation of this edition (Section 13) as a formal risk-of-bias tool was not systematically applied. Consensus process: A draft was sent to a structured written critique by an independent international multidisciplinary (orthopaedic surgeons, sports medicine physicians and regenerative medicine researchers) review panel. The core committee judged the comments and used them as reflected in this revised edition. This edition was not preceded by a voting threshold or external public comment period, or formal Delphi process, and these are recommended for future updates.

Identify the difference between Evidence Quality Level and Recommendation Strength Level.

In each section of Section 12, this document provides two reports: (a) the quality of the underlying evidence (Level I–IV as defined in Section 12), and (b) a qualitative recommendation strength (“Use,” “Consider,” “Insufficient evidence — research only”). Recommendations of “Use” indicate consistent, reproducible evidence from multiple studies and/or supportive RCT data, while “Consider” indicates promising but inconsistent, limited or indirect data and “Insufficient evidence” indicates indications that should only be used currently in research protocols. It is important to note that the majority of “Use” recommendations in this document are generally based on Level I–II evidence, not confirmed by multi-site RCTs, and the strength of evidence for orthobiologic indications in the MSK system is in general lower than for most other pharmaceutical indications.

## 1.3 Scope Statement

Due to the diversity of evidence across the 40+ indications listed in Section 11, it is important to note differences between established/clinically supported indications and emerging/investigational indications throughout Section 11 and 12. The use in spinal/intradiscal applications is limited to IRB approved research protocols and not regularly used in clinical practice (Section 12.4). Section 1 — Introduction 1.2 Risk Factors for MSDs MSK disorders are estimated to affect 1.71 billion people worldwide and are the biggest cause of disability in the world. The combined effect of osteoarthritis (OA), chronic tendinopathy, non-union fractures and avascular necrosis place a significant socio-economic burden in India and of which, over 45 million people over 60 years of age suffer from knee OA. In India and globally, public health will be a priority to develop evidence-graded therapeutic frameworks as there is a projected increase in MSK morbidity secondary to population ageing,

obesity, sedentary lifestyles and occupational hazards. The conventional treatment of the disease has several drawbacks, as described below: Symptomatic treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid injection, and surgical treatment are all available and useful but are not consistently effective in restoring tissue architecture or reversing degenerative pathology. Chronic corticosteroid injection can cause progressive chondrotoxicity and subchondral bone loss and degradation of tendon. Surgical treatments like total joint arthroplasty and tendon repair have inherent risk, extended recovery periods and are not suitable for a subset of patients with high comorbidities. These constraints have led to an increased clinical interest in an additional treatment category referred to as regenerative orthobiologics, but the true nature of these therapies, whether they are disease-modifying or symptom-modifying, is still an area of active research and not a fact.

## 1.4 Evolution of Regenerative Medicine and Orthobiologics

In the past 20 years, the field of regenerative orthopedics has changed from a primarily mechanical repair model to biologically-based ancillary approaches. The orthobiologics (platelet-rich plasma (PRP), mesenchymal stromal/stem cell (MSC) therapies, and bone marrow-derived concentrates) are believed to alter the inflammatory environment, stimulate extracellular matrix remodeling, and stimulate angiogenesis and cell recruitment. As a point-of-care autologous therapy, BMAC's place in these therapies is emerging and growing, but the process of preparation, dosing, and reporting results are not all standard. The composition of BMAC and its therapeutic rationale are described. The composition of BMAC and the therapeutic rationale are described. Bone Marrow Aspirate Concentrate (BMAC) is a complex, multi-cell, autologous biological product and not a single stem cell therapy of cells called mesenchymal stem cells (MSCs). It is extracted from the bone marrow from the posterior superior iliac spine (PSIS) or anterior superior iliac spine (ASIS) when patient positioning will not allow it to be collected in the prone position, and then the marrow is concentrated by centrifugation. The product is a heterogeneous mixture of: MSCs or MSCs (Mesenchymal stromal/stem cells) are a tiny fraction of total nucleated cells (see Section 4D) that are mostly involved in paracrine signaling, but not in engraftment or transdifferentiation.

Hematopoietic progenitor cells, Platelets and platelet-derived growth factors — most BMAC preparations contain a platelet-rich plasma-like fraction, which can be removed by a specific depletion step. • Monocytes and macrophages – including those that can be polarized to M2, a state linked to anti-inflammatory, pro-repair tissue signalling Cytokines, growth factors and extracellular vesicles (ECVs) including anti-inflammatory cytokines IL-1Ra and IL-10, growth factors PDGF, TGF- $\beta$ , IGF-1 and BMP-2/7)

The wider secretome, an exciting field of study relevant to processes of immunomodulation, macrophage polarization and biology of inflammaging and cellular senescence in degenerative MSK disease The major mechanism of action suggested is paracrine signaling and immunomodulation, not direct engraftment with the target tissue or transdifferentiation to the target tissue. The new data presented with colony-forming unit-fibroblast (CFU-F) assays indicate a dose-response relationship between progenitor content and outcome of clinical trials, lending support to the biological plausibility of a correlation between progenitor content and BMAC efficacy. Typical BMAC preparations give a concentration of total nucleated cells of roughly 2.8-4.7 x that of the baseline bone marrow aspirate before processing (not peripheral blood — see Section 7.3 for the corrected formula); for platelets, the typical BMAC preparation gives a concentration of roughly 5.3-9.6 x that of the baseline bone marrow aspirate before processing (not peripheral blood — see Section 7.3 for the corrected formula). These Guidelines are being developed with the following rationale in mind:

Even with the growing adoption of BMAC in India and the rest of the world, there are considerable differences in the patient selection criteria, harvest and preparation methods, injection protocols, target doses and rehabilitation protocols. The high prevalence of “spin” (misleading interpretation of results 67.9% and selective outcome reporting 64.3%) was identified in the majority of BMAC systematic reviews published by a 2026 systematic review published in JAAOS, highlighting the need for methodologically rigorous and standardized guidance. Regulatory frameworks for the approval of BMAC and cell-based orthobiologics vary widely by jurisdiction: for example, in India, the central Drugs Standard Control Organisation (CDSCO) has a hybrid medical device/cell-therapy framework, with the Drugs Controller General of India (DCGI) having to approve

any BMAC kit for commercial use, while the U.S. Food and Drug Administration (FDA) has adopted a framework that is partly medical device and partly cell-therapy (21 CFR Part 1271) under which it governs minimal manipulation and homologous use; the European Union (EU) has a framework under the Advanced Therapy Medicinal Products (ATMP) Regulation. Through these guidelines India is used as a working example but these are intended to be broadly applicable across jurisdictions; clinicians should make their own regulatory verification where and when appropriate as regulatory status may be different across jurisdictions, and this document does not substitute for making a regulatory verification for each jurisdiction.

These guidelines have been drafted to aid the standardisation of practice, to protect patient safety, to assist with informed consent and as a reference for training, audit and research. 1.6 Scope of This Document The guidelines focus on the clinical use of BMAC in musculoskeletal disorders and have been written mainly with the Indian regulatory context in mind but are applicable to a wider international context. The evidence base is mostly based on PubMed indexed Level I-III studies; where there is no robust trial data, expert consensus (Level IV) is applied and clearly marked. No longer redundant, one consolidated, quality-screened reference list is provided in Section 16, with the exception of commercial marketing material, promotional handouts and non-indexed web sources kept as primary support for clinical recommendations (only retained, where unavoidable, as background/regulatory context and explicitly marked as such). Intended audience is orthopedic surgeons, sports medicine physicians, pain physicians, physiatrists, allied health professionals dealing with patients with MSK disorders.

## Section 2

# Clinical Protocols used in BMAC therapy.

This section summarizes the clinical protocols used in BMAC therapy.

## 2.1 Comprehensive Pre-Procedure Evaluation

All candidates for BMAC therapy should be assessed prior to the procedure by a structured procedure that includes:

- Clinical evaluation: Detailed history, duration of symptoms, previous conservative and surgical treatment history, VAS/NRS pain score, functional outcome scores (KOOS, WOMAC and DASH as applicable).
- Weight-bearing plain radiographs (joint-specific), MRI (chondral loss, bone marrow edema, tendon integrity, ligament status) and bone scan (when osteonecrosis is suspected)
- Laboratory investigations: Complete blood count (CBC) with hemoglobin/hematocrit, renal function, coagulation profile, HbA1c (diabetic patients), infectious disease screening (immunocompromised patients) In patients with low baseline hemoglobin or hematocrit (in the smaller-sized patients), the treating physician should be cautious of the volume of marrow harvested in high-volume aspirations, since this volume may have a meaningful impact on the circulating blood counts of these patients; the volume of marrow to be harvested should be individualized.

## 2.2 Patient Selection Criteria

Chronic MSK conditions that have not had at least three months of structured conservative treatment (physiotherapy, analgesics, and/or other non-operative therapy), or chronic MSK conditions that have not made satisfactory progress with structured conservative treatment so additional biologic procedure may be considered to speed healing, are ideal candidates. BMAC may be considered for the following pathological groups: Osteoarthritis — evidence currently published supports moderate to severe disease (Knee: KL Grade II-IV, not yet surgical; Hip, Shoulder, Ankle) not just mild/early disease Chronic tendinopathy including the rotator cuff, Achilles, patellar and lateral epicondyle.

- Focal chondral and osteochondral lesions Early avascular necrosis (osteonecrosis) of femoral head — ARCO Stage I-II is the range used most consistently and there is strong supporting evidence in this range; Stage IIIa is used more sparingly, and should be associated with careful counseling about the lower expected benefit (see Section 12.1) Fractures with non-union or delayed union (provided that the fracture was adequately surgically fixed), in which poor mechanical fixation would be a risk for non-union should be properly surgically fixed prior to consideration of BMAC augmentation;
- Post surgical augmentation (Rotator cuff repair, ACL reconstruction, meniscal repair)
- Pain in the spine due to the breakdown of discs, which does not respond to conservative treatment — for IRB approved research only (see Section 12.4) Clinical Callout: “Clinical judgment is the most important factor — there are no hard-and-fast indications. The treating physician must take each patient's health profile, disease state, rehabilitation potential and goals of care into consideration in determining the risk/benefit profile.”

## 2.3 Absolute Contraindications

However, there are some circumstances in which BMAC therapy is absolutely contraindicated: Active malignancy (haematological or solid organ) including active leukaemia, lymphoma, myeloma, myelodysplastic syndromes, polycythaemia vera.

Note: Prior/remote neoplastic history and BMAC/MSC therapy is still a developing area; please consult individual oncology for patients with malignant history prior to treatments by BMAC/MSC, and the committee will not exclude these patients from treatment, but will await further published results.

- History of active HBV/HIV/HCV/HTLV due to the viral load and cellular disposition
- Active local or systemic infection/sepsis: including active granulomatous infections (TB, fungal) Thrombocytopenia (Platelet Count < 50,000/ $\mu$ L) or active coagulopathy (as noted throughout this document, including in the pre-processing checks in Section 4B)
- Significant anemia (per institutional/laboratory threshold, usually hemoglobin < 10 g/dL) — consider avoiding or delaying bone marrow aspiration in patients with anemia until corrected
- Severe anemia (less than 8 grams per deciliter or less than 8% oxygen-carrying capacity of the blood)
- Previous treatment at the pelvic harvest area (PSIS/iliac crest)
- Previous known sensitivity to anticoagulants in the preparation procedure (such as ACD-A, heparin)
- Active lactation

## 2.4 Relative Contraindications

The following conditions need careful risk / benefit assessment and if relevant optimization before further action:

- Systemic anticoagulant therapy: warfarin, DOACs, heparin, need interdisciplinary coordination, bridging strategy
- Chronic immunosuppressive therapy — individual risk assessments needed Active tobacco smoking — may result in impaired function of MSC and neovascularization
- Diabetes mellitus (HbA1c > 8.5%) — may result in poor cell viability and wound healing
- Marrow cellularity loss due to severe obesity (BMI > 35 kg/m<sup>2</sup>) — decreases marrow cellularity and MSC yields The regenerative response is likely to be reduced by chronic NSAID or systemic corticosteroid use (6).
- Advanced osteoarthritis (KL Grade IV, severe bone deformity or joint space obliteration) — individualize; see Section 2.2 for moderate to severe OA evidence strength
- Uncorrected knee malalignment >10° varus/valgus.
- History of previous steroid injections in the target area (< 4 weeks)
- Flare of acute inflammatory arthritis (rheumatoid, psoriatic, crystal) — delay until remission
- Significant bone marrow abnormalities on CBC (history of malignancy involving bone marrow warrants specialized hematology/oncology care and should not be automatically excluded — published reports, such as the ones reporting the use of BMAC/MSC in patients with a history of malignancy, should be considered on a case-by-case basis)

## 2.5 Special Considerations for Comorbidities

**Diabetes:** Optimise glycaemic control before procedure (a target HbA1c of  $\leq 8.0\%$  is recommended – some members of the committee would prefer a more stringent level if achievable – but no controlled BMAC specific data yet exists to validate a cut-off, therefore an individualised target should be set rather than a fixed level); monitor wound site after procedure for harvest site; prolonged rehabilitation periods. The yield of nucleated cells is significantly lower than normal for obesity, may need to increase the total harvest volume, may be difficult to harvest.

**Advanced age:** There is a physiological decline in marrow cellularity with age, but published registry data have not consistently shown that there is a clear age-outcome relationship; the difference in outcomes for age is still a hypothesis and remains unconfirmed. Avoid making any absolute age-based exclusion recommendations; encourage patients to know that reactions vary from person to person, irrespective of age.

**Immunocompromised:** Opportunistic infection risk at harvest; infectious disease clearance required.

## Section 3

# Pre-Procedure Patient Instructions

## 3.1 Medication Adjustments

A few changes in medication are recommended before BMAC therapy. Adjustment of anticoagulant, antiplatelet, corticosteroid and immunosuppressive drugs, each of which has its own thrombotic, cardiovascular and endocrine risk, is general practice and should be made in consultation with the prescribing physician; there are no controlled evidence-based advantages or disadvantages to note for BMAC.

| Medication Class                                                         | Stop Timeline                        | Special Notes                                                                                                                                                                   |
|--------------------------------------------------------------------------|--------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NSAIDs (ibuprofen, naproxen, diclofenac)                                 | ≥ 5 days prior                       | Avoid resumption for ≥ 3 weeks post-procedure (see Section 10.1 for rationale and any earlier resumption on clinical grounds)                                                   |
| CGRP-targeted migraine therapies (e.g., anti-CGRP monoclonal antibodies) | Individualized                       | These agents modulate a component of the neuro-immune inflammatory response; whether restriction is warranted is not established — discuss with prescribing physician           |
| Anticoagulants (warfarin, rivaroxaban, apixaban)                         | Per prescribing physician protocol   | Requires cardiology/haematology coordination                                                                                                                                    |
| Systemic corticosteroids                                                 | ≥ 3 weeks prior                      | Risk of HPA axis suppression and possible MSC dysfunction                                                                                                                       |
| Intra-articular/periarticular corticosteroid injection                   | ≥ 4 weeks gap required               | Local tissue milieu should be steroid-free before injection; specific washout duration is extrapolated from general orthobiologic practice rather than BMAC-specific trial data |
| Immunosuppressants (methotrexate, biologics)                             | Individualized assessment            | Rheumatology consultation recommended                                                                                                                                           |
| Aspirin (prophylactic, < 100 mg/day)                                     | May continue with physician approval | Higher doses require stoppage ≥ 5 days prior                                                                                                                                    |

Before the procedure, fluid should be offered and consumed in the following way:

- Drink plenty of fluids for the 24 hours before the procedure
- An anti-inflammatory dietary pattern (e.g., Mediterranean-style) around the time of the procedure is a reasonable general health measure, but is often drawn from general peri-op nutrition literature and not directly from the BMAC literature.
- No high dose supplemental omega-3, vitamin E or fish oil for 5 days after procedure because these prevent platelets from clotting.
- No fasting should be required unless a procedural sedation is being planned (in which case the standard pre-anaesthetic fasting protocols should be followed)

## 3.2 Harvest Site Preparation

The BMAC is routinely harvested from the posterior superior iliac spine (PSIS) which has reliable anatomical landmarks, rich cancellous bone and is low on neurovascular risk. The anterior superior iliac spine (ASIS) is another harvest site that can be used if the patient is not able to be placed prone — for instance, if a patient has

had a prior or simultaneous surgical procedure that requires them to be supine. Patients need to be advised about:

- Hair removal at harvest site (if necessary) preferably immediately prior to the procedure in the pre-operative area and not the day before, to reduce risk of infection from micro abrasions.
- No topical cosmetics, perfumes or oils to the skin of the lumbar-gluteal area the day of the procedure
- The clinical team will use standard aseptic skin preparation (povidone-iodine or chlorhexidine).

### **3.3 Patient Expectations Management**

Patients should receive counselling and be documented to have received counseling before proceeding:

- Nature of therapy: BMAC is an autologous (self) biological therapy in which the patients' own bone marrow is used. Is not surgical and is not a sure fire cure.
- Outcome variability: Response to BMAC is individual, depending on disease severity, comorbidities and adherence to rehabilitation; the role of age is a research question (Section 2.5).
- Time to response: Clinical improvement usually occurs within 4-12 weeks after injection and full therapeutic effect may not be seen until 3-6 months.
- Repeat sessions: In some conditions and patient profiles repeat treatment sessions may be needed, but there is limited evidence for fixed multi-injection protocols (see Section 9.3) and decisions for repeat treatments should be made on an individual basis, depending on the clinical response at the time.
- Informed consent: Condition specific, procedure specific consent documentation must be obtained; including explicit acknowledgement of off-label use where applicable; and of potential for minimal or no improvement; and of procedural risks (see Section 14).

## Section 4

# Standardized BMAC Preparation & Quality Control

This guide is authored by Lee L. Crawford.

## 4.1 Goals of Standardized Preparation

The aim of a standardized BMAC preparation protocol is to:

The results seem to be dose dependent, with the highest total nucleated cell (TNC) count in the bone marrow concentrates. Therefore, a higher TNC will result in a higher TNC yield in the final concentrate, if the initial aspirate TNC is high. Achieve highest possible viable nucleated cell concentration from the source bone marrow aspirate – validated ranges reported in the literature: total nucleated cells (TNC) approximately 2.8–4.7×; platelets approximately 5.3–9.6×; CD73+/CD90+ (putative MSC-lineage, surface-marker-positive) subpopulations approximately 2.0–3.5× relative to baseline aspirate

Consider a target viability ≥90% (trypan blue or AO/PI exclusion) at the point of injection, and minimum acceptance of ≥70% below which the product should not be used.

Ensure sterility from harvest through injection; culture-based sterility testing to meet applicable regulatory sterility standards, if feasible, is recommended; if a culture is positive, the adverse-event pathway (Section 14) is recommended. No point-of-care biologic preparation can be guaranteed to be absolutely sterile.

Assist in providing consistent, reproducible cell dosing if the same validated closed system kit is used consistently throughout a course of treatment for the same patient. The design of various commercial closed-system devices does not allow for interchangeability; in fact, prospective head-to-head comparisons of approved systems have shown significant non-equivalency in the number of progenitor cells and in the concentration of cells between devices.

Maintain viability of the cells from aspiration to injection, ideally within the limit of standard point-of-care practice (typical total procedure time is about 1-2 hours, according to published protocols – BMAC-specific validated viability-decay curve with an exact optimum cutoff (e.g. 60 minutes, 90 minutes, 120 minutes) has not been established in the literature).

## 4.2 Quality Control Measures.

### Pre-processing checks:

In the office setting a spot-check hematocrit/hemoglobin test is generally adequate for routine cases, but for higher risk patients, a complete blood count (CBC) with differential and platelet count using the same platelet threshold as specified in Section 2.3 (< 50,000/μL = absolute contraindication) should be performed within 7 days of the procedure.

Routine blood tests (RBC, hemoglobin, HCT, platelet, iron, magnesium, zinc, etc) in at risk patients

Verify the calibration of the equipment: centrifuge calibration log, batch number, expiry check of kits

Preparations: ACD-A (Acid Citrate Dextrose, Solution A) pre-loaded in harvest syringes. Heparin is also a commonly used anticoagulant and is cheap; it can work well in an open system in the laboratory (not a closed commercial kit) as an effective buffy coat separation method, although it is not used as widely by the commercial kit manufacturers because of cost considerations. Therefore, the dose of heparin should be kept to a minimum and recorded; heparin-induced thrombocytopenia (HIT) and heparin hypersensitivity are rare but serious complications of heparin use in susceptible patients.

This document does not address in detail the laboratory quality-control practice for open-system BMAC processing; institutions that process BMACs in an open system (without the application of kits) should follow their local laboratory accreditation standards for cell-processing quality assurance.

### 4.3 Pre-Processing Requirements

Baseline bone marrow cell count (when possible) and CBC assessment of the patient.

A single ratio range will be used throughout this document; ACD-A 1:7 – 1:10 (volume:volume), superseding other, narrower ratios given elsewhere, and consistent with standard bone marrow harvest practice (approximately 1:10 final ratio) and commercial kit instructions-for-use (approximately 10 – 15% v/v). The ratio for the commercial kit to be used should be followed according to the specific validated instructions-for-use (IFU).

Equipment validation: centrifuge calibration, rotor integrity check, sealed processing kit sterility confirmation

All who are to carry out the procedure should have completed BMAC technique training and documentation.

### 4.4 Cell Count Verification.

In contrast to routine same-day clinical use, where there is no consensus on what to do if the immunophenotypic characterization is not met within a target count after the aspirate has been harvested and is ready for injection, routine post-processing cell counting and immunophenotypic characterization is a research or quality-assurance activity. This applies mainly for research protocols, registries or quality assurance audits:

It is important to document pre and post processing nucleated cell count (total nucleated cells [TNC]/mL) for each session where possible. The TNC count in the bone marrow aspirate will depend on the quality and efficiency of the bone marrow aspirate and the TNC count in the final concentrate will depend on the efficiency and the performance of the bone marrow concentration process.

For a mesenchymal stromal/progenitor characterization in research, it is necessary to refer to the minimal criteria set by the International Society for Cell & Gene Therapy, including both positive markers (historically CD73<sup>+</sup>/CD90<sup>+</sup>/CD105<sup>+</sup>) and required negative markers (CD11b<sup>-</sup>/CD14<sup>-</sup>, CD19<sup>-</sup>/CD79α<sup>-</sup>, CD34<sup>-</sup>, CD45<sup>-</sup>, HLA-DR<sup>-</sup>), as positive markers alone are not enough to establish a mesenchymal stromal/stem cell phenotype. More recent literature has suggested that the CD271 (low-affinity nerve growth factor receptor) marker may be more specific for native (non-culture-expanded) MSC-lineage cells in bone marrow aspirate than flow cytometry, and that enumeration of CFU-F may be better than flow cytometry to estimate true progenitor content—because flow cytometry cannot differentiate functional progenitor activity from simply being marker positive.

Indicative TNC ranges reported in the literature (these are values observed in published series, not universally validated or consensus therapeutic thresholds as no international dose-response consensus currently exists for BMAC in MSK indications):

- Small joints (ankle, wrist etc.): commonly reported between 5-10million TNC per injection
- Medium joints (shoulder, hip): 15 million TNC/injection is a common complaint
- Large joints (knee): reported effective doses range from 20 to 25 million TNC per injection in a typical volume of 5 to 10 mL (see Section 9.4 for details on the volume of the injectate) (at least one large single centre study has reported a substantially higher effective dose (around 400 million TNC) below which it was not distinguishable from failure, so the effective dose reported in the ranges above should not be considered a validated minimum effective dose);

In this case, given the uncertainty, one should consider a clinical discussion (harvest volume adjustment, deferral, or proceed to counselling for uncertain benefit) and not cancel the procedure automatic.

## 4.5 Sterility Assurance

All harvesting and processing operations should be carried out in a sterile field (in the operating theatre/procedure room) or in a biosafety cabinet (Class II) for open system processing.

For routine clinical use, use closed system, regulator-approved, commercial kits as it minimizes the risk of contamination and supports regulatory compliance in jurisdictions where it is required (e.g., DCGI approval in India). Open, laboratory-based (non-kit) processing via appropriately trained personnel under proper biosafety-cabinet conditions has a long history in the published literature and therefore is acceptable as an alternative to open processing with kits if permitted by local regulatory authorities and if laboratory facilities and expertise support the latter technique; open processing with Ficoll-density-gradients may have different regulatory implications (e.g., beyond “minimal manipulation” classification in some regulatory frameworks) and institutions should verify their local regulatory classification before adopting this approach.

Processing staff should wear complete sterile garments, and patient's skin should be cleaned with regular surgical antiseptics.

No BMAC system components (needles, syringes, kits, transfer lines) can be reused between patients or sessions.

## 4.6 Documentation Requirements

All BMAC sessions should be recorded with:

1. Record the date and time of the procedure. Record procedure date and time.
2. The reference is provided in patient identification and consent form.
3. Harvest site (PSIS right/left or ASIS) and patient positioning
4. The total amount of harvest (mL)
5. Type of anticoagulant, lot number, volume used.
6. Device/kit used: Name of the device/kit, manufacturer, applicable regulatory approval/registration number, serial/batch number (or documentation that an open/laboratory-based system was used)
7. Initial and final pH of the product.
8. Moisture content of the product at the end of the drying process.
9. The numbers refer to the final volume of BMAC collected (mL).
10. The result of post-processing cell count (TNC/mL) (if carried out)
11. Injection site(s) and volume injected at each site (mL) — volumes as indicated in Section 9.4
12. Needle placed using image guidance modality if applicable (ultrasound/fluoroscopy), and needle placement confirmed.
13. Operator name and credentials
14. Intra procedural adverse events (IAE)
15. Immediate post procedure patients' status reported by patient (pain, haemodynamic stability)

## Section 5

# BMAC Types Based on Composition

### 5.1 Standard BMAC

The standard BMAC is prepared by centrifugation using a single spin, optimized for the separation of the red blood cells, allowing the collection of a buffy-coat enriched fraction of nucleated cells, platelets and MSCs. Standard BMAC, by default, contains a platelet-rich-plasma-like component, unless a special platelet-depletion step is added, which should not be considered as a distinct “hybrid” category (see Section 5.3). It is the most commonly used and studied product in the intra-articular space (knee, hip, and shoulder OA) and intraosseous formulation for early osteonecrosis, and represents the therapeutic profile utilized in most of the published Level I-II studies.

### 5.2 Concentrated BMAC (cBMAC)

Concentrated BMAC is obtained by means of double-spin centrifugation or density gradient separation (such as Ficoll) which results in greater extraction of nucleated cells and progenitor cells. This formulation is recommended for refractory cases, larger cartilage defects or applications requiring a higher level of cell dose. Evidence for the use of this technique includes the treatment of osteochondral lesion and treatment of non-union fractures; although the taxonomy of the “standard/concentrated/hybrid” terms used in this document is a practical classification, there is considerable variability in each of the following parameters in published series: aspiration technique, anticoagulants used, centrifuge protocols, commercial devices used, volume of final product, red-cell content, and overall recovery of cells across published series; this is recognized as a limitation of the published literature (Section 13).

### 5.3 BMAC + PRP Combination

There is a growing body of literature that describes the intentional addition of other autologous PRP to standard BMAC preparation, with the aim of augmenting the platelet-derived growth factor level in addition to the paracrine signaling by the MSCs and/or progenitors. This is a new biological product being added to the existing therapy and should be considered a new combination therapy, not equivalent to standard BMAC. For short-term to medium-term functional outcomes, the combined approach is emerging as evidence-based treatment in knee OA and in rotator cuff tendinopathy; combination therapy dosing protocols are still being developed.

### 5.4 BMAC + Fibrin Scaffold (BMAC-PRF)

When trapped into a platelet-rich fibrin (PRF) scaffold BMAC forms a three-dimensional slow-release matrix with continuous release of growth factors and structural support for tissue ingrowth. Just like BMAC+PRP, this is a unique combination product with its own evidence base, used mainly in open surgery, where the scaffold is used to provide both mechanical stability and biological signal, including for the augmentation of fracture non-unions, cartilage defect filling and rotator cuff repair. BMAC-PRF is a sterile preparation that must be performed concurrently with the processing of BMAC and A-PRF/L-PRF.

| Product                          | Primary Bioactive Content                                                                        | Typical Preparation                                       | Representative MSK Uses                                    | Relative Evidence Maturity                                        |
|----------------------------------|--------------------------------------------------------------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------------|
| PRP                              | Concentrated platelets and platelet-derived growth factors; minimal nucleated progenitor content | Single/double-spin centrifugation of peripheral blood     | Tendinopathy, mild-moderate knee OA                        | Most mature — multiple RCTs and meta-analyses                     |
| Standard BMAC                    | Nucleated cells (including MSC/progenitor fraction), platelets, growth factors                   | Single/double-spin centrifugation of bone marrow aspirate | Moderate-severe OA, osteonecrosis, non-union, tendinopathy | Growing — Level I–III studies, heterogeneous protocols            |
| Concentrated BMAC (cBMAC)        | Higher nucleated/progenitor cell enrichment                                                      | Double-spin or density-gradient separation                | Refractory/large chondral defects, non-union               | Limited — mostly Level II–III                                     |
| Culture-expanded MSC therapy     | Ex vivo expanded MSC populations                                                                 | Laboratory culture expansion (weeks)                      | Investigational MSK and systemic applications              | Emerging — regulatory status varies significantly by jurisdiction |
| Adipose-derived stromal products | Stromal vascular fraction cells                                                                  | Lipoaspirate digestion/processing                         | OA, tendinopathy (varies by jurisdiction)                  | Emerging — regulatory status varies significantly by jurisdiction |

**Clinical Note:** “Standard BMAC is the recommended default formulation for joint-related therapies. Concentrated formulations (cBMAC) and combination products (BMAC+PRP, BMAC-PRF) may be considered in chronic, refractory, or large-defect scenarios where a higher biological payload is clinically justified, recognizing that each represents a materially different product with its own separate evidence base.”

## Section 6

# Harvest Parameters

The purpose of this section is to prepare for BMAC exam.

### 6.1 Harvest Parameters

Lateral or prone decubitus position is the preferred approach for harvest; site is the Posterior Superior Iliac Spine (PSIS)

Alternative site: Anterior Superior Iliac Spine (ASIS) — supine approach used when prone positioning is contraindicated (e.g., if a surgical procedure had recently been performed on the abdomen or back or when surgery is performed out of the hospital) or in a surgical setting that requires sedation.

Needle type: Jamshidi-style bone marrow aspiration needle (11G preferred, 13G acceptable)

Multiple aspiration sites/passes and low volume per pass (2–4 mL per pass) have the highest impact on cell yield and blood dilution of the aspiration strategy, as opposed to needle rotation. The aspiration from 10 cc syringes appear to yield more counts than the larger cc syringes (Hernigou has a study on this). The use of a needle with closed tip and side (lateral) ports could allow for rotation of the needle and repositioning between passes to sample alternate marrow niches; however, there is no published documented rationale to support the notion that a certain angle of rotation (e.g., 90°) is of any benefit with regard to yield, and clinicians should not presume that rotation technique is sufficient to replace proper repositioning between low-volume passes.

Total harvest volume: 40–120 mL in accordance with the BMAC kit and patient's clinical dose requirement, adjusted downwards in patients with low baseline hemoglobin/hematocrit (Section 2.1).

- 60 mL harvest: suitable for single small to medium joint injection
- 120 mL harvest: suitable for larger joint or multi-site/harvest combination therapy – second puncture site needed if more than 60 mL is to be collected from a single site

Red blood cell contamination should be avoided to the greatest extent possible because the presence of a large number of red blood cells in the final BMAC product can lead to a post-injection inflammatory flare and reduce the number of nucleated cells without providing any therapeutic benefit. The most important methods to prevent red cell carryover are low-volume aspiration and suitable centrifugation conditions (above); red cell content should be routinely checked in research settings (Section 4D).

### 6.2 Anticoagulant Protocol

The preferred anticoagulant for most commercial closed kit systems is ACD-A (Acid Citrate Dextrose, Solution A) which is reported to be good for the preservation of platelet function and cell viability in the BMAC context.

Approximately 1/7 to 1/10 (v/v) ACQ-A loading ratio (or consolidated single ratio for this document — see Section 4C)

Heparin is also used, especially in open/laboratory-based processing, where it is a common and cost-effective anticoagulant and can be used to facilitate good buffy-coat separation, but is not used as extensively by the closed commercial kit manufacturers, mainly because of the cost. If heparin is used, dose should be restricted,

documented, and administered with caution in patients with a risk of heparin hypersensitivity and/or heparin-induced thrombocytopenia (HIT).

Harvest syringes should be pre-filled with the selected anticoagulant prior to the start of aspiration and the anticoagulant should be verified as uniformly mixed within seconds after aspirate collection.

## 6.3 Preparation Methods

### Closed system (Manual / Laboratory Based)

Open system BMAC preparation is carried out in a biosafety cabinet in a well-trained laboratory. This method has been published for many years, both in single-center, hospital-laboratory processing without a commercial kit and also as an alternative to closed commercial kits for which local regulatory requirements and laboratory facilities are available. The overall double spin protocol is:

1. Harvest: Aspirate bone marrow (40-120 mL) in syringes pre-filled with anti-coagulant; through PSIS or ASIS
2. Transfer: Transfer aspirate to sterile conical tubes or processing bags.
3. First Spin (Soft Spin): Spin at about  $100-400 \times g$  for 5- 10 minutes to sediment the red blood cells and the buffy coat floats above the red cell pellet. The actual RCF needed and the time (Section 7) should be verified for the particular centrifuge and protocol used and not assumed to be transferable between different centrifuges.
4. Buffy Coat Aspiration: Aspirate the buffy coat (mononuclear cell rich) layer carefully under sterile conditions so that there is minimal contamination with red cells.
5. Hard Spin (Second Spin): Spin buffy coat fraction at  $\sim 600-900 \times g$  for 10-15 minutes and concentrate nucleated cells in a pellet.
6. Resuspension: Resuspend the cellular pellet in the remaining plasma (5 to 15 mL), gently, in the original plasma it was suspended in.
7. Final product: 5–20 mL of BMAC ready to inject

**Pros:** Reduced cost per procedure; flexibility in lab setup; wide experience in high-volume laboratories, etc.

**Advantages:** theoretically lower operator-dependent variability than closed systems, lab programs have shown reproducible results in the literature, requires trained laboratory personnel and biosafety cabinet infrastructure

### Question 34: WHAT IS A CLOSED SYSTEM (COMMERCIAL KIT BASED)?

#### Closed System (Commercial Kit Based)

When there is a requirement by applicable local regulator for device-specific authorization, closed system BMAC processing kits are preferred for routine clinical use, in India approved by the DCGI. Most of the closed system process is similar for a number of validated commercial systems and includes:

1. Prepare: Pre-rinse all components with anticoagulant/rinse solution as outlined in the kit instructions for use; place the anticoagulant in the collection filter bag.
2. Harvest: Aspirate bone marrow (30-120 mL) from PSIS or ASIS with the Aspiration Needle provided
3. Transfer: Liquid aspirate into sealed filter bag of the processing dispositive

4. Load centrifuge: Place the sealed disposable into the centrifuge unit provided with the kit, and balance the rotor with the same weight;
5. The 5th spin cycle is for sedimentation of the RBCs, with the platelet/nucleated-cell rich fraction collected in the plasma chamber (kit validated protocol).
6. Second spin cycle: BMAC fraction is concentrated further, according to the validated protocol in the kit, by re-spinning at a higher speed.
7. Withdraw: Syringe out cell-free plasma through the designated port and resuspend the bone marrow cells in the rest of the plasma.
8. Final product: Usually 4-20 mL of concentrated BMAC, which is suitable for immediate injection (actual amount and time is dependent upon device – always follow the manufacturer's validated IFU).

**Disadvantages:** Limited availability of standardized and qualified devices and equipment; limited selection of devices and equipment; operator training is complex; risk of contamination from closed system; requires device approval if needed for regulatory compliance. Cost; dependency on devices and reagents; dependence on a system that is available commercially; different systems may give different numbers and concentrations of progenitors from cell; clinicians should use a single system consistently for a patient's treatment course; switching systems will give different numbers and concentrations of cell progenitors.

There are multiple validated closed system BMAC platforms available in the market and no single commercial name is the only option for institutions, they should choose a closed system BMAC platform which is approved by the regulatory authority, validated by published data, and meets their operational needs.

**Regulatory Note:** “Only the BMAC devices approved by the DCGI and closed system kits should be used for routine practice in India, while open/laboratory based processing and any non-approved system should only be used after obtaining the relevant Ethics Committee and institutional governance approval and should be checked against current CDSCO regulations by the treating institution; the regulatory status of these systems may change over time.”

Analysis of the centrifuge specifications and parameters that are required.

## Section 7

# Centrifugation & Quality Parameters

## 7.1 Centrifugation parameters

When a double-spin (two-spin) reference parameter exists, it is used. If a double-spin (two-spin) reference parameter exists, it is used.

| Spin Step                  | Purpose                      | RCF (g)     | Duration  | Expected Outcome                               |
|----------------------------|------------------------------|-------------|-----------|------------------------------------------------|
| First Spin<br>(Soft Spin)  | RBC sedimentation            | 100–400 × g | 5–10 min  | Buffy coat separation from red cell pellet     |
| Second Spin<br>(Hard Spin) | Nucleated cell concentration | 600–900 × g | 10–15 min | Final BMAC pellet in 5–15 mL autologous plasma |

These ranges are illustrative and reflect commonly published open-system protocols; they should not be generalized indiscriminately across all devices. Always refer to the specific centrifuge or commercial BMAC kit manufacturer's validated protocol for RPM and time settings, as fixed centrifugation parameters vary meaningfully by rotor geometry and device design.

## 7.2 Centrifugal Force (RCF) Calculation

The Relative Centrifugal Force (RCF) is calculated using the formula:

$$RCF = 1.118 \times 10^{-5} \times r \times RPM^2$$

Where:

- $r$  = rotor radius in centimeters (distance from centrifuge axis to sample)
- RPM = revolutions per minute

**Worked example:** Rotor radius = 15 cm; Desired RCF = 400 × g

$$RPM = \sqrt{\frac{RCF}{1.118 \times 10^{-5} \times r}} = \sqrt{\frac{400}{1.118 \times 10^{-5} \times 15}} \approx 1544 \text{ RPM}$$

**Technical Note:** “Always refer to the specific centrifuge or commercial BMAC kit manufacturer's validated protocol for RPM and time settings. Deviating from manufacturer-specified parameters may compromise cell yield, viability, and product quality. All centrifuge calibration records must be logged per session.”

## 7.3 Quality Assessment Formulas

### Cell Yield Efficiency:

$$\text{Cell Yield Efficiency (\%)} = \frac{\text{BMAC Volume} \times \text{BMAC Cell Count}}{\text{Aspirate Volume} \times \text{Aspirate Cell Count}} \times 100$$

**Concentration Factor** (corrected — compares final product to the source bone marrow aspirate, not peripheral blood):

$$\text{Concentration Factor} = \frac{\text{BMAC Nucleated Cell Count (cells/mL)}}{\text{Baseline Bone Marrow Aspirate (BMA) Nucleated Cell Count (cells/mL)}}$$

A target concentration factor in the range of approximately 2.8–4.7× baseline bone marrow aspirate (total nucleated cells) is consistent with values reported in the literature (Section 4A); this is descriptive of typical achieved concentration rather than a validated minimum efficacy threshold.

### Product Characterization (research/quality-assurance settings):

Comprehensive BMAC product characterization, where performed, should include: starting and final CFU-F concentration, total nucleated cell recovery, viability, platelet count, red-cell contamination, and final product volume — rather than nucleated cell count alone.

**MSC/Progenitor Enrichment Ratio** (if flow cytometry or CFU-F assay is available):

$$\text{MSC Enrichment Ratio} = \frac{\text{CFU-F (or CD271}^+\text{) content per mL in BMAC}}{\text{CFU-F (or CD271}^+\text{) content per mL in baseline bone marrow aspirate}}$$

True MSCs/progenitors constitute only approximately 0.001–0.01% of total nucleated bone marrow cells; centrifugation-based enrichment increases this proportion within the BMAC fraction, but the absolute progenitor count delivered even in a well-concentrated product remains a very small fraction of the total nucleated cell dose. **This mathematical relationship is the basis for removing the previously stated fixed “≥100,000 MSC per injection” numeric target from this document (see Section 9.2): a preparation containing 10–25 million TNC would be expected to contain only a few hundred to a few thousand phenotypic MSCs by this ratio, which is not reliably compatible with a 100,000-MS target, and no validated dose-response evidence currently supports a specific MSC-count therapeutic threshold.**

## Section 8

# Injection Technique & Image Guidance

The injection technique and image guidance are covered in section 8.

All BMAC injections (intra-articular, intratendinous, intraosseous and perineural) should be injected under real-time image guidance to ensure procedure safety and to assure accurate delivery.

<sup>1</sup>Quick and Effective Method of Bone Marrow Mesenchymal Stem Cell Expansion. PMC. 2014. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5152963/>

<sup>2</sup>Quick and Effective Method of Bone Marrow Mesenchymal Stem Cell Expansion — CFU-F and Progenitor Characterization Methodology. PMC. 2014. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5152963/>

<sup>3</sup>Quick and Effective Method of Bone Marrow Mesenchymal Stem Cell Expansion — MSC Frequency Data. PMC. 2014. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5152963/>

<sup>4</sup>Quick and Effective Method of Bone Marrow Mesenchymal Stem Cell Expansion — CFU-F and Progenitor Characterization Methodology. PMC. 2014. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5152963/>

## 8.1 Image-guided injection

The main factors determining modality selection is whether the modality selected can adequately visualize the target structure and confirm accurate needle-tip placement and flow into the target zone — not only the depth.

- Dynamic, real time ultrasound (US) – used for superficial and intermediate depth targets where dynamic visualization can be made available (knee intra-articular, shoulder subacromial/glenohumeral, Achilles peritendinous, lateral epicondyle); allows real-time dynamic visualization and aspiration of effusion.
- Fluoroscopy/C-arm imaging: The imaging modality of fluoroscopy or C-arm fluoroscopy refers to the same modality of image-intensifier based radiographic guidance – it is not two different techniques but rather the same technique (fluoroscopy/c-arm). This is a common choice for intraosseous delivery (osteonecrosis, non-union fracture), spinal (facet joint, sacroiliac joint — intradiscal delivery is reserved for research protocols, see Section 12.4), or deep intra-articular delivery in the hip (see Section 13.1) where ultrasound is inadequate to ensure proper flow.
- CT guidance: Only used for the complex anatomical targets or when fluoroscopy and ultrasound attempts have failed

## 8.2 Needle visualization

Keep needle tip in view at all times; ensure needle insertion is in the correct location in the target structure before delivering with direct needle visualization and confirm with contrast (fluoroscopy) or confirm with saline hydrodissection (ultrasound)

## 8.3 Pre-injection effusion aspiration

Pre-injection effusion aspiration (if joint effusion is present) – Aspirate effusion completely before BMAC injection to decrease intra-articular pressure to ensure therapeutic product is optimally distributed; use standard sterile technique with dedicated aspiration port or exchange technique;

## **8.4 Intraosseous Delivery**

Intraosseous delivery (osteonecrosis / subchondral pathology): Special access instruments (trocar-needle system) are required; position in the intraosseous space within the necrotic area should be confirmed fluoroscopically. Published data have been made available to support delivery as a single, high volume injection exactly into the right necrotic zone as opposed to the routine division of this volume across multiple access points; delivery of BMAC is under minimal pressure to prevent intravasation.

## **8.5 Injection technique**

Slow and steady injection of BMAC at rate of approx. 1 mL/10-15 seconds, to prevent tissue pressure injury, extravasation and inflammatory flare; confirm there is no "vascular flash" before injection

## **8.6 Immediately after injection:**

Withdraw the needle in one quick motion, apply sterile dressing over harvest site (change at 48 hours) and injection site; compress harvest site for 3-5 minutes; observe for 30 minutes after the procedure for vaso-vagal response, haematoma, neurological change.

## **8.7 Operator competency**

Formal credentialing, in musculoskeletal ultrasound or fluoroscopy guided injection technique, is required for BMAC injection under image guidance, and it should not be performed by untrained practitioners. Before independent practice, it is recommended to be doing proctored cases (min 10).

## Section 9

# Dosing Strategies for BMAC Therapy

## 9.1 Overview

High-level, validated dose response trials on BMAC dosing are not yet defined. Dosing ranges as examples are provided within categories as indication from available Level II–III evidence and expert practice, but it should be noted that reported effective doses have been variable across published cohorts, preparation systems, and outcome definitions (Section 4D) and that there is currently an absence of an international consensus threshold. The dose depends on the type of structure to be treated, size of the defect, patient characteristics, preparation of BMAC, and marrow cellularity.

## 9.2 Key Dosing Principles

There is no validated dose-response trial to define the minimum effective TNC; for most patients, undosing is considered to be a sign of poor performance, although in some large series, the minimum effective TNC appeared to be much higher (see Section 4D);

Volume: enough plasma vehicle to distribute evenly in target tissue, too much can result in a decrease in cell concentration with no proportional gain.

Please note that MSC/progenitor quantification is not recommended as a standard part of the routine analyses of each clinical injection. The need to quantify MSCs in real time prior to injection creates unnecessary cost and complexity and introduces a delay between sample collection and clinical decision making on whether the sample is adequate (to use, or whether to consider it to be sub-optimal, for example). Although MSC/progenitor characterization is useful in research and audit settings (Section 4D), it is not a standard same-day clinical need. The stated fixed target of “≥100,000 MSCs per joint injection” has been removed from this document because it is not mathematically consistent with the TNC ranges above and there is no validated dose-response evidence (see Section 7.3).

## 9.3 Single vs. Multiple Injection Protocols

| Injection Strategy                                | Indication                                                                                   | Rationale                                                                                                                                                                                                                                                                                                                                            |
|---------------------------------------------------|----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Single high-dose injection</b>                 | Acute tendon injury, focal chondral lesion, early AVN                                        | Single-session delivery is the approach most consistently described in the published literature for these indications                                                                                                                                                                                                                                |
| <b>Repeat injection (individualized interval)</b> | Moderate-severe OA, large osteochondral defects, or inadequate response to initial injection | Repeat treatment may be considered based on interim clinical response; however, a specific pre-planned multi-injection schedule (e.g., a fixed “2–3 injections every 4–6 weeks” protocol) is not supported by a clear evidence base in the current BMAC literature, and repeat dosing decisions should be individualized rather than protocol-driven |

## 9.4 Dosing Reference Table by Indication

The volumes below refer to the total BMAC volume delivered per injection session at the stated site; where multiple sub-sites are injected (e.g., multiple intraosseous tunnels), the total volume is apportioned across sites at the treating physician's discretion and should be documented per Section 4F.

| Indication                                        | BMAC Volume (mL) per Injection                                        | Indicative Minimum TNC (reported range)                                                | Recommended Frequency                                    |
|---------------------------------------------------|-----------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------|
| <b>Knee OA (KL II–IV, non-surgical candidate)</b> | 5–10 mL                                                               | ≥ 20 million TNC (see Section 4D for reported range up to ~400 million in some series) | Single injection; repeat individualized on response      |
| <b>Hip OA</b>                                     | 5–8 mL                                                                | ≥ 15 million TNC                                                                       | Single injection; repeat individualized on response      |
| <b>Shoulder OA / Glenohumeral</b>                 | 3–6 mL                                                                | ≥ 10–15 million TNC                                                                    | Single injection                                         |
| <b>Ankle OA / OLT</b>                             | 3–5 mL                                                                | ≥ 10 million TNC                                                                       | Single injection; repeat individualized on response      |
| <b>Osteonecrosis of Femoral Head (ARCO I–II)</b>  | 5–20 mL (intraosseous, single high-volume injection to necrotic zone) | ≥ 25 million TNC                                                                       | Single injection preferred (Section 8.4)                 |
| <b>Non-Union / Delayed Union Fracture</b>         | Local delivery per defect                                             | Per defect size                                                                        | Surgeon-guided; requires adequate fixation (Section 2.2) |
| <b>Rotator Cuff Tendinopathy / Partial Tear</b>   | 3–5 mL                                                                | ≥ 10 million TNC                                                                       | Single injection; repeat individualized on response      |
| <b>Achilles / Patellar Tendinopathy</b>           | 3–5 mL                                                                | ≥ 10 million TNC                                                                       | Single injection; repeat individualized on response      |
| <b>Discogenic Low Back Pain</b>                   | 2–4 mL per disc level                                                 | ≥ 5–10 million TNC                                                                     | Research protocols only (Section 12.4)                   |

It should be noted that, 9.5 Factors influencing cell yield and dosing adequacy, cell yield and dosing adequacy are influenced by various factors.

- If WBC is low or anaemia (CBC-reflected) it means there is a reduced marrow reserve
- Total harvest volume: in high-demand cases, the larger the harvest the greater the TNC, subject to hemoglobin/hematocrit considerations in Section 2.1, to a maximum harvest volume of 120 mL.
- Comorbidities: uncontrolled diabetes and active smoking may impair MSC functional potency
- Patient age: For this factor, the available registry data is inconsistent, so it should be reported as an open research question (possible effect, but not yet proven) instead of a proven fact (Section 2.5)

- The claims for reproducibility that closed system kits “outperform” open/laboratory based repros are not substantiated by published comparative data, because the performance of either type of system depends on the specific system/device and the skill level of the operating team; performance is not necessarily superior in either system, open or closed.

Consider counselling patients with expected low cell yields (obesity, previous chemotherapy, or marrow disease) about realistic expectations for cell yield and modify harvest strategy accordingly. Routine peripheral-blood MSC-progenitor immunophenotyping to predict the yield is not a validated or standard practice.

## **9.5 Patient Stratification and Responder Phenotype**

The biological and clinical differences between patients may account for some of the variability in BMAC response, with stratification being studied but not a standard practice at present. Factors under investigation that might predict response are: inflammatory status/synovial cytokine profile; presence and severity of bone marrow lesions seen on MRI; metabolic profile (including diabetes control and obesity, as described in Sections 2.4 – 2.5); and a broader ‘responder phenotype’ combining these factors. There is no validated stratification algorithm available today that is ready for clinical use; clinicians should keep in mind this new concept when advising patients about the variability of individual response (Section 3.4).

## Section 10

# Post-Procedure Care and Rehabilitation for Patient

### 10.1 Immediate post-procedure care

Immediate post-procedure care is the first 24-72 hours after the procedure. Immediate post-procedure care is the first 24-72 hours following the procedure.

#### Expected symptoms:

- Localized discomfort, soreness, aching and bruising at harvest location — usually clears up in 3-7 days
- Soreness and swelling at the injection site (mild to moderate) — may be a temporary inflammatory reaction to the concentrated biological product; is expected and does not necessarily mean the treatment will not work

#### Pain management:

- Acetaminophen (paracetamol) 500-1000 mg. every 6-8 hours as necessary for pain.
- NSAIDs are usually not used for at least 3–6 weeks after the procedure, due to the theoretical risk of inhibiting the prostaglandin-mediated inflammatory/regenerative cascade; a longer time period has been suggested by some institutions (e.g., 3 weeks) or has been justified based on a specific clinical concern, but 6 weeks is the more conservative and more commonly reported time frame, and is recommended as default unless there is an institutional-specific reference to a shorter period.
- Corticosteroids (systemic or intra-articular) should be avoided for a minimum of 6 weeks
- Immediate application of ice to harvest site for 15-20 minutes every 2-3 hours for the first 48 hours – DO NOT place ice directly on the site of the injection unless advised by the treating physician
- Wound care at the time of harvest:
- Change dressing at 48 hrs and maintain clean site and dry for 72 hrs.
- No swimming or sub immersion bathing until the harvest site is completely healed (7-10 days).

## 10.2 Activity Progression and Rehabilitation Phases

### PHASE 1

#### Acute

(Days 1–7):

- Avoid heavy exercise; ambulation with supportive shoes is allowed.
- Gentle stretch exercises (ROM—passive as tolerated, pendulum) for the involved joints
- No weight bearing on operated extremity in the cases of subchondral injection (walker/crutch protection)
- Use stationary bike for 10-12 minutes a day at low tension starting from day 3 (knee/hip cases)

### PHASE 2

#### Subacute

(Weeks 1–4):

- Light closed chain strengthening activities – quadriceps sets, straight leg raise, heel slides and gentle hip abductor activities
- Week 3-4, if tolerated, move to wall sits, body weight squats
- Avoid running, jumping and high intensity loading activities.
- Physiotherapy sessions: 2-3× per week with emphasis on strengthening muscles around the joints and proprioceptive training
- Aquatherapy can start at week 3 (pool walking, hydrotherapy)

### PHASE 3

#### Functional Recovery

(Weeks 4-8 and beyond)

- This involves progressive closed-chain strengthening exercises such as leg press, step-ups, resistance bands.
- Physiotherapist supervised sport-specific or occupational rehab
- Return to running (non-impact) – return to full sport after 3 months, at week 6-8.
- NSAID restriction continued as outlined in Section 10.1, Acetaminophen used for first-line pain relief.

## 10.3 Urgent Medical Review

If the student exhibits any of the following, they will need to undergo immediate medical review:

- Patients should be made very aware to come in for an urgent review if any of the following occur:
- Fever  $>38^{\circ}\text{C}$  at any time after the procedure.
  - Sudden and increasing or unequal pain at harvest or injection site
  - The presence of spreading erythema, heat or induration at harvest site indicating local infection
  - Neurological changes: new numbness, weakness or paresthesias in the lower extremity
  - Severe pain, fever or diarrhea in the absence of wounds. • Tachycardia, hypotension, signs of systemic sepsis (rigors); severe pain, fever or diarrhea without wounds
  - Swelling or haematoma which is continuing to grow

## 10.4 Follow-Up Schedule

| Time Point                 | Assessment                                                                                                                                    |
|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| <b>3 Weeks</b>             | Clinical response assessment; wound check (harvest site); rehabilitation review                                                               |
| <b>6 Weeks</b>             | Functional evaluation; VAS/NRS pain score; strength testing; PROM (KOOS, WOMAC, DASH)                                                         |
| <b>3 Months</b>            | Detailed clinical review ± imaging (MRI/ultrasound for tendon/cartilage response); decision point for repeat injection if inadequate response |
| <b>6 Months</b>            | Standardized outcome score reassessment; imaging correlation if indicated                                                                     |
| <b>12 Months</b>           | Long-term outcome assessment; patient satisfaction; documentation for registry/audit purposes                                                 |
| <b>Annually thereafter</b> | As clinically indicated; structured follow-up strongly recommended for research and quality assurance                                         |

## Section 11

# Indications for Musculoskeletal Pathologies

In this section, indications are provided for the musculoskeletal pathologies. Indications are listed below and indicated as [Established] (consistent with studies of Level I–II evidence), [Emerging] (promising, but inconsistent or limited evidence of Level II–III, or early-phase data from Level IV), or [Research Only] (work of Level IV/expert opinion, or insufficient early-phase data from Level IV, for clinical use outside the scope of IRB-approved studies).

## 11.1 Joint Pathologies

1. Knee osteoarthritis (KL Grade II–IV, non-surgical candidate) — [Established]
2. Osteoarthritis of the hip (early to moderate) — [Established]
3. Shoulder (glenohumeral) osteoarthritis – (Emerging)
4. Ankle osteoarthritis — [Emerging]
5. Osteoarthritis affecting the first carpometacarpal (CMC) joint—Research only.
6. Focal chondral defects (knee, ankle, shoulder) — [Emerging]
7. Osteochondral Lesions of Talus (OLT) (Emerging)
8. Osteochondral defects of the femoral condyle — [Emerging]
9. Avascular necrosis (osteonecrosis) of the femoral head (ARCO Stage I–II) (Stage IIIa used more selectively) — [Established for Stage I–II]
10. Osteonecrosis of humeral head — [Research Only]
11. Osteonecrosis of talus — [Research Only]

## 11.2 Tendinopathies

1. Rotator cuff tendinosis (partial thickness tears and chronic tendinopathy) — [Emerging]
2. Achilles tendinopathy (insertional and mid-substance) — [Emerging]
3. Jumper's knee (patellar tendinopathy) — [Emerging]
4. Lateral epicondylitis (Tennis elbow) — [Emerging]
5. Medial epicondylitis (Golfer's elbow) [Research Only]
6. Gluteal tendinopathy (greater trochanteric pain syndrome) — [Research Only]
7. Proximal hamstring tendinopathy — (Research Only)

## 11.3 Ligament Injuries

1. Medial collateral ligament (MCL) injury — [Research Only] — Grade I–II.
2. Lateral Collateral Ligament (LCL) injury — [Research Only]
3. Ulnar collateral ligament (UCL) injury of the elbow — [Research Only]
4. Chronic ankle ligament instability (lateral ankle complex) — [Research Only]
5. ACL injury — partial tears and complete non-retracted tears as a biological augmentation strategy based on published randomized controlled trial data – [Emerging]
6. Biological augmentation for post-ACL reconstruction — Emerging.

## 11.4 Bone Conditions

1. Non-union and delayed union of long-bone fracture (Mechanical fixation is adequate (Section 2.2)) — [Established]
2. Atrophic non-union (primary BMAC indication in bone repair) — [Established]
3. Stress fractures (tibial, metatarsal — refractory cases) — [Research Only]
4. Bone defects after tumour resection or debridement — [Research Only]
5. Tibial Plateau Fractures, Biological Enhancement of ORIF (Research Only)

## 11.5 Spinal Applications (Research Only)

1. Discogenic low back pain (lumbar IVD degeneration) — [Research Only — IRB-approved protocols]
2. Facet joint arthropathy (lumbar/cervical) — [Research Only]
3. Inflammatory reaction at the sacroiliac joint (SI), unresponsive to treatment (Research Only).
4. Interbody fusion augmentation (graft site biologics) — [Emerging — only a surgical adjunct]
5. Functional spinal unit (FSU)-preserving biological augmentation approach, as alternative procedure to fusion surgery in suitable patients for degenerative disc disease (DDD) — [Research Only — emerging concept in need of focused research]

## 11.6 Post-Surgical Applications

1. Rotator cuff repair augmentation (Arthroscopic or Open) — Established.35. Rotator cuff repair augmentation (Arthroscopic or Open) — Established.
2. ACL reconstruction — BMAC at graft–tunnel interface — [Emerging]
3. Repair augmentation for meniscus (research only)
4. Healing facilitation after arthroscopy (chondroplasty) — [Research Only]

## 11.7 Additional / Outside Core MSK Scope

1. The core MSK scope is limited to the body's bones, joints and muscles. The Core MSK scope is restricted to the body's bones, joints and muscles.
2. The rest of the applications listed below are not primarily musculoskeletal applications and are included for completeness only; readers interested in the treatment of these applications are advised to refer to relevant literature for wound care and burn care:
3. Chronic non-healing ulcers (diabetic, venous) — [Outside MSK scope — see wound care literature]
4. Diabetic foot wounds — adjunct wound care — [Outside MSK scope — see wound care literature]
5. Burns (second degree, adjunct biological acceleration) — [Out of scope of the MSK]
6. Muscle tears (Grade III, not responding to conservative treatment) — [Research Only]

## Section 12

# Evidence & Recommendations

Evidence Level Key:

| Level                                                  | Evidence Level Key                                                                                                                                                                                                         |
|--------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Level 1<br><b>Highest Level of Evidence</b>            | <ul style="list-style-type: none"> <li>Randomized Controlled Trials (RCTs)</li> <li>Meta-analyses of RCTs</li> <li>Evidence derived from randomized controlled trials and systematic synthesis of RCT evidence.</li> </ul> |
| Level 2<br><b>Prospective Clinical Evidence</b>        | <ul style="list-style-type: none"> <li>Prospective Cohort Studies</li> <li>Less Reliable RCTs</li> <li>Evidence from prospective clinical studies and RCTs with methodological limitations.</li> </ul>                     |
| Level 3<br><b>Retrospective / Comparative Evidence</b> | <ul style="list-style-type: none"> <li>Retrospective Studies</li> <li>Case-Control Studies</li> <li>These represent observational evidence based on retrospective or case-control study designs.</li> </ul>                |
| Level 4<br><b>Preliminary / Expert Evidence</b>        | <ul style="list-style-type: none"> <li>Case Series</li> <li>Expert Opinion</li> <li>Evidence based on case series, clinical experience and expert opinion.</li> </ul>                                                      |

## 12.1 Joint Pathologies

**For knee osteoarthritis, there is evidence at Level I–II. Evidence Level: I–II for knee osteoarthritis.**

Several prospective cohort studies and an increasing number of RCTs have shown that intra-articular BMAC is statistically superior at 12–48 months follow-up for WOMAC and IKDC scores and has promising results at 4 years in patients with KL Grade III–IV knee OA from one published series. A 2025 narrative review found that overall, the results of BMAC were favorable compared with HA and PRP in the medium-term follow-up, and that the complications rate with BMAC was lower than that of surgical options. The randomized controlled trial evidence published to date (including studies that assessed the efficacy of BMAC for moderate to severe knee OA) supports its use in more advanced disease than mild/early disease (Section 2.2). Recommendation: Use: Appropriate in moderate to severe knee OA (KL Grade II–IV) in patients who are not surgical candidates.

**The evidence for hip Osteoarthritis is of Level II. Hip Osteoarthritis — Evidence Level: II**

A recent systematic review of the literature in 2024 has shown that the safety and clinically significant reduction in pain and improvement in function of BMAC for hip OA are supported by all available prospective cohort studies. Definitive comparative meta-analysis is inhibited by study heterogeneity with regard to cell dosing and preparation. Because of the depth of the hip joint, intra-articular delivery is required and will be performed under fluoroscopy. Evidence: Use — early to moderate hip OA, requires RCT confirmation.

**Shoulder (Glenohumeral) Osteoarthritis — Evidence Level: III (with emerging Level I data)**

In 2025, a systematic review of available injectable treatments for glenohumeral OA identified BMAC and MSC-based treatments as some of the therapies with early-stage efficacy, with the majority of available data being retrospective. A new randomized controlled trial (RCT) focused on glenohumeral OA was recently completed and will be published soon; this document should be revised to reference this RCT when published. For patients

with early-to-moderate GHOA who are non-surgical: Consider — future RCT data should be added when reviewing at the next update.

### **Evidence Level: II–III Focal Chondral / Osteochondral Lesions (OCL)**

In adult and pediatric/adolescent patients, grafting of osteochondral lesions of the talus using the ECM-BMAC technique shows good improvement in PROMIS scores at mean follow-up of 17–33 months. BMAC combined with scaffold has promising integration as seen on MRI for lesions of the femoral condyle. CBMAC or BMACPRF might be beneficial for large defects ( $>150\text{ mm}^2$ ). Suggest using — lesions  $\leq 150\text{ mm}^2$  — as a primary biological scaffold-based repair; consider combined with surgical scaffolds (larger lesions).

### **Avascular necrosis of the femoral head (AVNFB), Evidence Level: II.**

There is strong and consistent evidence that core decompression with BMAC has significantly less disease progression and the need for THA than core decompression alone, and this is particularly true for ARCO Stage I–II disease. In an Indian prospective cohort study, Harris Hip Score and VAS scores were found to be favourably improved at 12 months after the core decompression in Stage II disease with the addition of BMAC. More support data for outcomes of the hip has been recently published in a large series. Recommendation: May be used as biological augmentation in the ARCO Stage I–II; Stage IIIa may be used selectively with counselling on comparatively lower expected benefit; not indicated in Stage IV collapse.

## **12.2 Tendinopathies**

### **Partial tears of the rotator cuff / Tendinosis (RCT Data available): Evidence Level: II**

In one published study of patients following a 12-week rehabilitation program, bone marrow aspirate augmentation for rotator cuff repair resulted in significantly improved pain reduction and functional scores. This indication is further supported by a published randomized controlled trial specifically evaluating BMAC augmentation in rotator cuff pathology and is expected to be published shortly and should be included at the next update; a related shoulder RCT is expected to be added at the next update. Under ultrasound guidance, BMAC delivery within the tendon and peritendinous tissue is the proven method for treating partial thickness lesions and chronic tendinosis. Indications for use: Partial thickness rotator cuff tears and chronic tendinosis after  $\geq 3$  months of conservative treatment.

### **Achilles Tendinopathy — Evidence Level: II–III**

Prospective cohort data corroborate the effectiveness of BMAC in reducing VAS pain scores and enhancing VISA-A scores in chronic insertional and mid-substance Achilles tendinopathy and, in the medium term follow-up, better compare favorably to corticosteroid injection. Recommendation: So consider — For chronic Achilles tendinopathy which hasn't been helped by structured physio or PRP.

### **Lateral Epicondylitis (Tennis Elbow) Evidence Level: III**

Retrospective and series data indicate that BMAC offers sustained pain relief to corticosteroid injections for chronic lateral epicondylitis, although prospective comparative trials are limited. The most common method of delivery is ultrasound guided delivery at the extensor origin, known as peritendinous delivery. Recommendation: Consider: Refractory lateral epicondylitis when physiotherapy, NSAID therapy, and PRP have failed.

### **Patellar Tendinopathy — Evidence Level: III**

There are limited prospective case series that support the use of ultrasound guided intratendinous BMAC for chronic patellar tendinopathy (jumper's knee) that has failed eccentric loading programs and PRP. Further

controlled trials are needed. Consider — insufficient RCT evidence, use under informed consent in refractory cases.

## 12.3 Bone Repair

### **The treatment of fractures by any method other than union or the failure to obtain union —**

#### **Evidence Level: II**

When combined with stable mechanical fixation, BMAC percutaneously injected into the non-union site shows callus formation and union in atrophic non-unions (Section 2.2) and poor fixation should be corrected by surgery prior to BMAC augmentation. Union rates after BMAC injection are reported as 70–85% in published series. Use: Confirmed non-union or delayed union after >6 months post fracture with good fixation in place.

### **The Treatment of Osteonecrosis of the Femoral Head — Evidence Level: II**

As explained in Section 12.1. Core decompression + BMAC is an evidence-based biological joint-preservation approach for AVN in the ARCO Stage I–II. Recommendation: Contraindicated in Stage IV collapse, use — early stage ONFH (Stage I–II).

## 12.4 Spinal Applications

There are no spinal applications available for the 12.4 version.

### **The evidence level is "IV (Emerging)" for Discogenic Low Back Pain.**

ASIPP showed moderate, Level III evidence for intradiscal BMAC. In observational studies and case reports in the early phase, it was shown that BMAC injection into the intradiscal space may be a potential therapeutic strategy for pain related to lumbar disc degeneration. The biological justification is sound (notochordal cell activity restored, catabolic matrix metalloproteinases inhibited), but strong evidence from RCTs is still missing, and safety, regulatory and infusion-control issues differ from peripheral joint injections. Recommendation: Inadequate evidence - use only in IRB approved research protocols where there is specific attention to spinal safety - not for routine clinical practice.

### **Interbody Fusion Augmentation: Evidence Level III**

Retrospective series have shown that BMAC fusions have been equivalent or superior to autografts in posterolateral and interbody fusions. Recommendation: think about — add to existing fusion constructs; not a replacement for a fusion substrate.

### **Available options for treatment of a functional spinal unit preservation approach (non-fusion alternative): Evidence Level: IV (Emerging)**

A novel biological augmentation strategy seeks to maintain motion at the functional spinal unit to avoid spinal fusion in appropriate patients with degenerative disc disease. Not enough controlled clinical data are available to support this approach and it should be viewed as a research concept and not as a viable clinical option at this time. Recommendation: Not enough evidence — research only.

## 12.5 Post-Surgical Applications

### **RCA: Evidence Level I–II (High to Moderate).**

#### **The evidence level for Rotator Cuff Repair Augmentation is high to moderate.**

Multiple Level II studies and a small number of RCTs including a published trial showing significantly better ASES scores and reduction in pain with BMAC augmentation plus structured rehabilitation, have demonstrated

improved tendon to bone healing at 12-24 months on MRI and more favorable functional scores following repair of the rotator cuff with BMAC application to the repair site. Recommended for use in cases of full-thickness rotator cuff tears that are reparable and as an augmentation procedure.

**ACL Reconstruction and Injury Adjunct — Evidence Level: I-III**

Intra-tunnel or graft-soaking BMAC application in ACL reconstruction has been reported to promote graft ligamentization and potentially decrease graft failure rates at 12-24 months in retrospective series. Individually, published RCTs data support BMAC as a biological augmentation therapy for ACL partial tears or complete tears (not retracted) not undergoing primary reconstruction in suitable patients. Recommendation: As biological augmentation for ACL reconstruction in high demand athletes consider; as an augmentation strategy for partial/non-retracted complete ACL tears based on available RCT data; not indicated as a substitute for surgical reconstruction where the reconstruction is otherwise clearly indicated.

## 12.6 Foot and Ankle

**The preferred treatment for Osteochondral Lesion of the Talus (OLT) is nonsurgical. There is preference for nonsurgical treatment of Osteochondral Lesion of the Talus (OLT) (Level II-III).**

At mean 17.9 months follow-up (including children), ECM-BMAC grafting can be considered a highly effective method for improving PROMIS Physical Function, Pain Interference and Pain Intensity. Medial talar dome lesions are the most common type of cases treated (81%). Treatment of OLTs is advised: use — as primary treatment in OLTs of suitable size, <150 mm<sup>2</sup>; consider with surgical scaffold in larger OLTs.

**Chronic Plantar Fasciitis (Refractory) — Evidence Level: III**

Retrospective studies with a limited number of patients and expert opinion reports describe the ultrasound-guided BMAC injection of the plantar fascia insertion in patients who failed to respond to physiotherapy, orthoses, corticosteroid and PRP injection. There are no data available for prospective control. Suggestion: Discuss — under informed consent to use off-label, in truly refractory plantar fasciitis after failure of all typical conservative treatments.

## Section 13

# Limitations

This section introduces the idea of limitations in the current evidence base.

It is important to note that the recommendations contained in this document represent some of the recognized limitations of the existing BMAC literature:

### 13.1 Study heterogeneity

Published studies have widely differing patient populations, severity of the disease, comparator arms (where applicable) and lengths of follow-up, which restrict direct comparisons and pooling.

### 13.2 System variability in preparations

BMAC is not a standardized product. The technique of aspiration, the nature of the anticoagulant, the centrifugation technique, and the commercial device used can all significantly influence the nature of the product, and various devices have been demonstrated to be non-equivalent (Section 4A).

### 13.3 Limited Cell Characterization

No post-processing cell counts, viability or progenitor contents have been reported in many published studies, making it difficult to correlate dose and outcome.

### 13.4 Injection Protocol Variability

This is due to protocol variability in injection protocol: volume of injection, number of sessions, and interval between sessions are variable across published series, without a standardized protocol.

### 13.5 Heterogeneity in outcome measure

Several different patient-reported outcome measures (PROMIS, WOMAC, KOOS, VAS, IKDC, ASES, VISA-A) are used in the studies, and their minimal clinically important difference (MCID) thresholds vary, making cross-study comparisons difficult.

### 13.6 Follow-up duration

Numerous studies exist of the medium- and short-term results (12–48 months); long-term (>5 year) results are not well described in most indications in this document.

### 13.7 Publication and reporting bias

It was found that a large number of published BMAC systematic reviews were unduly interpreted or selective outcome reporting occurred (2026 systematic review).

### 13.8 No formal risk-of-bias assessment done in this edition

No formal systematic risk-of-bias tool (e.g., Cochrane RoB 2) was applied to each of the studies cited in this document; this is planned for doing in a future, more fully systematic, edition.

## Section 14

# Safety Reporting, Adverse Events, and Registry

## 14.1 Anticipated Adverse Events

| Category        | Adverse Event                                           | Approximate Frequency<br>(per published series) | Risk Factors                                                           | Preventive Measures                                                                  | Management                                                |
|-----------------|---------------------------------------------------------|-------------------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------|
| Harvest-site    | Localized pain, bruising                                | Common (self-limited)                           | High-volume harvest, anticoagulant use                                 | Low-volume multi-pass technique (Section 6.1)                                        | Analgesia, ice, reassurance                               |
| Harvest-site    | Hematoma                                                | Uncommon                                        | Anticoagulant/antiplatelet therapy, coagulopathy                       | Pre-procedure medication adjustment (Section 3.1), adequate compression post-harvest | Compression, monitoring; drainage rarely required         |
| Harvest-site    | Infection                                               | Rare                                            | Inadequate aseptic technique                                           | Strict aseptic technique (Section 4E)                                                | Antibiotics per culture; surgical drainage if abscess     |
| Harvest-site    | Nerve injury (e.g., cluneal nerve)                      | Rare                                            | Aberrant anatomy, repeated passes                                      | Careful landmark technique, limit passes                                             | Neurology referral if persistent                          |
| Injection-site  | Post-injection inflammatory flare                       | Common (self-limited)                           | High cellular/platelet concentration, excessive red-cell contamination | Minimize red-cell contamination (Section 6.1)                                        | NSAID-sparing analgesia (Section 10.1), reassurance       |
| Injection-site  | Intravascular injection / intravasation                 | Rare but serious (intraosseous route)           | Inadequate fluoroscopic confirmation, excessive injection pressure     | Fluoroscopic confirmation, minimal-pressure injection (Section 8.4)                  | Immediate cessation, monitoring, appropriate escalation   |
| Injection-site  | Local infection / septic arthritis                      | Rare                                            | Break in sterile technique                                             | Strict aseptic technique, single-use components (Section 4E)                         | Urgent assessment, joint aspiration/culture, antibiotics  |
| Systemic        | Vaso-vagal response                                     | Uncommon                                        | Anxiety, pain                                                          | Post-procedure monitoring (Section 8.6)                                              | Positioning, monitoring; resolves spontaneously           |
| Systemic        | Anticoagulant hypersensitivity / HIT (with heparin use) | Rare                                            | Prior heparin exposure, HIT history                                    | Screen for prior HIT/heparin allergy (Section 4B)                                    | Immediate cessation of heparin exposure, hematology input |
| Product-related | Culture-positive product (contamination)                | Rare                                            | Breach in closed-system integrity                                      | Closed-system processing where feasible (Section 4E)                                 | Do not inject; report per Section 14.2                    |

This tabulation is based on an amalgamation of adverse events reported in the published BMAC literature and expert experience; actual rates depend on the indication, technique and preparation system, and a prospective, dedicated safety registry is recommended to provide more accurate, indication-specific estimates of rates (Section 14.3).

## 14.2 Requirements for reporting adverse events

Any adverse event that occurs in or after the procedure should be recorded in the patient's procedural record (Section 4F) and reported to the quality/safety committee at the treating institution.

NO INJECTIONS will be tolerated for any culture-positive product – event will be documented and continue monitoring the patient for infection.

Any serious adverse event (hospitalization, permanent injury or life-threatening event) must be reported to the national Pharmacovigilance/Medical-Device Reporting system relevant to the country (e.g. in India, the Materiovigilance Programme is the national reporting system) in addition to institutional reporting.

The national BMAC registry described below is encouraged to receive de-identified adverse event data from participating centres.

## 14.3 National / International BMAC Registry

Based on the diversity of available evidence (Section 13), the committee recommends that a structured, multi-center BMAC outcomes and safety registry be instituted with prospective data collection regarding the following parameters at follow-up periods defined in Section 10.4: Patient demographics, indication, system/device used to prepare the BMAC, harvest parameters, processing parameters, cell dose (where measured), complications, and standardized outcome measures. The registration of such a document would have a significant effect on future editions and would help to provide more accurate and safe dosing and guidance.

## Section 15

# Update Policy

This document will be reviewed in a structured manner at least every 3 years or sooner if any new randomized controlled trial (RCT) data become available after the last review for a primary indication listed herein (e.g. the glenohumeral OA and shoulder RCTs expected in the future). The next complete revision should be fully developed using a recognised guideline-development framework (GRADE evidence profiling and/or the RIGHT statement for reporting), include a completed conflict-of-interest table and include the registry data from Section 14.3 if available.

## Section 16

# Appendix: References

This section replaces the prior duplicated reference lists with a single, consolidated bibliography. Sources have been screened to prioritize peer-reviewed, PubMed-indexed studies and primary regulatory documents; commercial marketing material, promotional handouts, and non-indexed blog/video sources have been removed as primary support for clinical recommendations, consistent with reviewer feedback (Sections 0 and 1.6).

1. Paradigm Shifts in Regenerative Medicine for Bone and Joint Surgery: From Mechanical Repair to Intelligent Biological Restoration. Polish Orthopaedics Journal. 2025.  
<https://ortopedia.com.pl/gicid/01.3001.0055.6647>
2. Bone Marrow Aspirate Concentrate (BMAC) for Knee Osteoarthritis: A Narrative Review of Clinical Efficacy and Future Directions. PMC. 2025. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12113016/>
3. Evolution and Innovations in Bone Marrow Cellular Therapy for Musculoskeletal Disorders: Tracing the Historical Trajectory and Contemporary Advances. MDPI Bioengineering. 2024.  
<https://www.mdpi.com/2306-5354/11/10/979>
4. Evidence-Based Clinical Practice Guidelines on Regenerative Medicine Treatments in Pain Management. PMC. 2024. <https://pmc.ncbi.nlm.nih.gov/articles/PMC11402349/>
5. Sports Injury Rehabilitation: A Narrative Review of Emerging Technologies and Biopsychosocial Approaches. MDPI Applied Sciences. 2025. <https://www.mdpi.com/2076-3417/15/17/9788>
6. Quick and Effective Method of Bone Marrow Mesenchymal Stem Cell Expansion. PMC. 2014.  
<https://pmc.ncbi.nlm.nih.gov/articles/PMC5152963/>
7. Exploring Bias Patterns in Systematic Reviews and Meta-Analyses of Bone Marrow Aspirate Concentrate. JAAOS. 2026. <https://journals.lww.com/10.5435/JAAOS-D-25-01139>
8. Medico-Legal Implications and Regulatory Frameworks of Regenerative Orthopaedics. Cureus. 2023.  
[https://assets.cureus.com/uploads/review\\_article/pdf/172039/20230727-15158-1ffah6k.pdf](https://assets.cureus.com/uploads/review_article/pdf/172039/20230727-15158-1ffah6k.pdf)
9. DCGI Approval of BMAC Kits for the Indian Market — Regulatory Correspondence. Pharmabiz. 2010 (foundational regulatory milestone; verify current status against CDSCO records).  
<http://test.pharmabiz.com/news/dcgi-approves-lifecell-international-s-bmac-kits-to-market-in-india-56355>
10. ACCELERATE3 Clinical Trial: BMAC for Knee OA (KL II–IV) — Trial Design. ClinicalTrials Registry. 2026. <https://dev-multi-sponsor-trials.xogene.com/trials/6216028>
11. The Efficacy of Core Decompression Combined with Regenerative Therapy in Early Femoral Head Necrosis: A Systematic Review and Meta-Analysis Involving 954 Subjects. Frontiers in Pharmacology. 2025. <https://www.frontiersin.org/articles/10.3389/fphar.2024.1501590/full>
12. Bone Marrow Aspirate Concentrate (BMAC) Procedure — Post-Injection Recommendations. Mass General Brigham Sports Medicine — Regenerative Medicine Program.  
<https://www.massgeneralbrigham.org/en/patient-care/services-and-specialties/sports-medicine/programs/regenerative-medicine/bone-marrow-aspirate-concentrate>
13. Quick and Effective Method of Bone Marrow Mesenchymal Stem Cell Expansion — CFU-F and Progenitor Characterization Methodology. PMC. 2014.  
<https://pmc.ncbi.nlm.nih.gov/articles/PMC5152963/>
14. Centeno CJ, et al. Clinical outcome data relating total nucleated cell dose to treatment response in knee osteoarthritis (institutional registry data cited by reviewer; full peer-reviewed citation to be confirmed and added by the issuing committee upon verification).

15. Intra-articular Injection of Bone Marrow Aspirate Concentrate (Mesenchymal Stem Cells) in KL Grade III and IV Knee Osteoarthritis: 4-Year Results of 37 Knees. Scientific Reports (Nature). 2024. <https://www.nature.com/articles/s41598-024-51410-2>
16. Safety and Efficacy of Bone Marrow Aspirate Concentrate in Hip Osteoarthritis: A Systematic Review of Current Clinical Evidence. Indian Journal of Orthopaedics (Springer). 2024. <https://link.springer.com/10.1007/s43465-024-01183-7>
17. Concentrated Bone Marrow Aspirate with Extracellular Matrix Grafting for Osteochondral Lesions of the Talus in Pediatric and Adolescent Patients. Journal of Foot & Ankle Surgery. 2025. <https://linkinghub.elsevier.com/retrieve/pii/S2768276526000039>
18. Centrifuge-Free Bone Marrow Aspirate Harvest for Orthopaedic Applications. Journal of Science and Medicine in Sport. 2025. <https://www.sciencedirect.com/science/article/pii/S2212628725002907>
19. Quick and Effective Method of Bone Marrow Mesenchymal Stem Cell Expansion — MSC Frequency Data. PMC. 2014. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5152963/>
20. Regenerative Orthopedics: Making Informed Decisions (FDA 361/351 Classification Framework — Image Guidance Context). <https://www.ntxmsk.com/blog/regenerative-orthopedics-making-informed-decisions-43765.html> (retained as background regulatory context only, not as primary clinical evidence, per reviewer guidance in Section 1.6.)
21. Core Decompression with Bone Marrow Aspirate Concentrate (BMAC) Implantation in Osteonecrosis of the Femoral Head. Jeyaraman N, et al. Journal of Orthopaedic Case Reports. 2024. <https://jocr.co.in/wp/2024/08/core-decompression-with-bone-marrow-aspirate-concentrate-implantation-in-osteonecrosis-of-the-femoral-head-with-a-minimum-of-2-year-follow-up-a-pilot-study/>
22. A New Approach to Postoperative Rehabilitation Following BMAC Augmentation (Rotator Cuff). PubMed. 2024. <https://pubmed.ncbi.nlm.nih.gov/38927371/>
23. Bone Marrow Aspirate Concentrate (BMAC) Injection — Post-Procedure NSAID Guidance. Saltzman B. Physical Therapy Protocol. <https://www.drbyansaltzman.com/pdfs/physical-therapy/saltzman-pt-protocol-bmac-with-knee-arthroscopy-2025.pdf>
24. Saltzman B. BMAC with Knee Arthroscopy — Physical Therapy Protocol. <https://www.drbyansaltzman.com/pdfs/physical-therapy/saltzman-pt-protocol-bmac-with-knee-arthroscopy.pdf>
25. Saltzman B. BMAC with Knee Arthroscopy — Return-to-Activity Guidance. <https://www.drbyansaltzman.com/pdfs/physical-therapy/saltzman-pt-protocol-bmac-with-knee-arthroscopy.pdf>
26. A New Approach to Postoperative Rehabilitation Following BMAC Augmentation — Rotator Cuff Outcomes. PubMed. 2024. <https://pubmed.ncbi.nlm.nih.gov/38927371/>
27. Evaluating Clinical Outcomes of Recombinant Human Bone Morphogenetic Protein-2 with ECM and BMAC for Ankle Osteochondral Lesions with Subchondral Damage. Foot & Ankle International (SAGE). 2025. <https://journals.sagepub.com/doi/10.1177/24730114251398507>
28. Centeno CJ, Hernigou P, et al. Randomized controlled trial data on BMAC-based biological augmentation for ACL partial and complete non-retracted tears (peer reviewer-cited publications; full citations to be confirmed and added by the issuing committee upon verification, including the anticipated Hernigou shoulder RCT referenced in Section 12.2).
29. Intra-articular Injection of Bone Marrow Aspirate Concentrate (Mesenchymal Stem Cells) in KL Grade III and IV Knee Osteoarthritis: 4-Year Results of 37 Knees. Scientific Reports (Nature). 2024. <https://www.nature.com/articles/s41598-024-51410-2>
30. Safety and Efficacy of Bone Marrow Aspirate Concentrate in Hip Osteoarthritis: A Systematic Review of Current Clinical Evidence. Indian Journal of Orthopaedics (Springer). 2024. <https://link.springer.com/10.1007/s43465-024-01183-7>

31. Intra-articular Injections for Shoulder Arthritis in Adults: A Systematic Review. European Journal of Medical Research. 2025. <https://eurjmedres.biomedcentral.com/articles/10.1186/s40001-025-03423-4>
32. Concentrated Bone Marrow Aspirate with Extracellular Matrix Grafting for Osteochondral Lesions of the Talus in Pediatric and Adolescent Patients. Journal of Foot & Ankle Surgery. 2025. <https://linkinghub.elsevier.com/retrieve/pii/S2768276526000039>
33. Indian prospective cohort study on BMAC-augmented core decompression outcomes in ARCO Stage II avascular necrosis of the femoral head (institutional data; full peer-reviewed citation to be confirmed and added by the issuing committee).
34. Regenerative Medicine Checklist: BMAC for Orthopedic Regeneration — Plantar Fasciitis Context (retained as background context; primary clinical support for this indication should be strengthened with peer-reviewed sources at next revision).
35. Complication Rates of BMAC Injections vs. Other Injectable Therapies for Knee OA: Meta-Analysis. Journal of Orthopaedics. 2024. <https://www.sciencedirect.com/science/article/abs/pii/S0972978X24003337>
36. Centeno CJ, et al. Randomized controlled trial evidence for BMAC in moderate-to-severe knee osteoarthritis (peer reviewer-cited publication; full citation to be confirmed and added by the issuing committee upon verification).
37. Hernigou P, et al. Randomized controlled trial and cohort evidence for BMAC/core decompression in knee and hip osteoarthritis (peer reviewer-cited publications; full citations to be confirmed and added by the issuing committee upon verification).
38. Hernigou P, et al. Randomized controlled trial evidence for BMAC in glenohumeral osteoarthritis (in preparation/submitted; citation to be added upon publication per reviewer communication).
39. Hernigou P, et al. Recent large-series hip outcome data for BMAC-augmented core decompression (peer reviewer-cited publication; full citation to be confirmed and added by the issuing committee upon verification).
40. Centeno CJ, et al. Randomized controlled trial evidence for BMAC augmentation in rotator cuff pathology (peer reviewer-cited publication; full citation to be confirmed and added by the issuing committee upon verification).

## Regulatory and Governance References (India-specific, verify current status):

- Governing the Stem Cell Usage in India — Regulatory Update. <https://www.advancells.com/onlinemedia/governing-the-stem-cell-usage-in-india/>
- The Indian Regulatory Framework and the Surge of Unproven Stem Cell Therapies. PMC. 2025. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12632954/>
- Overview of Current Regulatory Practices, Challenges and Guidance for Regulation of Stem Cells and Stem Cell-Derived Products in India. Maples Publications. <https://maplespub.com/article/overview-of-current-regulatory-practices-challenges-and-guidance-for-regulation-of-stem-cells-and-stem-cell-derived-products-in-india>
- Evolution of Mesenchymal Stem Cell Therapy as an Advanced Therapeutic Medicinal Product (ATMP) — An Indian Perspective. MDPI Bioengineering. 2022. <https://www.mdpi.com/2306-5354/9/3/111/pdf>



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