National Institute for Health and Care Excellence

1098/1 – Microstructural scaffold (patch) insertion without autologous cell implantation for repairing symptomatic chondral knee defects

Consultation Comments table

IPAC date: Thursday 14th April 2016

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Company Finceramica Faenza	**General**	We have been informed about the consultation document GID-IPG10004 on *"Microstructural scaffold (patch) insertion without autologous cell implantation for repairing symptomatic chondral knee defects".* With regard to such document, we'd like to inform you that the ongoing "Multicenter Randomized Controlled Trial for the Treatment of Knee Chondral and Osteochondral Lesions: Marrow Stimulation Techniques vs MaioRegen" is about to be completed. The final report is likely to be available by the end of May 2016. Considering that the RCT results will be critical for your assessment, we kindly ask you to postpone its deadline in order to include the Study results.	Thank you for your comment. The Committee is aware about this ongoing study (NCT01282034 –included in the overview) which is due to be completed by May 2016. Normally efficacy data from unpublished or non-peer reviewed studies are not considered. Only relevant papers that are accepted for publication are included provided that the publication date is before the guidance is published (June 2016).

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2	Consultee 2 Professional Organization International Cartilage Repair Society	**General**	Numerous surgical approaches have been proposed over the years to treat chondral and osteochondral lesions. Currently, the standard treatment for end-stage degenerative joint pathology is total joint replacement, a successful procedure in older population but unsuitable in younger active high physical demand patients. Early surgical intervention for symptomatic cartilage lesions, as bone marrow stimulation techniques, have been suggested to provide a clinical benefit and slow down further joint deterioration but often result in lesser structural quality and biomechanical properties compared to native tissue which reduce the durability of the clinical results [1,2] The limitations of this surgical approach are further amplified in the Early Osteoarthritis setting where older patients with degenerative lesions showed even less satisfactory results. Also a recent survey evaluating orthopaedic surgeons' advice in the management of younger (< 60 years old) physically active Early Osteoarthritis patients has highlighted a treatment gap for this pathology which cannot be properly addressed neither by bone marrow stimulation technique nor by UKA or TKA[3]. The use of biomaterials to favor the regeneration of articular defects has become popular in the last decades, showing promising results initially in combination with autologous chondrocytes[4]. Chondral scaffolds are usually monophasic, collagen or hyaluronic acid are currently applied cell-free as an augmentation for microfractures to stabilize the blood clot and favor the regenerative process. Promising clinical results have been obtained so far[5–14] and the number of published papers reporting short to mid-term follow-up is rapidly increasing[15].	Thank you for your comments. Consultee highlights about chondral and osteochondral treatments including bone marrow stimulation techniques and scaffold based repair. References listed by the consultee (8, 9 and13) are included in table 2 in the overview. Other related publications (references 5, 6, 10, 12, 14 and 15) are included in Appendix A of the overview. References 7, 11 are small studies related to this topic and have been added to Appendix A in the overview.

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3	Consultee 2 Professional Organization International Cartilage Repair Society	**General**	Further developments in this field have been provided by the increasing knowledge on the importance of the subchondral bone in the etiopathogenesis of degenerative lesions, which led to the development of targeted strategies to regenerate the entire osteochondral unit. New matrices with different layers to address both cartilage and subchondral bone have been developed and used in clinical practice. The clinical benefit of cell-free scaffold in the treatment of osteochondral lesions has been reported in several publications[16–27] and confirmed also in complex cases otherwise doomed to a poorer outcome with the other cartilage treatment procedures[16,23].	Thank you for your comment. Papers related to osteochondral lesions and complex large cases (references 21, 24 and 26) are included in table 2 in the overview. Other related publications (references 16, 18, 20, 22, 23, 25) are included in Appendix A of the overview. References 17, 19 and 11 are small studies related to this topic and have been added to Appendix A in the overview.

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4	Consultee 2 Professional Organization International Cartilage Repair Society	**1.1**	It is clear that long-term studies and also RCT comparing different techniques are needed to confirm the efficacy of cell-free scaffolds and further clarify the most appropriate clinical indications. It is also important to specify that several devices have been developed, with substantial differences regarding the material chosen and their intended use[29]. In this scenario, it is difficult to release a unique recommendation regarding the use of all scaffolds for cartilage and osteochondral repair. For our opinion, strong restriction in the use of these techniques will damage the possibility to perform further clinical research and also limit the patient's possibility to have access to the treatment for a pathology which actually doesn't present gold standard of treatment.	Thank you for your comment. Section 1.3 has been amended as follows: *NICE encourages further data collection, including randomised controlled trials on microstructural scaffold insertion without autologous cell implantation for repairing symptomatic chondral knee defects. Studies should clearly describe patient selection, clinical indications and adjunctive treatments. Outcome measures should include symptom relief, functional ability, long-term outcomes measured by appropriate imaging techniques and patient-reported outcomes.* A committee comment was added in section 6.1 as follows: *The committee was informed that there are several devices and substantial differences in the materials used.* Section 1.1 of the guidance states that the procedure should be used with 'special' arrangements in place. This means that clinicians

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4				using the procedure should inform the clinical governance lead in their trust, tell the patient about the uncertainties regarding the safety and efficacy of the procedure and collect further data by means of audit or research. The Committee recommends these arrangements when using a procedure because there are significant uncertainties in the evidence on efficacy or safety, or an inadequate quantity of evidence. The Committee may also consider the balance of risks and benefits of the procedure is such that special arrangements should be in place. This recommendation is often made when the procedure is considered to be emerging practice in the NHS.

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5	Consultee 2 Professional Organization International Cartilage Repair Society	**1.3**	The ICRS have taken steps to encourage responsible innovation by establishing a global ICRS registry of all non-arthroplasty cartilage injury and repair. The ICRS Registry has been developed in conjunction with the British company Amplitude who already run seven registries to standards consistent with UK guidance on information governance, consent and privacy. Cell-free scaffolds for cartilage repair could be entered into this registry for continuing independent monitoring of patient and device outcome. The Registry is free of charge to patients, surgeons and hospitals, and the anonymized data is owned and governed by the ICRS; a non-profit education and research society for the advancement of cartilage repair. The ICRS Registry will go live in September 2016. We expect the utilization of these devices to increase over time with proper identification of the best target population, thus we strongly encourage responsible innovation and close collaboration among clinicians, Scientific Societies, industry and Health Authorities to provide patients with the most suitable therapeutic solution.	Thank you for your comment. After reviewing and confirming that the global ICRS registry meets the criteria set by NICE, a committee comment was added in section 6.2 as follows: – *The committee was made aware of a register of all non-arthroplasty cartilage injury and repair that was being established by the International Cartilage Repair Society Registry. Clinicians are encouraged to submit data from appropriate patients to that register once it becomes available.*

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6	Consultee 2 Professional Organization International Cartilage Repair Society	**General**	**<u>References</u>** 1. Filardo, G., Kon, E., Roffi, A., Di Martino, A. & Marcacci, M. Scaffold-based repair for cartilage healing: a systematic review and technical note. *Arthrosc. J. Arthrosc. Relat. Surg. Off. Publ. Arthrosc. Assoc. N. Am. Int. Arthrosc. Assoc.* **29,** 174–186 (2013). 2. Angele, P. *et al.* Chondral and osteochondral operative treatment in early osteoarthritis. *Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA* (2016). 3. Li, C. S., Karlsson, J., WinemakerM., Sancheti, P. & Bhandari, M. Orthopedic surgeons feel that there is a treatment gap in management of early OA: international survey. *Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA* **22,** 363–378 (2014). 4. Filardo, G., Kon, E., Roffi, A., Di Martino, A. & Marcacci, M. Scaffold-Based Repair for Cartilage Healing: A Systematic Review and Technical Note. *Arthrosc. J. Arthrosc. Relat. Surg.* **29,** 174–186 (2013). 5. Schiavone Panni, A., Cerciello, S. & Vasso, M. The manangement of knee cartilage defects with modified amic technique: preliminary results. *Int. J. Immunopathol. Pharmacol.* **24,** 149–152 (2011). 6. Dhollander, A. a. M. *et al.* Autologous matrix-induced chondrogenesis combined with platelet-rich plasma gel: technical description and a five pilot patients report. *Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA* **19,** 536–542 (2011). 7. Dhollander, A. a. M. *et al.* The combination of microfracture and a cell-free polymer-based implant immersed with autologous serum for cartilage defect coverage. *Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA* **20,** 1773–1780 (2012).	Thank you for your references. Please see response to comment 2.

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7	Consultee 2 Professional Organization International Cartilage Repair Society	**General**	8. Gille, J. *et al.* Mid-term results of Autologous Matrix-Induced Chondrogenesis for treatment of focal cartilage defects in the knee. *Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA* **18,** 1456–1464 (2010). 9. Kusano, T. *et al.* Treatment of isolated chondral and osteochondral defects in the knee by autologous matrix-induced chondrogenesis (AMIC). *Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA* **20,** 2109–2115 (2012). 10. Pascarella, A. *et al.* Treatment of articular cartilage lesions of the knee joint using a modified AMIC technique. *Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA* **18,** 509–513 (2010). 11. Vannini, F., Battaglia, M., Buda, R., Cavallo, M. & Giannini, S. 'One step' treatment of juvenile osteochondritis dissecans in the knee: clinical results and T2 mapping characterization. *Orthop. Clin. North Am.* **43,** 237–244, vi (2012). 12. Siclari, A., Mascaro, G., Gentili, C., Cancedda, R. & Boux, E. A cell-free scaffold-based cartilage repair provides improved function hyaline-like repair at one year. *Clin. Orthop.* **470,** 910–919 (2012). 13. Gille, J. *et al.* Outcome of Autologous Matrix Induced Chondrogenesis (AMIC) in cartilage knee surgery: data of the AMIC Registry. *Arch. Orthop. Trauma Surg.* **133,** 87–93 (2013). 14. Buda, R. *et al.* Osteochondral lesions of the knee: a new one-step repair technique with bone-marrow-derived cells. *J. Bone Joint Surg. Am.* **92 Suppl 2,** 2–11 (2010).	Thank you for your references. Please see response to comments 2 and 3.

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8	Consultee 2 Professional Organization International Cartilage Repair Society		15. Lee, Y. H. D., Suzer, F. & Thermann, H. Autologous Matrix-Induced Chondrogenesis in the Knee: A Review. *Cartilage* **5,** 145–153 (2014).16. Kon, E., Delcogliano, M., Filardo, G., Altadonna, G. & Marcacci, M. Novel nano-composite multi-layered biomaterial for the treatment of multifocal degenerative cartilage lesions. *Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA* **17,** 1312–1315 (2009). 17. Kon, E. *et al.* How to Treat Osteochondritis Dissecans of the Knee: Surgical Techniques and New Trends: AAOS Exhibit Selection. *J. Bone Joint Surg. Am.* **94,** e11–18 (2012). 18. Filardo, G., Di Martino, A., Kon, E., Delcogliano, M. & Marcacci, M. Midterm Results of a Combined Biological and Mechanical Approach for the Treatment of a Complex Knee Lesion. *Cartilage* **3,** 288–292 (2012). 19. Marcacci, M. *et al.* Unicompartmental osteoarthritis: an integrated biomechanical and biological approach as alternative to metal resurfacing. *Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA* (2013). 20. Filardo, G. *et al.* Treatment of Knee Osteochondritis Dissecans With a Cell-Free Biomimetic Osteochondral Scaffold: Clinical and Imaging Evaluation at 2-Year Follow-up. *Am. J. Sports Med.* (2013). 21. Kon, E. *et al.* Clinical results and MRI evolution of a nano-composite multilayered biomaterial for osteochondral regeneration at 5 years. *Am. J. Sports Med.* **42,** 158–165 (2014).	Thank you for your references. Please see response to comments 2 and 3.

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9	Consultee 2 Professional Organization International Cartilage Repair Society		22. Delcogliano, M. *et al.* Use of innovative biomimetic scaffold in the treatment for large osteochondral lesions of the knee. *Knee Surg. Sports Traumatol. Arthrosc. Off. J. ESSKA* (2013). 23. Filardo, G. *et al.* Osteochondral scaffold reconstruction for complex knee lesions: a comparative evaluation. *The Knee* **20,** 570–576 (2013). 24. Kon, E. *et al.* A one-step treatment for chondral and osteochondral knee defects: clinical results of a biomimetic scaffold implantation at 2 years of follow-up. *J. Mater. Sci. Mater. Med.* (2014). 25. Kon, E., Filardo, G., Venieri, G., Perdisa, F. & Marcacci, M. Tibial plateau lesions. Surface reconstruction with a biomimetic osteochondral scaffold: Results at 2 years of follow-up. *Injury* (2014). 26. Berruto, M. *et al.* Treatment of Large Knee Osteochondral Lesions With a Biomimetic Scaffold: Results of a Multicenter Study of 49 Patients at 2-Year Follow-up. *Am. J. Sports Med.* (2014). 27. Verdonk, P., Dhollander, A., Almqvist, K. F., Verdonk, R. & Victor, J. Treatment of osteochondral lesions in the knee using a cell-free scaffold. *Bone Jt. J.* **97-B,** 318–323 (2015).	Thank you for your references. Please see response to comment 3.