National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89)

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	British Association for Surgery of the Knee (BASK)	Accurate summary	Comment noted.
	British Orthopaedic Association	We support the BASK (British Association for Surgery of the Knee) comments for all sections. In addition, we have provided further comments in the section on 'Population'.	Comment noted.

Section	Consultees	Comments	Action
	Sanofi	Sanofi Biosurgery does not consider Knee replacement and osteotomy as suitable comparators to the whole population of patients with single isolated cartilage lesions of the knee. These therapy options are usually reserved for specific patients as either salvage, particularly for TKR, or in patients with early osteoarthritis in whom other less radical cartilage repair options are unsuitable. TKR and osteotomy are indicated for patients with osteoarthritis and not for isolated cartilage lesions[1, 2] which is the focus of this appraisal. Osteotomy is a treatment option generally reserved for patients who have coexisting joint malalignment[3]. The population appropriate for cell based therapy is a young, active population and knee replacement is clinically and medically unwarranted and most surgeons will try to avoid early TKR due to the well-documented limited lifespan of knee prostheses[4, 5] and as revision surgery becomes very complicated with a high degree of morbidity. References 1. Liddle AD et al Maturias 2013; 75 131-136; 2. Griffin T et al ANZ J. Surg 2007; 77 214-221 3. Dettoni F et al Iowa Orthopaedic Journal 2010; 30 131-140 4.Total Knee Replacement Royal Surrey Hospital www.royalsurrey.nhs.uk 5. Labek G et al JBJS Br 2011; 93 (3) 293-7	Comment noted. It is agreed at this stage for the scope to be inclusive therefore comparators in this section have not been removed/changed as these were agreed at the scoping workshop; however, the wording in this section has been amended to account for the appropriate comparator for a given size of lesion ('as appropriate for lesion size').
	TiGenix	No comment	Comment noted.
The technology/ intervention	British Association for Surgery of the Knee (BASK)	Yes	Comment noted.
	British Orthopaedic Association	No comments	No action required.

Section	Consultees	Comments	Action
	Sanofi	**Clarification for the background information**: MACI® should be described as "matrix applied characterised autologous cultured chondrocyte implant" as per the SmPC[1]. MACI® is an approved Advanced Therapy Medicinal Product (ATMP) defined as a combined tissue-engineering product (TEP)[2]. The final product undergoes Viability, Identity and Potency assays to ensure that the seeded cells are live chondrocytes capable of producing the matrix proteins required for cartilage repair. MACI is the only product capable of utilising these proprietary, approved assays. References 1. MACI Summary of Product Characteristics 2. European Medicines Agency MACI Assessment Report EMA/CHMP/25287/2013	Comment noted. The purpose of this section of the scope is to give a brief overview of the technology and is not intended to address the regulatory framework. However, this section of the scope has been updated to describe MACI as 'matrix applied characterised autologous cultured chondrocyte implant' as detailed in the Summary of Product Characteristics.
	TiGenix	We suggest adding the words 'using a standardised, reproducible, proprietary process' between the words 'expanded in the laboratory' and the words 'to provide enough cells'. This is more complete. We suggest deleting the words '..to make up a suspension..." between "..enough cells to..."and "...that can be used to treat the cartilage defect." This is more accurate. We suggest substituting the words 'A mini-arthrotomy' for the words 'Open knee surgery' We suggest adding the words " ..glued or.." in front of the words "...sutured over the cartilage defect or the cells..." and "...sutured over the cartilage defect(cell-seeding technique) The document states that "'Traditional' ACI can be carried out without the branded products above under hospital exemptions from the 'advanced therapy medicinal products' regulation". While this is correct, the information is incomplete. The ATMP regulations permit products to be used under the hospital exemption under certain circumstances, but such products are not	Comments noted. The purpose of this section of the scope is meant to be a brief overview of the technology. No changes to the scope required. The wording in the technologies section has been amended to a more accurate description. Details about ChondroCelect's MA wording has not been added as this section is not intended to be exhaustive description of each technology. The wording in of the

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		'approved' under the ATMP regulations because by definition they are one-off therapies and not a distinct product. We suggest that the draft scope background reflect this. Given the position, we propose that the 'hospital exemption' therapies be removed from the interventions to be considered. By definition, there will be no studies of 'a product', and therefore there can be no basis for assessing the comparative cost-effectiveness of a treatment pathway involving a hospital exemption product.	intervention of the PICO table has been changed to Characterised Chondrocyte Implantation using ChondroCelect'. Comment noted. With regard to the use of traditional ACI under hospital exemptions from the advanced therapy medicinal products' regulation, the DH and MHRA have agreed that it is appropriate for traditional ACI to be included within the scope of this appraisal to update the guidance in TA89.
Population	British Association for Surgery of the Knee (BASK)	Patients with symptomatic articular cartilage lesions of the retropatella surface should be considered for inclusion. The RCTs have concentrated on condyle lesions, but the evidence for patella lesions is emerging from long-term cohort studies.	Comment noted. The population of the scope has been broadened so that it covers all cartilage defects so that each can be explored within the marketing authorisation as appropriate. The wording of the population has therefore been amended to remove the reference to specific articular surfaces of the knee 'Adults with symptomatic defects in the cartilage of the knee with no advanced osteoarthritis'

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	British Orthopaedic Association	The BASK comments recommend extending the Appraisal to include cartilage lesions of the retropatella surface. In our view, this should be extended further, to also include the tibia and trochlear portion of the femur. There is literature available on this. We believe it is too restrictive to consider ChondroCelect only in relation to femoral lesions. We believe that this is important because if the appraisal comes to the conclusion that the procedure is cost effective, then it should be considered for all knee lesions. In this way, surgeons performing this procedure could apply just one technique with which they are familiar to the lesions they find in their patients, rather than having to use a different technique depending on where in the knee they find the lesions.	Comment noted. The population of the scope has been broadened so that it covers all cartilage defects so that each can be explored within the marketing authorisation as appropriate. The wording of the population has therefore been amended to remove the reference to specific articular surfaces of the knee 'Adults with symptomatic defects in the cartilage of the knee with no advanced osteoarthritis'

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	Sanofi	For the classification of cartilage lesion the Modified Outerbridge Scale Grade III & IV should be added to the ICRS criteria (as per the MACI SmPC[1]). The Modified Outerbridge Scale is a more user friendly and practical assessment tool used by surgeons in their daily practice[2] as compared to the ICRS Grading Scale which is more usually used in clinical trials. The bullet – "Patients should have any concomitant joint malalignment must be corrected prior to or at the time of cartilage repair" should be added to this definition of the population. It is well recognised that irrespective of the repair technique joint instability and/or malalignment is a risk factor for a poor outcome[3,4]. References 1. MACI Summary of Product Characteristics 2. Cameron ML et al Am J Sp Med 2003; 31(1) 83-86 3.Bentley G et al Injury, Int. J. Care Injured 44 (2013) S1, S3–S10 4. Moran J et al JBJS AM 2014 96(4) 336- 344	Comment noted. The background section of the scope has been amended to include details of the International Cartilage Repair Society and the Modified Outerbridge grading systems as commonly used methods for classifying the severity of lesions to cartilage. Comment noted. The 'other considerations' section of the scope has been amended to include 'and for cartilage defects secondary to malalignment' as a subgroup.

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	TiGenix	We suggest adding the words 'which meet the following criteria: • ICRS grade III-IV; • lesion size: ≥ 2 cm²; • onset of symptoms ≤ 3 years; • patient aged 18 to 50 years; • no signs of advanced osteoarthritis.' after the words 'femoral condyle of the knee'. This is more complete.	Comment noted. The different interventions for cartilage repair will be considered within their marketing authorisation therefore specific reference to ICRS grade, lesion size and age and the articular surface of the lesion have been removed from the population although the exclusion of signs of advanced osteoarthritis has been retained as this is relevant to all interventions. In addition, specifying an age-range is too restrictive and may not reflect the use of this technology in clinical practice in England. The scope has been amended accordingly.
Comparators	British Association for Surgery of the Knee (BASK)	The comparators are appropriate. Microfracture should perhaps also include 'augmented microfracture' which is a variant where a membrane is sutured over the defect. However, there is little good evidence to support augmented microfracture and it is more costly than traditional microfracture	Comment noted. 'Augmented microfracture' would be considered to be a sub-category of 'microfracture comparator' which would therefore fall within the scope of the appraisal. No additional action is needed.

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	Sanofi	Sanofi Biosurgery strongly believes that due to the limited treatment options open to surgeons and the huge variation in patient presentations, symptomatology and concomitant pathologies, it is more appropriate to consider lesions > 1cm^2 as a single group. With respect to the comparators Sanofi Biosurgery do not consider either knee replacement or osteotomy as applicable to the cartilage patient population as a whole. The use of these therapeutic options would be for a small minority of patients with specific clinical requirements and not reflective of the usual patient with an isolated cartilage defect treated within the parameters of these products licensed indications. Sanofi Biosurgery considers these surgical options inappropriate to apply to a wider population and could result in many patients undergoing major radical surgery needlessly or at the least many years earlier than would be necessary. *(Please see comments in Background Information).* Furthermore it is the aim of surgeons treating this active population of patients to try to preserve knee health as long as possible and to either prevent or delay the need for knee replacement surgery which is indicated in patients with osteoarthritis and not isolated cartilage lesions. Current guidelines and consensus statements do not limit the use of microfracture on the basis of lesion size. Microfracture has been used by many centres internationally for larger lesions[1-3] and as such should be considered an active comparator across all lesions at this time There are data available to support the short term use of microfracture and mosaicplasty, and for long term use of ACI and MACI, across a range of lesion sizes. References 1Steadman JR et al J Arthro Rel Surg 2003 19(5) 477-484 2. Mithoefer K et al Am J Sp Med 2009; 7(10) 2053-63 3. Gobbi A et al Knee Surg Sports Traumatol Arthrosc 2005 13 : 213–221	Comment noted. The scope of the appraisal has been broadened to include all relevant technologies for cartilage repair which will be appraised within their marketing authorisations. The interventions will be compared with each other where appropriate. Therefore references to specific articular surfaces have been removed and references to specific lesion size has been replaced with ‘as appropriate for lesion size’.

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	TiGenix	We suggest deleting 'Mosaicplasty' because: • it is little used in the UK (in 2011-12 only 84 hospital admissions were coded to a primary procedure osteochondral autograft, against probably 2250+ microfracture (all relevant codes are not absolutely specific for microfracture); • although IPAC considered that current evidence on safety is adequate, data on long-term efficacy are inadequate; • there are no data of which we are aware to support cost-effectiveness, the evidence on CCI comes from a trial vs microfracture, and there are no data comparing CCI against mosaicplasty or any clear way of making a robust indirect comparison. We suggest that there is a need to define 'small' and 'large'. • We do not consider that knee replacement is a realistic comparator for the population of interest.	Comment noted. Attendees at the workshop noted that both mosaicplasty and microfracture as used in clinical practice in England although mosaicplasty is technically demanding and is used less than microfracture. References to lesions sizes have been removed from the final scope .
Outcomes	British Association for Surgery of the Knee (BASK)	Appropriate	Comment noted.
	Sanofi	Sanofi Biosurgery would suggest that for Health related quality of life outcome measure, disease specific scales such as the QoL component of the KOOS and WOMAC scores are considered rather than a general QoL scale.	Comment noted. Specific outcome measures (such as KOOS and WOMAC) are not usually included in NICE scopes to avoid exclusion of clinical trials that use other relevant outcome measures.

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	TiGenix	We suggest adding the words 'measured by KOOS' after the words 'knee function'. We suggest replacing the wording 'including long term function' with the words 'avoidance of OA including knee replacement'. We suggest adding 'structural quality of cartilage repair tissue'	Comment noted. See previous comment about the wording 'measured by KOOs'. In response to the advice of clinicians at the scoping workshop 'Avoidance of osteoarthritis including knee replacement', and The outcome 'including long term function' has been replaced with the words 'avoidance of osteoarthritis including knee replacement' 'Structural quality of cartilage repair tissue' has been added as outcomes in the scope.
Economic analysis	British Association for Surgery of the Knee (BASK)	Appropriate	Comment noted.

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	Sanofi	Given that NICE is considering outcomes such as development of osteoarthritis and TKR and that these patients are young and active, we would suggest that a lifetime horizon, based on UK life expectancy, would be the appropriate time horizon for the model.	Comment noted. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
	TiGenix	We suggest inserting the words 'in the reference case' between the word 'Costs' and the words 'will be considered;. This is more accurate.	Comment noted. NICE appraisals always consider the reference case. therefore no action needed
Equality and Diversity	British Association for Surgery of the Knee (BASK)	No comments	Comment noted.
	Sanofi	No comments	Comment noted.
	TiGenix	No comments.	Comment noted.

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Innovation	British Association for Surgery of the Knee (BASK)	Yes, this represents a step-change in the regenerative potential of articular cartilage. However, the technology has been available for some time and has been limited in availability due to cost and previous NICE recommendations. The first ACI was performed 29 years ago. There is quality of life data published by Saris, by Brittberg, and by Bentley.	Comment noted. The innovative nature of the interventions will be considered by the Committee during the course of the appraisal. No changes required.
	Sanofi	Sanofi Biosurgery would consider the MACI implant to be a step change to microfracture and Chondrocelect. The Short-Form Health Survey (SF-12) HRQoL scores from the SUMMIT Trial show that treatment with MACI implant results in statistically significant improvements versus microfracture in HRQoL after 2 years, resulting in an SF-12 score which more closely resembles that of the overall US population[1]. References 1 Price A et al Poster Abstract 9.2.1 ICRS 11th World Congress Izmir 2013	Comment noted. The innovative nature of the interventions will be considered by the Committee during the course of the appraisal. No changes required.
	TiGenix	ATMP regulations represent a significant break with the regulations governing cell-based therapies in the past. ChondroCelect, the first cell-based therapy to be approved under the new ATMP regulations. ChondroCelect offers a proven treatment option for people with symptoms for whom current treatments are recognised to be unsatisfactory. We believe CCI to be an effective and innovative cell therapy which meets the needs of patients with significant cartilage damage in the knee and whose lifestyle places significant demands on the knee.	Comment noted. The innovative nature of the interventions will be considered by the Committee during the course of the appraisal. No changes required.

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Other considerations	British Association for Surgery of the Knee (BASK)	The International Cartilage Repair Society (ICRS) is introducing an international web-based registry that will be available to surgeons and patients to be included from Q4 2014. Inclusion of patients in such a registry would be of benefit to evaluation of existing and emerging treatments. There is a Cartilage Consensus Meeting of UK cartilage Repair Surgeons in March 2014. The remit is that surgical experts will produce a consensus algorithym of expert opinion based on best available published evidence.	Comment noted. No changes required
	Sanofi	We agree that the guidance should only be issued in accordance with the marketing authorisation.	Comment noted. No changes required
	TiGenix	The term marketing authorisation (certainly without qualification) is inaccurate in relation to hospital exemption products. We suggest that the text should be amended.	Comment noted. The scope has been amended appropriately.
Questions for consultation	British Association for Surgery of the Knee (BASK)	No comments	Comment noted.
	Sanofi	No comments	Comment noted.

Section	Consultees	Comments	Action
	TiGenix	The patients in which clinical efficacy is statistically significantly better are those with symptom onset < 3 years prior to treatment. This is in line with findings in previous studies of various cartilage repair techniques. We propose that the scope is confined to this subgroup. ChondroCelect is innovative: it is the first cartilage repair product to meet the requirements of the new ATMP regulations. These require ChondroCelect to meet biopharmaceutical-standard criteria. Unlike previous autologous chondrocyte offerings, the ATMP defined "medicinal product" standard of ChondroCelect addresses previous regulatory "grey areas" by providing a supportive pharmacovigilance concept, a risk-management plan and proof coming from a SmPC. In addition, quality assurance, reproducibility, standardisation of manufacture, specific potency etc apply, offering performance which is materially different from earlier products, including those previously reviewed by NICE in TA89. ChondroCelect involves a proprietary expansion process designed to preserve the integrity and function of chondrocytes, in particular to maintain their ability to produce hyaline cartilage. This distinguishes ChondroCelect from older ACI products (those reviewed in TA89) which suffer from such problems as dedifferentiation, non-standardised production techniques, and variable potency	Comments noted. Attendees at the workshop agreed that If evidence allows consideration will be given to subgroups stratified by duration of symptoms (less or more than 3 years), size of lesion, and previous exposure to surgical treatment, and for cartilage defects secondary to malalignment. Comments noted. The innovative nature of the interventions will be considered by the Committee during the course of the appraisal. No changes required
Additional comments on the draft scope.	British Association for Surgery of the Knee (BASK)	No comments	Comment noted.
	Sanofi	No comments	Comment noted.
	TiGenix	No comments	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Health Improvement Scotland
Royal College of Nursing

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89) [ID686]

Response to consultee and commentator comments on the provisional matrix of consultees and commentators

Summary of comments, action taken, and justification of action:					
	Proposal:	*Proposal made by:*		*Action taken:* Removed/Added/Not included/Noted	*Justification:*

1.	As ChondroCelect is a cell-based therapy, NICE may wish to include the following in the matrix of consultees: Organisations with a special interest in the repair of cartilage injuries which NICE may wish to consider including in the matrix are – • International Cartilage Repair Society (ICRS) • UK Cartilage Club • UK Stem Cell Foundation • UK Stem Cell Bank • Arthritis Research UK • Cell Therapy Catapult Ltd • Alliance for Regenerative Medicine(ARM) • UK Regenerative Medicine Community (UKRMC) • London Regenerative Medicine Network (LRMN) • Regenerative Medicines in Europe(REMEDiE) • Regenerative Medicine (RM) Alliance for Advanced Therapies (AAT) • UK Regenerative Medicine Community Medical Technologies Innovation Knowledge Centre, University of Leeds	Tigenix			Arthritis Research UK – already on matrix UK Stem Cell Foundation – added as a research group The following organisations do not meet the criteria for consultees or commentators: International Cartilage Repair Society UK Cartilage Club UK Stem Cell Bank ACell Therapy Catapult Alliance for Regenerative Medicine UK Regenerative Medicine London Regenerative Medicine Network Regenerative Medicines in Europe