Response from Leela C Biant. BASK Representative Clinician Expert.

Comments on the ACD on Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee.

The consultation document above

1. Has not taken into account all the relevant evidence
2. Has not appropriately interpreted the evidence
3. The provisional guidance is entirely unsound
4. The suggestions for further research are inappropriate and unethical

Errors in the ACD

2.7 and 5.3 "There are no UK guidelines or internationally accepted treatment on how to treat cartilage lesions"
The Committee was provided with the UK Cartilage Consensus Paper, which is in press. It is due to be published in April 2015. It had 72 signatories of clinicians involved in cartilage repair in the UK at the time it was submitted to NICE. It now has close to 100, which represents the majority of orthopaedic surgeons who perform this surgery. The Dutch Orthopaedic Society and the German Orthopaedic Society have previously published similar papers.
One of the reasons the UK Cartilage Consensus Meeting was convened, was due to the previous NICE Appraisal being cited by NHS and other health providers to deny patients access to treatments where the clinicians consider the evidence to be strong enough to recommend ACI in appropriate patients. There is considerable variation in access to these services across the UK. Furthermore, clinicians were concerned that doing comparator treatments such as microfracture is less effective and compromises the chance of subsequent repair with ACI.

4.1 The Committee's summary of the AG review of clinical evidence demontrates misinterpretation of the AGs evidence.
First generation ACI (ACI-P) has a higher rate of patch hypertrophy which is amenable to correction by day-case arthroscopy, but there is no higher failure rate of the repair itself. There are comparative trials of different forms of ACI which show no difference in clinical result.
The AG stated CONCLUSIVELY from their review that ACI was more effective than microfracture. The opposite is stated in 4.1.

4.6 The summary suggests that the AG regard the TIG/ACT trial as good quality. This is true. "However, the AG regards ACI-P as obselete". This implies that the trial is now irrelevant to the current therapy. This is a misinterpretation of the AG evidence and the clinical situation.
ACI-P uses a different patch than ACI-C or MACI. The repair is just as good with ACI-P, as stated in the AG addendum, but the small complication of patch hypertrophy is much less in ACI-C and MACI, which is one reason they are favoured now. The trial is of relevance and should not be discounted or considered less valuable on these grounds. In fact, any evidence from this study is that shows the superiority of ACI over microfracture is likely to be greater

with ACI-C or MACI, as stated in the AG report. There is no difference in the re-operation rate between ACI-c and ACI-P in the ACTIVE Trial.

Publication	Comparison	Results
Schneider et al. Orthop. Ihre Grenzgeb. 2003	ACI Gen I vs ACI Gen III	No difference
Bartlett et al. JBJS(Br) 2005	ACI Gen II vs ACI Gen III	No difference
Gooding et al. Knee 2006	ACI Gen I vs ACI Gen II	No difference
Zeifang et al. AJSM 2010	ACI Gen I vs ACI Gen II	No difference

5.2 "The Committee did not consider best supportive care (including physiotherapy) to be a relevant comparator because the Committee heard that best supportive care had already failed by the time clinicians consider ACI"
6.3 " Further research is recommended to compare ACI, mosaicplasty and microfracture with conservative treatment"

The ACD contradicts itself entirely here. It was explained that surgeons do not consider surgery unless conservative methods have failed. It is therefore illogical, if not unethical to recommend research against a comparator treatment the patient has already failed by the time the present to the clinician and the Committee itself does not consider an appropriate comparator.

5.3 "It (The Committee) noted 3 small studies with relatively short follow-up"
These studies are not small surgical studies, and should not be benchmarked against drug studies. The studies mentioned are adequately powered, appropriate and methodologically sound enough to show a difference between ACI and microfracture. Indeed they all have, even at 'relatively short follow-up". If longer follow-up evidence is required, there are cohort studies and an RCT against mosaicplasty with data at minimum 10 years, and a total of 15 RCTs involving ACI.

Publication	Comparison	Results	Period
Visna et al. Acta Orthop. Belgica 2004	ACI Gen III vs Abrasion	ACI better	1 year
Knutsen et al. JBJS(Am) 2007	ACI Gen I vs MFX (in arthritis)	No difference	5 years
Basad et al. KSSTA 2010	ACI Gen III vs MFX	ACI better	2 years
VanLauwe et al. AJSM 2011	ACI Gen I vs MSF	ACI better	5 years
Cole et al. AJSM 2011	ACI Gen IV vs MFX	ACI better	2 years
Crawford et al. JBJS(Am) 2012	ACI Gen III vs MFX	ACI better	2 years
Saris et al. AJSM 2014	ACI Gen III vs MFX	ACI better	2 years
Lim et al. Clin Orthop Rel Res 2012	ACI Gen I vs MFX vs Mosaicplasty	No difference	1 year
Horas et al. JBJS(Am) 2003	ACI Gen I vs Mosaicplasty	No difference	1 year
Bentley et al. JBJS(Br) 2003	ACI Gen I vs Mosaicplasty	ACI better	2 years
Dozin et al. Clin J Sports Med. 2005	ACI Gen I vs Mosaicplasty	No difference	1 year
Bentley et al. JBJS(Br) 2012	ACI Gen I vs Mosaicplasty	ACI better	10 years

4. 5.3 “Lysholm, Tegner and Cincinnati scores were not regularly used in clinical practice and some were of limited relevance to the general population with cartilage defects” This is a misinterpretation of what the clinician experts reported. These measures were used in cartilage repair patients in earlier studies before articular cartilage-specific scores were developed. The Lysholm Score has been validated in patients with chondral leasions (Kocher MS et al JBJS Am 2004). They were used for general soft-tissue knee problems including meniscal damage or ligament damage and reflect pain and function in an active population (as opposed to an elderly arthritic population). They are reasonable measures of pain and function and allow intra-study comparison between treatments and comparison between studies.

   5.3 “The Committee concluded that, although there is more clinical-effectiveness data than at the time of the previous NICE technology appraisal guidance on the use of ACI for the treatment of cartilage defects in the knee joints, the evidence base for the technology is still emerging”
   The Committee seem to have only considered 3 RCTs against microfracture and have ignored the large evidence base on ACI clinical effectiveness (several long-term cohort studies over 10 years and an RCT against mosaicplasty at minimum 10 years. There are 15 published RCTs of some form of ACI against a comparator). The RCTs favour ACI, and the several cohorts over 10 years would suggest that the evidence has already emerged. This conclusion is also in direct contradiction to the AG conclusion of the evidence base.

   5.4 “The Committee heard that the clinical experts differed with respect to how effective they perceived ACI to be compared with microfracture. The Committee heard that this may in part reflect a clinician’s experience and preference. When asked to judge the clinical effectiveness of ACI, clinical experts stated that there was some evidence to show that ACI is clinically effective, but also stated that this evidence was not definitive. They also stated that, although ACI, microfracture, and mosaicplasty were probably clinically effective, evidence was lacking for the natural history of lesions treated by debridement and lavage”

   This is absolutely not what the clinicians expressed. It was the stated opinion of one of the clinicians present, not the other two who were given insufficient opportunity to respond, because one had to leave part-way through the meeting (having been invited at too short notice to cancel a clinic) and because the other was part of the AG, who are not invited to make any presentation. The one clinician is not representative of the vast majority of surgeons who perform this surgery, and who have put their signatures to the UK Cartilage Consensus Paper. The Committee may have given too much weight to the opinion of one, who was in contradiction with the majority of surgeons, the evidence in the literature and the AG.
   The evidence for ACI is solid and multiple, and irrespective of preference and experience and is absolutely definitive. Around 100 clinicians have signed the UK Cartilage Consensus Paper.

“They also stated that there was evidence lacking for the natural history of lesions treated by debridement and lavage”
This is not an accurate interpretation of what was said, nor is it accurate based on the literature. Large cartilage lesions become arthritis

5.5 “The Committee noted that it was presented with no clinical effectiveness data beyond 5 years” and “insufficient long-term evidence to support a conclusion on the long-term effectiveness of ACI”
This data is available, and the Committee should avail itself of this. The AG or two of the clinical experts could have presented this had they been asked.

5.7 “It (The Committee) noted that the claimed advantages of ACI over microfracture in its use for larger lesions was not supported by the study of Minas and colleagues (2009)”
The paper by Minas has been misinterpreted entirely by the Committee, and the paper in fact has evidence exactly to the contrary.

5.8 and 5.10 “significant uncertainty in the cost-effectiveness results” (of the AG)
I know as a co-author of the assessment report that the economic modelling of the AG has itself been independently assessed for quality and has been deemed to be of very good academic quality with a score of 5/6 by an independent referee chosen by the HTA programme editors.

6.3. “Further research is recommended to compare ACI, mosaiclasty and microfracture with conservative treatment, for example, sham (placebo) procedure, lavage and debridement, or intensive physiotherapy that reflects the rehabilitation following ACI”
This is illogical, and likely unethical. The Committee itself has already stated that conservative measures are an inappropriate comparator in section 5.2 “The Committee did not consider best supportive care (including physiotherapy) to be a relevant comparator because the Committee heard that best supportive care had already been failed by the time clinicians consider ACI”

NICE has not taken into account all the available evidence and has not accurately interpreted the evidence presented to it. The guidance is inappropriate and will deny effective treatment to patients, based on their flawed interpretation of clinical effectiveness data. The Committee was, perhaps, also inappropriately influenced by a clinician who did not represent the majority view, nor a sound evidence base for his statements.

Leela C Biant 19th March 2015.