

Chair's presentation

Autologous chondrocyte implantation in the knee (review of TA16 and TA89)

3rd Appraisal Committee B meeting

Chair: Amanda Adler

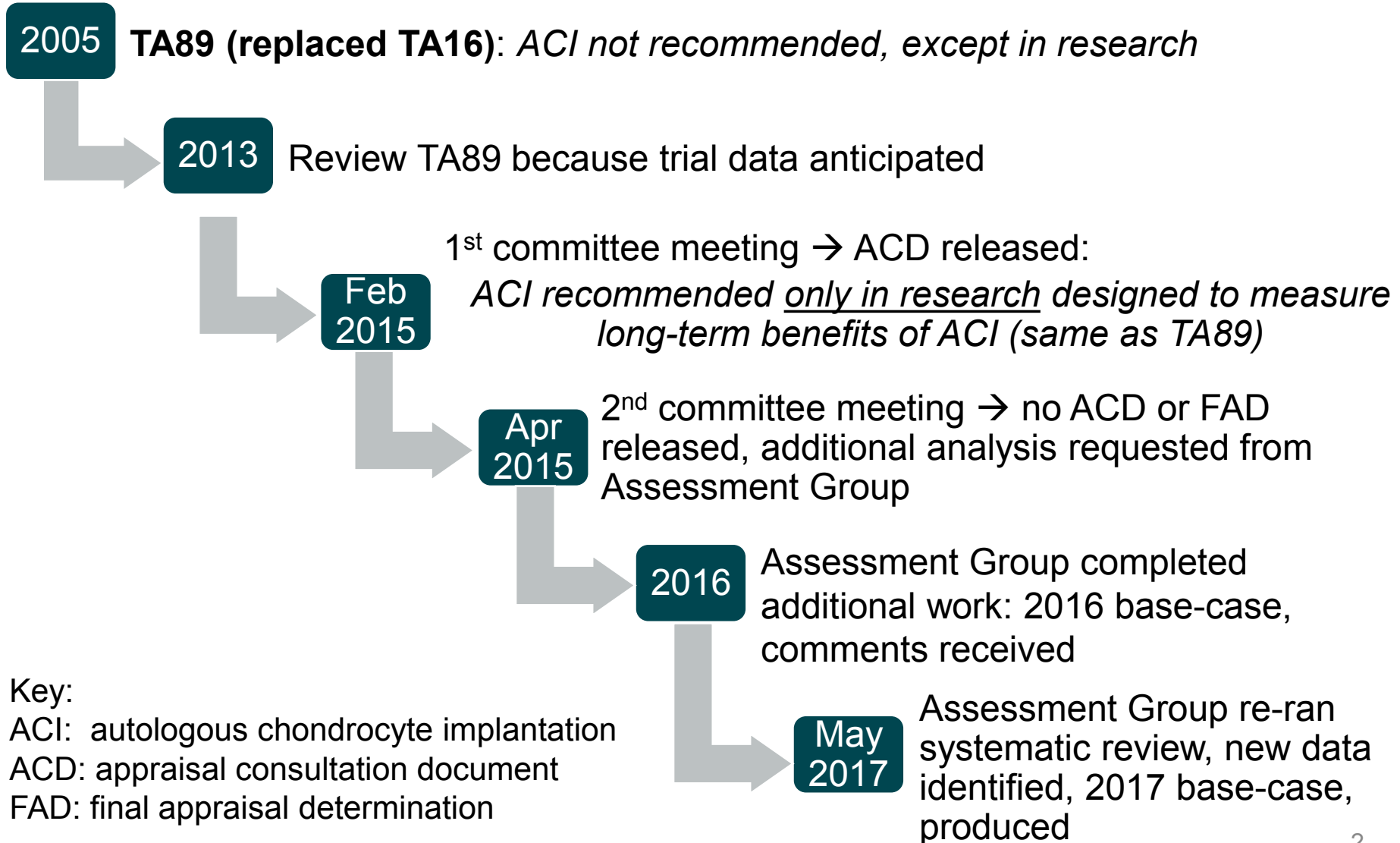
Lead team: Ken Stein, Steve Palmer, Cliff Snelling

Assessment Group: Warwick Evidence

NICE technical team: Mary Hughes, Ahmed Elsada

21st June 2017

History of appraisal



Technologies and companies: update

Company	Technology	Regulatory status
OsCell John Charnley Laboratory (NHS Laboratory) at Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry (RJAH)	Traditional ACI	Used under hospital exemptions from the 'advanced therapy medicinal products' regulation for products 'prepared on a non-routine basis'
Vericel	Matrix associated chondrocyte implantation (MACI)	2013 marketing authorisation granted, 2014 company closed EU manufacturing site, marketing authorisation currently suspended until new site registered
Swedish Orphan Biovitrium (Sobi), Marketing authorisation holder: TiGenix	ChondroCelect	Product <u>withdrawn</u> for commercial reasons by TiGenix (2017)

Decision Problem

Population

Adults with symptomatic defects in the cartilage of the knee with no advanced osteoarthritis

Intervention

- Traditional ACI
- Matrix associated chondrocyte implantation (MACI)
- ~~ChondroCelect~~

Comparators

- As appropriate for lesion size:
1. Microfracture
 2. Mosaicplasty
 3. Osteotomy
 4. Knee replacement
 5. Best supportive care

Outcomes

Pain, knee function, re-treatment, activity, osteoarthritis, health related quality of life

ACI procedures

Extract healthy chondrocytes → culture chondrocytes → return chondrocytes to lesion where they produce cartilage

Can differ in:

- Whether cells ‘characterised’ - selected to produce hyaline cartilage
- Whether cells seeded onto cap or matrix (ACI-M = ‘3rd generation’)
- Material of cap: periosteum (ACI-P – 1st generation) or collagen (ACI-C – 2nd generation)

Cell type	Cells seeded onto	
	Cap	Matrix
Characterised - No	Traditional ACI	
Characterised - Yes	-	MACI

Comparators

	Description	Committee conclusion at previous meetings
Microfracture (MF)	Perforate bone marrow - release stem cells and growth factors to repair cartilage	Most relevant comparator, most widely used
Mosaicplasty	Harvest grafts from non-weight bearing regions of knee, transplant in mosaic pattern	Variable use in clinical practice
Osteotomy	Cut bone - change alignment	Variable use in clinical practice, may be used if MF or ACI not successful – not a comparator
Knee replacement	-	Not comparator, used later in treatment pathway
Best supportive care	Exercise, weight loss, analgesia, corticosteroid injections, TENS, heat/cold, crutches	Not a comparator, ACI would be used when best supportive care inadequate

Key clinical effectiveness trials

Original assessment group report 2014

Tech	Compare	Study	1° outcome	Follow up yrs	Results	In 2017 model?
ACI (mixed, some 'traditional')	Mostly MF, mosaicplasty	ACTIVE (n=390)	Lysholm Assessor Score	8	No difference yrs 1 to 4	No
MACI	MF	SUMMIT (n=144) 'Basad' (n=60)	KOOS Tegner/ Lysholm	2 2	MACI better (within 2 years)	No
Chondro-Celect	MF	TIG/ACT (n=118)	Overall KOOS	5	Chondro Celect better (within 2 years)	Yes, used for modelling MF

SYMPTOM OUTCOME SCORES

- Lysholm score: pain, function, swelling
- Knee Injury + Osteoarthritis Outcome Score (KOOS): pain, function, quality of life
- Tegner score: function
- Clinical experts: Lysholm and Tegner not regularly used in clinical practice, KOOS sometimes used.

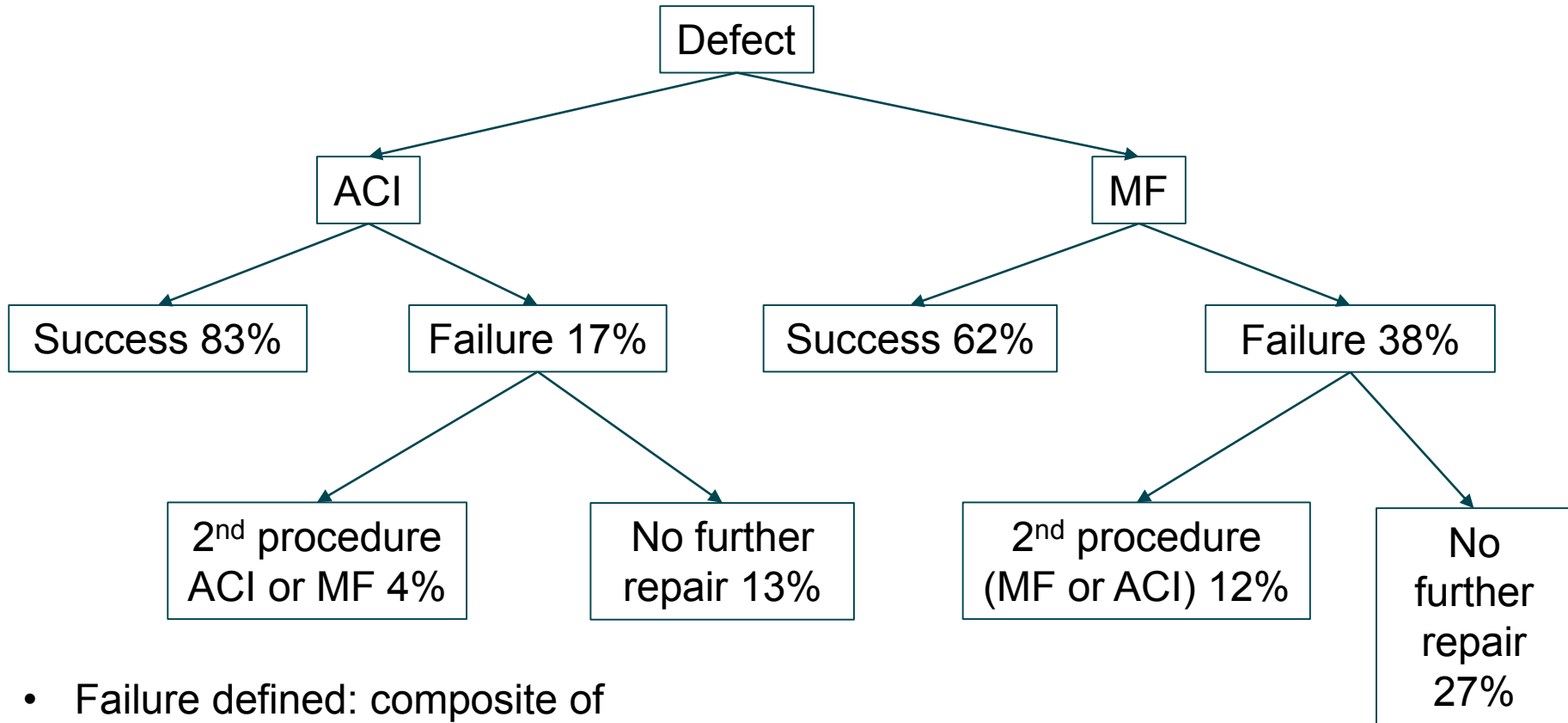
Cost effectiveness model

Original assessment group report 2014

- Assumed all ACIs (traditional ACI, MACI, ChondroCelect) **equally effective**
- Compared ACI with MF
- Lifetime time horizon (100 years), cycle length 1 year
- Modelled cohort average age 33 years (people over 55: no ACI, knee replacement instead)
- Model allowed up to 2 procedures (ACI, MF) before knee replacement
 - People could have repeated ACI or repeated MF
 - Success of 2nd procedure assumed same as 1st
- Failure rate assumed constant of model horizon

Failure rates at 36 months - lower for ACI

(original assessment group report 2014)



- Failure defined: composite of
 - 1. time-to-treatment failure (re-intervention)
 - 2. lack of response measured by KOOS
- Used to model transitions out of 1st repair and 2nd repair health states

Assessment report (2014) Figure 6. Data from: Saris et al 2009 [TIG/ACT, ChrondroCelect vs. microfracture]; Saris et al 2014 [SUMMIT, MACI vs. microfracture]

Utility values (original Assessment Group report 2014)

Health State	Utility value	Source
Before primary repair	0.654	Gerlier et al (2010) SF-36 questionnaire in TIG/ACT trial
Successful primary repair (1 st year after repair)	0.760	
Successful primary repair (2 nd year onwards)	ACI: 0.817 MF years 2 - 4: 0.817 thereafter*: 0.654	
Non-successful repair, but choosing not to have further surgery	0.691‡	

* To reflect that the benefit of microfracture may decline after 5 years

‡ sensitivity analysis around this assumption:

- 1) 0.654 utility is same as before surgery
- 2) 0.817 utility is the same as a successful repair
- 3) 0.746 utility is midway between same as before surgery and successful repair¹⁰

Committee conclusions 1st + 2nd meetings

Short term clinical data

- Uncertainties, but ACI may improve symptoms vs. MF
- SUMMIT+ TIG/ACT show benefit with ACI <2 years; ACTIVE did not. Reason for difference unclear:
 - ACTIVE = pragmatic trial (21% different tx to that allocated)
 - Broader range of patients than SUMMIT +TIG/ACT
 - MF with collagen cap in ACTIVE different than traditional MF

Long-term data

- Not enough evidence to conclude effectiveness >5 years
- ACI-P likely to have longer data. Relevant to include.
- Final results from ACTIVE (pending) will be important

Relative effective different types ACI

- Indirect comparisons → no clinically important differences
- Included trials too small to detect differences?
- Clinical experts: little evidence that different forms of ACI differ

Treatment

- Clinical experts: people would not have 2nd MF after a 1st one

Overall

- Available data did not robustly support that ACI better than comparators
- Committee preferred Assessment Group model to ChondroCelect's

Further analysis requested by NICE

- New systematic review by Assessment Group. Include RCTs and observational studies with outcomes for ACI (all) + MF
- Patient level data from ACTIVE trial (requested from RJAH, Oswestry)
- Review evidence for minimum age 55 for knee replacement
- Utility value results from SUMMIT (requested from manufacturer)
- Assessment Group Modelling
 - Remove repeated MF
 - Include new data
 - Include changes in Assessment Report Addendum
 - Include committee's preferred cost assumptions
 - Subgroup analysis
 - lesion size $> 4 \text{ cm}^2$
 - duration of symptoms < 3 years
 - no previous knee repairs
 - Sensitivity analysis around
 - utility values
 - clinical effectiveness
 - price of cells
 - defining treatment failure

N.B. Committee's key questions to be addressed

- 1) Is ACI effective compared with MF?
- 2) What are the long term outcomes for each treatment (5 years +)?
- 3) Are there groups of people for whom ACI or MF performs better/worse?
- 4) What are the uncertainties around the cost effectiveness estimates?

Summary: received from Assessment Group

Clinical effectiveness

- New observational data presented from larger cohorts (including 2 UK cohorts for ACI) for treatment failure rates
- New 15 year follow up on treatment failure rates from Swedish RCT comparing ACI and MF (n=80)
- 5 to over 10-year data presented (≤ 5 year data in original submission)

Modelling

- Reconstructed individual patient data from available Kaplan Meier data + tested different ways to extrapolate data beyond observed data
- Presented naïve comparison cost-effectiveness results (comparison using different data sources for modelling ACI and modelling MF arms)

Subgroups

- Data permitted stratifying ACI by
 - previous treatment/ no previous treatment
 - osteoarthritic damage

Sensitivity analyses

- Data sources and extrapolation method
- Utility values (including new published utility values from SUMMIT Trial)
- Price of cells

New base case (2016 base case + updated 2017 base case)

Summary: key trials/studies for new modelling of failure rates (2016*/17†)

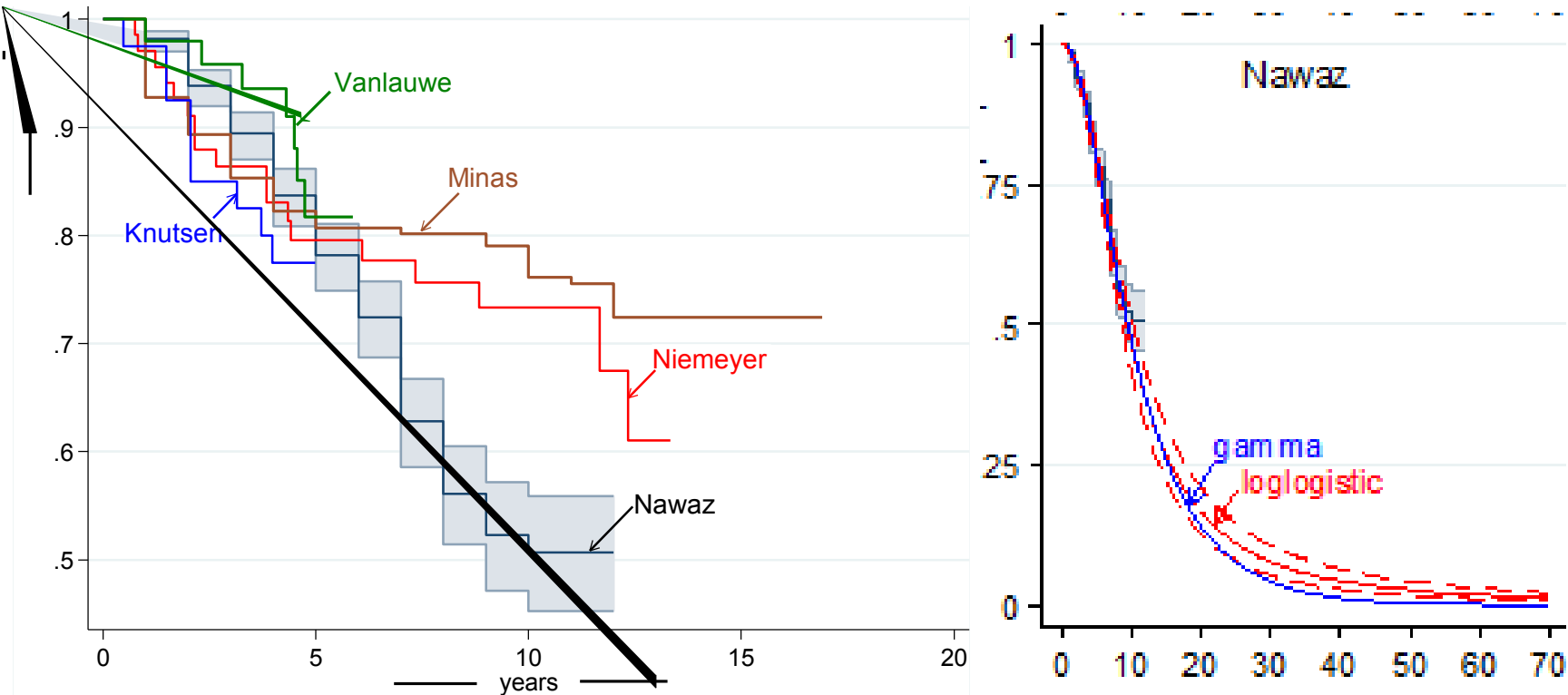
Data source	RCT or Cohort	Trial/study details	Follow up (years)	Failure definition	used in 2017 base case?
ACI					
Nawaz 2014*	Cohort	UK study: n= 827 ACI-C/P or MACI Subgroups	Ave 6.2 [2 to 12]	Re-intervention, graft delamination or symptom scores close to/worse than pre-op.	ACI- Yes
Dugard 2017†	Cohort	Traditional ACI n=170	Ave 10.9 [4.6-18.6]	Knee replacement	
Microfracture					
Knutsen 2007*	RCT	ACI-P vs. MF n=80	5	Re-intervention	
Layton 2015*	Claims database	US claims database n=3,498 MF	5		
Saris 2009 *	RCT (TIG/ACT)	RCT n=118 characterised ACI-P vs. MF	5		MF- Yes, pooled data from these studies
Knutsen 2016†	RCT	ACI-P vs. MF	15		

Patient characteristics

	ACI			MF		
	Nawaz	Dugard	Knutsen	Knutsen	Saris	Layton‡
N	827	170	40	40	61	3,498
Age [range]	34 [14-56]	37.2 [15.1- 65.8]	33.3 [NR]	31.1 [NR]	33.9 [NR]	47 [NR]
Male (%)	59.6	65	60	NR	67	NR
Mean Defect size (cm²)	4.09 [0.64-20.7]	4.0 [median, IQR 2.4-6]	5.1 [NR]	4.5 (SD NR)	2.4 (SD 1.2)	NR
Previous (%)	34	>90	93	93	77	NR
Symptom duration years	NR	NR	3 (median)	3 (median)	1.57 (0 to 18)	NR
Defect site						
Med fem %	51	60*	89.0	89	NR	NR
Lat fem %	13	23*	11.0	11	NR	NR
patellar %	24.0	8*	0	0	NR	NR
trochlea %	6.0	6*	0	0	NR	NR
Multiple %	6.0	27	0	0	NR	NR

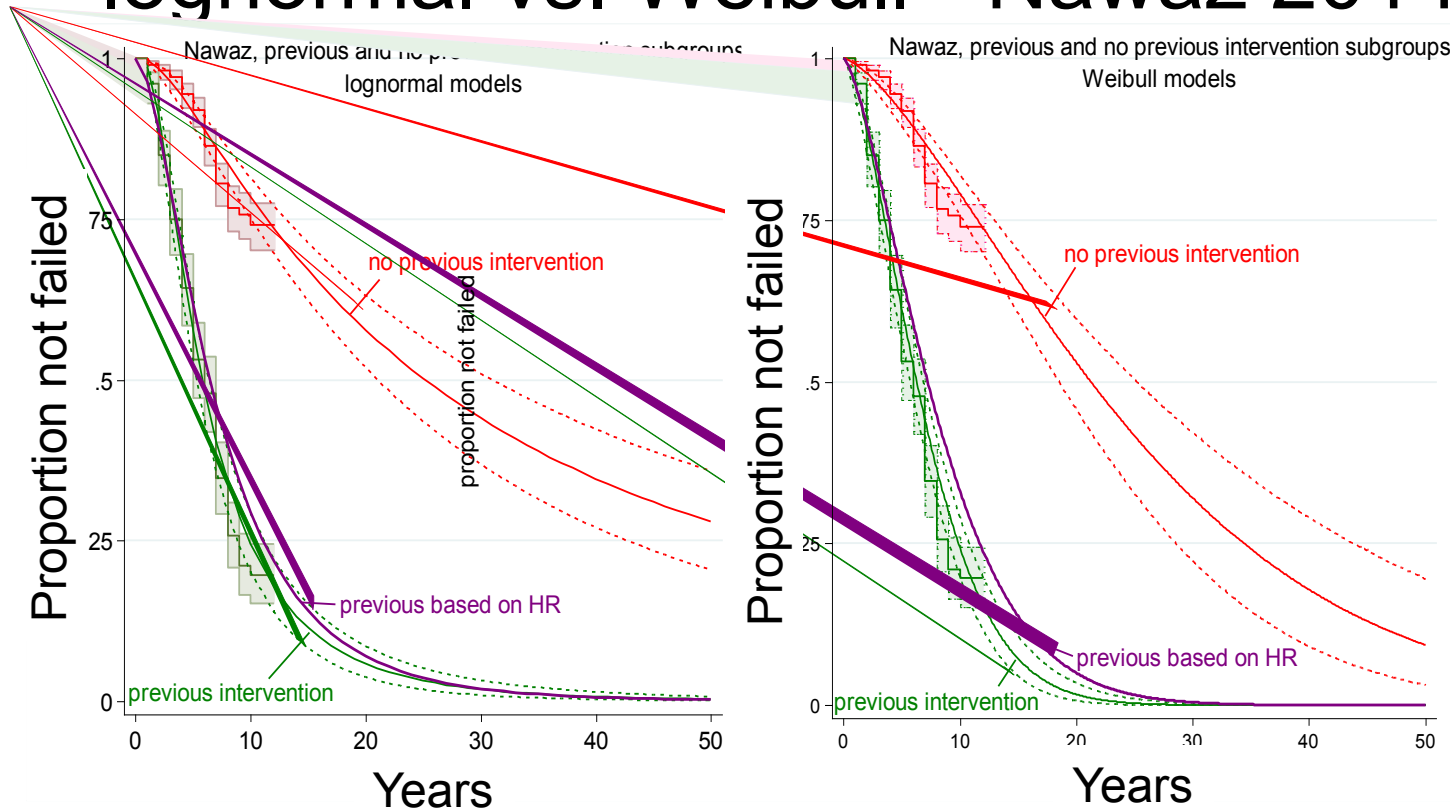
SD = standard deviation; NR = not reported; Med fem = medial femoral; Lat rem = lateral femoral;; * of single site lesions ‡ conference abstract. Data from assessment report 2016: table 1 Dugard et al 2017; tables 3 + 4 pages 35 and 42

Time to failure: ACI (Nawaz 2014)



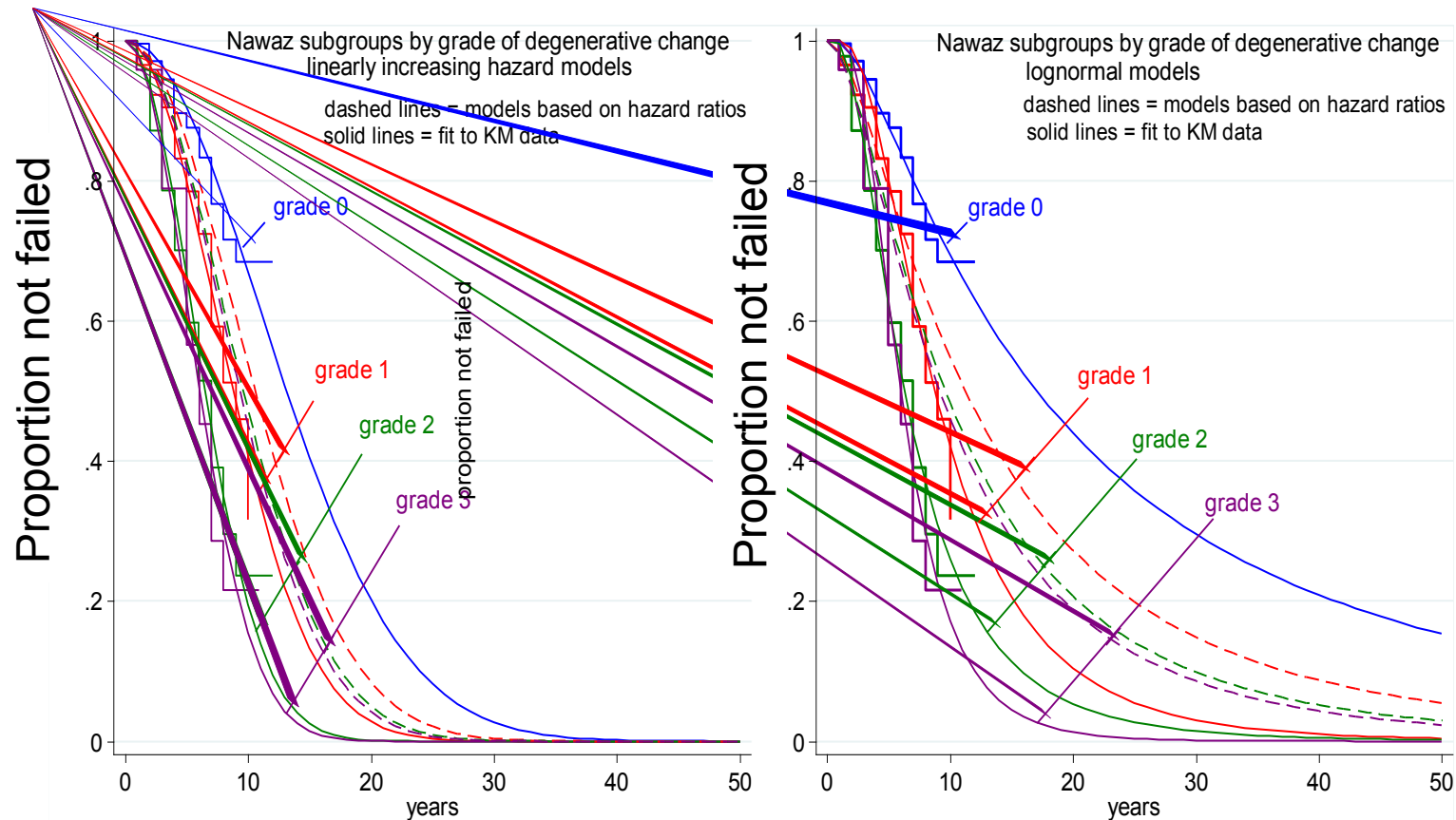
- Up to 6 years, Nawaz observed data consistent with other smaller studies (N.B. Minas $n=210$, Vanlauwe $n=50$, Niemeyer $n=70$, Knutsen $n=40$, failure defined as re-intervention)
- Best statistical fit to Nawaz: log-logistic and gamma
- No difference between ACI (P or C) and MACI time to failure
- Defect size not associated with risk of failure

Subgroup - time to failure: people who have/haven't had previous intervention by lognormal vs. Weibull - Nawaz 2014



- 34% (282) had previous treatments.
- Assessment Group: previous treatments in clinical practice may include palliative (debridement and lavage), repair (microfracture and drilling), restoration (mosaicplasty- small lesions only), reconstruction (knee replacement and allografts)
- ACI failure rate greater in people who had previous repair attempts

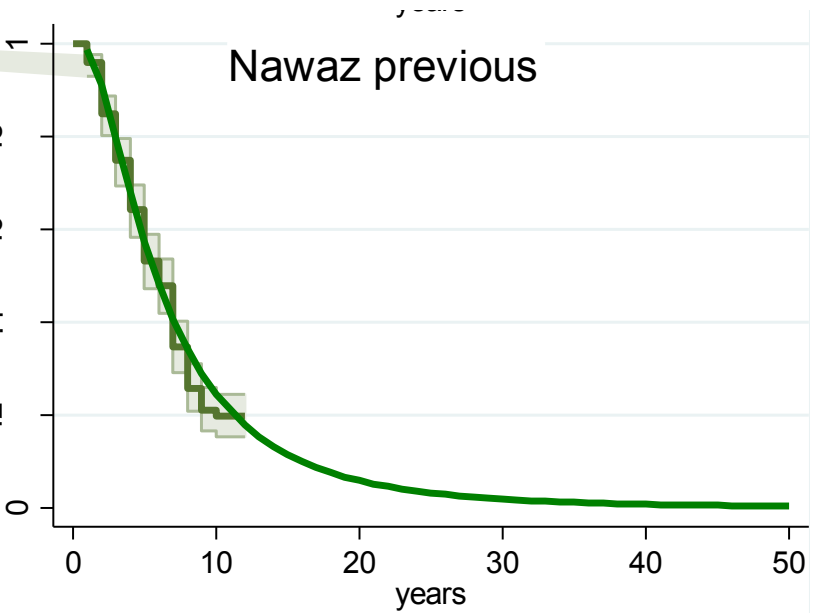
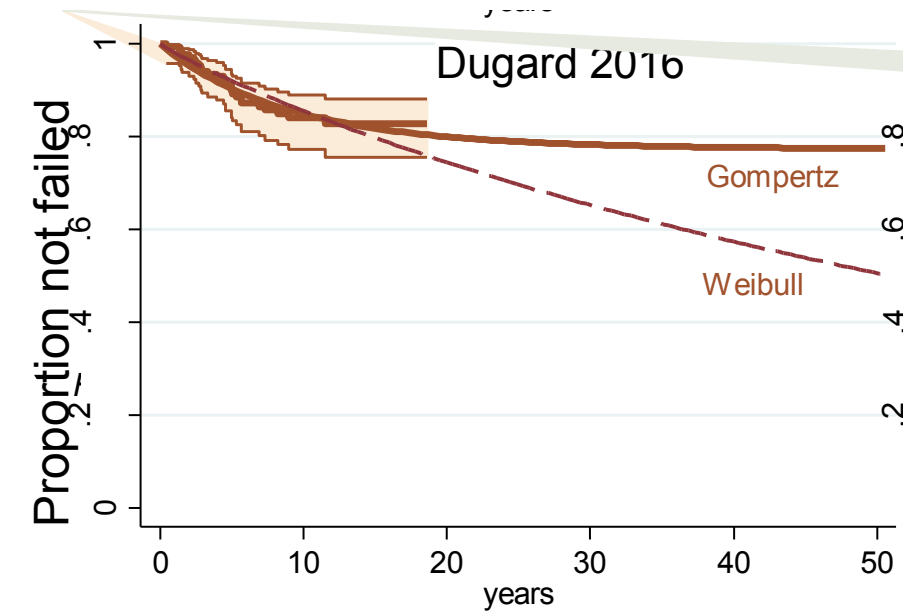
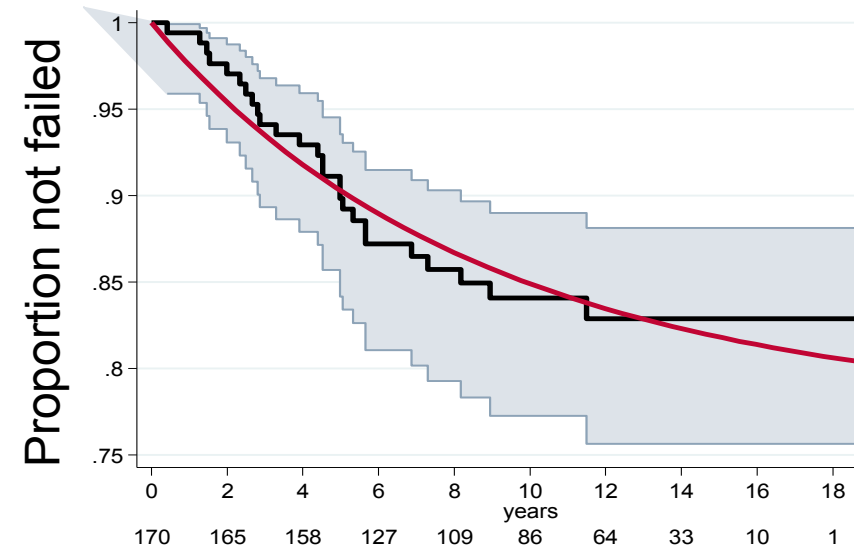
Subgroup: time to failure by osteoarthritic damage at time of surgery -Nawaz 2014



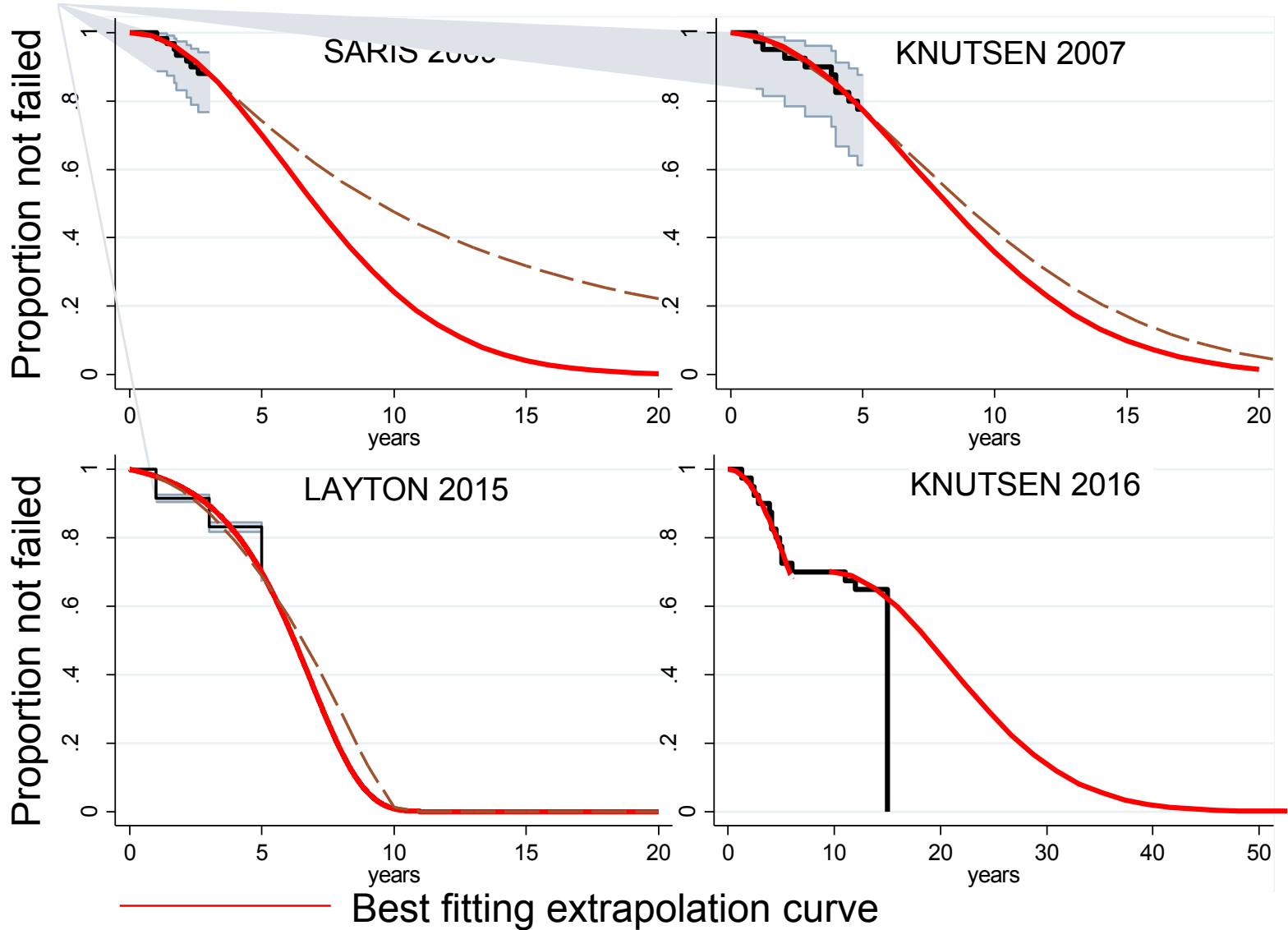
- Failure rates higher with **increasing osteoarthritic damage** at time of ACI

Time to failure traditional ACI-Dugard 2017

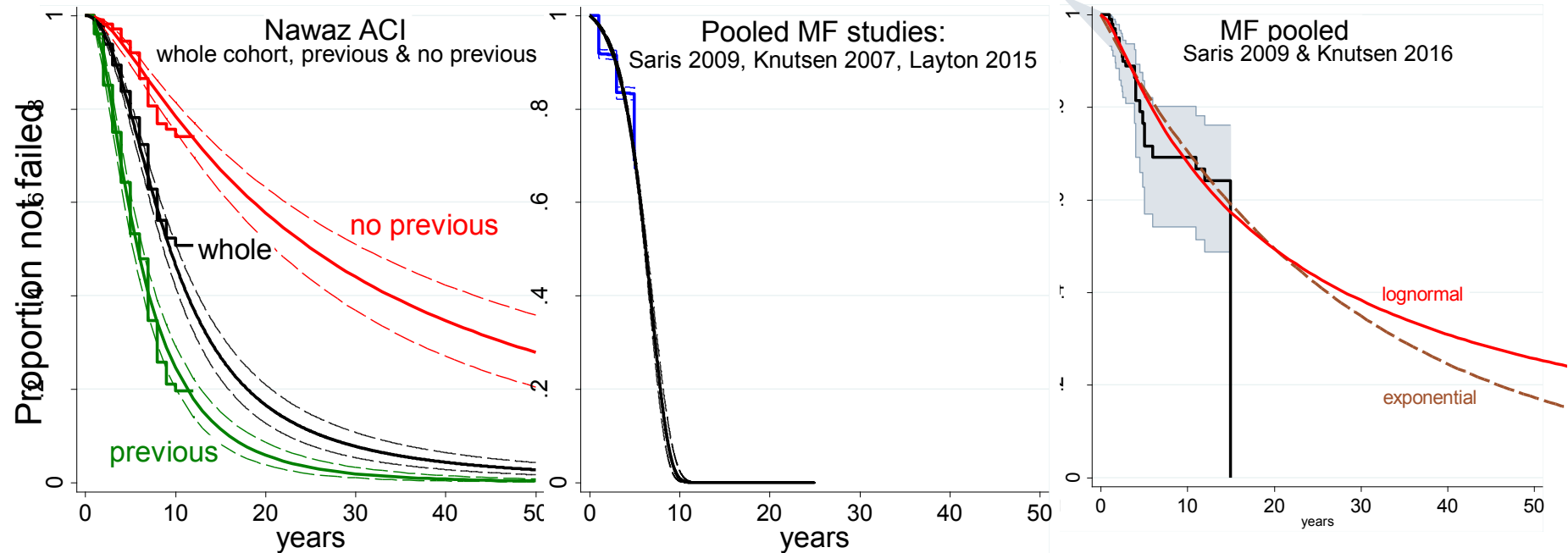
- UK observational study of ACI n = 170
- Data comes from RJAH hospital in Oswestry “traditional ACI” (N.B. separate study/patients from ACTIVE)
- >90% had previous treatment
- Weibull fit data best
- Failure rate in Dugard lower than Nawaz but failure defined as knee replacement (N.B. Nawaz definition broader)



Time to failure MF- Saris, Layton, Knutsen



Data used in assessment group base case



ACI Nawaz

**MF pooled Saris,
Knutsen 2007, Layton**

**MF pooled Saris +
Knutsen 2016**

2016 + 2017 base cases

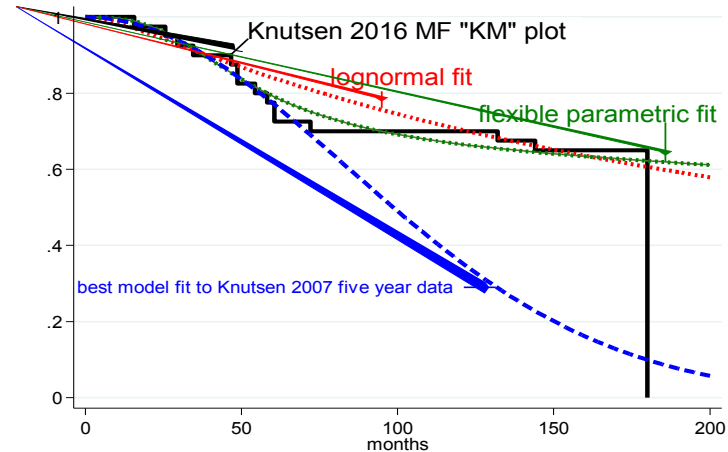
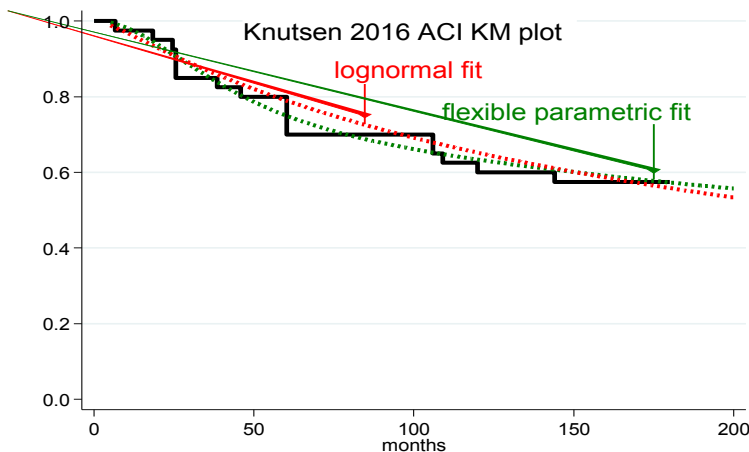
2016 base case

2017 base case

N.B. failure definitions differed between studies. Assessment Group noted Solheim (2016) prospective cohort, n=110. 10-14 years after MF in a 46% had a 'poor outcome', defined as needing knee replacement or a Lysholm score under 64. Symptom scores did improve from baseline but few had normal knee function. 39% had additional surgery.

Knutsen 2016 direct comparison of MF vs ACI

- Only study with long term Kaplan Meier data for both MF and ACI
- At 15 years 17/40 failures with ACI, 13/40 failures with MF
- Cost effectiveness results using extrapolated Knutsen data for ACI and MF presented as sensitivity analysis



- Assessment group also noted potential 'phases of failures'
 - Regular 'event' phase between 0 and ~6 years
 - 'no events phase' between ~6 to ~11 years with MF, between ~5 to 9 years ACI
 - ≈50% of 'non failure' knees had early OA at mean age of 48 years – increased failure rate expected after 15 years?

Additional data on utility values from Vericef (MACI) submitted to NICE 2016

- In 2014 Assessment Group aware of an abstract from SUMMIT trial - patients with chondral defects had a baseline utility of 0.484 (N.B. Assessment Group base case =0.654)

	MACI	Microfracture
Baseline		
N	141	
Mean utility value (SD)	0.484 (0.296)	
Response at week 52		
N	71	68
Mean utility value (SD)	0.7848 (0.2113)	0.7472 (0.2270)
Response at week 104		
N	70	70
Mean utility value (SD)	0.8051 (0.1899)	0.7188 (0.2969)
Response at week 156		
N	65	59
Mean utility value (SD)	0.8131 (0.2105)	0.7769 (0.2553)

Assessment Group 2016 base case and subgroups

Subgroup	ICER ACI (MF) vs. MF (ACI)	ICER, ACI (ACI) vs. MF (ACI)
Base case (all)	£19,050*†	£18,844
Previous repairs	£42,628*†	£38,262
No previous repair	£9,227	£9,363*
Osteoarthritis		
• Kellgren grade 0	£12,138	£12,275*
• Kellgren grade 1	£17,166*†	£17,104
• Kellgren grade 2	£20,424*†	£20,096
• Kellgren grade 3	£21,665*†	£21,207

ACI failure rates: Nawaz (2014).

MF failure rates: pooled data whole pop (Layton, Knutsen (2007), Saris).

* pairwise ICER calculated by NICE,

† ACI (MF) extendedly dominated by MF(ACI) and ACI (ACI) in incremental analysis (data tables 7, 13-17 additional analyses 2016)

Kellgren Lawrence grades of osteoarthritis 0 (no arthritis) - 4 (severe arthritis)

Sensitivity analysis (2016): utility values

Parameter	Sensitivity analysis		ICER ACI (MF) vs. MF (ACI)	ICER, ACI (ACI) vs. MF (ACI)
Base case			£19,050*†	£18,844
Utility, people whose surgery failed + chose no 2 nd repair (0.691 in base case)	0.654 (as before 1 st repair)		£15,769*†	£15,634
	0.817 (as successful repair)		£65,310*†	£62,658
	0.746 (as mid-point between success/before 1 st repair utility value)		£27,594*†	£27,123
Utility data Vericel	MACI	MF	£15,667*†	£15,648
Baseline	0.484			
Week 52	0.7848	0.7472		
Week 104	0.8051	0.7188		
Week 156	0.8131	0.7769		

Assessment Group additional analyses 2016 (tables 10-12, 24). * pairwise ICER calculated by NICE, †ACI (MF) extendedly dominated in incremental analyses

Assessment Group 2017 base case

Data for ACI failure	Data for MF failure	Pairwise ICER ACI (MF) vs. MF (ACI)	Pairwise ICER ACI (ACI) vs. MF (ACI)	table
Nawaz 2014 whole population	Knutsen 2016, Saris 2009 pooled	£14,002	£14,129*	6
Nawaz 2014 previous repair		£22,820* †	£22,288	6
Nawaz 2014 no previous repair		£8,022	£8,155*	6

* Pairwise calculated by NICE, † ACI (MF) extendedly dominated in incremental, ‡ dominated in incremental. Green rows base case 2017. Assessment group addendum 2017 tables 3-7 (see 'table' column)

Assessment Group sensitivity analyses: data sources and extrapolation

Data for ACI failure	Data for MF failure	Pairwise ICER ACI (MF) vs. MF (ACI)	Pairwise ICER ACI (ACI) vs. MF (ACI)	table
Nawaz 2014 whole population	Layton 2015, Knutsen 2016, Saris 2009 pooled	£17,480*†	£17,401	5
Nawaz 2014 previous repair		£35,268*†	£32,636	5
Nawaz 2014 no previous repair		£8,868	£9,005*	5
Knutsen 2016 lognormal model		£9,351	£9,561*	4
Dugard 2017	Layton 2015, Knutsen 2016, Saris 2009 pooled	£7,050	£7,143*	7
Dugard 2017	Knutsen 2016, Saris 2009	£6,556	£6,333*	7

* Pairwise calculated by NICE, † ACI (MF) extendedly dominated in incremental, ‡ dominated in incremental, Green rows base case 2017. Assessment group addendum 2017 tables 4, 5, 7 (see 'table' column)

Sensitivity analyses changing cost of cells

Cost of cells	ICER ACI (MF) vs. MF (ACI)	ICER, ACI (ACI) vs. MF (ACI)	Table
2016 base case £16,000‡	£19,050*†	£18,844	
£8000	£9,803*†	£9,700	21
£12,000	£14,427*†	£14,272	22
2017 base case £16,000‡	£14,002*	£14,129*	
£8000	4126	£4196*	9
£12,000	6074	£6175*	9

- ‡ Approximate list price of ChondroCelect and MACI.
- N.B. Confidential discounts provided by companies to NHS by companies make evaluating *real* cost difficult
- RJAH, Oswestry state cost of cells produced in hospital affiliated lab £9,159 to £12,361 (in own Trust £9,266)
- In both 2016 and 2017 modelling, Assessment Group used committee's preferred costs for cell harvesting (£870) and implanting (£2,396)
- * Pairwise ICER calculated by NICE, † ACI (MF) extendedly dominated

Consultation comments on Assessment Group's additional analyses

2016 additional analyses sent to all consultees.

2017 addendum sent to Vericel and RJAH, Oswestry

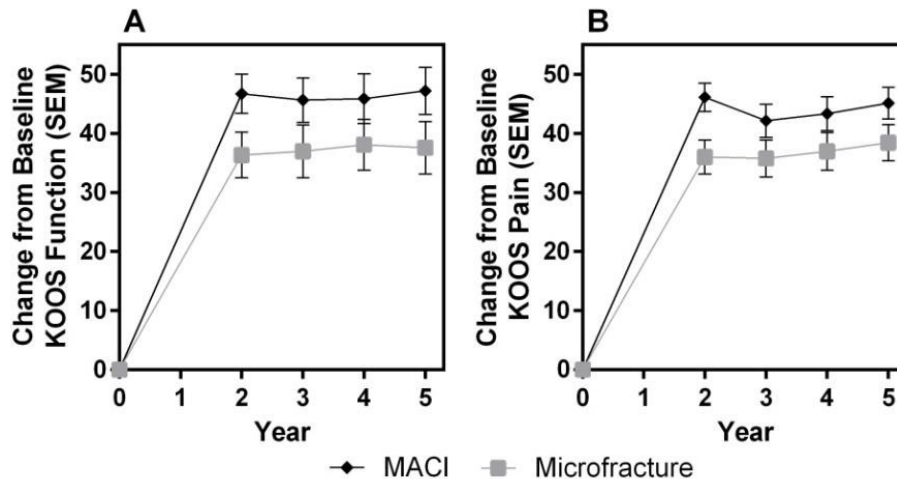
- Comments on the 2016 additional analyses were received from:
 1. Cartilage Research Foundation (submitted via Vericel)
 2. International Cartilage Repair Foundation (submitted via Vericel)
 3. British Association for Surgery of the Knee (BASK)
 4. Vericel
 5. RJAH, Oswestry
- In 2016 (after 2nd committee meeting), 29 statements from patients who had ACI

Consultation comments: themes

Theme	Comments
Evidence base	30 year anniversary of ACI - clinical benefit documented
Assessment Group 2016 analyses	Concur with [2016] report conclusions. Nawaz suitable for modelling ACI. “By using the full cohort (including patients with prior interventions and early degenerative joint disease).....this study represents a very conservative estimate of effectiveness of ACI, but provides insight into the true UK experience”
Treatment pathway	<p>ACI works best as 1st treatment</p> <p>ACI only option for:</p> <ul style="list-style-type: none"> • Cartilage defects from previous operations • Large cartilage defects <p>“ACI often reserved for more challenging lesions: early OA, degenerative lesions, large chronic lesions having failed multiple treatments.”</p>
Price and service provision ACI	Cost of procedure £9,159 to £12,361. Patients eligible for ACI ~300 /year. ‘..other centres (who we would happily assist ..) would be encouraged to grow cells.’ (RJAH, Oswestry).

Consultation comments: data for Assessment Group modelling (2)

- **Vericel:** SUMMIT (MACI vs. MF) extension study. Improvements in KOOS pain and function scores maintained at 5 years



3 studies (Australia, Germany and Austria) with minimum 5 year follow-up. Outcomes consistent with SUMMIT (improvements in pain and function by 36 weeks and maintained at 5 years)

- **Vericel:** Brigham and Women's Hospital 20 year database. >800 patients. Majority had > 1 cartilage defect. Few treatments able to treat larger lesions or lesions in patellofemoral joint - in these people 80% patient satisfied with ACI
- **International Cartilage Repair Society:** Systematic review (Kon et al 2017). Failure rates with ACI (n=1974) + MACI (n=1493). Failure rates over mean follow up of 7.2 years: All ACI 15%; MACI 10%

29 statements from patients (2016)

- Symptoms include pain, swelling, locking and instability
- Injuries impact quality of life and self esteem. Couldn't be active when sport had been important part of lives had negative effect on mood
- ACI/MACI carried out at different centres
- Typically patients were <60 years when had surgery and had been active and sporty before knee injuries
- Recovery time long, but benefits made up for it.
- People were able to resume a level of activity with which they were satisfied; considered the degree of symptom reversal good.
- Quality of life restored

Key issues for consideration

Theme	Issue
Intervention	Chondrocelect is no longer available. Is MACI available?
	Is it still reasonable to assume a class effect between different types of ACI in decision making?
Comparators	<p>What treatment options are available for people With osteoarthritic damage to the knee? Who have had previous knee cartilage repair surgery? With larger lesions?</p>
Outcomes	<p>Do new data/ analyses suggest ACI is an effective treatment post 5 years? Which data sources are appropriate for modelling long-term success rates of ACI and MF?</p>
Naïve comparison	How would differences in definition of failure and study populations affect the modelled estimate of clinical and cost effectiveness of ACI compared with MF?
Costs	What is the price of ACI used in current practice?
Subgroups	Is there evidence that effectiveness differs by subgroup?
	Is there evidence that cost effectiveness differs by subgroup?
	Are there any other potential subgroups of interest?

Decision tree

