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Safety Notices and Vigilance - a Healthcare Professional's view Opportunities and Challenges

**Mr Tim Wilton MA FRCS Medical Director National
Joint Registry (UK)**



Conflict of Interest Statement

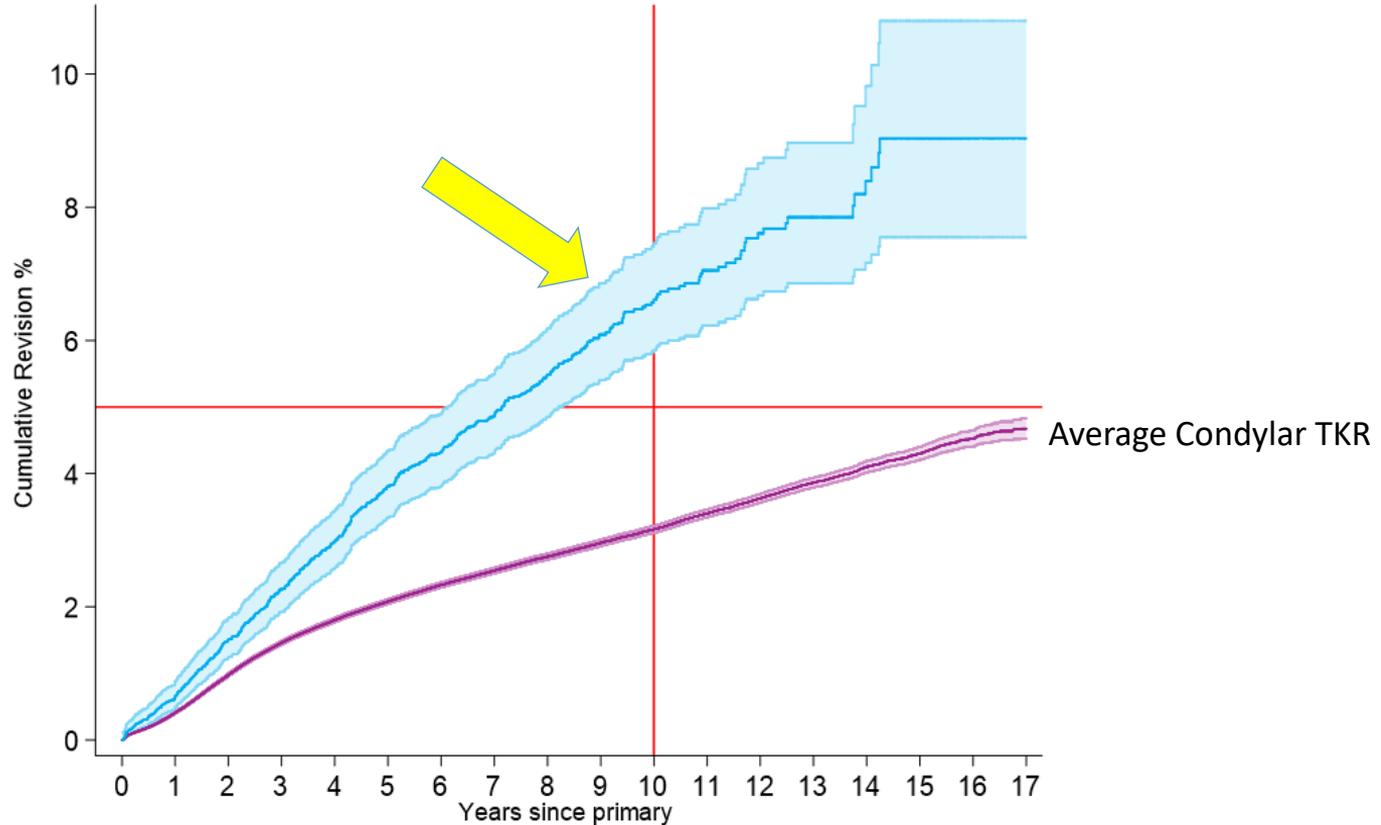
- Medical Director National Joint Registry
- Previously Chairman and Council member of Bone and Joint Journal
- President British Orthopaedic Association 2016
- President BASK 2010-2012
- Member of Orthopaedic Data Evaluation Panel (ODEP)
- Design Consultant Smith and Nephew 2003-2009
- No royalties at any time
- No shares or financial interests in any related company
- No financial support for Unit or Research from Industry

Post Market Vigilance

- Can be by 'after event' reporting eg 'yellow card' system in UK
- Can be by routine collection of data eg in Registries
- Registries rely on pre-determined outcome collection (eg Revision)
- Registries have the capacity to link to other databases (eg Mortality)
- Registries are more likely to capture all cases and all specified failures
- Registries can't identify outcomes where the data are not either collected in the registry OR a linked database



If an Implant had this revision rate would you want to know / do something about it?



HOW BEST TO DETECT FAILED DEVICES?

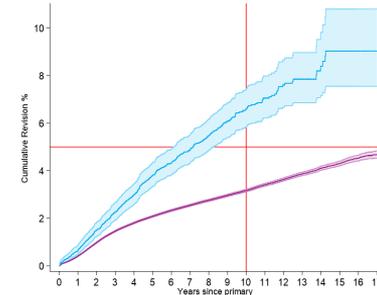
- Any MISSED complication delays or prevents detection
- Reporting systems for 'Failure' are not usually robust
- Reports to MHRA about devices numbered about 15000 per year in 2012
- The same year there were 15000 revision hip and knee replacements
- About 2% of these were reported to the MHRA



Registry Background

- NJR usual analysis has been on the basis of ‘whole brand’ with REVISION operation as the outcome measure
- In recent years this has been subdivided for knees according to Cruciate Retaining or Posterior Stabilised knees and also separated by patella resurfacing/not resurfacing (ie 4 groups)
- Statistically significant differences between large cohorts are common (?important)
- ‘Outlier’ implants are defined as showing 50% (Alert) or 100% (Alarm) higher than expected revision rate **compared to the Combined CR/PS average**

That device happens to be part of the Nexgen family



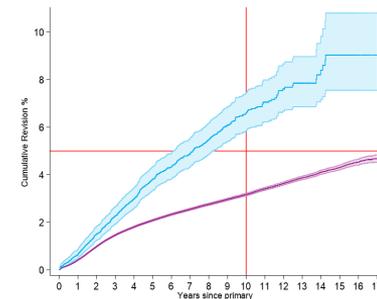
- Overall performance one of the more satisfactory knees

NJR Annual Report Data 2022

Brand ¹	N	Median (IQR) age at primary	Male (%)	Time since primary					
				1 year	3 years	5 years	10 years	15 years	18 years
Nexgen Hinge Type[Fem:Tib]	1,056	73 (64 to 80)	26	1.19 (0.68-2.09)	2.67 (1.79-3.97)	3.88 (2.72-5.54)	7.47 (5.11-10.84)	9.36 (6.22-13.95)	
Nexgen LCCK[Fem] Nexgen[Tib]	1,181	71 (64 to 79)	36	1.22 (0.72-2.04)	2.67 (1.85-3.85)	3.26 (2.30-4.62)	4.85 (3.29-7.11)	8.20 (4.17-15.76)	
Nexgen[Fem:Tib]	183,105	70 (64 to 76)	42	0.38 (0.35-0.41)	1.26 (1.20-1.31)	1.97 (1.90-2.04)	3.38 (3.27-3.49)	4.52 (4.33-4.71)	5.32 (4.80-5.90)
Nexgen[Fem] LPS (Legacy Posterior Stabilised ZimmerBiomet)[Tib]	3,319	67 (59 to 75)	46	0.46 (0.28-0.76)	1.84 (1.43-2.37)	2.56 (2.06-3.18)	4.20 (3.49-5.04)	5.90 (4.84-7.17)	7.11 (5.51-9.14)
Nexgen[Fem] TM Monoblock[Tib]	4,286	64 (58 to 71)	57	0.61 (0.42-0.90)	2.60 (2.16-3.13)	3.28 (2.78-3.87)	4.35 (3.76-5.05)	5.24 (4.41-6.08)	5.62 (4.75-6.64)
Optetrak CR[Fem] Optetrak[Tib]	1,641	70 (63 to 76)	43	0.86 (0.51-1.45)	3.44 (2.65-4.46)	4.89 (3.93-6.08)	8.17 (6.84-9.74)	10.72 (8.75-13.10)	



Nexgen Knee Family (Brand)



- Many surgeons have reported good outcomes
- *Keohane et al 2020* and *Brown et al 2021* expressed concern over high failure rate in some variants
- In 2016 the Sub-Brand Nexgen LPS was highlighted by NJR Implant Scrutiny Committee as having a high Revision Rate and referred to MHRA

Further Process

- What happens after reporting an implant?
- Discussions between Regulator and Manufacturer?
- Discussions with Clinical organisations?
- Requests for **Independent** study results?

Nexgen is a Complex Family

- There are similar designs which have different surface treatment
- The bearings can be mobile or fixed
- The ligaments can be retained or removed
- The Kneecap can be resurfaced or not
- Two different polyethylene materials can be used
- Most of these combinations are permitted

Detailed Nexgen Analysis

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Variants

CR Constructs Tibial - Bearing	All CR Nexgen Femoral Components	CR Option	CR Precoat	CR Porous	CR Flex Precoat	CR Flex GSF Precoat	CR Flex Porous
Stemmed Cemented Option - CR Flex Std	82,684	62,190	848	561	12,807	6,276	2
Stemmed Cemented Option - CR Flex Prolong	1,605	208	0	2	986	344	5
Stemmed Precoat - CR Flex Std	8,203	2,305	138	49	4,409	1,299	3
Stemmed Precoat - CR Flex Prolong	2,090	9	3	0	1,443	628	7
TM Tray - CR Flex Std	219	4	0	147	2	1	65
TM Tray - CR Flex Prolong	91	0	0	7	0	1	83
TM CR Monoblock	4,264	140	6	3,676	74	52	316
All Poly Tibia	952	803	1	0	39	109	0
All Tibial Components	100,108	66,339	998	4,594	19,773	8,715	481

PS Constructs Tibial - Bearing	All LPS Nexgen Femoral Components	LPS Option	LPS Porous	LPS Flex Option	LPS Flex GSF Option	LPS Flex Titanium
Stemmed Cemented Option - LPS Flex Std	69,372	58,779	86	6,859	3,571	77
Stemmed Cemented Option - LPS Flex Prolong	696	76	0	345	74	201
Stemmed Precoat - LPS Flex Std	9,184	6,041	4	2,610	488	41
Stemmed Precoat - LPS Flex Prolong	881	8	0	248	168	457
LPS Fluted Precoat - LPS Std Mobile	501	0	0	345	156	0
TM Tray - LPS Flex Std	370	10	359	1	0	0
TM Tray - LPS Flex Prolong	4	0	3	0	0	1
TM LPS Monoblock	1,888	74	1,796	7	4	7
All Tibial Components	82,896	70,704	2,263	11,458	4,652	785

Large numbers so Statistical significance quite likely

NEXGEN VARIANTS

Revised / Expected vs. all other NJR TKR: Comparison with average

Revision rate vs. all other bicondylar knees	All CR Nexgen Femoral Components	CR Option	CR Precoat	CR Porous	CR Flex Precoat	CR Flex GSF Precoat	CR Flex Porous
Stemmed Cemented Option - CR Flex Std	0.76 (0.72 - 0.81)	0.75 (0.71 - 0.80)	0.84 (0.44 - 1.48)	0.47 (0.22 - 0.86)	0.80 (0.70 - 0.91)	0.81 (0.66 - 0.98)	0.00 (0.00 - 50.76)
Stemmed Cemented Option - CR Flex Prolong	0.51 (0.27 - 0.87)	0.37 (0.01 - 2.06)		0.00 (0.00 - 67.38)	0.61 (0.29 - 1.12)	0.32 (0.04 - 1.15)	0.00 (0.00 - 30.86)
Stemmed Precoat - CR Flex Std	0.72 (0.61 - 0.84)	0.79 (0.57 - 1.08)	0.58 (0.07 - 2.11)	0.00 (0.00 - 2.06)	0.63 (0.50 - 0.78)	1.00 (0.68 - 1.41)	0.00 (0.00 - 62.37)
Stemmed Precoat - CR Flex Prolong	1.13 (0.85 - 1.48)	0.00 (0.00 - 10.78)	0.00 (0.00 - 59.00)		1.01 (0.70 - 1.42)	1.45 (0.91 - 2.20)	0.00 (0.00 - 9.50)
TM Tray - CR Flex Std	0.58 (0.16 - 1.50)	0.00 (0.00 - 44.06)		0.66 (0.14 - 1.93)	0.00 (0.00 - 109.05)	0.00 (0.00 - 133.71)	0.46 (0.01 - 2.58)
TM Tray - CR Flex Prolong	0.71 (0.09 - 2.58)			0.00 (0.00 - 11.82)		0.00 (0.00 - 41.63)	0.83 (0.10 - 3.01)
TM CR Monoblock	1.00 (0.86 - 1.16)	0.60 (0.16 - 1.54)	0.00 (0.00 - 14.98)	0.99 (0.84 - 1.15)	0.81 (0.22 - 2.07)	1.64 (0.45 - 4.19)	1.42 (0.81 - 2.31)
All Poly Tibia	0.67 (0.34 - 1.16)	0.64 (0.31 - 1.18)	0.00 (0.00 - 137.10)		3.27 (0.40 - 11.81)	0.00 (0.00 - 2.12)	
All Tibial Components	0.79 (0.75 - 0.82)	0.76 (0.71 - 0.80)	0.78 (0.42 - 1.30)	0.89 (0.77 - 1.04)	0.77 (0.70 - 0.86)	0.88 (0.75 - 1.03)	1.16 (0.70 - 1.80)

Revision rate vs. all other bicondylar knees	All LPS Nexgen Femoral Components	LPS Option	LPS Porous	LPS Flex Option	LPS Flex GSF Option	LPS Flex Titanium
Stemmed Cemented Option - LPS Flex Std	1.35 (1.30 - 1.41)	1.24 (1.18 - 1.30)	1.14 (0.28 - 2.6)	2.04 (1.83 - 2.26)	1.85 (1.58 - 2.16)	2.34 (0.64 - 6.00)
Stemmed Cemented Option - LPS Flex Prolong	1.55 (1.01 - 2.29)	2.02 (0.65 - 4.71)		1.45 (0.72 - 2.55)	0.57 (0.01 - 3.17)	1.88 (0.81 - 3.70)
Stemmed Precoat - LPS Flex Std	0.93 (0.82 - 1.06)	0.72 (0.59 - 0.87)	0.00 (0.00 - 18.89)	1.32 (1.08 - 1.61)	1.07 (0.55 - 1.87)	2.62 (0.32 - 9.47)
Stemmed Precoat - LPS Flex Prolong	1.63 (1.10 - 2.33)	0.00 (0.00 - 25.74)		1.69 (0.81 - 3.10)	1.29 (0.42 - 3.02)	1.78 (1.00 - 2.93)
LPS Fluted Precoat - LPS Std Mobile	1.18 (0.54 - 2.24)			1.17 (0.43 - 2.54)	1.21 (0.25 - 3.54)	
TM Tray - LPS Flex Std	1.26 (0.71 - 2.08)	0.00 (0.00 - 13.93)	1.29 (0.72 - 2.13)	0.00 (0.00 - 293.12)		
TM Tray - LPS Flex Prolong	5.01 (0.13 - 27.91)		0.00 (0.00 - 19.98)			66.53 (1.68 - 370.70)
TM LPS Monoblock	0.83 (0.64 - 1.06)	0.90 (0.25 - 2.31)	0.79 (0.60 - 1.02)	1.87 (0.05 - 10.44)	8.74 (1.06 - 31.56)	2.30 (0.06 - 12.80)
All Tibial Components	1.27 (1.22 - 1.32)	1.17 (1.12 - 1.22)	0.87 (0.69 - 1.09)	1.76 (1.61 - 1.91)	1.65 (1.42 - 1.90)	1.98 (1.34 - 2.81)

Revised / Expected (95% CI)
Adjusted for patient age and gender

p < 0.001	p < 0.001
p < 0.05	p < 0.05

Outlier status requires 50% or 100% increase compared to class average

NEXGEN VARIANTS

Potential Outlier status vs. all other NJR TKR

Potential outlier status cf. all other bicondylar knees	All CR Nexgen Femoral Components	CR Option	CR Precoat	CR Porous	CR Flex Precoat	CR Flex GSF Precoat	CR Flex Porous
Stemmed Cemented Option - CR Flex Std	0.76 (0.72 - 0.81)	0.75 (0.71 - 0.80)	0.84 (0.44 - 1.48)	0.47 (0.22 - 0.86)	0.80 (0.70 - 0.91)	0.81 (0.66 - 0.98)	0.00 (0.00 - 50.76)
Stemmed Cemented Option - CR Flex Prolong	0.51 (0.27 - 0.87)	0.37 (0.01 - 2.06)		0.00 (0.00 - 67.38)	0.61 (0.29 - 1.12)	0.32 (0.04 - 1.15)	0.00 (0.00 - 30.86)
Stemmed Precoat - CR Flex Std	0.72 (0.61 - 0.84)	0.79 (0.57 - 1.08)	0.58 (0.07 - 2.11)	0.00 (0.00 - 2.06)	0.63 (0.50 - 0.78)	1.00 (0.68 - 1.41)	0.00 (0.00 - 62.37)
Stemmed Precoat - CR Flex Prolong	1.13 (0.85 - 1.48)	0.00 (0.00 - 10.78)	0.00 (0.00 - 59.00)		1.01 (0.70 - 1.42)	1.45 (0.91 - 2.20)	0.00 (0.00 - 9.50)
TM Tray - CR Flex Std	0.58 (0.16 - 1.50)	0.00 (0.00 - 44.06)		0.66 (0.14 - 1.93)	0.00 (0.00 - 109.05)	0.00 (0.00 - 133.71)	0.46 (0.01 - 2.58)
TM Tray - CR Flex Prolong	0.71 (0.09 - 2.58)			0.00 (0.00 - 11.82)		0.00 (0.00 - 41.63)	0.83 (0.10 - 3.01)
TM CR Monoblock	1.00 (0.86 - 1.16)	0.60 (0.16 - 1.54)	0.00 (0.00 - 14.98)	0.99 (0.84 - 1.15)	0.81 (0.22 - 2.07)	1.64 (0.45 - 4.19)	1.42 (0.81 - 2.31)
All Poly Tibia	0.67 (0.34 - 1.16)	0.64 (0.31 - 1.18)	0.00 (0.00 - 137.10)		3.27 (0.40 - 11.81)	0.00 (0.00 - 2.12)	
All Tibial Components	0.79 (0.75 - 0.82)	0.76 (0.71 - 0.80)	0.78 (0.42 - 1.30)	0.89 (0.77 - 1.04)	0.77 (0.70 - 0.86)	0.88 (0.75 - 1.03)	1.16 (0.70 - 1.80)

Potential outlier status cf. all other bicondylar knees	All LPS Nexgen Femoral Components	LPS Option	LPS Porous	LPS Flex Option	LPS Flex GSF Option	LPS Flex Titanium
Stemmed Cemented Option - LPS Flex Std	1.35 (1.30 - 1.41)	1.24 (1.18 - 1.30)	1.02 (0.28 - 2.66)	2.04 (1.83 - 2.26)	1.85 (1.58 - 2.16)	2.34 (0.64 - 6.00)
Stemmed Cemented Option - LPS Flex Prolong	1.55 (1.01 - 2.29)	2.02 (0.65 - 4.71)		1.45 (0.72 - 2.59)	0.57 (0.01 - 3.17)	1.88 (0.81 - 3.70)
Stemmed Precoat - LPS Flex Std	0.93 (0.82 - 1.06)	0.72 (0.59 - 0.87)	0.00 (0.00 - 18.89)	1.32 (1.08 - 1.61)	1.07 (0.55 - 1.87)	2.62 (0.32 - 9.47)
Stemmed Precoat - LPS Flex Prolong	1.63 (1.10 - 2.33)	0.00 (0.00 - 25.74)		1.69 (0.81 - 3.10)	1.29 (0.42 - 3.02)	1.78 (1.00 - 2.93)
LPS Fluted Precoat - LPS Std Mobile	1.18 (0.54 - 2.24)			1.17 (0.43 - 2.54)	1.21 (0.25 - 3.54)	
TM Tray - LPS Flex Std	1.26 (0.71 - 2.08)	0.00 (0.00 - 13.93)	1.29 (0.72 - 2.13)	0.00 (0.00 - 293.12)		
TM Tray - LPS Flex Prolong	5.01 (0.13 - 27.91)		0.00 (0.00 - 19.98)			66.53 (1.68 - 370.70)
TM LPS Monoblock	0.83 (0.64 - 1.06)	0.90 (0.25 - 2.31)	0.79 (0.60 - 1.02)	1.87 (0.05 - 10.44)	8.74 (1.06 - 31.56)	2.30 (0.06 - 12.80)
All Tibial Components	1.27 (1.22 - 1.32)	1.17 (1.12 - 1.22)	0.87 (0.69 - 1.09)	1.76 (1.61 - 1.91)	1.65 (1.42 - 1.90)	1.98 (1.34 - 2.81)

Revised / Expected (95% CI)
Adjusted for patient age and gender

LCI > 2x expected	UCI < 1/2 expected
LCI > 1.5x expected	UCI < 2/3 expected
LCI > 1.2x expected	UCI < 5/6 expected

Potential Outlier Status just for Tibial Loosening

NEXGEN VARIANTS

Potential Outlier Status - Aseptic Tibial Loosening	All CR Nexgen Femoral Components	CR Option	CR Precoat	CR Porous	CR Flex Precoat	CR Flex GSF Precoat	CR Flex Porous
Stemmed Cemented Option - CR Flex Std	1.14 (1.02 - 1.27)	1.13 (0.99 - 1.28)	2.13 (0.58 - 5.46)	0.20 (0.01 - 1.14)	1.13 (0.85 - 1.48)	1.43 (0.98 - 2.02)	0.00 (0.00 - 308.32)
Stemmed Cemented Option - CR Flex Prolong	1.20 (0.33 - 3.08)	0.00 (0.00 - 10.16)		0.00 (0.00 - 441.81)	2.01 (0.55 - 5.15)	0.00 (0.00 - 3.91)	0.00 (0.00 - 158.23)
Stemmed Precoat - CR Flex Std	0.89 (0.63 - 1.22)	1.20 (0.60 - 2.14)	0.00 (0.00 - 6.05)	0.00 (0.00 - 8.19)	0.64 (0.37 - 1.02)	1.72 (0.82 - 3.16)	0.00 (0.00 - 494.07)
Stemmed Precoat - CR Flex Prolong	0.80 (0.29 - 1.74)	0.00 (0.00 - 70.77)	0.00 (0.00 - 549.99)		0.62 (0.13 - 1.81)	1.18 (0.24 - 3.46)	0.00 (0.00 - 43.97)
TM Tray - CR Flex Std	0.00 (0.00 - 3.05)	0.00 (0.00 - 202.73)		0.00 (0.00 - 4.60)	0.00 (0.00 - 674.89)	0.00 (0.00 - 758.69)	0.00 (0.00 - 9.72)
TM Tray - CR Flex Prolong	0.00 (0.00 - 7.65)			0.00 (0.00 - 63.55)		0.00 (0.00 - 139.27)	0.00 (0.00 - 9.28)
TM CR Monoblock	0.36 (0.21 - 0.59)	0.00 (0.00 - 2.53)	0.00 (0.00 - 73.58)	0.39 (0.22 - 0.64)	0.00 (0.00 - 3.29)	0.00 (0.00 - 6.93)	0.49 (0.01 - 2.75)
All Poly Tibia	0.00 (0.00 - 1.66)	0.00 (0.00 - 1.92)	0.00 (0.00 - 1077.67)		0.00 (0.00 - 46.28)	0.00 (0.00 - 16.80)	
All Tibial Components	1.01 (0.91 - 1.11)	1.11 (0.97 - 1.25)	1.56 (0.43 - 4.00)	0.36 (0.21 - 0.58)	0.94 (0.74 - 1.18)	1.41 (1.03 - 1.88)	0.34 (0.01 - 1.90)

Potential Outlier Status - Aseptic Tibial Loosening	All LPS Nexgen Femoral Components	LPS Option	LPS Porous	LPS Flex Option	LPS Flex GSF Option	LPS Flex Titanium
Stemmed Cemented Option - LPS Flex Std	2.92 (2.74 - 3.12)	2.52 (2.33 - 2.72)	3.31 (0.68 - 9.6)	5.41 (4.64 - 6.28)	4.49 (3.55 - 5.62)	0.00 (0.00 - 11.13)
Stemmed Cemented Option - LPS Flex Prolong	3.21 (1.47 - 6.09)	3.97 (0.48 - 14.33)		4.28 (1.59 - 5.56)	0.00 (0.00 - 12.13)	2.42 (0.29 - 8.75)
Stemmed Precoat - LPS Flex Std	1.33 (1.03 - 1.70)	0.77 (0.49 - 1.16)	0.00 (0.00 - 91.24)	2.27 (1.61 - 3.12)	1.88 (0.51 - 4.80)	0.00 (0.00 - 26.35)
Stemmed Precoat - LPS Flex Prolong	2.14 (0.86 - 4.42)	0.00 (0.00 - 345.54)		0.97 (0.02 - 5.43)	0.00 (0.00 - 5.40)	3.88 (1.42 - 8.45)
LPS Fluted Precoat - LPS Std Mobile	0.91 (0.02 - 5.07)			0.00 (0.00 - 5.18)	2.00 (0.07 - 14.42)	
TM Tray - LPS Flex Std	0.44 (0.01 - 2.42)	0.00 (0.00 - 73.50)	0.45 (0.01 - 2.48)	0.00 (0.00 - 3449.84)		
TM Tray - LPS Flex Prolong	0.00 (0.00 - 95.59)		0.00 (0.00 - 98.95)			0.00 (0.00 - 2813.41)
TM LPS Monoblock	0.27 (0.09 - 0.62)	0.00 (0.00 - 3.34)	0.29 (0.09 - 0.67)	0.00 (0.00 - 26.30)	0.00 (0.00 - 72.67)	0.00 (0.00 - 33.53)
All Tibial Components	2.41 (2.27 - 2.55)	2.20 (2.05 - 2.35)	0.43 (0.20 - 0.82)	3.76 (3.30 - 4.26)	3.67 (2.92 - 4.55)	2.70 (1.16 - 5.31)

Worst outcomes for Tibial Loosening

- Combination of THREE associated factors-
- Flex Femoral Component
- LPS Components
- Absence of PMMA Precoat on Tibial Baseplate
- It does NOT appear to be simply the Non-Precoat Tibia so removing that from the market is likely to address only part of the issue

Formal Notification to MHRA

- Early 2022 these problematic combinations were reported
- Further discussion occurred with manufacturer and MHRA then FDA
- Manufacturer noted that these UK findings were not identified globally
- They suggested 'rationalisation' of the implant portfolio without safety concerns being raised
- Pressure applied by MHRA and FDA to issue a Safety Notice

FSN Issued and 'Option' Tibia withdrawn

- December 2022 Field Safety Notice issued identifying the 'Option' Tibial component as having a high revision rate
- 'Option' tibial implant withdrawn from market and limited follow-up advice given
- Concerns expressed by many surgeons that they should notify all existing patients with affected devices and consider follow-up examination
- Urgent consultation required with professional organisations, surgeons and registry about how much intervention is required and from whom

Registry Actions

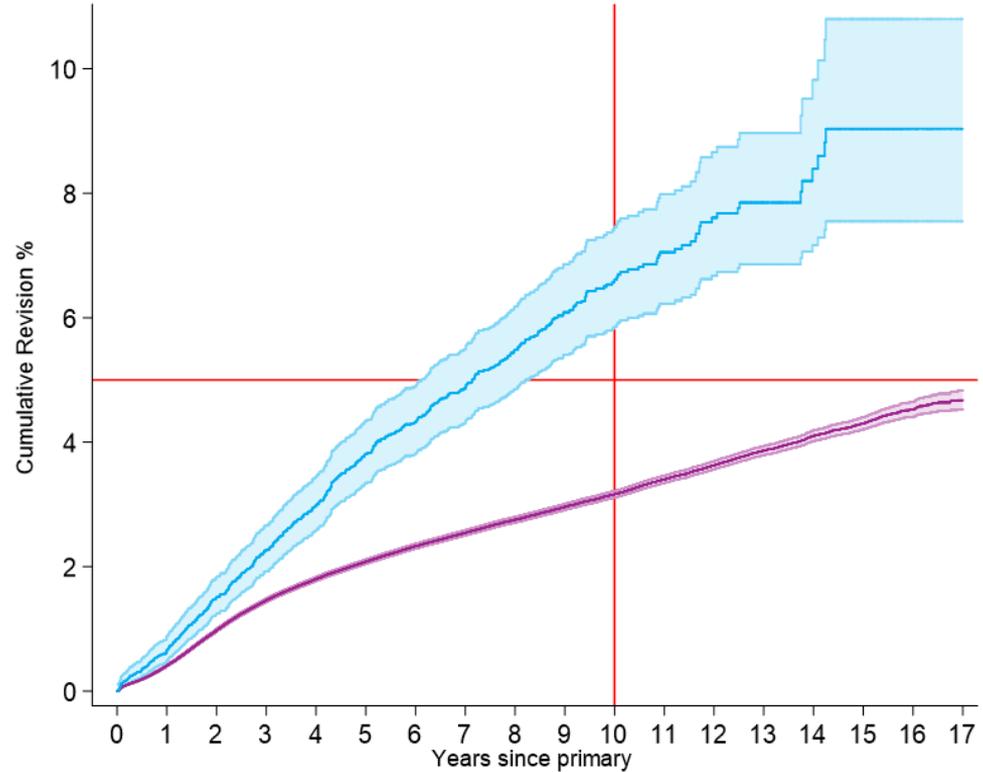
- The Registry can identify the problem – IF the correct analysis is done
- The Registry can identify every case with the affected device
- The Registry can inform each hospital which of their patients is affected
- Clinical advice with full information about the devices concerned is essential to giving the appropriate plan for further action
- This must be available at the time the FSN is issued to avoid confusion



How best to identify this variant?

Where should the threshold be for identifying a problem?

How should advice be developed, WHEN and by whom?



Key:

— Nexgen PS Option Option Fle:
— All Bicon. Knees

Numbers at Risk	
11,755	10,474
8,249	6,051
4,153	2,467
1,323	466
107	18,218

1,205,788	1,039,642	816,821	604,908	423,709	273,241	155,133	66,258	18,218
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Conclusions

- Identifying a problem implant is difficult but requires comprehensive data
- Once identified should the device be formally withdrawn?
- Is it enough to allow the manufacturer to remove the device from the market?
- Many devices with much worse revision rates have been withdrawn for 'commercial reasons' and not for **SAFETY** reasons



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THANK YOU / QUESTIONS

Mr Tim Wilton NJR Medical Director

Timothy.wilton@njr.org.uk

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