NICE advice

FLEXISEQ for osteoarthritis

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is FLEXISEQ, a topically applied drug-free gel indicated for treating the symptoms of osteoarthritis. A potential **innovative aspect** is that it is described as having a novel, physical mode of action and contains no active drug. It consists of an aqueous gel containing hydrophilic, nanoscale lipid vesicles made from phospholipid bilayer (Sequessome vesicles), which are designed to pass through the skin into the joint. FLEXISEQ is regulated as a medical device.
- The **intended place in therapy** is as a pain-relieving treatment for people with all stages of osteoarthritis, especially those for whom non-steroidal anti-inflammatory drugs (NSAIDS) are not suitable. It would be used in addition to core treatments such as exercise and weight loss.
- The **key points from the evidence** summarised in this briefing are from 4 randomised controlled trials (RCTs), including a total of 3,213 patients with knee osteoarthritis, and a meta-analysis. The RCTs, in which FLEXISEQ was used as the placebo arm for studies of topical ketoprofen and oral celecoxib, showed that FLEXISEQ was, in some cases, at least non-inferior to active comparators. The meta-analysis reported that the magnitude of the effect with FLEXISEQ is unlikely to be a result of the placebo effect alone.

- **Key uncertainties** are the limited evidence base for FLEXISEQ's analgesic mode of action and the major limitation of all trials in that there was no topical placebo control (inactive gel) with which to compare the effectiveness of FLEXISEQ. The meta-analysis was of poor methodological quality. A randomised controlled trial comparing FLEXISEQ to a topical gel placebo in people with knee osteoarthritis is currently ongoing with results expected in late 2016.
- FLEXISEQ is not yet available on the NHS, but the current retail **cost** for a 50 g tube bought over the counter is about £18.00, including VAT.

The technology

FLEXISEQ (often referred to as TDT 064 in the scientific literature) is an aqueous gel containing hydrophilic, nanoscale lipid vesicles with a phospholipid bilayer (Sequessome vesicles). The manufacturer claims that, because of their composition, Sequessome vesicles can pass through the skin to reach a joint. Sequessome vesicles are ultra-deformable, meaning that they are structurally robust and can stay intact while passing through the intercellular spaces of the skin (44 nm), despite their larger size (70 to 198 nm in diameter; Conaghan et al. 2014). The movement of these vesicles is said to be driven by the osmotic gradient between the surface of the skin and sub-dermal tissues (Cevc et al. 2003). FLEXISEQ is classed as a medical device because it has a physical mode of action and contains no active drug.

According to the manufacturer's instructions for use, FLEXISEQ should be applied twice daily, in the morning and the evening, to the soft tissues around the affected joint. Following application, it must be left to dry for at least 10 minutes before covering the area. As the gel dries, the water evaporates and this is reported to trigger the movement of the hydrophilic Sequessome vesicles through the skin, towards the aqueous environment of the synovial fluid within the joint.

The innovation

Although the analgesic mechanism of FLEXISEQ is unclear, the manufacturer claims that once localised in the joint, the Sequessome vesicles may act as a lubricant by coating the cartilage. Although a lubricant action would not be expected to provide an analgesic effect directly, the reduction in friction between cartilage surfaces may minimise further inflammation, and might reduce the release of fragments and debris from the damaged

cartilage (Conaghan et al. 2014).

Current NHS pathway

Current treatments for osteoarthritis focus on managing symptoms such as pain because there is no medication that has been proven to prevent the disease or modify its course. According to the NICE guideline on osteoarthritis: care and management, healthcare professionals should take a holistic approach in assessing the impact of osteoarthritis on a person's function, quality of life, work, mood, relationships and leisure. Recommended core treatments for osteoarthritis are physical activity and exercise, weight loss (if the person is overweight or obese), and providing verbal and written information to increase the person's understanding of the condition. The use of locally applied heat or cold (thermotherapy) should be considered in addition to core treatments. Other options which can be considered include electrotherapy (transcutaneous electrical nerve stimulation [TENS]) for pain relief; advice on footwear for people with lower limb osteoarthritis; assessment for bracing, joint supports and insoles for people with instability; and use of assistive devices (for example walking sticks and tap turners).

Pharmacological management is also recommended in addition to core treatments to help manage pain. Paracetamol and/or topical non-steroidal anti-inflammatory drugs (NSAIDs) should be considered before oral NSAIDs, cyclo-oxygenase 2 (COX-2) inhibitors or opioids. Where paracetamol or topical NSAIDs do not provide enough pain relief, addition of oral analgesics (NSAIDs, COX-2 inhibitors and opioids) should be considered, taking into account individual patient risks (such as age) and potential benefits. Oral NSAIDs and COX-2 inhibitors should be used at the lowest effective dose for the shortest possible period of time.

The Medicines and Healthcare Regulatory Agency (MHRA) is currently reviewing non-prescription analgesics, after which time NICE will review the evidence on the pharmacological management of osteoarthritis.

Topical capsaicin cream can be considered in addition to core treatments for knee or hand osteoarthritis. For the relief of moderate to severe pain, intra-articular corticosteroid injections may be considered.

Referral for joint surgery is recommended for people if osteoarthritis has a substantial impact on quality of life and does not respond to non-surgical treatment.

Population, setting and intended user

Osteoarthritis is one of the most common chronic diseases in the UK, with 8.75 million people having sought treatment (Versus Arthritis). An estimated 4 million people in England have osteoarthritis of the knee and 2.5 million have osteoarthritis of the hip (Versus Arthritis).

FLEXISEQ is promoted for use by anyone with osteoarthritis and seems likely to be used in those for whom oral or topical NSAIDS are contraindicated, as an adjunct to other treatments for symptom management. FLEXISEQ is designed to be used in any setting, including at home by the patient and it should be applied according to the manufacturer's instructions for use.

FLEXISEQ is contraindicated for people with known sensitivity to any of its ingredients. It has not been tested on pregnant women in clinical trials, and therefore its use during pregnancy is not advised.

Costs

Device costs

The current retail list price for a 50 g tube of FLEXISEQ gel bought over the counter is £18.49 from UK high-street retailers (including VAT). Though not available on the NHS, the manufacturer is planning to apply for inclusion in the NHS Drug Tariff and states that an NHS prescription would cost £30.82 (excluding VAT) for a 125 g tube. The manufacturer claims that with the recommended application of twice a day, a 125 g tube will last for 28 days on average, but this will vary based on the number and size of joints being treated.

Costs of standard care

When FLEXISEQ is used as in addition to core treatments, it will add to immediate costs.

NICE's guideline on osteoarthritis: care and management groups standard care into 3 categories: core treatments (self-management, exercise and non-pharmacological treatments), pharmacological treatments and joint surgery. Adults with osteoarthritis are supported with non-surgical core treatments for at least 3 months before any referral for

consideration of joint surgery (NICE's quality standard on osteoarthritis). In most cases the costs of self-management, exercise and weight loss programmes will be borne by individuals and not by the NHS and social care services. The unit costs of a 1 hour session of physiotherapy or occupational therapy are about £38 (PSSRU 2015). These unit costs cover a wide range of resources including labour time, facility overheads, facility capital and all clinical equipment. These unit costs are inclusive of mobility aids (shoe inserts, walking aids, bracing and tap turners) that physiotherapists and occupational therapists may supply. Thermotherapy can also be provided by these professionals (NHS website) and relevant costs are likely to be included in the clinical element. TENS can be recommended and the TENS machine and pads, which cost a total of around £35 (Lewis et al. 2015), can sometimes be loaned to patients (NHS website).

Pharmacological treatments can be considered as well as core treatments. Table 1 provides the costs of standard pack sizes and also the maximum monthly cost which assumes continual treatment for the month and was based on the maximum daily dose a patient should take. A GP appointment (unit cost for which is £45 (PSSRU 2015) will be required for prescription purposes with these treatments. In addition, the full cost of a corticosteroid injection will include the costed labour time of a hospital-based nurse or consultant. Assuming a 15 minute appointment these would add £10 or £34, respectively (PSSRU 2015).

Table 1: Pharmacological treatment unit costs

Pharmacological treatment	Unit	Pack cost	Max monthly cost	Source
Oral analgesics (e.g. paracetamol)	32 tablets (500 mg)	£0.20	£1.40	BNF 2016
Topical NSAIDs (e.g. felbinac)	100 g tube (30 mg per 1 g)	£8.00	£56.00	BNF 2016
Topical capsaicin	45g tube (250 mcg per 1 g)	£17.70	£49.20	BNF 2016
Oral NSAIDs (e.g. dexibuprofen)	60 tablets (400 mg)	£10.00	£14.00	BNF 2016
Intra-articular injections (corticosteroid)	1 100 mg vial of solution	£0.90	N/A	BNF 2016

A variety of surgical procedures can be used to treat severe osteoarthritis in different joints and unit costs will vary by procedure and joint. The most common cases are knee arthroplasty (knee replacement), hip arthroplasty (hip replacement) and resurfacing arthroplasty (NHS website). A UK evaluation comparing different knee prostheses stated the unit cost of the knee arthroplasty procedure (depending on brand and patient gender) ranged from £4,574 to £5,491 (Pennington et al. 2016). Another UK economic evaluation found the unit costs of hip arthroplasty and resurfacing hip arthroplasty were £6,091 and £6,275, respectively (Edlin et al. 2012).

Resource consequences

According to the manufacturer, FLEXISEQ has been available over the counter since 2013 and is not currently prescribable. FLEXISEQ is a topically applied gel and does not need special preparation, additional facilities or equipment. No other practical difficulties have been identified in using the technology.

No published evidence on the resource consequences of adopting FLEXISEQ in the relevant indication was identified in the systematic review of evidence. It is unclear if FLEXISEQ will be cost-effective for the NHS compared to standard care. In cases where FLEXISEQ is used as an add-on treatment, the immediate costs of treatment will increase. This may not be the case when it is used as a substitute for topical NSAIDs.

Regulatory information

FLEXISEQ was CE-marked as a class IIb device in March 2016. The product is regulated under the Medical Devices Directive (93/42/EEC).

A search of the Medicines and Healthcare Products Regulatory Agency (MHRA) website revealed that no manufacturer Field Safety Notices or Medical Device Alerts have been issued for this technology.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to:

promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

People with osteoarthritis that has had a substantial adverse effect on their ability to carry out normal day to day activities for at least 12 months are likely to be considered disabled under the Equality Act 2010. Osteoarthritis is more common in women and older people. Twenty percent of people aged between 50 and 59 have symptomatic osteoarthritis whereas 50% of people aged over 80 years have the condition. Age and sex are protected characteristics under the Equality Act 2010.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the published process and methods statement. This briefing includes the most relevant/best available published evidence relating to the clinical effectiveness of the technology. The literature search strategy, evidence selection methods and detailed data extraction tables are available on request by contacting mibs@nice.org.uk.

Published evidence

Evidence in this briefing is taken from 1 meta-analysis and 4 randomised controlled trials (RCTs). The total number of patients included in the 4 RCTs was 3,213. The results varied among the studies.

Table 2 summarises the clinical evidence as well as its strengths and weaknesses.

Table 2 Summary of selected studies

Study	Details of intervention and comparator	Outcomes	Strengths and limitations

Conaghan et al. 2013 1,395 patients, randomised, double-blinded, placebo and active-controlled trial. Multicentre (Czech Republic, Germany, Poland, UK).	IDEA-033 (ketoprofen in ultradeformable vesicle gel; not a marketed product). Oral celecoxib. FLEXISEQ (TDT 064) (ketoprofen-free topical placebo). Oral placebo.	When using the WOMAC index to assess pain, IDEA-033 was not superior to FLEXISEQ in reducing osteoarthritis knee pain. IDEA-033 and FLEXISEQ were superior to oral placebo and non-inferior to celecoxib in reducing osteoarthritis knee pain. The most frequent types of treatment-related adverse events reported were gastrointestinal symptoms for oral (celecoxib, oral placebo) and skin reactions for topical applications (IDEA-033, FLEXISEQ).	The study was a randomised controlled trial (RCT), which is a strength of the study design. FLEXISEQ was designed to be the topical placebo gel arm so there was no comparison of FLEXISEQ with a true topical placebo (such as an inactive gel) which would have controlled for any placebo effects of administering a topical treatment, such as patient expectation of benefit. The study reported a detailed sample size calculation and justification. As with all patient-reported primary outcomes, the WOMAC score may be subject to bias (this scale is commonly used to assess the condition of patients, based on their symptoms and physical functioning, it measures 5 items for pain [score range 0 to 20], 2 for stiffness [score range 0 to 8], and 17 for functional limitation [score range 0 to 68]).

			The WOMAC index is the recommended methodology for assessing efficacy in osteoarthritis trials (Dieppe, 1995). The use of the baseline-observation-carried-forward (BOCF) approach to handle missing data could have resulted in an underestimation of the treatment effects. The study received funding from the manufacturer of IDEA-033 which may introduce bias.

Kneer et al. 2013 866 patients, randomised double-blind placebo-controlled parallel group, multicentre (Germany, Poland, Serbia, Croatia).	IDEA-033. FLEXISEQ (topical placebo).	All 4 treatments improved WOMAC pain scores by 50% or more. The 50 and 100 mg IDEA-033 doses (but not the 25 mg) were marginally superior to FLEXISEQ in reducing pain. The superiority was not demonstrated for the WOMAC function score. The percentage of patients who responded was significantly higher for all the IDEA-033 groups versus the FLEXISEQ group. Skin reactions were the only relevant drug-related adverse	RCT with blinding. However, as FLEXISEQ was designed to be the topical placebo gel arm, there was no comparison of a true topical placebo with FLEXISEQ. The study reported a detailed sample size calculation and justification. As a patient-reported outcome, the WOMAC score may have been subject to bias. A large number of patients in the IDEA-033 groups withdrew from the study at an early stage and this may have contributed to the lower than expected effect size in these treatment groups. Equally the larger number of drop-outs could reflect dissatisfaction with either effectiveness or side effects. The study received funding from the manufacturer of the IDEA-033.

		events. No significant differences were reported between the groups in terms of adverse event frequency.	
Rother and Conaghan 2013 555 patients, randomised double-blind trial, multicentre (USA).	IDEA-033. FLEXISEQ (topical placebo).	IDEA-033 was inferior to FLEXISEQ in relieving mild-to-moderate pain associated with knee osteoarthritis and improving joint function. IDEA-033 was associated with a higher frequency of withdrawals due to adverse events compared to FLEXISEQ.	RCT with blinding. However, as FLEXISEQ was designed to be the topical placebo gel arm, there is no comparison of a true topical placebo and FLEXISEQ. The study reported a detailed sample size calculation and justification. As a patient-reported outcome, the WOMAC score may have been subject to bias. The study received funding from the manufacturer of IDEA-033 which may introduce bias.

Rother et al. 2007 397 patients, randomised, double-blind, controlled trial, multicentre (Germany).	IDEA-033. Oral celecoxib. FLEXISEQ (topical placebo). Oral placebo.	IDEA-033 was superior to placebo and comparable to celecoxib in relieving pain associated with an acute flare of knee osteoarthritis. Most adverse events were evenly spread throughout the groups, but IDEA-33 caused more skin irritations than FLEXISEQ.	RCT with blinding. However, as FLEXISEQ was designed to be the topical placebo gel arm, there is no comparison of a true topical placebo and FLEXISEQ. The study reported a detailed sample size calculation and justification. As a patient-reported outcome, the WOMAC score may have been subject to bias. The study received funding from the manufacturer of IDEA-033 which may introduce bias.

Rother et al. 2014 Meta-analysis of 5 RCTs with FLEXISEQ using formal parametric meta-analysis methods to investigate the overall effect size (ES) of FLEXISEQ across all studies, versus the standard placebo effect (pooled data of 198 osteoarthritis trials).	Intervention: FLEXISEQ (5 RCTs, n=1,320). Comparator data from Zhang et al. (2008): all placebo-controlled knee osteoarthritis groups (122 trials, n=10,300); all placebo groups for topical NSAIDs (13 trials, n=896); all untreated controls (14 trials, n=1,167).	The combined ES for FLEXISEQ for pain relief and improvement in function was higher than the values reported for placebos in knee osteoarthritis studies, and for the placebo arms reported in topical and oral NSAIDs studies. The effect sizes for the individual FLEXISEQ studies were higher than the effect size reported by Zhang et al. (2008).	Funding for the 5 RCTs in this study was provided by the manufacturer of IDEA-033; funding for the meta-analysis was provided by the manufacturer of FLEXISEQ. Four of the 5 RCTs in the meta-analysis have been published as peer reviewed papers. The fifth RCT was reported as a conference abstract. The meta-analysis seemed to be of poor quality. The search strategy was not reported and it was unclear what process was adopted for sifting and data extraction. For the included studies, no assessment of study bias is reported, with the exception of conflicts of interest.
Abbreviations: baseline-observation-carried-forward (BOCF) approach; RCT, randomised controlled trial; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.			

Strengths and limitations of the evidence

All 4 identified studies were RCTs and included a detailed sample size calculation and

justification. The majority of the data on the efficacy of FLEXISEQ are derived from the clinical development programme for IDEA-033 which included RCTs with FLEXISEQ as the drug-free control (IDEA-033 is a topical gel in development, which contains ketoprofen in Transfersome vesicles, using the same core technology as Sequessome vesicles; Pro Bono Bio, Transferosomes, 2016). This means that there was no placebo topical treatment with an inactive gel that would control for any placebo effects of administering a topical treatment, such as patient expectation of benefit, making this a major limitation in all 4 RCTs.

The risk of selection bias in Kneer et al. (2013) was unclear. The paper did not report the method of randomisation, and it was unclear whether there was adequate concealment of allocation for investigators and patients. The risk of selection bias in the other 3 studies was deemed to be low, as either a computer-generated list or a random permuted block scheme was used to randomise patients into groups. In all 4 studies, the treatment groups were comparable at baseline, with only Kneer et al. (2013) reporting that they did a test on statistical significance.

None of the studies was deemed to be at high risk of performance bias because in each study, the treatment groups had the same care other than the intervention. All 4 studies are reported as double-blind, but it is not clear how patients were kept blind to their treatment.

All 4 RCTs had 12-week follow-up, which is typical for studies of treatments for osteoarthritis. A Cochrane review of topical NSAIDs for chronic musculoskeletal pain (April 2016) identified 39 studies that were generally of high quality, none of which lasted longer than 12 weeks.

In Kneer et al. (2013), the effects of FLEXISEQ administered alone were evaluated through the 'NSAID-responder enrichment design', which involves enrolling patients experiencing an increase in symptoms (flare) following withdrawal of NSAID treatment. This study design has been used in studies of COX-2 inhibitors, and has been associated with a greater treatment effect than non-enrichment designs (Trijau et al. 2010; Bjordal et al. 2007). Therefore, the selection of patients likely to respond to NSAIDs in this study may have contributed to the statistical superiority of the IDEA-033 groups compared with FLEXISEQ. In the other 2 phase III trials (Conaghan et al. 2013 and Rother and Conaghan 2013), a non-flare design was used and these showed stronger FLEXISEQ effects.

Only 1 of the studies included a UK centre (Conaghan et al. 2013) which may therefore

limit the generalisability to the NHS.

All 4 studies received funding from the manufacturer of IDEA-033 and the manufacturer of FLEXISEQ provided publication support for the meta-analysis. Manufacturer-sponsored studies may introduce bias into publication results and conclusions.

Rother et al. (2014) used a network meta-analysis to compare the effect size of FLEXISEQ (from 5 RCTs) with the placebo effect, using a large dataset of pooled placebo response results from a systematic review and meta-analysis of 198 RCTs on osteoarthritis (including 193 placebo groups; Zhang et al. 2008). The meta-analysis seemed to be of poor quality. Four of the RCTs that involved FLEXISEQ were published in peer reviewed journals and 1 was reported as a conference abstract. Although the methodology used by Rother et al. (2014) is similar to that used in the meta-analysis of RCTs looking at osteoarthritis treatments in Zhang et al. (2008), there are issues with the comparator (pooled placebo effect from the Zhang et al. study) that could potentially introduce bias. Firstly, Zhang et al. (2008) used study level variables for the regression analysis so the sensitivity analysis may have been lower than expected. Secondly, the limited information provided in some of the Zhang et al. studies made it difficult to properly assess their quality before including them in the meta-analysis and pooling the data.

Recent and ongoing studies

One ongoing trial has been identified:

- Study of FLEXISEQ for treatment of osteoarthritis of the knee in NSAID-compromised patients (NCT02594176). Double-blind randomised controlled trial, comparing FLEXISEQ to a topical gel placebo. Recruitment has been completed and data are expected in late 2016.

Specialist commentator comments

Five specialist commentators noted the limited evidence base for FLEXISEQ's physical and analgesic mechanism of action. One commentator questioned the plausibility of the migration of the Sequessome vesicles to the joint in significant amounts and for a sufficient amount of time to provide symptomatic relief. Another commentator suggested that the synovium and bone are more likely sources of pain in osteoarthritis than cartilage and questioned FLEXISEQ's analgesic mechanism of action. A third specialist commentator

expressed concern that although FLEXISEQ is drug-free and may not have the risks associated with drug treatments, it could potentially accumulate in the joint. Another commentator highlighted the need for robust evidence of Sequessome vesicles localisation in the joint from in vivo models.

One specialist commentator felt that the clinical effectiveness of FLEXISEQ has not been demonstrated. The absence of an adequate placebo (an inactive topical gel) for FLEXISEQ was highlighted as a limitation by 3 commentators. One commentator said that without it, the clinical effectiveness of FLEXISEQ could be attributed to the placebo effect of rubbing a gel onto the knee, instead of the Sequessome vesicles reaching the joint. Another commentator noted that pooling the results from studies using different placebo treatments may introduce bias into the meta-analysis results.

Three specialist commentators recognised the importance of long-term studies for a chronic condition, such as osteoarthritis. Two commentators considered that studies with short-term follow-up are of value because many people experience osteoarthritis through flares (as opposed to constant symptoms) which they tend to treat at home for short-term periods, with the occasional use of topical gels or creams.

With regard to the FLEXISEQ indication, one specialist commentator clarified that patients unable to tolerate oral non-steroidal anti-inflammatory drugs (NSAIDs) can often tolerate topical NSAID therapy. Two commentators suggested that FLEXISEQ will most probably be used in combination with oral NSAIDs and other add-on therapies, with one of them noting that its additional benefit may be negligible. One commentator questioned the rationale behind the manufacturer's claim that although FLEXISEQ can be used by anyone with osteoarthritis, it would be most useful for people in whom NSAIDs are contraindicated, who have limited treatment options. The same commentator stated that in these people, the number of affected joints will be a deciding factor on potential benefit.

One specialist commentator noted that, in practice, paracetamol is currently considered as a less efficient NSAID and is not recommended as a first line therapy. Patients prefer to use gels and cream for flares rather than taking oral NSAIDs. One commentator remarked that current treatments for osteoarthritis focus on managing symptoms because there is no medication that has been proven to prevent the disease or modify its course and patients have shown a preference for efficient pain management.

One commentator highlighted the significantly higher cost of FLEXISEQ per month compared to alternative treatments. Another noted that although use of FLEXISEQ would

add to costs (as an adjunctive therapy), it could reduce the cost of treating side effects if patients use it as a substitute for oral NSAIDs.

Specialist commentators

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

The following clinicians contributed to this briefing:

- Dr John Dickson, General Practitioner with a Special Interest, Darlington Clinical Commissioning Group. Dr Dickson declared the following conflicts of interest:
  - Dr Dickson has a consultancy agreement with the manufacturer of FLEXISEQ and has done fee paid work for them.
  - He has about $10,000 worth of shares in Pfizer.
  - He is a Trustee of the Primary Care Rheumatology Society.
- Dr Yee Ho (Michael) Chiu, Consultant Rheumatologist, Arrowe Park Hospital, no conflicts of interest declared.
- Dr Pamela Mangat, Consultant Rheumatologist, Royal Free London, no conflicts of interest declared.
- Dr Mark Porcheret, Senior Lecturer in General Practice, Keele University, no conflicts of interest declared.
- Dr Benjamin Schreiber, Consultant Rheumatologist, Royal Free London, no conflicts of interest declared.

- Dr Elspeth Wise, General Practitioner with a Special Interest, Northern Doctors Urgent Care Ltd. Dr Wise declared the following conflicts of interest:
  - Ran a recruitment site for CL033-III-03. The surgery she works for was paid per patient recruited and she personally received some of the payment.
  - Involved in a review paper of the technology which was sponsored by FLEXISEQ manufacturer (Pro Bono Bio). She received expenses and hospitality for the meeting arranged to discuss this.
  - Presented a summary of the research behind FLEXISEQ to the Primary Care Rheumatology Society but received no financial support/compensation for this. The review article stated that evidence supported the usage of FLEXISEQ in osteoarthritis.
  - A family member buys FLEXISEQ over the counter for knee osteoarthritis.

Development of this briefing

This briefing was developed for NICE by the King's Technology Evaluation Centre. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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