NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation: GID-MT570 AposHealth for osteoarthritis (OA) of the knee

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
3. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
4. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
5. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
    a. **Part 1 - clinical**
    b. **Part 2 - economic**
6. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
    a. **Clinical expert questionnaires**
    b. **Patient expert questionnaires**
7. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.

8. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

Document cover sheet

Assessment report: AposHealth for osteoarthritis of the knee

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0.1	Subheadings added for appendix A	HM	14/07/22	
0.2	Addition of appendix A and search critique in section 4.1	SW	18/07/2022	
0.3	Edited Appendix A and search critique in section 4.1 Details add to coversheet/decision problem/clinical context/ Additions to Overview of technology (Section 2.0) Edited Appendix A company search strategy for economic evidence Ongoing Studies (Section 8.2) additions Clinical Evidence (Section 4) and Evidence Synthesis and Meta-Analysis (Section 7) additions	SW SO'C AR SW AR AR	25/07/2022 28/07/2022 16/08/2022 24/08/2022 25/08/2022	

0.4	Additions to Clinical Context (Section 3) and Clinical Evidence (Section 4) QA of data in tables Additions to Sections 4-8 and 10 for draft submission QA of data tables, addition to study selection diagram Further preparation of clinical sections for draft submission	SB SW AR SW AR	31/08/2022 31/08/2022 02/09/2022 05/09/2022 06/09/2022	
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0.6	Amendments after internal draft review	AR/MD	08/09/2022	
1.0	Draft version to NICE	AR/SO'C	09/09/2022	09/09/2022
1.1	Addressing NICE comments post draft submission	AR/SO'C/SB	14/09/2022	
1.2	Economic section updated, report checked and formatted	SO'C	21/09/2022	
1.3	Amendments to clinical sections after internal review	AR	22/09/2022	
1.4	Amendments to economic sections after internal review	MD	22/09/2022	
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2.1	Post-fact check.	AR/MD/SO'C/SB	29/09/2022	
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Medical technologies guidance

MTG570 AposHealth for osteoarthritis (OA) of the knee External Assessment Group report

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Contains confidential information: Yes

Number of attached appendices: 5

Purpose of the assessment report

The purpose of this External Assessment Group (EAG) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

None

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Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Any ‘commercial in confidence’ information in the submission document should be underlined and highlighted in turquoise.

Any ‘academic in confidence’ information in the submission document should be underlined and highlighted in yellow.

Contents

Abbreviations

Term	Definition
ALF	Aggregated Locomotor Function
CI	Confidence interval
DHSC	Department of Health and Social Care
EAG	External Assessment Group
IQR	Interquartile range
K&L	Kellgren and Lawrence system for classification of osteoarthritis
KOFG	Knee osteoarthritis functional grade classification
KSS	Knee Society Score
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
OA	Osteoarthritis
PFJOA	Patellofemoral Joint Osteoarthritis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised controlled trial
SD	Standard deviation
TKR	Total Knee Replacement
VAS	Visual analogue scale
Vs	Versus
WOMAC	Western Ontario and McMaster Osteoarthritis Index

Executive summary

AposHealth (previously AposTherapy) is a non-invasive device worn on the foot to adjust the gait of the user to improve symptoms of knee osteoarthritis (OA), a condition that results in joints becoming stiff and painful. It is proposed as an addition to non-surgical standard care, or as an alternative. The comparators included alternative devices such as supports, splints and braces or intra-articular corticosteroid injections.

Clinical evidence primarily from low quality non-comparative, observational studies indicates that users of AposHealth experience improvements in symptoms of knee OA including pain, function and stiffness. Quality of life outcomes also show improvements and both clinical and patient experts supported these findings from their own experience. Two comparative studies, one high quality randomised trial and one prospective comparative study, did report improvements with AposHealth however both studies compared with a sham device rather than standard care.

There is a lack of evidence comparing AposHealth to non-surgical standard care treatment options such as manual therapy, walking aids, and intra-articular corticosteroid injections and their respective impacts on pain and function. Additionally, there is a lack of evidence relating to the outcome of TKR surgery delay or avoidance and in general there is a lack of long-term follow-up data (beyond 2 years). This is a key gap in the evidence and has a particular impact on the economic assessment.

There are no published economic evaluations of AposHealth. The company submitted a Markov decision model comparing standard care to standard care with AposHealth. An NHS perspective was used, with a 3.5% discount rate, 1-month cycles and results reported at a 2, 5 and 10-year time horizons. Both the company's submitted model and the EAG base case are cost saving for AposHealth at 5 years, and the company's 10-year model is also cost saving, by £246. The EAG base case becomes cost incurring at 10 years by £46, and this increases as the model is extended to 20 years. This result should be treated with caution as the existing evidence for delay to surgery is only over 2 years, and the model may not include all costs that could be considered over a longer duration.

The early cost savings were due to modelled delays in TKR surgery, with far fewer procedures for patients in the AposHealth arm. Over a longer time horizon, patients in the AposHealth arm continued to move to TKR surgery and the difference in the total number of procedures performed for each arm of the model was decreased.

A number of potential subgroups were identified as being likely to benefit from use of AposHealth including people who cannot have surgery and people who do not want to have surgery. Clinical experts indicated that a proportion of people with knee OA wish to avoid surgery and this was supported by the patient expert, however currently the clinical evidence does not inform outcomes for specific subgroups.

Currently, areas of greatest uncertainty that would benefit from further research include avoidance/delay in surgery, long term follow-up and the need to identify subgroups most likely to benefit from AposHealth. These uncertainties should be balanced against the observed improvements in symptom management and impact of patient quality of life, as well as the fact that there is a proportion of people who would prefer to avoid surgery, findings which were supported by both clinical experts and a patient expert.

1 Decision problem

The scope included adults over the age of 16 years with knee osteoarthritis (OA) that have not sufficiently benefited from non-surgical standard care treatment options such as education and advice, exercise and manual therapy, weight loss (for people who are overweight) and pain relief (oral, topical or transdermal).

AposHealth is proposed as an addition to non-surgical standard care or as an alternative and the comparators included alternative devices such as supports, splints and braces or intra-articular corticosteroid injections.

The company has not proposed any variation to the scope, however it has added further clarification to the subgroups to be considered (Table 1). The scope identifies two specific population sub-groups of interest:

- People for whom total knee replacement is recommended
- People who do not want or cannot have surgical intervention.

The company has further defined the subgroups to note that consideration should be given to people with unicompartmental OA, patellofemoral joint osteoarthritis (PFJOA), people who have not responded sufficiently to previous treatments but who may not be at surgical threshold, people who may benefit from delayed surgery and people for whom surgery is the only remaining option. The EAG agrees that this additional information does not represent a variation to the scope (Table 1). Where possible, the EAG will report the clinical evidence according to the groups identified by the company.

Table 1: Variation to Scope

Decision problem	Scope	Proposed variation in company submission	EAG comment
Subgroups	• People for whom total knee replacement is recommended • People who do not want or cannot have surgical intervention	• Unicompartmental OA • Patellofemoral Joint Osteoarthritis (PFJOA) • Anyone who has not responded sufficiently to previous treatments (may not necessarily be at surgical threshold yet), or • People for whom there is benefit in delaying surgery • People for whom surgery is the only remaining choice.	The EAG agrees that this information provided by the company is for clarification purposes only and does not represent a variation to the scope.

2 Overview of the technology

AposHealth (previously AposTherapy) is a non-invasive device worn on the foot to adjust the gait of the user to improve symptoms of knee OA, a condition that results in joints becoming stiff and painful.

The device consists of a pair of shoes with two pods attached to the underside of each shoe with screws. The two pods (pertupods) are positioned on the heel and the forefoot of the shoe and are available in various sizes and levels of hardness which facilitate personalisation of the device. Positioning of the pertupods is performed by trained healthcare professionals and can be aided by gait analysis software and/or hardware. AposHealth is a Class I CE marked device.

The company claims that the device works to reduce pain by adjusting the gait of the user to redistribute pressure placed on the knee during movement. It is also claimed that the device re-educates the muscles in the knee to correct abnormal gait, resulting in an improvement in symptoms even when the user is not wearing the device.

The AposHealth 4-step treatment plan takes place over the course of 1 year and consists of an initial patient assessment, personalisation of the device, at-home treatment and ongoing monitoring. The at-home treatment step involves the user wearing the device for short periods of time during daily activities, for a total of up to 60 minutes per day.

AposHealth is not recommended for use for people with balance issues, people who require walking aids and people with especially severe osteoporosis.

3 Clinical context

Osteoarthritis is a condition that can affect any joint in the body and is particularly common in weight-bearing joints such as the knees.

Knee OA occurs as a result of damage to the cartilage in the joint which subsequently undergoes changes as the body attempts to repair the damage. In the UK, knee OA is the most common form of osteoarthritis. It is estimated that 18% of the population aged over 45 years have sought treatment for knee OA (NICE Clinical Knowledge Summary of Osteoarthritis).

Current treatment options depend on the severity of symptoms and patient characteristics. They include pharmacological and non-pharmacological treatments. Referral for joint surgery may be offered if management through pharmacological and/or non-pharmacological treatment options is insufficient.

Non-pharmacological:

- Weight loss
- Therapeutic exercise
- Devices e.g. walking aids
- Physiotherapy (manual therapy)

Pharmacological:

- Analgesics (oral, topical)
- Intra-articular corticosteroid injections

The company has positioned AposHealth as a treatment option for people who do not respond to non-surgical treatment.

The EAG identified a number of potentially relevant guidelines including NICE guidance and a NICE-accredited commissioning guide published by the Royal College of Surgeons:

- NG 193: Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain (2021)
- NG157: Joint replacement (primary): hip, knee and shoulder (2020)
- IPG637: Platelet-rich plasma injections for knee osteoarthritis (2019)
- CG177: Osteoarthritis: care and management (2014) (currently being updated, publication expected October 2022).
- RCS: Painful Osteoarthritis of the Knee (2017)

Of the identified guidelines, NICE clinical guideline (CG177) which is currently being updated (GID-NG10127) and the RCS guidelines are the most directly relevant. RCS guidance recommends that most people can be managed in primary care by following NICE CG177 for the management of OA. Referral for surgery should be considered for people that are refractory, that is, non-responders, for up to 3 months of non-surgical treatment. RCS guidance again recommends following NICE guidance (CG177) for people referred for surgery.

Table 2 outlines some of the key recommendations from the relevant published guidance. It should be noted that the NICE guideline is for the management of all osteoarthritis and is not specifically for management of knee OA. Of particular relevance to this topic, the draft recommendations include a recommendation to consider walking aids (such as walking sticks) for people with lower limb osteoarthritis. The recommendations on non-pharmacological care also state that insoles, braces, tape, splints or supports should not routinely be offered to people with osteoarthritis. This is due to a lack of evidence for efficacy of devices, with little data available to guide healthcare professionals on which people would benefit most from these aids. The draft guidelines include a recommendation for research on such devices. The draft guidelines states that other non-pharmacological therapies, including therapeutic exercise, should routinely be offered.
Although the draft guideline included evidence relating to AposHealth, this was limited to Reichenbach (2020), the guideline was reviewed before publication of Drew (2022) and Greene (Unpublished).

The British Orthopaedic Association (BOA) Getting It Right First Time (GIRFT) programme has been designed to improve the quality of care in the NHS through reduction of unnecessary variation. The GIRFT total knee replacement pathway outlines a pathway from first presentation in primary care to surgery and beyond to discharge and follow-up. In line with RCS guidelines, the GIRFT pathway includes conservative management with review and referral for surgery if still symptomatic at 3 months. The GIRFT

also incorporates the relevant NICE clinical guidance at each stage of the pathway.

Clinical experts reported that while people would be referred for surgery when treatment refractory, there is no clearly defined time limit for this and the 3-month time specified in the RCS guidance should be interpreted in line with people's symptoms and need.

Table 2: Potentially relevant guideline recommendations related to management of knee OA

Guideline	Recommendations
GID-NG10127 (updating NICE CG177)	**Please note that these guidelines are a draft and may change. Final updated recommendations will be published on 19th October 2022 at which point the Assessment Report will be updated to reflect any changes.** • When giving information to people with osteoarthritis, their families and carers, tailor it to their individual needs (such as language and culture), ensure it is in an accessible format and follow the recommendations on: - enabling patients to actively participate in their care in NICE's guideline on patient experience in adult NHS services. **[2012, amended 2021]** - putting shared decision making into practice in NICE's guideline on shared decision making. **[2021]** - delivering an approach to care that takes account of multimorbidity in NICE's guideline on multimorbidity. **[2016]** • Explain to people with osteoarthritis that: - the core treatments for the condition are therapeutic exercise and weight loss (if appropriate), along with information and support.
	Non-Pharmacological management • Therapeutic exercise - Offer tailored therapeutic exercise to all people with osteoarthritis (for example, local muscle strengthening, general aerobic fitness). • Weight loss - Guidance and information on weight management, including recommended interventions to support weight loss, see NICE's webpage on obesity. • Manual therapy

Guideline	Recommendations
	- If discussing manual therapy, explain to people with osteoarthritis that there is not enough evidence to support its use alone for managing osteoarthritis. • Devices - Consider walking aids (such as walking sticks) for people with lower limb osteoarthritis. • Do not routinely offer insoles, braces, tape, splints or supports to people with osteoarthritis. Research recommendation Which biomechanical interventions (such as footwear, insoles, braces and splints) are most beneficial in the management of osteoarthritis, and in which subgroups of people with osteoarthritis do they have the greatest benefit?
	Pharmacological management • Topical, oral, and transdermal medicines - Use them alongside non-pharmacological treatments and to support therapeutic exercise. - Offer a topical non-steroidal anti-inflammatory drug (NSAID). - If topical medicines are ineffective or unsuitable, consider an oral NSAID. - Do not routinely offer weak opioids unless for short-term pain relief. - Do not routinely offer strong opioids. - Do not routinely offer paracetamol and glucosamine. • Intra-articular injections • Consider intra-articular corticosteroid injections when other pharmacological treatments are ineffective or unsuitable. Explain to the person that these will only provide short-term relief.
	Follow-up and Review • Consider patient-initiated follow-up for most people with osteoarthritis. • Consider planned follow-up for people with osteoarthritis when their individual needs and preferences suggest that this is necessary, taking into account: - treatments or interventions that need monitoring - their ability to seek help for themselves - their occupation and activities - the severity of their symptoms or functional limitations.

Guideline	Recommendations
	• People with multiple long-term conditions are likely to benefit from a tailored approach in line with NICE's guideline on multimorbidity. • Advise people with osteoarthritis to seek follow-up if planned management is not working within an agreed follow-up time or they are having difficulties with the agreed approaches.
	Referral for joint replacement • Consider referring people with hip, knee or shoulder osteoarthritis for joint replacement if: – their joint symptoms (such as pain, stiffness and reduced function) are – substantially impacting their quality of life and – non-surgical management (for example, therapeutic exercise, weight loss, pain relief) is ineffective or unsuitable. • Use clinical assessment when deciding to refer someone for joint replacement, instead of systems that numerically score severity of disease. • Do not exclude people with osteoarthritis from referral for joint replacement because of: – age – sex – smoking – comorbidities – overweight or obesity, based on measurements such as BMI. If discussing referral for joint replacement, explain to the person being referred that the risks of joint replacement can vary depending on BMI.

Special considerations, including issues related to equality

AposHealth is intended for people with knee OA. The technology is contraindicated in people who have severe imbalance or vertigo issues. The technology is also not suitable for people considered at high risk of falls or those with severe osteoporosis. The technology should be worn for at least an hour a day so may not be suitable for people with very limited mobility or those who use walking aids to get around at home, depending on clinical judgment. Osteoarthritis is more common in people who are older, in women and in people with obesity. The company reported that one meta-analysis conducted in North America found that pain severity and disability is higher for people with an African family background compared with people with a European family background (Vaughn 2019). Age, sex, disability and race are protected characteristics under the Equalities Act.

4 Clinical evidence selection

4.1 *Evidence search strategy and study selection*

The company submission did not include a search strategy. The company stated that they tracked all peer-reviewed research, but did not provide information on how tracking was conducted. The company identified a total of 48 studies. Following exclusion of 24 studies, the company submission included 17 published studies and 7 ongoing studies, totaling 24 studies. No details on decisions for exclusion were reported.

The EAG conducted their own literature searches to ensure that all relevant evidence had been identified. The EAG literature searches identified a total of 367 records. Two studies (Drew 2022 and Herman 2018) included in the company submission were not picked up through EAG searches and added to the database. The company also provided an additional manuscript which has been accepted for publication in the Journal of Orthopaedic Experience and Innovation (Greene, Unpublished), giving a total of 370 records. Details of the EAG searches are provided in Appendix A.

Two EAG researchers screened the 370 records by title and abstract in accordance with the scope. Of these, 310 were excluded as they did not meet the scope, leaving 60 records for screening against the criteria of the decision problem. Nine of these were trial database records. The remaining 51 publications were retrieved and reviewed by two EAG researchers, and disagreements on inclusion and exclusion were discussed until a consensus was reached. Twenty-two publications were excluded, leaving 29 publications for inclusion. Of these publications, 14 were full-texts, 1 was an unpublished manuscript, 9 were abstracts associated with the included full-texts, and 5 were additional abstracts. Three of the 9 trial database records were National Clinical Trial (NCT) records with associated full-text publications and are discussed in the clinical evidence section. One trial database record was identified as a duplicate and was excluded. The remaining 5 trial database records are discussed in section 8.2.

Table 3 Full text publications included and excluded by company and the EAG

Publication	Included in Company Submission	Included in EAG Assessment Report	EAG Comment
Reichenbach 2020	✓	✓	Randomised controlled trial comparing AposHealth vs. sham device.
Bar-Ziv 2010	✓	✓	Prospective controlled study comparing AposHealth vs. sham device.
Bar-Ziv 2013	✓	✓	Two-year follow-up results for Bar-Ziv 2010.
Debbi 2015	✓	✓	Prospective cohort study of AposHealth.
Drew 2022	✓	✓	Retrospective study of AposHealth users with a cohort undergoing TKR as a control but no comparisons made.
Drexler 2012	✓	✓	Retrospective cohort study of AposHealth.
Elbaz 2010	✓	✓	Retrospective cohort study of AposHealth.
Elbaz 2013	✓	X	AposHealth for patients diagnosed with large complex medial meniscal tear, outside scope of MTG.
Elbaz 2014	✓	✓	Prospective cohort study of AposHealth.
Goryachev 2011	✓	✓	Prospective cohort study of AposHealth.
Haim 2012	✓	✓	Prospective cohort study of AposHealth.
Haim 2013	✓	X	AposHealth for patients diagnosed with anterior knee pain with no diagnosis of knee OA and so is outside scope of MTG.
Herman 2018	✓	✓	Retrospective cohort study of AposHealth.
Lador 2013	✓	✓	Retrospective cohort study of AposHealth.
Lubovsky 2017	✓	✓	Retrospective cohort study of AposHealth.
Miles 2020	✓	✓	Retrospective cohort study of AposHealth.
Greene Unpublished	✓	✓	Unpublished at the time of EAG literature search, provided by company. Retrospective cohort study of AposHealth.

4.2 *Included and excluded studies*

There were 14 studies (Bar-Ziv 2010 and Bar-Ziv 2013, Debbi 2015, Drew 2022, Drexler 2012, Elbaz 2014, Elbaz 2010, Goryachev 2011, Greene Unpublished, Haim 2012, Herman 2018, Lador 2013, Lubovsky 2017, Miles 2020, and Reichenbach 2020) included. Nine abstracts (Bar-Ziv 2009, Bar-Ziv 2013, Elbaz 2015, Goryachev 2012, Haim 2011, Lador 2011, Miles 2022, Mor 2014, and Reichenbach 2018) related to 13 studies were identified. An additional 5 abstracts (Elbaz 2012, Elbaz 2009, Hagen 2018, Van Ginckel 2021 and Veeramachaneni 2016) were included in the evidence base.

Of the 17 studies included in the company submission, the EAG excluded 2 because the populations were not relevant to the decision problem (Elbaz 2013 and Haim 2013) (Table 3). The company did not include any published abstracts.

The EAG has included evidence from a total of 29 publications (14 full-text publications, 1 unpublished manuscript, and 14 abstracts) covering a total of 19 unique studies.

A full study flow diagram outlining the number of studies identified by the EAG and excluded at each stage can be found in Appendix A.

A summary of the included studies (Table 4) and additional abstracts (Table 5) is presented below. It should be noted that the traffic light system used in table 4 relates only to whether the study can be considered applicable to the decision problem as outlined in the scope. While it briefly highlights some of the potential limitations and areas for concern it is not a quality appraisal. Critical appraisal of all the included studies is reported in section 5 and Appendix B.

Table 4: Studies selected by the EAG as the evidence base

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Bar-Ziv (2010) **Location:** Israel **Study dates:** December 2005 – February 2006	**Design:** Pseudo-randomised sham-controlled trial. **Intervention:** AposHealth used daily for eight weeks. **Control:** Sham device identical in appearance to the intervention, minus the biomechanical elements. Daily use for eight weeks. Patients could use any other medical or physical therapy. GREEN	**Active group (n=31)** • 8 male, 23 female • Average age: 64 ± 8.1 years • K&L grade 2: 3 (10%) • K&L grade 3: 11 (36%) • K&L grade 4: 17 (55%) • BMI: 30.03 ± 4.3 **Control group (n=26)** • 7 male, 19 female • Average age: 66 ± 7.8 • K&L grade 2: 7 (27%) • K&L grade 3: 5 (19%) • K&L grade 4: 14 (54%) • BMI: 29.7 ± 3.79 All patients diagnosed with symptomatic bilateral medial compartment knee OA. No statistically significant difference between groups at baseline. **Setting:** Orthopaedic department at an Israeli hospital. GREEN	Follow ups at 4 and 8 weeks after the start of treatment. WOMAC ALF SF-36 health survey KSS Statistically significant difference in all outcomes between groups at 8 week follow up. GREEN	Partially meets the scope. AposHealth is being compared against a sham device rather than standard care. There was no randomisation, patients were assigned based on when they were able to attend the clinic. There is no mention of any other care patients might be receiving. Only 8 weeks of treatment. Study demonstrates statistically significant effectiveness of AposHealth in reducing pain, improving functioning and quality of life in knee OA.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Bar-Ziv (2013) **Location:** Israel **Study dates:** Not reported **Bar-Ziv (2009)** – related abstract **Bar-Ziv (2013)** – related abstract	**Design:** 2 year follow-up of pseudo-randomised sham-controlled trial (Bar-Ziv 2010). **Intervention:** AposHealth use daily for 12 weeks. **Control:** Sham device identical in appearance to the intervention, minus the biomechanical elements. Daily use for 12 weeks. GREEN	**Active group (n=40)** • 75% female • Average age: 64.1 ± 7.5 years • K&L grade 2: 17.5% • K&L grade 3: 25% • K&L grade 4: 57.5% **Control group (n=16)** • 69% female • Average age: 69 ± 8.6 years • K&L grade 2: 18.8% • K&L grade 3: 31.2% • K&L grade 4: 50% All patients diagnosed with symptomatic bilateral medial compartment knee OA. No statistically significant difference between groups at baseline. **Setting:** Orthopaedic department at an Israeli hospital. GREEN	Follow up at 6,12, and 24 months from the start of treatment for the active group. For the control group it was only at 24 months. WOMAC ALF SF-36 KSS Statistically significant difference in all outcomes at the 24 month follow up. GREEN	Partially meets scope. Treatment is with AposHealth, but it is compared against a sham device rather than standard care. However, patients could use standard care available to them. Although this was not controlled for, nor reported. There was no blinding or randomisation in this phase of the trial, in contrast to the initial 8 week trial period (Bar-Ziv 2010). Additionally, participants underwent unspecified crossover between trial arms during the 2 year follow-up period. The follow up schedules for each group were different. Study demonstrated that AposHealth improves function and pain in knee OA patients two years after treatment.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Debbi (2015) **Location:** Israel **Study dates:** Not reported	**Design:** Prospective single-arm cohort study **Intervention:** AposHealth use daily for 9 months. **Control:** N/A AMBER	• 25 female patients • Average age: 62 ± 7 years • Height: 159 ± 5.65 • Weight: 77.27 ± 9.99kg • K&L: 3 ± 0.9 Patients diagnosed with symptomatic bilateral medial compartment knee OA. **Setting:** Orthopaedic department at an Israeli hospital. GREEN	Follow up at 3 and 9 months after the start of treatment. Gait analysis WOMAC SF-36 Statistically significant improvement in WOMAC and SF-36 (except those relating to mental health) scores, and gait pattern scores after 9 months. GREEN	Partially meets scope. Treatment is with AposHealth, but it is not compared against anything. No control arm or randomisation. Only female patients. Study demonstrates statistically significant effectiveness of AposHealth in reducing pain, improving functioning and quality of life in knee OA.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Drew (2022) **Location:** USA **Study dates:** March 2018 – March 2019	**Design:** Retrospective case series **Intervention:** AposHealth **Control:** Surgery (at baseline only) AMBER	• 237 patients • 35% female / 65% male • Average age: 68.7 ± 9.2 years Patients with end-stage knee OA. **Setting:** Clinics in the USA GREEN	Follow up at 3, 6 and 12 months after the start of treatment. TKR surgery avoidance Gait analysis WOMAC SF-36 Statistically significant improvement in WOMAC and SF-36 (except those relating to mental health) scores after 12 months. 204/237 participants in the AposHealth arm did not progress to TKR surgery at 24 months. GREEN	Partially meets scope. Compares patients that chose AposHealth treatment against those that chose surgical treatment at baseline only. Comparisons post-AposHealth and post-surgery are not made. Study demonstrates statistically significant effectiveness of AposHealth in reducing pain, improving functioning and quality of life in knee OA. The study also reports 86% of AposHealth users avoided TKR surgery at 24 months.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Drexler (2012) **Location:** Israel **Study dates:** April 2009 – September 2010	**Design:** Retrospective case series **Intervention:** AposHealth use daily for 12 weeks. **Control:** N/A **AMBER**	• 654 patients • Average age: 64.7 ± 8.9 years • Height: 162.3 ± 9.1cm • Weight: 84.4 ± 31.1kg All patients diagnosed with symptomatic bilateral medial compartment knee OA. **Setting:** Orthopaedic department at an Israeli hospital. **GREEN**	Follow up at 12 weeks after the start of treatment. WOMAC SF-36 Statistically significant improvement in WOMAC and SF-36 scores after treatment. **GREEN**	Partially meets scope. Treatment is with AposHealth, but it is not compared against anything. Only 12 weeks of treatment. Study demonstrates statistically significant effectiveness of AposHealth in reducing pain, improving functioning and quality of life in knee OA.
Elbaz (2010) **Location:** Israel **Study dates:** Not reported	**Design:** Retrospective case series **Intervention:** AposHealth use daily for 12 weeks. **Control:** N/A **AMBER**	• 46 patients • Average age: 62.5 ± 7.7 years • Height: 1.61 ± 0.7m • Weight: 83.3 ± 15.9kg • BMI: 32.1±5.8 All patients diagnosed with symptomatic bilateral medial compartment knee OA. **Setting:** APOS Therapy Centre in Israel **GREEN**	Follow up at 12 weeks after the start of treatment. Gait analysis WOMAC SF-36 health survey Statistically significant difference in WOMAC pain and function scores and SF-36 scores (except those relating to mental health) after 12 weeks of treatment. No significant difference in outcomes when age and BMI are accounted for. **GREEN**	Partially meets scope. Treatment is with AposHealth, but it is not compared against anything. Only 12 weeks of treatment. Study demonstrates statistically significant effectiveness of AposHealth in reducing pain, improving functioning and quality of life in knee OA.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Elbaz (2014) **Location:** Singapore **Study dates:** Not reported **Elbaz (2015)** – related abstract **Mor (2014) –** related abstract	**Design:** Prospective single-arm cohort study **Intervention:** AposHealth use daily for 6 months. **Control:** N/A AMBER	• 58 patients • 39 female, 19 male • Average age: 59.7 ± 6.1 years • BMI: 30.7 ± 14.6 • K&L 2: 37% • K&L 3: 38.9% • K&L 4: 24.1% Singaporean patients diagnosed with symptomatic bilateral medial compartment knee OA. **Setting:** APOS Therapy Center in Singapore. GREEN	Follow up at 3 and 6 months after the start of treatment. Gait analysis WOMAC SF-36 Statistically significant improvement in WOMAC and SF-36 scores, and gait pattern scores after 6 months. GREEN	Partially meets scope. Treatment is with AposHealth, but it is not compared against anything. No control arm or randomisation. Study demonstrates statistically significant effectiveness of AposHealth in reducing pain, improving functioning and quality of life in knee OA.
Goryachev (2011) **Location:** Israel **Study dates:** Not reported **Goryachev (2012) –** related abstract	**Design:** Prospective single-arm cohort study **Intervention:** AposHealth use daily for 12 weeks. **Control:** N/A AMBER	• 14 patients (all female) • Average age: 59.9 ± 6.2 years • Height: 160.7 ± 6.3cm • Weight: 77.4 ± 8.9kg All patients diagnosed with symptomatic bilateral medial compartment knee OA. **Setting:** Orthopaedic department at an Israeli hospital. GREEN	Follow up at 12 weeks after the start of treatment. Gait analysis through muscle activity of the lower limb muscles. WOMAC Statistically significant improvement in WOMAC, an increase in gait velocity, and greater peak muscle activity after treatment. GREEN	Partially meets scope. Treatment is with AposHealth, but it is not compared against anything. Only 12 weeks of treatment. Small sample size of only females. Study demonstrates statistically significant effectiveness of AposHealth in reducing pain, and improving functioning, gait and quality of life in knee OA.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Greene (Unpublished) **Location:** UK **Study dates:** November 2017 – November 2019	**Design:** Retrospective case series **Intervention:** AposHealth use daily for at least two years. **Control:** N/A **AMBER**	• 365 patients47% male and 53% female Patients diagnosed with knee OA. **Setting:** Physiotherapy clinics offering AposHealth in the UK **GREEN**	Follow up at 3, 6, 12, and 24 months from the start of treatment. Surgery avoidance at 2 years after starting treatment. WOMAC Oxford Knee Score Rate of having a TKR was 6% in year one and 10% in year two, 16% overall. AposHealth led to a statistically significant improvement in WOMAC and Oxford Knee Score at 24 months. **GREEN**	Partially meets the scope. AposHealth is used but not compared against anything. Demonstrates that AposHealth can improve pain and function in knee OA after 24 months of treatment. Also demonstrates that the rate of AposHealth patients having a TKR is 16% after two years of treatment.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Haim (2012) **Location:** Israel **Study dates:** Not reported **Haim (2011) –** related abstract	**Design:** Prospective single-arm cohort study **Intervention:** AposHealth use daily for 12 weeks. **Control:** N/A **AMBER**	• 25 patients (all female) • Average age: 62 ± 7 years • Height: 159 ± 5.65cm • Weight: 77.2 ± 9.99kg • K&L grade: 3 ± 0.9 All patients diagnosed with symptomatic bilateral medial compartment knee OA. **Setting:** Orthopaedic department at an Israeli hospital. **GREEN**	Follow up at 12 weeks after the start of treatment. KAM magnitude (knee adduction impulse, loading response (1st) peak and terminal stance (2nd) peak) Knee and hip sagittal kinematics Spatiotemporal parameters (cadence, stride time, stride length, step length, walking speed, and step width) WOMAC SF-36 Statistically significant improvement in WOMAC and SF-36 scores after treatment. **GREEN**	Partially meets scope. Treatment is with AposHealth, but it is not compared against anything. Only 12 weeks of treatment. All female patients. Study demonstrates statistically significant effectiveness of AposHealth in reducing pain, improving functioning and quality of life in knee OA.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Herman (2018) **Location:** Israel **Study dates:** Not reported	**Design:** Retrospective case series **Intervention:** AposHealth use daily for 12 months. **Control:** N/A AMBER	• 518 patients • 336 females, 182 males • Average age: 63.4 ± 12.9 years • K&L 1: 17.6% • K&L 2: 36.94% • K&L 3: 32.5% • K&L 4: 13.5% Patients diagnosed with symptomatic bilateral medial compartment knee OA. Patients BMI> 30 kg/m2 **Setting:** APOS Therapy Center in Israel. GREEN	Follow up at 3, 6, 9, and 12 after the start of treatment. Gait analysis WOMAC SF-36 KOFG classification Statistically significant reduction in pain, stiffness, and functional limitation after 3 months of therapy. No statistically significant improvement between 3 and 12 months of therapy. GREEN	Partially meets scope. Treatment is with AposHealth, but it is not compared against anything. No control arm or randomisation. Study demonstrates statistically significant effectiveness of AposHealth in reducing pain, improving functioning and quality of life in obese patients with knee OA. This study aimed to validate the use of KOFG classification as a tool to assess time dependent changes in knee OA.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Lador (2013) **Location:** Israel **Study dates:** Not reported **Lador 2011** – related abstract	**Design:** Retrospective case series **Intervention:** AposHealth use daily for 4 months. **Control:** N/A AMBER	• 988 patients • 652 female, 336 male • Average age: 65.5 ± 8.8 years • Height: 162.7 ± 8.8cm • Weight: 81.8 ± 15.8kg • BMI: 30.8 ± 5.1 All patients diagnosed with symptomatic bilateral medial compartment knee OA. **Setting:** Orthopaedic department at an Israeli hospital. GREEN	Follow up at 4 months after the start of treatment. Spatiotemporal parameters (velocity, step length, cadence, base of support, stance phase, single-limb support phase) WOMAC SF-36 Statistically significant improvement in WOMAC, SF-36, and spatiotemporal parameters after treatment. GREEN	Partially meets scope. Treatment is with AposHealth, but it is not compared against anything. Only 4 months of treatment. No control arm or randomisation. Study demonstrates statistically significant effectiveness of AposHealth in reducing pain, improving functioning and quality of life in knee OA.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Lubovsky (2017) **Location:** Israel **Study dates:** April 2009 – December 2012	**Design:** Retrospective case series **Intervention:** AposHealth use daily for 12 months. **Control:** N/A AMBER	• 105 patients • 73 females, 32 males • Average age: 65.6 ± 7.9 years • Height: 162.1 ± 9.3cm • Weight: 92.4 ± 15.7kg • BMT: 35 ± 4.1 Obese patients diagnosed with symptomatic bilateral medial compartment knee OA. **Setting:** APOS Therapy Center in Israel. GREEN	Follow up at 3 and 12 months after the start of treatment. Gait analysis WOMAC SF-36 Statistically significant reduction in pain, stiffness, and functional limitation after 3 months of therapy, and further improvement after 12 months. GREEN	Partially meets scope. Treatment is with AposHealth, but it is not compared against anything. No control arm or randomisation. Study demonstrates statistically significant effectiveness of AposHealth in reducing pain, improving functioning and quality of life in obese patients with knee OA.
Miles (2020) **Location:** UK **Study dates:** 2009 – 2017 **Miles (2022) –** related abstract	**Design:** Retrospective case series **Intervention:** AposHealth use daily for 6 months. **Control:** N/A AMBER	• 455 patients • 247 females, 208 males • Average age: 62.2 ± 9.5 years • 20% recommended surgery • 80% not recommended surgery Patients diagnosed with symptomatic unilateral and bilateral medial compartment knee OA. **Setting:** Physiotherapy clinics in the UK that offer AposTherapy treatment. GREEN	Follow up at 3 and 6 months after the start of treatment. Gait analysis WOMAC SF-36 KOFG classification Statistically significant reduction in WOMAC, SF-36, and KOFG scores after 6 months of treatment. GREEN	Partially meets scope. Treatment is with AposHealth, but it is not compared against anything. Short follow up of only 6 months. No control arm or randomisation. Study demonstrates statistically significant effectiveness of AposHealth in reducing pain, improving functioning and quality of life in patients with knee OA. This is one of the only studies that is based in the UK with UK patients.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Reichenbach (2020) **Location:** Switzerland **Study dates:** April 2015 – January 2017 **Reichenbach (2018) –** related abstract	**Design:** Single blinded, sham controlled, randomised control trial **Intervention:** AposHealth use daily for 24 weeks. **Control:** Sham device near identical to the active AposHealth shoe. The biomechanical elements were encased in a transparent outsole so they were visible but didn't create a convex surface. Patients were given a sham calibration. Daily use for 24 weeks. Patients could use any other medical or physical therapy. **GREEN**	**Active group (n=111)** • 60 male, 51 female • Average age: 65.3 ± 9.2 years • K&L grade 2: 33 (29.7%) • K&L grade 3: 50 (45%) • K&L grade 4: 28 (25.2%) • BMI: 27.7 ± 4.8 **Control group (n=109)** • 56 male, 53 female • Average age: 65 ± 9.3 • K&L grade 2: 36 (33%) • K&L grade 3: 46 (42.2%) • K&L grade 4: 27 (24.8%) • BMI: 28.3 ± 4.3 All patients diagnosed with symptomatic unilateral and bilateral medial compartment knee OA. No statistically significant difference between groups at baseline. **Setting:** University hospital in Switzerland. **GREEN**	Follow ups at 4, 8, 12, 16, and 24 weeks after the start of treatment. WOMAC SF-36 health survey Gait analysis Statistically significant improvement between groups in WOMAC pain and function after 12 weeks of treatment, and in stiffness after 24 weeks. No statistically significant difference between groups in SF-36 mental and physical subscores after 24 weeks. No statistically significant difference in healthcare and analgesic use between groups after 24 weeks. **GREEN**	A controlled comparison of AposHealth against a sham device whereby patients were also allowed to use other physical and medical therapies, this meets the scope. It was only single blinded. The paper notes that while results are statistically significant for the primary outcome, they cannot be certain of the clinical importance of the overall results.

Table 5: Relevant Abstracts

Study	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Elbaz (2012) **Location:** Israel **Study dates:** Not reported	**Design:** Retrospective case series **Intervention:** AposHealth use daily for 12 months. **Control:** N/A AMBER	• 745 patients Patients diagnosed with symptomatic bilateral medial compartment knee OA. **Setting:** Clinic GREEN	Follow up at 12 weeks after the start of treatment. Gait analysis WOMAC SF-36 Statistically significant reduction in WOMAC pain and function after treatment. GREEN	This is an abstract only, so many details are unavailable. Partially meets scope. Treatment is with AposHealth, but it is not compared against anything. Short follow up of only 3 months. No control arm or randomisation. Study demonstrates statistically significant effectiveness of AposHealth in reducing pain and improving function in patients with knee OA.
Elbaz (2009) **Location**: Israel **Study dates**: Not reported	**Design:** Prospective cohort **Intervention:** AposHealth use daily for 12 months. **Control:** N/A AMBER	47 patients Patients diagnosed with symptomatic bilateral medial compartment knee OA. Setting: Clinic and at home GREEN	Follow up at 12 weeks after the start of treatment. Gait analysis WOMAC SF-36 Following treatment, there was a statistically significant improvement in WOMAC pain and function. SF-36 scores significantly increased. Gait velocity, step length and single limb support increased significantly.	This is an abstract only, so many details are unavailable. Partially meets scope. Treatment is with AposHealth, but it is not compared against anything. Short follow up of only 12 weeks. No control arm or randomisation. Study demonstrates statistically significant effectiveness of AposHealth after 12 weeks in reducing pain and improving function in patients with knee OA.

Study	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
			GREEN	
Hagen (2018) **Location:** USA **Study dates:** January 2009 - November 2017	**Design:** Case-control study **Intervention:** AposHealth use daily for one year. **Control:** Patients with a diagnosis of knee OA that didn't receive AposHealth. **GREEN**	• 179,398 patients Patients between 40-64 years old who have completed a one-year course of AposHealth for knee OA. **Setting:** Academic medical centre **GREEN**	**Active arm:** The number of opioid prescriptions filled by patients for one year. **Control arm:** Overall claims data for opioid prescriptions. 16.7% of AposHealth patients received any opioid prescriptions during the year. 34.5% of knee OA patients received a prescription. **GREEN**	This is an abstract only, so many details are unavailable. Study meets the scope in that it's comparing patients on standard care with those receiving AposHealth. However, the specifics of the standard care are not apparent. Study is used as evidence that AposHealth leads to less opioid use.
Van Ginckel (2021) **Location:** Belgium **Study dates:** Not reported	**Design:** Meta-analysis **Intervention:** Customised shoes, knee braces, insoles, canes, or gait retraining for knee OA. **Control:** Non-biomechanical treatment for knee OA. **GREEN**	27 trials involving 2,413 patients with knee OA receiving one of ten different treatments. **Setting:** N/A **GREEN**	Efficacy of different biomechanical treatments for knee OA. Most comparisons had low to very low certainty of evidence. Considering all biomechanical treatments, combined bracing showed the most pain relief, with significant differences versus shoes. **GREEN**	This is an abstract only, so many details are unavailable. Study meets the scope. It is comparing AposHealth within a meta-analysis against other devices used for treatment of OA. Evidence suggests that AposHealth is not any more effective at treating knee OA than other biomechanical treatments.

Study	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Veeramachaneni (2016) Location: USA Study dates: Not reported	**Design:** Prospective cohort **Intervention:** AposHealth use daily for one month. **Control:** N/A AMBER	22 patients 30.4% male and 69.5% female Patients diagnosed with knee OA. Setting: Clinic GREEN	Follow up at one month after the start of treatment. Gait analysis WOMAC SF-36 After one month of AposHealth there was a statistically significant improvement in WOMAC pain, function, and stiffness scores, and in SF-36 scores. GREEN	This is an abstract only, so many details are unavailable. Partially meets the scope. AposHealth is used but not compared against anything. Demonstrates that AposHealth can improve pain and function in knee OA after one month of treatment.

5 Clinical evidence review

5.1 *Overview of methodologies of all included studies*

Of the 14 studies, 1 was a randomised controlled trial (Reichenbach 2020), 1 was a prospective comparative study (Bar-Ziv 2010 and Bar-Ziv 2013) and 12 were observational cohort studies (Debbi 2015, Drexler 2012, Drew 2022, Elbaz 2010, Elbaz 2014, Greene Unpublished, Goryachev 2011, Haim 2012, Herman 2018, Lador 2013, Lubovsky 2017, and Miles 2020).

In discussion with the company, the EAG queried the relationship between the publications by Bar-Ziv (2010) and Bar-Ziv (2013) as it was noted that they have the same NCT registration identifier. The company advised the 2010 publication reported on the first phase of the trial results in an 8-week follow-up period. This phase of the trial was blinded and pseudo-randomised. The 2013 publication is a report of a 2-year follow-up period of the trial but the participants were unblinded and cross-over between treatment arms was permitted.

The RCT (Reichenbach 2020) compared AposHealth to a sham device, as did the prospective comparative study by Bar-Ziv (2010 and 2013). The EAG noted the use of a sham device as a control assumes there would be no biomechanical impact on the user's knee joints from use of the sham device.

Many studies lacked direct comparators. Seven of the observational cohort studies were retrospective and consisted of the analysis of data retrieved from a single database of AposHealth users (Drexler 2012, Elbaz 2010, Greene Unpublished, Herman 2018, Lador 2013, Lubovsky 2017, and Miles 2020). Four of the observational cohort studies were prospective and reported on the outcomes of a single group of patients who received the AposHealth intervention, with post-treatment measurements being compared with baseline measurements (Debbi 2015, Elbaz 2014, Goryachev 2011, and Haim 2012).

The retrospective cohort study by Drew (2022) reported on the rate of progression to TKR surgery in a cohort of patients that received AposHealth

as an intervention for knee OA. The study authors reported clinical information from a cohort of patients that elected to undergo TKR as an intervention for knee OA (and did not receive AposHealth) for comparison at baseline only. As the study only compared its two cohorts at baseline, and not post-intervention, the study was treated as a single-arm observational study with results extracted from the AposHealth arm only.

5.2 *Critical appraisal of studies and review of company's critical appraisal*

Critical appraisal of full publications was completed by 2 EAG researchers (Appendix B) with key strengths and limitations discussed below. Abstracts were not critically appraised due to a lack of data.

The Biomechanical Therapy for Osteoarthritis of the Knee (BIOTOK) study was a single-centre randomised controlled trial that compared AposHealth with a sham device (Reichenbach 2020). The EAG considers the quality of this RCT to be high as the groups were similar at baseline, true randomisation and concealed allocation was used, and the participants were blind to their treatment assignment. The outcomes were measured in the same, reliable way for both groups.

The prospective comparative study (Bar-Ziv 2010 and Bar-Ziv 2013) was similar to the RCT in that the comparator was a sham device. The limitation of this study is primarily the unclear description of participants moving between phases of the trial which undermines the robustness of the results. The initial 8-week study (Bar-Ziv 2010) was blinded and pseudo-randomised. However, in the 2-year follow-up period, participants were unblinded and cross-over between treatment arms was permitted. The study by Bar-Ziv (2010 and 2013) is treated as one study in the results section but the manuscripts were critically appraised separately due to the variation in their methods and design.

Most included studies were observational with no comparator. It was unclear if complete and consecutive inclusion was carried out in the majority of the studies where participants were retrieved from a database (Drexler 2012, Elbaz 2010, Herman 2018, Lador 2013, Lubovsky 2017, Miles 2020, and

Greene Unpublished). Four of the observational studies did report a systematic selection of participants from a database based on the dates they received AposHealth treatment (Drexler 2012, Drew 2022, Miles 2020 and Greene Unpublished). Some patients were excluded from these studies as per the study's pre-specified exclusion criteria. The EAG acknowledges that the outcomes reported across the observational studies are relatively consistent with Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores, SF-36 questionnaire results and gait outcomes frequently being reported. The EAG noted that the WOMAC scores reported in the included studies were not all on the same scale, with some studies using a visual analogue scale (VAS) with a range of 0-10, others using a VAS with a range of 1-100 and others not reporting the format of scale used (Table 7). The EAG therefore believes that caution should be taken when comparing WOMAC scores between studies and interpreting the evidence.

The EAG considers the body of evidence for AposHealth to be generally of low quality methodologically based on critical appraisal checklists. This is attributed to the majority of the evidence being observational, retrospective and non-comparative. There is one RCT (Reichenbach 2020) which is highlighted in the company submission as a pivotal study and one pseudo-randomised trial (Bar-Ziv 2010, Bar-Ziv 2013), both of which compare AposHealth with a sham device. Drew (2022) reports rates of progression to TKR surgery in a cohort receiving AposHealth and compares clinical parameters at baseline to a cohort that have elected to undergo TKR surgery. No comparison of rates of progression to TKR with other non-surgical interventions for knee OA is reported. A key limitation in the evidence base is a lack of comparator however this may be driven by uncertainties in the care pathway making it difficult to design and conduct a comparative study. Limited UK studies makes assessment of the generalisability of the findings to the NHS setting less certain. A lack of long-term follow-up (beyond 2 years) to understand how long people with knee osteoarthritis can avoid surgery for while using AposHealth and to clearly assess use of any additional treatments such as pain relief is another limitation of the evidence. Although the methodological quality of the included studies is considered low, this should

be balanced against the extent to which the evidence meets the criteria set out in the NICE real-world evidence framework. The NICE real-world evidence framework sets out best-practices for planning, conducting and reporting real-world evidence studies to improve the quality and transparency of evidence. In terms of planning, the included studies largely appear to meet the criteria set out in the framework, with study conduct and reporting also in line with the framework. Overall, despite methodological limitations in individual studies, the body of evidence consistently reports improvement in a number of outcomes for people using AposHealth (see results section).

5.3 *Results from the evidence base*

The results from the included studies are discussed in detail in this section. The results from the evidence base have been grouped by outcome with results from the most commonly reported outcome measures summarised in Table 8 and Table 9. The EAG noted the lack of evidence regarding the comparison of AposHealth to non-surgical standard care treatment options such as manual therapy, walking aids, and intra-articular corticosteroid injections and their respective impacts on pain and function. Additionally, there is a lack of evidence relating to the outcome of TKR surgery delay or avoidance beyond 2 years.

5.3.1 *Gait Analysis*

Although not an outcome in the scope, AposHealth functions through adjustment of gait and the EAG notes that there are a number of approaches to gait analysis ranging from visual analysis to digital apps and more comprehensive gait analysis laboratories. Twelve of the 14 studies identified by the EAG utilised a gait analysis device in some form to either calibrate AposHealth or assess outcomes post-intervention, details of which can be found in Table 6. The correlation between modification of gait and subsequent changes in clinical outcomes, such as a reduction in pain and function, is not explored consistently across the evidence base. However, the studies by Lador (2013) and Miles (2020) both reported high correlation between changes in gait parameters and changes (improvement) in self-evaluation clinical outcome questionnaires. One clinical expert using AposHealth in both the NHS and private settings used a comprehensive gait analysis system

using cameras, walkways and software for calibration and outcome assessment but noted that many physiotherapy clinics were unlikely to have such a comprehensive gait analysis system. The patient expert also stated a similar gait-analysis tool was used during their AposHealth calibration sessions.

Table 6: Gait Analysis Tools used in each study

Study	Type of Gait Analysis Used	Gait analysis results
Bar-Ziv 2010 and 2013	Visual/observational	• Gait analysis not reported as an outcome.
Debbi 2015	Vicon motion analysis	• At 3-month follow-up: all patients showed a small but significant increase in walking velocity of 0.07 m/s (from 1.00 ± 0.13 to 1.07 ± 0.14 m/s, p = 0.017). • Cadence increased by 5 steps/min (from 105.54 ± 9.54 to 110.08 ± 7.59 step/min) but was not significant (p = 0.058).
Drexler 2012	Visual/observational	• Gait analysis not reported as an outcome.
Drew 2022	Visual and 'computerised' gait analysis (tool not named)	• Gait analysis not reported as an outcome.
Elbaz 2010	GaitRite	• Improved gait (SLS) in all groups regardless of age or BMI level.
Elbaz 2014	GaitMat	• All gait parameters significantly improved at 3 months (except SLS phase of the less symptomatic knee). • All gait parameters significantly improved compared to baseline at 6 months.
Goryachev 2011	Gait lab	• Small but significant increase in gait velocity (7.74% increase) after AposHealth. • No significant difference in cadence. • Greater peak activity in muscles after AposHealth.
Greene Unpublished	OptoGait	• Velocity (cm/s), step length (cm) and SLS phase all improved over time with AposHealth treatment.
Haim 2012	Vicon motion analysis	• Significant reduction observed in KAM magnitude after three and nine months of treatment with AposHealth (speculated by study authors to be linked with improvement in symptoms).
Herman 2018	GaitMat	• Gait analysis used to calculate knee osteoarthritis functional grade (KOFG) which was an outcome of the study.
Lador 2013	GaitMat	• A significant improvement in all gait measures at 4 months.

Study	Type of Gait Analysis Used	Gait analysis results
		• Male patients improved from 46.7 to 54.8 (17.3%) and female patients improved from 41.0 to 50.6 (23.4%). • High correlation between the improvement in SLS and improvement pain and function.
Lubovsky 2017	GaitMat	• Significant improvements in all gait pattern in all parameters when measured at 3 months (P = 0.03 overall). These improvements further improved following 12 months of therapy. However, the improvements in the 3-month scores and the 12-month scores did not reach a level of significance.
Miles 2020	OptoGait	• All spatial-temporal gait parameters p < 0.01 after 3 months. • p < 0.01 between 3 and 6 months, except SLS on both sides (p = 0.554 and 0.452). • All parameters p < 0.01 after 5 months.
Reichenbach 2020	Zeno walkway	• Between-group differences in velocity, step length, and SLS were superior in the AposHealth group between 12 and 24 weeks of follow-up when compared to the sham device group.
Abbreviations: KAM: knee adduction moment; KOFG: knee osteoarthritis functional grade; SLS: single-limb support.		

5.3.2 *Pain, function, and stiffness*

Pain, function and stiffness outcomes were consistently reported across the evidence base, reported in one high quality RCT (Reichenbach 2020), 1 low quality comparative study (Bar-Ziv 2010 and Bar-Ziv 2013) and 12 observational studies (Debbi 2015, Drexler 2012, Drew 2022, Elbaz 2010, Elbaz 2014, Greene Unpublished, Goryachev 2011, Haim 2012, Herman 2018, Lador 2013, Lubovsky 2017 and Miles 2020). Pain, function, and stiffness were primarily measured using the Western Ontario and McMaster Universities Arthritis Index (WOMAC). The Aggregated locomotor function (ALF) score is used in 1 study (Bar-Ziv 2010 and 2013) as a measure of function. The Oxford Knee Score (OKS) is used as a measure of pain and function in the study by Greene (unpublished).

The WOMAC is widely used in the evaluation of knee OA outcomes and is made up of 24 questions divided into 3 subscales with 5 questions relating to

pain, 17 questions relating to function, and 2 questions relating to stiffness. As previously mentioned, the scales used for the WOMAC scores in each paper varied, details of which can be found in Table 7. The low end of the scales represents low pain, low stiffness, and low functional limitation. The high end of the scales represents high pain, high stiffness, and high functional limitation. WOMAC scores were reported in all included studies and the total scores, pain subscale scores, function subscale scores, and stiffness subscale scores are summarised in Table 8.

Table 7: WOMAC Scales used in each study

Study	WOMAC Scale Used (unit)	Format
Debbi 2015	0-10 (cm)	VAS
Drew 2022	0-100 (mm)	VAS
Elbaz 2010	0-10 (cm)	VAS
Elbaz 2014	0-10 (cm)	VAS
Goryachev 2011	0-10 (cm)	VAS
Greene Unpublished	0-100 (mm)	VAS
Haim 2012	0-10 (cm)	VAS
Herman 2018	0-100 (not reported)	Not reported
Lador 2013	0-100 (mm)	VAS
Lubovsky 2017	0-100 (mm)	VAS
Miles 2020	0-100 (mm)	VAS
Reichenbach 2020	0-10 (not reported)	VAS

The ALF scale is used to measure locomotor functions. The total score is the sum of the mean scores on three physical tests which include walking a specified distance, ascending and descending stairs, and transferring from sitting to standing (measured in seconds).

The OKS is a measure that consists of a 12-item questionnaire, resulting in a total score on a scale of 0-48 where 0 represents poorest function and 48 represents highest function. The questions ask the participant to describe their ability to complete physical tasks and their experiences of pain while doing such physical tasks (such as descending stairs, completing housework, and using transport).

Where AposHealth is compared to a control group (Reichenbach 2020, Bar-Ziv 2010 and Bar-Ziv 2013), the differences in WOMAC scores between

groups (totals and subscales) are statistically significant (all p<0.02), showing better outcomes for the AposHealth group. However, there is uncertainty that the improvement observed in the study by Reichenbach (2020) is clinically important. The longest follow-up of these comparative studies was 2 years (Bar-Ziv 2013). In this study, the results of the ALF score did not differ significantly between groups over time. The study authors suggested this could have been due to the control group having access to additional therapies during the study period.

Drew (2022) reported statistically significant improvements in WOMAC pain and function scores after 12 months of treatment with AposHealth (p<0.001). These scores were not compared to post-surgery WOMAC pain and function scores of the cohort that received TKR. However, the study authors did report that baseline WOMAC pain and function scores of the TKR cohort were significantly worse than the group that were treated with AposHealth. Greene (unpublished) reported an improvement in OKS in the first 6 months of treatment (by 7.6 points) and by the end of 2 years of treatment (by 10.6 points. The authors state that this meets a designated clinical minimally important change of 7 points. The EAG noted that the OKS is an outcome measure that was initially created for post-TKR outcome assessment and has since been adopted for the assessment of knee OA outside of this context.

Miles (2020) conducted a sub-analysis on participants that had been recommended for TKR prior to commencing treatment with AposHealth (20% of study population). The study concluded that WOMAC pain and stiffness subscales were significantly higher at the 6-month follow-up time point in the participants that had been recommended for TKR. However, improvements were seen from baseline to the 6-month follow-up period which suggested AposHealth did benefit this group of participants, but not to the same degree that it benefited participants that had not been recommended for surgery.

In the study abstracts that reported on pain, function and/or stiffness, positive impacts were observed as a result of intervention with AposHealth (Elbaz 2012, Elbaz 2009, Hagen 2018, and Veeramachaneni 2016).

Overall, results from the evidence base show a consistent decrease in pain, function limitation, and stiffness as measured by WOMAC scores after AposHealth is given as an intervention compared to baseline measurements. This is supported by the experience of a patient expert who stated that using AposHealth has significantly improved their pain, mobility, and ability to participate in physical activity. Clinical experts also stated that they had observed improvements in pain and mobility in patients they had provided with AposHealth.

Table 8: Pain, Function, and Stiffness Results

Pain, function, and stiffness as measured by the WOMAC Index: Mean ± SD													
Study	**Treatment**	**Baseline**				**Follow-up 1**				**Follow-up 2**			
		Pain	**Function**	**Stiffness**	**Total**	**Pain**	**Function**	**Stiffness**	**Total**	**Pain**	**Function**	**Stiffness**	**Total**
Reichenbach 2020	AposHealth	4.3 ± 1.8	3.5 ± 1.8	5.0 ± 2.4	3.8 ± 1.7	*At 12 weeks:* 2.3 ± 1.7	*At 12 weeks:* 2.1 ± 1.4	*At 12 weeks:* 2.9 ± 2.0	*At 12 weeks:* 2.2 ± 1.4	*At 24 weeks:* 1.3 ± 1.3	*At 24 weeks:* 1.4 ± 1.2	*At 24 weeks:* 1.6 ± 1.5	*At 24 weeks:* 1.4 ± 1.2
	Control (Sham Device)	4.0 ± 2.0	3.4 ± 1.8	4.4 ± 2.4	3.6 ± 1.7	*At 12 weeks:* 2.6 ± 2.1	*At 12 weeks:* 2.5 ± 2.0	*At 12 weeks:* 2.8 ± 2.3	*At 12 weeks:* 2.5 ± 2.0	*At 24 weeks:* 2.6 ± 2.0	*At 24 weeks:* 2.4 ± 1.8	*At 24 weeks:* 2.8 ± 2.2	*At 24 weeks:* 2.5 ± 1.8
Bar-Ziv 2010	AposHealth	5.4 ± 2.7	5.1 ± 2.6	5.7 ± 3.0	5.4 ± 2.6	*At 4 weeks:* 3.1 ± 2.2	*At 4 weeks:* 3.1 ± 1.9	*At 4 weeks:* 3.7 ± 2.5	*At 4 weeks:* 3.3 ± 2.0	*At 8 weeks:* 1.9 ± 1.6	*At 8 weeks:* 1.9 ± 1.5	*At 8 weeks:* 1.9 ± 2.3	*At 8 weeks:* 1.9 ± 1.7
	Control (Sham Device)	5.0 ± 2.7	5.2 ± 2.3	5.4 ± 3.3	5.2 ± 2.6	*At 4 weeks:* 5.1 ± 2.2	*At 4 weeks:* 5.5 ± 2.2	*At 4 weeks:* 5.4 ± 3.0	*At 4 weeks:* 5.3 ± 2.3	*At 8 weeks:* 5.4 ± 2.7	*At 8 weeks:* 5.7 ± 2.6	*At 8 weeks:* 5.2 ± 3.2	*At 8 weeks:* 5.4 ± 2.6
Bar-Ziv 2013	AposHealth	5.0 ± 2.8	4.9 ± 2.6	5.5 ± 3.1	NR	*At 2 years:* 1.9 ± 1.6	*At 2 years:* 1.9 ± 1.3	*At 2 years:* 2.1 ± 1.7	NR	N/A			
	Control (Sham Device)	5.5 ± 3.3	5.9 ± 2.5	5.6 ± 3.3	NR	*At 2 years:* 6.8 ± 2.0	*At 2 years:* 6.6 ± 1.7	*At 2 years:* 7.7 ± 1.5	NR	N/A			
Debbi 2015	AposHealth	4.1 ± 2.3	4.6 ± 2.2	5.2 ± 3.2	NR	*At 3 months:* 1.7 ± 1.3	*At 3 months:* 2.1 ± 1.6	*At 3 months:* 2.5 ± 2.1	NR	*At 9 months:* 1.6 ± 1.5	*At 9 months:* 1.7 ± 1.2	*At 9 months:* 1.6 ± 1.5	NR

Pain, function, and stiffness as measured by the WOMAC Index: Mean ± SD													
Study	Treatment	Baseline				Follow-up 1				Follow-up 2			
		Pain	Function	Stiffness	Total	Pain	Function	Stiffness	Total	Pain	Function	Stiffness	Total
Drew 2022 [b]	AposHealth	54.7 ± 1.6	47.6 ± 1.7	NR	NR	*At 3 months:* 41.1 ± 1.9	*At 3 months:* 34.6 ± 1.9	NR	NR	*At 12 months:* 35.1 ± 3.3	*At 12 months:* 31.2 ± 3.0	NR	NR
Elbaz 2014 [a]	AposHealth	Unable to extract [a]			NR	*At 3 months:* Unable to extract [a]				*At 6 months:* 68.3% decrease [a]	*At 6 months:* 75.6% functional limitation decrease [a]	*At 3 months:* Unable to extract [a]	NR
Goryachev 2011	AposHealth	4.6 ± 2.3	4.9 ± 2.4	5.8 ± 3.4	NR	*At 3 months:* 1.7 ± 1.3	*At 3 months:* 2.0 ± 1.5	*At 3 months:* 2.7 ± 2.1	NR	N/A			
Haim 2012	AposHealth	4.1 ± 2.3	4.6 ± 2.2	5.2 ± 3.2	NR	*At 3 months:* 1.7 ± 1.3	*At 3 months:* 2.1 ± 1.6	*At 3 months:* 2.5 ± 2.1	NR	*At 9 months:* 1.6 ± 1.5	*At 9 months:* 1.7 ± 1.2	*At 9 months:* 1.6 ± 1.5	NR
Drexler 2012	AposHealth	5.0 ± 2.0	4.9 ± 1.9		NR	*At 3 months:* 3.5 ± 2.1	*At 3 months:* 3.5 ± 2.0		NR	N/A			
Elbaz 2010	AposHealth	4.4 ± 2.1	4.6 ± 2.3		NR	*At 12 weeks:* 3.4 ± 1.8	*At 12 weeks:* 3.5 ± 2.2		NR	N/A			

Pain, function, and stiffness as measured by the WOMAC Index: Mean ± SD													
Study	**Treatment**	**Baseline**				**Follow-up 1**				**Follow-up 2**			
		Pain	**Function**	**Stiffness**	**Total**	**Pain**	**Function**	**Stiffness**	**Total**	**Pain**	**Function**	**Stiffness**	**Total**
Greene Unpublished [b]	AposHealth	55.8 ± 18.8	54.3 ± 19.8	NR	NR	*At 6 months:* 32.2 ± 22.6	*At 6 months:* 33.0 ± 22.7	NR	NR	*At 2 years:* 27.4 ± 20.2	*At 2 years:* 29.2 ± 20.5	NR	NR
Herman 2018[b]	AposHealth	46.1 ± 1.0 (SE)	4.3 ± 1.0 (SE)	47.4 ± 1.3 (SE)	43.8 ± 1.0 (SE)	*At 3 months:* 30.6 ± 1.0 (SE)	*At 3 months:* 30.6 ± 1.0 (SE)	*At 3 months:* 33.4 ± 1.2 (SE)	*At 3 months:* 30.8 ± 0.9 (SE)	*At 12 months:* 27.1 ± 1.0 (SE)	*At 12 months:* 27.7 ± 1.1 (SE)	*At 12 months:* 29.3 ± 1.2 (SE)	*At 12 months:* 27.7 ± 1.0 (SE)
Lador 2013[b]	AposHealth	51.4 ± 20.2	49.9 ± 19.7	NR	NR	*At 4 months:* 35.4 ± 22.1	*At 4 months:* 36.0 ± 22.3	NR	NR	N/A			
Lubovsky 2017	AposHealth	Unable to extract [a]			NR	*At 3 months:* 34.7% decrease	*At 3 months:* 35.0% decrease	*At 3 months:* 29.7% decrease	NR	*At 12 months:* 45.7% decrease	*At 12 months:* 44.7% decrease	*At 12 months:* 8.7% decrease	NR
Miles 2020[b]	AposHealth	46.7 ± 19.7	39.0 ± 21.6	38.97 ± 21.6	NR	*At 3 months:* 27.4 ± 19.7	*At 3 months:* 24.1 ± 19.8	*At 3 months:* 24.1 ± 19.8	NR	*At 6 months:* 24.0 ± 18.9	*At 6 months:* 21.2 ± 18.5	*At 6 months:* 21.2 ± 18.5	NR

Notes:

[a] WOMAC Scores in these publications are reported in a line graph format where exact values cannot be visually extracted. Percentage decreases taken from text.

[b] WOMAC Scale in these studies reported as 1-100 in contrast to all other studies which report WOMAC Scale as 0-10.

Abbreviations: N/A: Not Applicable; NR: Not Reported; SD: Standard Deviation; SE: Standard Error; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

5.3.3 *Quality of Life and Patient Satisfaction*

Quality of life outcomes were consistently reported across the evidence base, reported in one high quality RCT (Reichenbach 2020), one low quality comparative study (Bar-Ziv 2010 and Bar-Ziv 2013) and 10 observational studies (Debbi 2015, Drexler 2012, Drew 2022, Elbaz 2010, Elbaz 2014, Haim 2012, Herman 2018, Lador 2013, Lubovsky 2017 and Miles 2020).

The SF-36 is a standardised questionnaire used to evaluate self-reported quality of life in various settings, including osteoarthritis patients. The questionnaire consists of 36 items grouped into 8 dimensions: physical function, pain, role limitation due to physical health, energy/fatigue, emotional well-being, role limitation due to emotional health, social functioning, and general health. The results from these 8 domains can be converted into 2 summary scores, a physical component score (PCS) and a mental component score (MCS). SF-36 scores are reported in all included studies except Greene (Unpublished) and Goryachev (2011) and are summarised in Table 9.

From one high quality RCT (Reichenbach 2020) no statistically significant difference in SF-36 scores (total, PCS, and MCS) between active and control groups was observed. One comparative study (Bar-Ziv 2010) reported a significant difference in SF-36 scores between active and control groups and between time points (baseline, 4 weeks, and 8 weeks). At 2-year follow-up there were significant differences in total and PCS SF-36 scores between active and control groups (Bar-Ziv 2013). However, there was no significant difference in improvement over time between groups for the SF-36 MCS.

In the study by Drew (2022), the SF-36 overall score was significantly improved after 1 year. The PCS SF-36 component increased significantly after 1 year but no significant changes in MCS SF-36 component were observed. Comparisons in SF-36 scores were made at baseline between the AposHealth arm and the arm receiving TKR, and no significant differences were noted. SF-36 scores were not reported post-surgery for the participants in the arm receiving TKR.

In the non-comparative studies, the impact on SF-36 scores from baseline to post-treatment follow-up points was mixed. All subscale scores of the SF-36 were significantly improved in 4 studies (Drexler 2012, Herman 2018; Lador 2013; and Miles 2020). Significant improvements in all subscales except emotional well-being were reported in 2 studies (Elbaz 2014 and Haim 2012). Significant improvements were reported in all subscales except the subscales of limitation due to emotional health and emotional well-being (Debbi 2015) and significant improvements were reported in all subscales except role limitation due to emotional health, emotional well-being, and social functioning (Elbaz 2010). Significant improvements in all subscales except role limitation due to emotional health were reported in one study (Lubovsky 2017).

In the study abstracts that reported on quality of life, positive impacts on quality of life were observed as a result of intervention with AposHealth (Elbaz 2012, Elbaz 2009, Hagen 2018, and Veeramachaneni 2016).

The company provided 2 unpublished patient satisfaction surveys, one from people in an NHS setting (n=218) and one from a private setting (n=165). The questions in the NHS survey were agreed upon jointly by the company and an NHS Clinical Commissioning Group (CCG). The results from the surveys indicate high patient satisfaction and compliance rates with AposHealth. This was aligned with the input from one patient expert who expressed great satisfaction in the improvement to their quality of life since using AposHealth. The EAG noted these reports were not peer-reviewed or published.

Overall, there is some evidence that AposHealth can improve quality of life for people with knee OA, with stronger evidence for improvements to physical aspects and weaker evidence for improvements to emotional aspects. There is generally a lack of long-term data to evidence continued improvements and/or the maintenance of any observed improvements.

Table 9: SF-36 Results

SF-36 Scores: Mean (SD)										
Study	**Treatment**	**Baseline**			**Follow-up 1**			**Follow-up 2**		
		PCS	**MCS**	**Total**	**PCS**	**MCS**	**Total**	**PCS**	**MCS**	**Total**
Reichenbach 2020	AposHealth	40.4 ± 7.1	57.0 ± 7.4	NR	*At 12 weeks:* 43.1 ± 7.6	*At 12 weeks:* 57.1 ± 7.0	NR	*At 24 weeks:* 45.9 ± 7.4	*At 24 weeks:* 56.8 ± 6.7	NR
	Control (Sham Device)	40.3 ± 6.2	56.4 ± 8.8	NR	*At 12 weeks* 43.8 ± 7.3	*At 12 weeks* 56.2 ± 8.9	NR	*At 24 weeks:* 44.5 ± 8.0	*At 24 weeks:* 56.0 ± 9.0	NR
Bar-Ziv 2010	AposHealth	46.0 ± 18.6	57.5 ± 45.3	56.0 ± 21.1	*At 4 weeks:* 61.8 ± 19.2	*At 4 weeks:* 73.6 ± 38.2	*At 4 weeks:* 68.1 ± 17.7	*At 8 weeks:* 69.2 ± 21.0	*At 8 weeks:* 90.8 ± 23.4	*At 8 weeks:* 77.1 ± 15.1
	Control (Sham Device)	43.7 ± 21.1	56.0 ± 39.3	53.5 ± 18.9	*At 4 weeks:* 36.7 ± 20.9	*At 4 weeks:* 42.7 ± 40.3	*At 4 weeks:* 51.1 ± 19.5	*At 8 weeks:* 38.7 ± 22.1	*At 8 weeks:* 44.0 ± 39.3	*At 8 weeks:* 48.5 ± 22.1
Bar-Ziv 2013	AposHealth	51.9 ± 19.2	64.7 ± 19.6	NR	*At 2 years:* 67.6 ± 16.3	*At 2 years:* 73.7 ± 13.1	NR	N/A		
	Control (Sham Device)	39.7 ± 17.8	50.3 ± 19.7	NR	*At 2 years:* 37.1 ± 14.9	*At 2 years:* 56.8 ± 12.5	NR	N/A		
Debbi 2015	AposHealth	NR [a]								
Drew 2022	AposHealth	43.2 ± 1.6	64.4 ± 1.6	51.5 ± 1.2	*At 3 months:* 52.1 ± 1.7	*At 3 months:* 69.2 ± 1.6	*At 3 months:* 58.8 ± 1.4	*At 12 months:* 48.8 ± 2.9	*At 12 months:* 67.7 ± 2.8	*At 12 months:* 56.9 ± 2.4
Elbaz 2014	AposHealth	44.7 ± 14.5	58.5 ± 16.0	NR	*At 3 months:* 59.0 ± 18.0	*At 3 months:* 67.0 ± 16.3	NR	*At 6 months:* 65.3 ± 17.7	*At 6 months:* 71.7 ± 13.4	NR
Haim 2012	AposHealth	NR [a]								

SF-36 Scores: Mean (SD)											
Study	**Treatment**	**Baseline**			**Follow-up 1**			**Follow-up 2**			
		PCS	**MCS**	**Total**	**PCS**	**MCS**	**Total**	**PCS**	**MCS**	**Total**	
Drexler 2012	AposHealth	47.4 ± 17.2	60.5 ± 18.9	NR	*At 3 months:* 54.6 ± 18.2	*At 3 months:* 66.4 ± 17.9	NR	N/A			
Elbaz 2010	AposHealth	NR [a]									
Herman 2018	AposHealth	NR	NR	51.6 ± 0.73	NR	NR	*At 3 months:* 59.4 ± 0.74	NR	NR	*At 6 months:* 59.8 ± 0.82	
Lador 2013	AposHealth	43.0 ± 15.4	57.1 ± 18.9	NR	*At 4 months:* 52.1 ± 17.9	*At 4 months:* 64.0 ± 18.5	NR	N/A			
Lubovsky 2017	AposHealth	42.9 ± 16.3	56.8 ± 18.1	NR	*At 3 months:* 52.0 ± 16.9	*At 3 months:* 63.4 ± 17.5	NR	*At 12 months:* 54.3 ± 18.3	*At 12 months:* 65.1 ± 18.2	NR	
Miles 2020	AposHealth	45.7 ± 18.4	64.0 ± 19.5	53.5 ± 16.1	*At 3 months:* 57.7 ± 19.9	*At 3 months:* 72.3 (18.2)	*At 3 months:* 62.6 ± 16.6	*At 6 months:* 61.4 (20.0)	*At 6 months:* 73.6 ± 18.1	*At 6 months:* 65.2 ± 16.9	
Notes: [a] The SF-36 questionnaire scores are not reported in the 2 summary score formats in these studies (PCS and MCS).											
Abbreviations: MCS: Mental Component Score; N/A: Not Applicable; NR: Not Reported; PCS: Physical Component Score; SF-36: Short-Form 36 Item Quality of Life Questionnaire											

5.3.4 *Surgery Avoidance or Delay*

There is extremely limited, low quality evidence that AposHealth can delay surgery for people with knee OA through symptom management.

Surgery avoidance is being defined in this context as an individual with knee OA who would have been referred for total knee replacement (TKR) under current guidelines but who does not progress to surgery and instead continues to manage their symptoms through non-surgical interventions. Surgery delay is defined in this context as increasing the time period an individual manages their symptoms with non-surgical intervention before progressing to surgery. Surgery avoidance and/or delay is the primary outcome of the economic model submitted by the company.

The company emphasises the potential of AposHealth for altering and improving gait patterns of people with knee OA and states an assumption that this is the reason patients may be able to delay or avoid TKR. While there is some evidence that gait is modified by the provision of AposHealth, only two studies included by the EAG include surgery avoidance as the primary outcome (Drew 2022 and Greene Unpublished) and neither included correlation analysis exploring the relationship between gait modification and surgery avoidance/delay. The study by Greene (Unpublished) reported that 84% of people (305/365) that met the criteria for being referred for TKR in an NHS Trust did not progress to having a TKR after being provided with the AposHealth device. The study by Drew (2022) reported that 86% of the participants who received AposHealth avoided TKR at 2 years (204/237). These studies are retrospective case series with no comparator to assess if AposHealth has a higher rate of surgery avoidance in comparison to other non-surgical knee OA therapies. Additionally, there is no data beyond the 2-year follow-up periods to establish if TKR was avoided completely or just delayed. The study authors in both Drew (2022) and Greene (unpublished) note that there were significant differences between the individuals that progressed to have TKR and those that did not. In the study by Drew, baseline pain and function were worse in the group of patients who progressed to TKR. In the study by Greene (unpublished) the Oxford Knee Scores were worse in those who progressed to TKR.

In the study by Bar-Ziv (2013) that compared AposHealth (active group) with a sham device (control group), the authors observed a difference in the number of TKRs performed in the active and control groups at the 2-year follow-up time point, although this was not a pre-specified outcome of the study. One patient (2.6%) in the active group underwent a TKR while 5 patients (31%) in the control group underwent a TKR.

The consensus amongst clinical experts was that there is insufficient long-term data to determine how long AposHealth can delay TKR for or whether patients can avoid TKR altogether by using AposHealth. A patient expert stated they have been 'avoiding' surgery for approximately 3 years by using AposHealth to manage their symptoms. The EAG noted this patient expert expressed personal wishes to avoid surgery and clinical experts agreed that this would be the case for a proportion of people with knee OA.

5.3.5 *Reduction in the use of standard care or conventional therapies*

There is limited, low quality evidence that use of AposHealth results in a reduction in the use of pain medication, physical therapy and other non-pharmacological interventions.

The company submission included unpublished evidence in the form of survey and audit data that suggested the use of AposHealth resulted in a reduction in outpatient consultations regarding knee pain, a reduction of opioid use, a reduction in physical therapy and other non-pharmacological interventions

In the RCT by Reichenbach (2020), the rates of analgesic use were not different between the AposHealth group and the control group. The study by Bar-Ziv (2010) reported that overall, the control group utilised more of the rescue medication provided (647 pills) in comparison to the active group (273 pills).

In the study abstract by Hagen (2018), it is reported that use of opioid medication was lower in people who had completed a course of therapy with AposHealth in comparison to a general population of people with knee OA.

6 Adverse events

The EAG did not identify any adverse events from searches on the MHRA and FDA databases. The company did not report results of searches on these databases. The company highlighted the study by Reichenbach (2020) which reported no significant adverse events associated with the treatment compared to controls.

The EAG are satisfied that there are no significant safety concerns for AposHealth. The possibility that AposHealth may impact on balance and incidence of falls is mitigated by patients with balance issues being excluded from the recommended population for AposHealth. The clinical experts agreed that they have not been alerted to any adverse events from the use of AposHealth in their experience.

7 Evidence synthesis and meta-analysis

The company submission did not include meta-analysis, and did not cite reasoning for this.

The EAG note that while there is consistency in the outcomes reported, there is an absence of a consistent comparator across the studies. In addition, there are variable follow-up periods (ranging from 8 weeks to 2 years). The EAG therefore consider that meta-analysis of the available data will not provide any further certainty of the effectiveness of AposHealth compared with other non-surgical treatments. The EAG has therefore not conducted a meta-analysis.

8 Interpretation of the clinical evidence

The EAG acknowledges the potential for AposHealth to improve pain, function, stiffness, and quality of life for patients with knee OA, as evidenced by improvements in outcome measures such as WOMAC and SF-36.

The EAG notes there is limited evidence with standard care as the comparator but recognises that there are inconsistencies in the standard care pathway in the NHS that may make it difficult to identify clear comparators. Due to its proposed positioning in the knee OA care pathway, comparison of

AposHealth against other non-surgical interventions for knee OA would be beneficial to determine its relative effectiveness. As the evidence is largely non-comparative, it cannot be determined that AposHealth is superior to other forms of non-surgical OA therapy for improving symptoms and increasing quality of life. The EAG notes that where AposHealth is compared to another intervention (or control), it is compared to a sham device. The EAG is cautious of potential issues with the validation of the sham device and its ability to act as a true control. This aligns with the draft NICE guideline for the management of osteoarthritis (expected publication October 2022) which recognises that the difficulty in designing an appropriate sham device is a significant limitation for studies involving shoe devices.

The EAG recognises there is potential for AposHealth to be effective at delaying surgery for people who do not wish to, or cannot, undergo surgery when it is the recommended treatment option for them. However, with the lack of long-term follow-up reporting on surgical delay and/or avoidance, this potential is currently not well supported.

Overall, the EAG considers there are uncertainties in the evidence surrounding: the clinical importance of improvements in symptoms, how these observed improvements compare to existing non-surgical interventions for knee OA, and the ability of AposHealth to result in delay or avoidance of TKR surgery. The need for further evidence generation should be considered, acknowledging that the evidence indicates positive outcomes, which is supported by patient expert testimony, clinical expert input and an NHS patient satisfaction survey.

8.1 *Integration into the NHS*

The positioning of AposHealth in the care pathway for osteoarthritis is unclear. The company submission states that AposHealth would be provided alone or alongside standard non-surgical interventions for knee OA. Clinical experts indicated that AposHealth would be utilised after standard care options had been exhausted, as a method of delaying TKR. One clinical expert raised concerns that AposHealth was adding another ‘layer’ of treatment to the pathway and potentially adding extra costs for the NHS.

The evidence available is mostly in settings outside of the NHS. The company states that there are no expected differences between the participants in the included studies and those receiving routine care in the UK NHS. AposHealth is currently being used in 3 NHS Trusts and also in private settings. A clinical expert using AposHealth in both private and NHS settings stated that AposHealth is beneficial to patients who are not responding to standard non-surgical intervention and have been recommended for surgery. However, the same clinical expert proposed that AposHealth may hold more benefit to patients if introduced at an earlier point in the care pathway as the effect on neuromuscular training would be greater. The EAG has not identified any published evidence regarding the optimal point at which to introduce AposHealth to a patient's care pathway.

Clinical experts suggested that the current care pathway for knee OA is largely patient-led with an individual's tolerance to pain and discomfort alongside their personal wishes to avoid surgery being major factors in influencing their progression to TKR. Individuals with a strong aversion to undergoing surgery (TKR) may be assumed to have a higher compliance to devices such as AposHealth in comparison to individuals that are not strongly against undergoing TKR. The evidence review by the EAG did not include details on patient compliance with the device and the relationship to personal preferences on avoiding surgery.

AposHealth is a device that has components (pertupods) that can be altered as per the requirement of the user and replaced should wear and tear occur, as confirmed by the patient expert. The implications of the provision of follow-up appointments and physiotherapy sessions is discussed in more detail in Section 9.

The company claims that AposHealth can be used without the need for an additional gait analysis device, and can be calibrated and evaluated using a combination of clinicians' observations and patient-reported feedback, which the EAG accepts. However, clinical experts noted that use of additional gait analysis tools beyond a visual assessment and patient feedback are likely to be used. The EAG noted that AposHealth can be used with a variety of gait

analysis tools, and is not limited to use with a particular system, as demonstrated in the evidence base.

AposHealth requires additional training of staff to calibrate and assess the device and its outcomes. This training is provided by company and included in the economic model, this is discussed in greater detail in Section 9.

It should be considered that the type of gait analysis used, the accuracy of pertupod positioning by physiotherapists/clinicians and the software used in conjunction with calibration will all have an impact on the outcomes of AposHealth. Efficacy in practice may therefore not be reflective of efficacy in trial settings.

8.2 *Ongoing and unpublished studies*

The EAG searched the Clinical Trials.gov and International Clinical Trials Registry Platform (ICTRP) registries for relevant ongoing trials and identified five studies where AposHealth was used or mentioned.

The company submission identified 7 ongoing or unpublished studies, one of which is the study by Greene (Unpublished) which has now been accepted for publication. One of the studies (NCT04732962) was also identified by the EAG. The EAG identified 4 additional NCT registered trials that mentioned AposHealth or AposTherapy, although these are either of a 'terminated' or 'unknown status'. Details of these can be found in Table 10.

The remaining 5 studies identified by the company were not registered to a trial database. Two were documents relating to unpublished studies, one of which reports a range of research proposals relating to AposHealth; the other is a report on a study performed to assess the impact of AposHealth (AposTherapy) on outcomes in those with knee OA and lower back pain. The company stated the aforementioned research studies are not due for publication. One study is a summary of data on file evidencing surgery avoidance rates which the EAG agree is relevant to the economic model. The remaining 2 studies identified by the company are reports of survey data regarding patient satisfaction or audit. The EAG acknowledges the relevance of this information provided by the company but as it is not peer-reviewed and/or due for publication, it is not considered to be robust evidence.

Table 10: Ongoing Studies

NCT Identifier	Country	Primary Outcomes	Intervention	Comparator	Design	Enrolment	Start Date	End Date	Status
NCT03153956	USA	Knee pain, improvement in function	AposTherapy	Sham Device	Prospective, Randomised Double-Armed	77 (Actual)	16/04/15(Actual)	15/11/18 (Actual)	Terminated
NCT00492674	Israel	Gait, pain, function and quality of life	AposHealth	Sham device, physical therapy	Randomised, controlled and double blind prospective	NR	NR	NR	Unknown (last update 2007)
NCT03171168	USA	Knee Pain and Function	AposTherapy	Conventional physical therapy	Single-centre, randomised controlled trial	45 (Actual)	30/11/16 (Actual)	30/09/19 (Actual)	Terminated
NCT04732962	USA	Pain	AposHealth	TKR	Non-randomised parallel assignment	150 (Estimated)	22/07/21 (Actual)	12/22 (Estimated)	Recruiting
NCT01266382	Israel	Gait, pain, function and quality of life	AposHealth	NR	Interventional	NR	NR	NR	Unknown (last update 2010)

Abbreviations: NR: Not Reported; TKR: Total Knee Replacement; USA: United States of America.

9 Economic evidence

9.1 *Published economic evidence*

Search strategy and selection

The company conducted a combined search for both clinical and economic evidence, identifying 48 records in total, however no economic evidence was identified. The EAG also conducted a combined search for clinical and economic evidence but did not identify any studies relevant to the economic section.

Published economic evidence review

No relevant evidence

Results from the economic evidence

No relevant evidence

Additional economic evidence

No economic evidence was found for AposHealth. Some costs for OA were identified and these are discussed in the parameters section below. Additional clinical papers that were out of scope, but of importance for the model are also discussed in section 9.2.

9.2 *Company de novo cost analysis*

9.2.1 *Economic model structure*

The company submitted a Markov decision model comparing standard care to standard care with AposHealth. An NHS perspective was used, with a 3.5% discount rate, 1-month cycles and results reported at a 2- and 5-year time horizon.

The model comparator and structure were appropriate to the scope, and the time horizons chosen were based on the duration of available evidence. While the EAG accept that there is a lack of evidence beyond two years, it is important to explore the longer-term impact for chronic conditions.

The standard care arm assumed that all patients started with osteoarthritis of the knee, and receiving standard care. They could then move to TKR surgery,

and following the first 6 months were also able to move to TKR on their other (contralateral) knee. Following knee surgery there were follow up costs for the first two years only. Death could occur in all states.

Figure 1: Model Structure

DIAGRAM 1. STANDARD CARE ARM

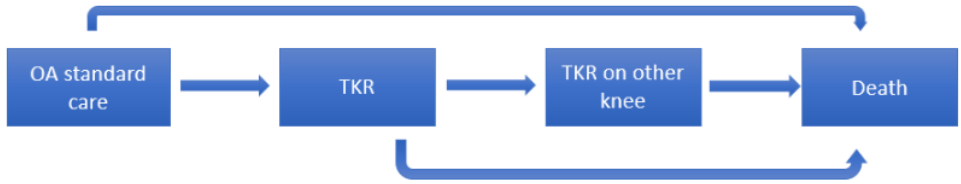
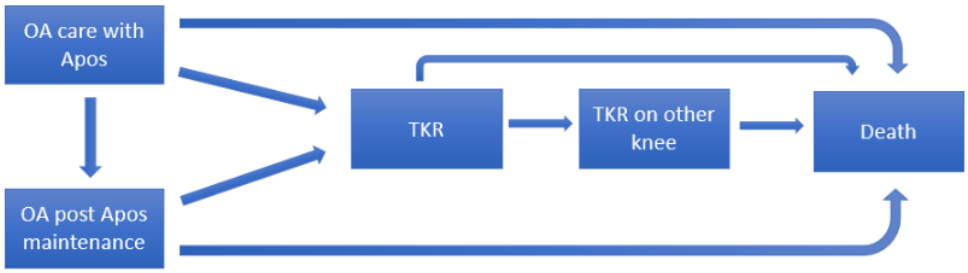


DIAGRAM 2. APOS ARM



The AposHealth arm has a similar structure, however the initial standard care state has adjuvant AposHealth treatment. After active treatment with AposHealth for the first 12 months, all patients who have not yet had knee surgery move to a post-maintenance state. This assumes that the benefits of AposHealth (including a 15% reduction in use of health care resources for standard care) will continue beyond the active treatment duration. Patients may move to TKR both during and after the active treatment phase. Death can occur from all states.

Revised company 10-year model

Following queries from the EAG about the time horizon, the company submitted an additional model with an extended 10-year time horizon and some altered parameters. The model structure and main assumptions remained unchanged. The key changes were:

- Change in mortality calculations
- Inclusion of revisions past year 2
- Reduction of follow up appointments with AposHealth from 2 per year to 1 per year after year 5.

These are discussed together with the original company submission and EAG base case throughout the remainder of the assessment report.

Table 11: Assumptions in economic model

Assumption	**Justification** (summary, see company submission for full text)	**EAC Comment**
Two-year TKR rate for AposHealth: 16% (monthly: 0.72%)	Greene (Unpublished) report a 2-year TKR probability of 16% in a cohort of patients with end-stage knee OA who meet the clinical criteria for referral for elective primary TKR, and this cohort matches the cohort in our model. Supported by Drew 2022	The EAG accept this and discuss further in section 9.2.2
Yearly TKR rate – standard care: 33% (monthly: 3.28%)	McHugh (2011), reports a 1-year TKR probability of 33% in a cohort of patients with OA newly referred by GPs to an orthopaedic surgeon for consideration for TKR	The EAG accept this and discuss further in section 9.2.2
Mortality: 0.8% (0.07% monthly)	Leal (2022), reports an annual mortality rate of 0.8% for patients eligible for TKR/underwent TKR	Based on the initial year post procedure
Post-operative complications (Of those receiving TKR): 6%	Leal (2022), reports a 6% post-operative complication rates associated with TKR	Based on the initial year post procedure
Revision during year 1 (Of those receiving TKR): 0.5%	Leal (2022), reports a 0.5% of patient will require revision post primary TKR during the first year of surgery	Based on the initial year post procedure
Utilisation of other interventions – AposHealth: 15% savings relative to standard care costs	Patients treated with AposHealth will continue to consume standard care interventions. However, the Apos intervention is associated with a significant reduction in pain and improvement in function that affect the utilisation of other health resources. Multiple data sets suggest an average saving of 15% in healthcare utilisation while using AposHealth. [redacted])	The EAG accept this assumption, and variations are considered in the sensitivity analysis. Further information is discussed in section 9.2.2.
Five-year rate of 2nd TKR (Probability is applied 6 months after having the first TKR): 33.5% (monthly: 0.8%)	Patients that have had a primary TKR are likely to have a secondary TKR in the contralateral knee. (Sanders 2017)	The EAG accept this assumption, and variations are considered in the sensitivity analysis. Further information is discussed in section 9.2.2
Percent of patients in cohort who have a prior TKR 33.6%	The probability of a patient undergoing a TKR in their other knee is scaled down by 33.6% when applied to patients who have undergone a first TKR in the model.(Chitnavis 2000)	The EAG agree that some patients will have previous knee replacements. The percentage and impact is likely to vary with site.

Table 12: Additional Assumptions Identified by the EAG

Additional assumptions identified by the EAG	
There is no requirement for additional gait analysis equipment or training	The company stated that formal gait analysis is not a requirement and this is not included in the submitted model. The EAG have accepted this in the base case, but carried out sensitivity analysis to investigate the impact of gait analysis equipment.
Constant mortality rate	This is a conservative assumption. The submitted model is 5 years, and the importance of background mortality rates is greater with an extended time horizon. A higher mortality rate will increase any modelled cost saving due to AposHealth, as knee surgery is delayed and may not occur for some people. This is amended in the EAG model and also the company 10-year model.
Mortality is the same for both arms and at all stages of the model	Mortality is the same with or without a knee replacement and with or without AposHealth. The EAG agree that this is a reasonable assumption, and the evidence is discussed in the clinical parameters section (9.2.2)
There are no ongoing care costs for people with knee replacements after two years post-op.	This is a conservative assumption. Patients in the standard care arm will move to knee replacement more rapidly and therefore spend more time in the model in a post-op state. Patients in the AposHealth arm spend more time in the standard care pre TKR states, and less time in the post-op state. This assumption becomes more important if the time horizon is extended. Both the EAG and the company 10-year model have addressed this with revisions, but not other care costs.
Revisions of TKR only occur in the first two years	This is a conservative assumption, particularly with an extended time horizon. The EAG base case and the 10-year company submission both include revisions for subsequent years.
The reduced likelihood of needing a TKR remains at a reduced level after active treatment with AposHealth and continues at the same level for the duration of the model.	The clinical evidence submitted is for 2 years duration, although the company state there has been some follow up for 3.5 years.
The completion of training requires supervised sessions. The supervisor is provided at no additional cost, and there is an assumption that the sessions incur no additional staff time, as they will be part of patient care.	The EAG believe this to be a reasonable assumption.

9.2.2 *Economic model parameters*

The key clinical parameters are the rates of surgery for TKR, and this is reported in only a limited number of the selected papers. Costs come from standard sources and are reported in detail later.

Clinical parameters and variables

Key clinical parameters include TKR, subsequent contralateral knee replacement, post-operative complications and mortality.

Total Knee Replacement (TKR)

The model is based on movement of patients from standard care (with or without an Apos device) to TKR, and subsequently to a TKR of the other knee. The majority of the clinical evidence identified for AposHealth does not report rates of surgical intervention, with only one UK based paper available, which is non-comparative (Greene Unpublished). Therefore, the model has used a separate source for the comparator arm (McHugh 2011). Table 13 compares the baseline data and outcomes for the two studies. Both cohorts of patients were based in the UK, were being treated within the NHS as part of normal practice (rather than as a trial), and all had a diagnosis of knee OA. Both studies used inclusion criteria that consider suitability for TKR.

With two single arm pragmatic studies, conducted in different time periods and locations, it is difficult to determine how appropriate comparison of outcomes is. However, there are similar inclusion criteria and baseline characteristics and the EAG have not been able to identify any more robust evidence sources. The company 10-year model did not change the probability of TKR for the first knee.

Table 13: Comparison of baseline data

	Greene Unpublished	McHugh 2011	Drew (2022)	Bar- Ziv (2013)
Intervention	Apos device	Standard care	AposHealth device, or surgery	Apos health or control
Setting	UK, unnamed single CCG	UK, NW England, 10 orthopaedic surgeons	USA, single payer	Israel, single centre
Type	Retrospective clinical audit	Prospective follow up of referred patients.	Retrospective data analysis	Pseudo randomised trial – randomised for first 8 weeks after which study was unblinded and cross-over allowed.
Number	365	123 with 12 month follow up 106 with surgical outcome known	237 AposHealth, 294 Surgical option	40 AposHealth 16 Sham deviice
Dates	Retrospective analysis of data from 2017-2019	Recruitment 09/2006 – 06/2007 Follow up 07/2008	Retrospective analysis of data with enrollment 2018-2019	Not reported
Age (mean)	72.1	65.7	68.7	AposHealth 64.1, control 67.4
Female	53%	50.4%	35%	AposHealth: 75% Control: 69%
WOMAC pain score	55.8 (18.8) of score 0-100	10.7 (3.4) of score 0-20	54.7	AposHealth 5 (2.8) Control 5.5 (3.3) (VAS, 0-10 score)
Oxford knee score 0-48 (48 being the best outcome)	21.4 (7.5)	20.9 (8.7) Converted from 39.1 (8.7) (reported using the 60-12 scale (12= least difficulties))	n/a	n/a
Key inclusion criteria	• Surgical threshold for Orthopaedic referral (Oxford Knee Score<19) AND radiological evidence of moderate /severe osteoarthritis	• GP letter sent to surgeon to consider surgery. Letters were screened, and patients included if they had:	• Patients were eligible for TKR • Offered either AposHealth or surgery	• All patients diagnosed with symptomatic bilateral medial compartment knee OA

	Greene Unpublished	McHugh 2011	Drew (2022)	Bar- Ziv (2013)
Intervention	Apos device	Standard care	AposHealth device, or surgery	Apos health or control
	• Radiological features of severe disease are present • The patient complains of intense or severe symptomatology	• Confirmed diagnosis of OA • Considered potentially suitable for TKR		
Surgery	**AposHealth only:** 6% at 1 year 16% after 2 years	**Standard care only:** 40 TKR (37% of 106 known outcomes, or 33% of 123 with1 year follow up complete) at 1 year	**AposHealth:** 34/204 (14%) **Surgical arm:** 259/294 (88%) Over 2 year follow up	**AposHealth:** 1/40 (3%) **Sham device arm:** 5/16 (31%)

Alternative data sources for the intervention are Drew (2022) and Bar-Ziv (2013). Drew (2022) retrospectively analysed data from patients who were eligible for TKR surgery between 2018-19, but may have chosen either AposHealth or surgery. They reported that 34/237 (10.3%) of patients using AposHealth had received TKR after two years. For the comparator, this number was 88% reflecting that these were patients who had already decided to proceed with TKR.

Bar-Ziv (2013) is discussed in the clinical evidence section, and (although not stating surgery as an outcome) reports that 1 patient (2.6%) in the AposHealth group underwent a TKR while 5 patients (31%) in the control (sham device) group underwent a TKR during the two-year follow up.

For the comparator, Abraham (2022) considered data from 3123 patients in the UK with moderate to severe OA pain (in any joint). Of these, 13.4% had a total joint replacement (this may not have been knee) during the two-year follow up. For the subgroup of 1,922 patients with severe OA pain, 22.2 had one or more total joint replacements.

Total Knee Replacement for second knee

The model assumes that there will be a minimum of 6 months TKR on the first knee and any possible joint replacement on the opposing knee. The National Joint Registry report (2021) records only 1 percent of primary knee procedures being bilateral.

After the initial 6 months, the monthly probability of a knee replacement is based on two studies. Sanders (2017) for the probability of a second knee replacement and Chitnavis (2000) for the proportion of patients entering the model who already have a knee replacement on the opposing knee and are therefore not included in the calculation for a second knee.

Sanders (2017) is a retrospective cohort study based in the US that identified and 2,139 patients who had a TKR between 1969 and 2008. With a mean follow up of 11 years per patient, there were 45% contralateral knee arthroplasties at 20 years, or 38.7% at 10 years. The company chose to use a graph from the paper to extract a value of 33.5% at 5 years for the model. The

EAG repeated the data extraction using WebPlotDigitizer and found a value of 33% at 5 years. By using the 5-year value, the monthly probability of a second procedure is 0.739%, whereas using a 20-year value, the monthly probability is 0.249%. The lower probability would result in a small reduction in cost saving. The EAG have used a 10-year value of 37.8% due to their extended time horizon.

In addition, the following sources were considered:

Huang (2021) carried out a retrospective study of 502 patients in China with bilateral KOA who received a unilateral knee replacement between 2015 and 2019. They reported an incidence for contralateral TKR of 38.64%, although there is no additional data on the mean follow up, or analysis of time to the contralateral procedure.

Lamplot (2018) analysed data from 53,931 patients in the US who had a TKA between 2006 and 2008 recorded in administrative data for continental US states. They reported that 27.5% of patients with an initial TKA for osteoarthritis received a contralateral TKA within 5 to 8 years.

Gillam (2013) obtained data for patients with 122,096 knee arthroplasties from the Australian Orthopaedic Association National Joint Replacement Registry and 12,082 knee arthroplasties from the Norwegian Arthroplasty Register, where the first procedure took place between 2002 and 2010. Within the study 21% and 22% respectively received a contralateral knee, however rates over time are not presented. Although the study undertook complex analysis and reported hazard rates for some transitions, there was no further data reported for contralateral second procedures on the knee.

Sayeed (2011) studied data from 646 patients with a primary knee procedure between 1984 and 1994 in the US. They found a 36% probability of having a subsequent contralateral knee procedure at 10 years.

The same study found a 4.8% probability of a revision of the original surgery at 10 years, with this being much higher for younger patients.

Overall, the evidence points to an increased probability of contralateral total knee replacement following a primary procedure. The values used by the company are within a plausible range from the available evidence, and have been accepted by the EAG. Sensitivity analysis will be used to explore this further.

The submitted model assumes that some patients in the modelled cohort will enter with an existing knee replacement, and therefore not be eligible for a contralateral knee replacement. This is used to reduce the transition probability from single to bilateral knee replacements. The company used a retrospective analysis of records from 125 patients from the UK who had undergone a primary TKR or revision between 1995 and 1996, and who did not have a definite identifiable cause for OA in the replaced joint. They found that 33.6% of these patients had bilateral knee replacements. The EAG query if this is a reliable source of data given the relatively small number of patients, inclusion criteria and age of the study. However, the assumption that some patients will have an existing knee replacement is a conservative one (patients have knee replacements earlier in the standard care arm, and therefore will be more likely to also experience a contralateral knee replacement). In addition, given the evidence on likelihood of a contralateral knee replacement following the primary procedure, the assumption is also plausible. The actual proportion seen in clinical practice is likely to vary between hospitals (and may also vary over time if the criteria for referring to AposHealth changed). The EAG have therefore accepted the value, and used sensitivity analysis to understand the impact of any uncertainty. The company 10-year model did not change the probability of TKR for the second knee.

Mortality

The company submission used a rate for one-year mortality post total knee replacement, taken from a paper by Leal (2022). This is a large retrospective study of 391,691 patients in the UK with knee replacements, taken from the National Joint Registry (NJR Report 2021). While this is a very robust and appropriate source, the one-year mortality may not be appropriate for a longer time horizon as the cohort ages. The EAG considered life tables available from ONS (using pre-COVID data from 2017-19). For a patient who is 68

years old the probability of mortality at 1 year is 1.57% for men and 1.03% for women. As these are higher than the condition specific mortality, the EAG opted to use general mortality rates, incorporating the change in mortality over time, as the patient cohort ages.

The company 10 year model also included a variable mortality rate, but based on the mortality rate reported in the NJR report (2021, table 3.K12) of 26% at 10 years after all primary TKR procedures, with the mean age for all primary TKR procedures being 70. This is used to estimate rates for 1 year, 2-5 years and 6-10 years for both arms.

After 10 years, the EAG model has 18% mortality, and the company model 24%. However, in the EAG model, patients enter the model aged 68, with 50% of those in the comparator arm having received a knee replacement by age 70. At 12 years (10 years after 50% have received TKR), the EAG models a mortality of 24%, which is close to that reported in the NJR for 10 years post procedure. The EAG believe that using the ONS life tables are a more accurate method to model mortality.

Post-operative complications and revisions

The probability of post-operative complications or revisions in the first year is taken also taken from Leal (2022), with a one-year probability of 6% and 0.5% respectively. For the second year, the company model uses the difference between year 2 costs and the costs collected in the year prior to TKR as an indication of the change due to TKR.

From the third year there is an assumption of no cost in the submitted company model. This is a conservative assumption as more patients are affected in the standard care arm (due to earlier TKR procedures). Both the EAG and the company 10-year model have included revisions in all follow-up costs, and based this on data from the National Joint Registry (NJR). The National Joint Registry (2021) has evidence for the number of revisions on primary TKRs over time, and at different ages (the cohort modelled by the EAG enter the model at 68, with over 50% having received a TKR by age 70). For all patients (median age 70), the Kaplan Meier estimate of cumulative

revision at 10 years is 4.13, or 6.43 at 17 years. For those under 55 this is higher (15.45 for males, 15.2 for females at 17 years), For the age range 65 to 74, it is lower (5.24 for males, 4.74 for females at 17 years).

Both the company and EAG have deducted 0.5% of patients who receive revisions in the first year (based on Leal 2022) and use the NJR for a cumulative revision rate, however the company 10-year model takes the figure of 4.1% at 10 years and the EAG chose to use the cumulative revision rate of 6.43% at 17 years. The impact of either choice on the model results is very small.

Either approach remains likely to be a simplification of the actual situation, where there would be additional care costs associated with the years immediately before and after revision, and subsequent risks of re-revision. However including these in the submitted model would be very complex and unlikely to materially change any decision making.

Table 14: Clinical parameters used in the company's model and any changes made by the EAG

Parameter	Company submission	Source	EAG value	Comment
Average patient starting age	Not included (variable mortality added for 10 year model)		68	Starting age is not included in the submitted model. The EAG have included a start age based on the mean age of those receiving a primary knee replacement (70 years, NJR annual report 2021), and the time for 50% of the standard care arm to have received a knee replacement (2 years). For reference the mean age reported in studies used for clinical parameters is stated below: McHugh (2011) Mean age: 66 Greene (2022) Mean age: 72 Sanders (2017) Mean age: 69 Chitnavis (2000) Mean age: 69 (m), 73(f) Leal (2022) Mean age 69.5
Monthly probability of TKR (rates are constant over time, and constant during and post Apos delivery period)				
OA standard care to TKR	3.282%	McHugh 2011.	No change	Taken from a TKR probability in a cohort 123 patients with OA newly referred by GPs to an orthopaedic surgeon for consideration for TKR. 33% over 1-year duration. Sample size of 123 patients. Mean age: 66. 50.4% female.
OA care with Apos to TKR	0.724%	Greene Unpublished	No change	2-year TKR probability in a cohort of patients with end-stage knee OA who meet the clinical criteria for referral for elective primary TKR, and are treated with

Parameter	Company submission	Source	EAG value	Comment
				AposHealth. 23/365 (6%) in first year and an additional 36/365 (10%) in second year. 16% total TKR at two years.
TKR on other knee	0.500%	Sanders 2017. 33.5% over 5 years	0.395%	Patients that have had a primary TKR are likely to have a secondary TKR in the contralateral knee. This does not occur during first 6 months after first TKR. The figure of 33.5% is taken from a graph, and the EAG obtained 33% for a 5-year period. As the EAG extended the time horizon, the figure of 37.8% over 10 years was preferred in the EAG model.
Percent of patients in cohort who have a prior TKR	33.6%	Chitnavis 2000 33.6%	No change	From submission: The probability of a patient undergoing a TKR in their other knee is scaled down by 33.6% when applied to patients who have undergone a first TKR in the model.
Monthly probability of death				
Death	0.067% (variable rate in 10 year model)	Leal 2022	Variable rate	Leal (2022) reports an annual mortality rate of 0.8% for patients eligible for TKR /underwent TKR for the first year post-procedure. The EAG have used life tables from ONS 2017-19 (pre COVID) to introduce variable mortality as the cohort progresses through an extended model.
Adverse events				
Post-operative complications (Of those receiving TKR)	6%	Leal 2022	No change	Leal (2022) reports a 6% post-operative complication rates associated with TKR for the first year post procedure. It is also applied to year two in the model.
Revision during year 1 (Of those receiving TKR)	0.5%	Leal 2022	No change	From submission: Leal (2022) reports a 0.5% of patient will require revision post primary TKR during the first year of surgery
Adverse events during year 2				These are not explicitly calculated, but costs are derived to include revisions.
Adverse events during years 3+	0.34% (10 year model only)	NRJ 2021, 10 years	0.32%	Monthly rate for revisions for company 10 year and EAG models. NJR 2021, 17 years

Resource identification, measurement and valuation

Technology costs and training

The AposHealth system consists of a pair of Apos shoes and a supply of pods to fit on the heel and forefoot of the shoes. The pods can be changed to give the desired impact on gait, and can be swapped over time as needs change. The company states that following the purchase of the AposHealth system additional pods can be ordered free of charge as needed. They expect that one patient may require up to 3 sets of pods during their use of the system.

The company state that the cost of the AposHealth system is £875 excluding VAT.

Training is provided by AposHealth free of charge. It would normally be delivered by a physiotherapist who has been trained by AposHealth in use of the system. Training consists of 6 hours theory training, delivered by AposHealth either online or face to face. This is followed by 5 to 10 observed calibrations that are delivered as part of the routine service provision.

Costs for training are the 6 hours of theory time per physiotherapist delivering AposHealth. A service may require several staff to be trained, and each of them will treat a number of patients, over a number of years. There is no requirement for retraining after a certain time. The model assumes that each trained member of staff will treat 250 patients, resulting in a training cost of £1.31 per patient. While the EAG feels that the company justification of this volume within a year is optimistic, the training will last for longer than one year, and therefore the cost has been accepted by the EAG. Changes in this assumption have only a very small impact on overall costs.

Physiotherapists may use gait analysis tools or equipment when making assessments of the patient's gait. These are additional to AposHealth devices and have not been included in the modelled costs, as the company advises they are not necessary. The EAG noted that the use of gait analysis equipment is described in the clinical evidence studies and has included a scenario where the equipment is costed.

Standard care costs

The company identified a number of papers that contained costs, and used two of these to inform the model (Abraham 2022, Leal 2022), the EAG identified an additional 3 papers (Cole 2022, Lohan 2021 (abstract only), Dakin 2012), and used data from Cole (2022) for an additional scenario

Abraham (2022) and Lohan (2021) both consider patients with a diagnosis of OA and an OA pain episode that is used as an index event. A matched cohort without OA is used as a comparator in both of these studies, and the methodology is broadly similar. Abraham (2022) is based on data obtained

nationally, whereas Lohan (2021) is based on data from a single region, and is only available as an abstract. On this basis the choice of Abraham (2022) is supported by the EAG. The EAG note that the difference between OA and the comparator reported in Lohan (2021) is greater than in Abraham (2022), and that that higher standard care costs prior to TKR would reduce any cost savings due to AposHealth.

The company used the difference in standard care cost between the OA and comparator cohort as the model input for standard care. As the studies included patients who underwent TJR during the follow up, the company subtracted the cost of surgery and follow up for the proportion of patients who were reported as experiencing this (22.2% had one or more joint replacements, converted to 11.8% per year, Abraham 2022).

The EAG supports the use of Abraham (2022) but has also considered costs from one study that reports costs over 5 years (Cole 2022) to create an alternative scenario. This approach uses the information from a single paper to supply costs pre and post TKR. This requires a different assumption, that the year prior to TKR is representative of standard care costs, even if TKR is delayed by several years. Cole (2022) was used for the additional scenario due to data availability for 5 years, however there are other limitations to this study, which relies on patient recall over 12 month periods for collecting resource use.

The EAG summarised the findings from each of the studies in Appendix C.

Reduction in standard care costs due to AposHealth

The company have assumed a 15% reduction in standard care costs prior to TKR. This is based on published studies showing a reduction in pain and function limitation, and unpublished audits that reported resource use.

The EAG agreed that the clinical evidenced showed a consistent decrease in pain, function limitation, and stiffness as measured by WOMAC scores after AposHealth is given as an intervention compared to baseline. The included studies had very limited evidence of reduced use of pain medication, physical therapy and other non-pharmacological interventions

Two unpublished studies reported changes in resource use, and were provided to NICE by the company.

One was based on US healthcare insurance records, and reported on the pre and post healthcare costs for 214 patients with knee OA (n=88) or lower back pain (n=126) who received AposHealth between 2015-2017, and who had at least 12 months data pre and post the index intervention. The mean age of patients with Knee OA at baseline was 57.9 which is younger than the clinical studies under consideration. Due to the skewed nature of the cost data, median results are presented. Although economic models require mean data, the results are not used directly for the model inputs.

There were non-significant reductions in median all cause costs, and for median direct costs. There were some significant changes for components of direct costs in the Knee OA group which were

- The proportion of patients having a direct OP office visit (79.5% to 52.3%; p<0.00)
- The mean number of direct OP office visits decreased (2.2 +2.2 vs. 1.5 +2.7, p<0.0001)
- The proportion of patients using non-NSAID, non-opioid pain medications (“other pain medications”) decreased (37.5% to 25.0%, p=0.029)

Changes in health care resource use have limited applicability to the scope, due to the US setting.

The second study was based in the UK reported results of a short phone survey amongst 165 patients using AposTherapy via a private healthcare provider, and with severe knee pain, in 2012. When asked about consultant visits, 72% of patients said they had less visits concerning knee pain since starting AposTherapy. For other treatment types the following reductions were reported as in table 15:

Table 15 Patient reported change in additional treatments for knee pain

	n	Stopped	Used less	Same	Used more
Over the counter painkillers	87	38%	44%	17%	1%
Prescription painkillers	60	45%	35%	18%	2%
Oral anti-inflammatories	76	39%	39%	21%	0%
Injections	29	72%	14%	10%	3%
Physiotherapy	70	66%	17%	14%	3%
Osteopathy	18	72%	17%	6%	6%
Knee brace	36	50%	28%	19%	3%
Orthotics	43	37%	14%	42%	7%

The company shared slides with results for the survey and limited reporting of methodology, however the whole survey tool is not available and the EAG is not able to fully critique the information.

Total knee replacement costs

Total knee replacement costs in the submitted model were based on NHS best practice tariffs. The EAG have substituted NHS Reference Cost data from 2019/20 (to avoid the impact of COVID) and inflated to 2022/23. There is only a small impact on the results from this change.

Follow up costs after total knee replacement

Following knee replacement, the company have used costs from the analysis by Leal (2022) which reports costs for 457,747 patients with TKR, using data from the NJR. Costs are given for the year prior to TKR, the year in which TKR occurs and a follow up year.

The total costs after TKR are calculated as costs following TKR minus costs pre-TKR.

Table 16: Cost parameters used in the company's model and changes made by the EAG

Parameter	Company value	Source	EAG value	Comment
Apos Health costs				
Cost of device	£875	Device cost: from company	No change	

Parameter	Company value	Source	EAG value	Comment
Apos Health Training cost				
Band 6 physiotherapist per hour	£54.67	Band 6 hospital physiotherapist, PSSRU 2021, £52 per hour Inflated to 2022/3	No change	
Training time per staff member	6 hours	Company estimate	No change	Training cost calculation: 6 hours of training x £54.67 = £328.01
Devices per staff member per year	250 patients per clinician	Company estimate	No change	Given that AposHealth will be only a part of the work load for most NHS physiotherapists, 250 per year is a high number. There is however no re-training requirement, and any changes have only a small impact on the overall cost.
Total training cost per device	**£1.31**	Calculated from above	No change	See below
This is the cost of staff time for training. The training resources, courses and supervision are supplied free of charge. There is an assumption that supervised sessions are not an additional staff cost, as they will be used in patient care.				
Initial assessment cost				
Total cost for device, training and initial evaluation	£79.82	Band 6 hospital physiotherapist, PSSRU 2021, £52 per hour. Inflated to 2022/3 PSSRU 2010 uplift for indirect time = 1.46)	No change	This uplift for patient facing time is taken from PSSRU 2010 as unavailable in current versions.
Total cost for device, training and initial evaluation	**£956.13**		No change	
Follow up costs				
Year 1: Follow up cost	Year 1: £119.72 (3 x 30 min yearly, or £9.98 per month)	Band 6 hospital physiotherapist, PSSRU 2021, £52 per hour. Inflated to 2022/3, and uplifted to allow 1.46 for patient facing time.	No change	This uplift for patient facing time is taken from PSSRU 2010 as unavailable in current versions.
Year 2: Follow up cost.	Year 2: £1,093.64 (2 x 30 min yearly, or £6.65 per month)		No change	
Year 3 Follow up cost	Year 3 + (1 x 30 min yearly or £		Unchanged from year 2 £1,093.64	
Total costs if followed up for entire two years	**£1,155.67**		No change	

Parameter	Company value	Source	EAG value	Comment
OA Standard Care Costs				
Severe OA	£3389	Abraham 2022	No change	Fig.5 and table 4 UK (Salford) based observational retrospective cohort study. Healthcare resource use and costs were collected between 2010 and 2017, it is unclear if there was any inflation applied to earlier costs. The model assumes that all costs are 2017/18
Control	£1397	Abraham 2022	No change	(Figure 5)
Additional OA costs (cost of severe OA – cost of Control arm without OA)	£2258 (£1992 prior to inflation)	Abraham 2022. Costs inflated from 2017/18 to 2022/23 using PSSRU.	No change	This includes GP encounters, inpatient admissions, outpatient visits, A&E attendances and analgesic drugs.
% of those in cohort who have surgery during study period (costs excluded from std care)	11.8%	Abraham 2022	No change	22.2% of the severe cohort in Abraham (2022) have surgery during the 24-month study period (11.8% annualised probability). Source. figure is for severe OA generally, not knee specific.
Estimated annual cost of surgery alone = (year 1 costs + year 2 costs) *11.8%	£971.25	Company calculations based on NHS Tariffs and Leal.	£1034.63	EAG calculation unchanged, but value depends on cost of surgery (see EAG changes)
Annual cost of OA care (total additional OA care – cost of surgery) for std care arm	**£1286.63** (107.22 monthly)	Company calculation	**£1,233.25** (£101.94 monthly)	As above
Reduction in health care resource use post AposHealth	**15%**	Company assumption based on clinical data	**15%**	15% reduction to standard care, due to improvements in health and reduced need for healthcare resource
Annual cost of OA care for Apos arm	**£1093.64** (91.14 monthly)	Standard care minus 15% Company estimate	**£1,039.77**(86.65 monthly)	.
Total Knee replacement costs				
Knee surgery: HRG HN22D	£6,624	National Tariff Workbook 22/23. Elective best practice tariff	£6,765.73	EAG: Very Major Knee Procedures for Non-Trauma with CC Score 2-3. NHS Cost Collection 2019/20

Parameter	Company value	Source	EAG value	Comment
Knee surgery: HRG HN22E	£6,313	National Tariff Workbook 22/23. Elective best practice tariff	£6,413.92	EAG: Very Major Knee Procedures for Non-Trauma with CC Score 0-1. NHS Cost Collection 2019/20
Mean surgical cost	**£6,468.50**	Non-weighted mean	**£7,131.47**	EAG: weighted mean, inflated to 2022/23
Additional TKR costs (year 1)				
Rehabilitation: post-discharge for Knee replacement	£620	National Tariff Workbook 22/23. Complexity Resource Group (Tariff section 5	£504.70	EAG: VC18Z Rehabilitation for joint replacement. £453.37 inflated to 2022/23
Outpatients, first attendance, Consultant led	£169	National Tariff Workbook 22/23.	£155	EAG: Single Professional, Trauma and Orthopaedics Service, WF01B, £142.96 inflated to 2022/23
Outpatients, follow-up attendance, Consultant led	£67	National Tariff Workbook 22/23.	£133	EAG: - Single Professional, Trauma and Orthopaedics Service (110). WF01A, £122.85 inflated to 2022/23
Total follow up	**£244.71**	Assume 1 pre-surgery and 1 post surgery	**£305.36**	
Primary care cost due to TKR (year 1)				
Primary care due to TKR (1st year) GP consultation	£42.26	PSSRU 2021, Per surgery consultation including direct care staff and with qualification costs. £39.23 inflated to 2022/23	No change	
TKR complications and revisions (year 1)				
Outpatient consultations for complications and revisions (year 1)	£8.71	Assumption: 2 additional follow up consultations for each revision (0.5%) or complication (6%)	£17.31	Based on previous cost of follow up consultation (£133 x 2 x 6.05%)
Inpatient care for complications and revisions (year 1)	£487.47	Leal 2022	No change	From Leal 2022 (table 4): Post op complications £10,406, inflated to 2022/3 and applied to 6% Year 1 revisions: £6,220, inflated to 2022/23 and applied to 0.5%
Year 2 additional costs				

Parameter	Company value	Source	EAG value	Comment
Inpatient costs	£367.98	Leal 2022 (figure 1 and supplementary data)	No change	Cost of year 2 (Leal, 2022) minus cost of year pre-surgery. In patient costs £389 Primary care costs £37 Outpatient costs - £105 = £321, inflated to 2022/21
Overall TKR cost				
Estimated year 1 TKR cost	**£7,862.94**	Sum of year 1 costs as described above	**£8,400.03**	Includes: Surgery, revisions and complications, rehabilitation, OP care and GP visits
Monthly costs in year 1	£92.29		£76.75	
Estimation of additional costs in Y2	**£367.98**	Sum of year 2 costs as described above	No change	
Monthly costs in year 2	£30.67		No change	
Monthly costs in year 3	£0 (£4.08 in 10 year model)		£3.80	Revisions calculated from NJR rate (2021)

9.2.3 *Sensitivity analysis*

The company carried out deterministic sensitivity analysis with both one- and two-way tables for a number of key parameters, all of which were varied by 20%. This was also provided for the company 10-year model. The EAG repeated this with the amended model, extended it to 20 years and added additional parameters and ranges (Appendix D). The EAG results were displayed as both tables and a tornado diagram, together a threshold graph.

The EAG also created two additional scenarios. The first included the cost of gait analysis equipment in the AposHealth arm. The second scenario used costs from Cole (2022) to test the impact of using an alternative cost source for healthcare resource use before and after TKR. In addition the EAG explored how modelling could reflect patients who did not want TKR or were not suitable for TKR.

To include gait analysis equipment, the EAG used the average cost of 2 sources for the OptoGait device, resulting in a cost of £12,151.80. It was assumed that the equipment had a lifetime of 5 years, and would be used for 100 patients per year (these do not have to be related to AposHealth). The resulting per patient cost of £24.30 was applied to the initial AposHealth evaluation, but not to future follow-up appointments.

The costs available from Cole (2022) have been discussed earlier, and were used to replace the submitted costs for an exploratory scenario. The change in monthly costs is summarised in Table 17, with the largest change being in OA care prior to TKR

Table 17: Summary of standard care costs in EAG base case and alternative scenario

	EAG base case	EAG alternative cost scenario (Cole 2022)
OA care prior to TKR	£101.94	£32.07
1-year monthly costs post TKR	£76.75	£63.59
2-year monthly costs post TKR	£30.67	£23.34
3 year + monthly costs post TKR	£3.80	£5.47

At the fact check, the company asked for the modelling to consider changes in the likelihood of surgery as patients age. They highlighted information from National PROMs data (NHS Digital 2019-20) that shows a lower number of knee replacements per 100,000 of the general population (at that age group) for patients in the over 85 years age group. The EAG have not included this as part of the base case, due to the uncertainties of how this may translate to the modelled population, or the different impact on the standard care and AposHealth arms of the model. The EAG have produced an exploratory scenario, that changes the initial probability of surgery by a ratio based on the PROMS data, for both arms of the model. The transition probabilities are multiplied by 1.1 for 75-79 years, 0.87 for 80-84 years and 0.36 for the 85+ age group.

9.3 *Results from the economic modelling*

9.3.1 *Base case results*

Both of the company's submitted model and the EAG base case are cost saving for AposHealth at 5 years, and the company's amended 10-year model is also cost saving at 10 years. However, the EAG base case becomes cost incurring at 10 years, and this continues when the model is extended to 20 years. This result should be treated with caution as the existing evidence for delay to surgery is only over 2 years, and the model may not include all costs that could be considered over a longer duration. The EAG have addressed some of these, but as an additional scenario due to the limited evidence available, and the ability to fit this to the existing model structure

The base case results for both the company models and the EAG at 5 years are very similar, shown in Table 18. The key differences are the extension of the model to a longer time horizon, and some additional modifications to accommodate this change.

Overall, any cost savings come from a reduction in TKR and subsequent complications and follow up. There is also a 15% reduction in monthly standard care costs due to the impact of AposHealth in the model, however this does not result in a total cost saving in standard care costs over either model time horizon due to the longer time prior to surgery for patients in the AposHealth arm.

Table 18 shows the distribution of costs between AposHealth, care prior to TKR, and TKR procedures and follow up for the two company models and the EAG base case. Table 19 summarises the cost savings at different time horizons for each model.

Table 18: Detailed summary of base case results

	Company's result 5-year time horizon			Company's result 10-year time horizon			EAG's result 5-year time horizon			EAG's result 20-year time horizon		
	Technology	Comparator	Cost saving per patient	Technology	Comparator	Cost saving per patient	Technology	Comparator	Cost saving per patient	Technology	Comparator	Cost saving per patient
AposHealth provision	£1,292		-£1,292	£1,355		-£1,355	£1,288	£0	-£1,288	£1,531	£0	-£1,531
Care prior to total knee replacement	£4,076	£2,584	-£1,492	£5,893	£2,805	-£3,089	£3,829	£2,432	-£1,397	£6,999	£2,710	-£4,289
Total knee replacements and 2 year follow up	£2,915	£7,557	+£4,642	£4,759	£9,449	+£4,690	£2,953	£7,596	+£4,643	£6,475	£10,264	+£3,789
Total	**£8,283**	**£10,141**	**+£1,858**	**£12,007**	**£12,254**	**+£247**	**£8,069**	**£10,027**	**+£1,958**	**£15,005**	**£12,974**	**-£2,032**
Time at which 50% haveTKR	**>5 years**	**20 months**		**107 months**	**21 months**					**103 months**	**21 months**	
Primary TKRs (%)	**34.69%**	**85.31%**		**53.19%**	**94.2%**		**34.28%**	**84.47%**		**71.38%**	**96.15%**	
Contralateral TKRs (%)	**4.23%**	**12.98%**		**13.08%**	**29.95%**		**2.27%**	**6.99%**		**19.12%**	**31.79%**	

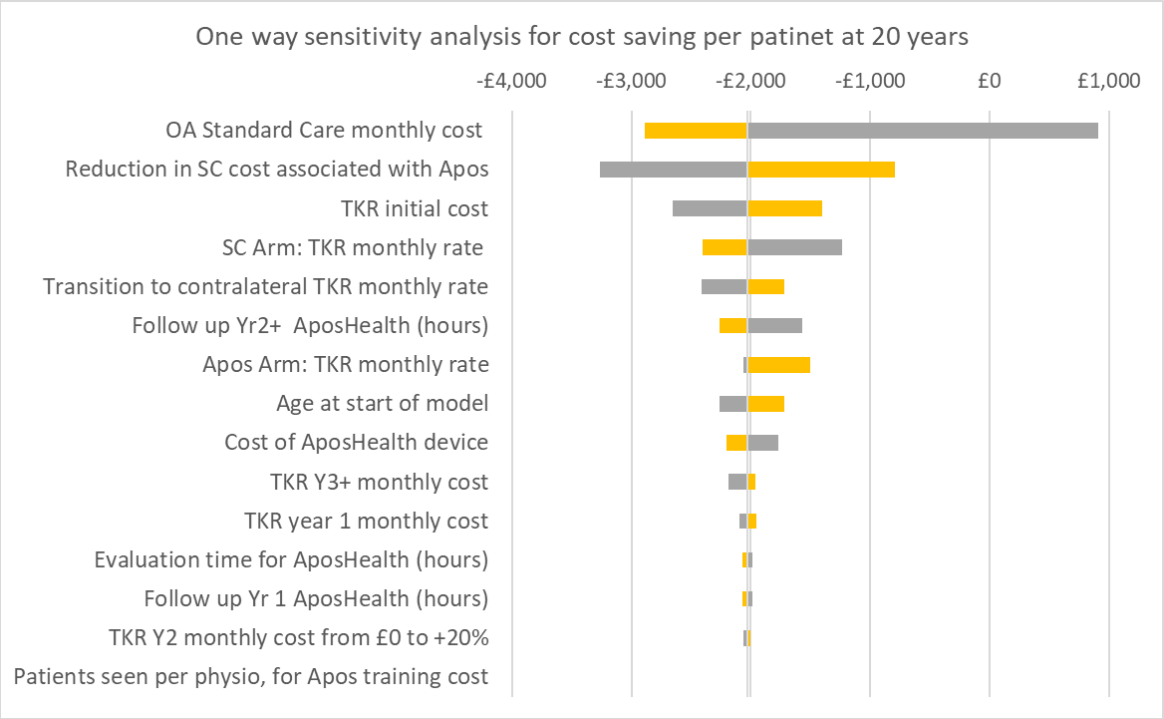
Table 19 Summary of base case results

	Cost saving per patient		
Time horizon	**Company original submission**	**Company 10-year extended time horizon**	**EAG Base Case**
5 years	+£1,858	+£1,886	+£1,958
10 years		+£247	-£46
15 years			-£1,396
20 years			-£2,032

9.3.2 *Sensitivity analysis results*

The tornado diagram for the EAG base case at 20 years is shown in Figure 2, with the full list of parameter values used available in Appendix D.

Figure 2: Tornado Diagram for EAG base case at 20 years



The costs of care, both before and after TKR, use parameter variations based on lower costs from Cole (2022) and a 20% increase from the base case input. This results in the cost of OA care prior to TKR being the only parameter that makes the sensitivity analysis cost saving at 20 years.

In addition to the key parameters of OA care prior to TKR; reduction in cost due to AposHealth; and transitions to TKR, two other parameters are noted. The cost of TKR surgery and associated resource use was varied by 20% due to observed cost variations during COVID-19, however this may not reflect future uncertainties. AposHealth follow up beyond the first year is continued for the duration of the model therefore variations are multiplied over the years. It is uncertain if this level of follow up is likely to be used, and the company 10 year model reduced follow up appointments after 3 years.

The tornado diagram demonstrated the importance of the cost of standard care prior to TKR and its reduction due to AposHealth, and both have

considerable uncertainty attached. Table 20 considers 2-way variation in both inputs, with the base case values shown in bold.

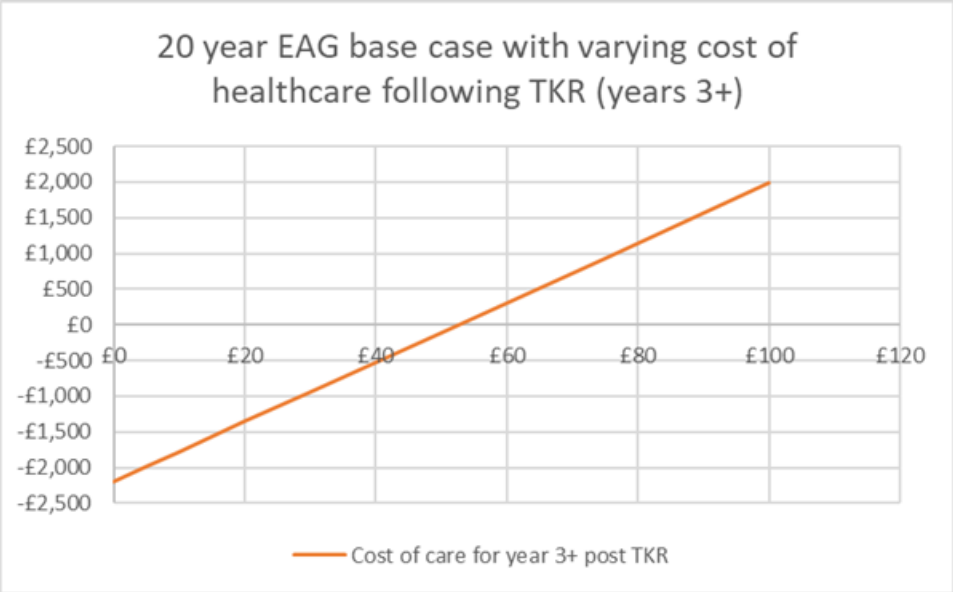
Table 20: Two-way table for the monthly cost of OA care prior to TKR and the percentage reduction due to AposHealth (base case value in bold)

20 year Cost Saving per patient due to AposHealth						
	Monthly cost of OA care prior to TKR					
	£25	£50	£75	**£102**	£125	£150
0%	+£903	-£452	-£1,807	-£3,267	-£4,517	-£5,872
10%	+£1,105	-£48	-£1,201	-£2,444	-£3,507	-£4,660
15%	+£1,206	+£154	-£898	**-£2,032**	-£3,002	-£4,054
30%	+£1,508	+£759	+£10	-£797	-£1,488	-£2,237
40%	+£1,710	+£1,163	+£616	+£27	-£478	-£1,025
50%	+£1,912	+£1,567	+£1,222	+£850	+£532	+£187

Lower costs of OA care prior to TKR tend towards a cost saving outcome, as fewer costs are accumulated by patients with delayed TKR procedures.

Figure 3 demonstrates the impact of changes in the reduction the cost of care after TKR (with all other parameters unchanged).

Figure 3: Threshold Analysis



9.3.3 *Additional results*

The company did not report any additional results for sub-groups or different scenarios.

The EAG scenario that includes the use of gait analysis equipment for initial calibration of AposHealth (but not subsequent appointments) found only a very small change in the 20-year cost saving due to AposHealth, from -£2,032 to -£2,056.

The EAG also explored a scenario using an alternative set of costs for standard care before and after TKR. This resulted in a change from cost incurring to cost saving at 20 years, with the total cost saving due to AposHealth being £879. This should be considered with caution as the costs reported by Cole (2022) were lower than several other studies considered, relied on patient recall over 12 months and were only for costs related to the primary TKR knee. This does illustrate the importance of changes in these costs for the model, with the largest change in input being a reduction in standard care prior to TKR.

For patients that do not want, or would be unable to have a TKR, the EAG explored the impact of setting all transitions to TKR to 0%. This considered the cost of using AposHealth balanced with the assumed reduction in cost of standard OA care prior to TKR, along with improved patient outcomes. Using the EAG base case, with a 15% reduction in standard care costs for AposHealth, there is a negative cost saving of -£538 at 5 years, and -£40 at 20 years. However, if the cost reduction was 20% this becomes a cost saving of +£259 at 5 years, and +£701 at 20 years.

The EAG exploratory scenario that included variation in the likelihood of surgery, with age, as patients progressed through the model had only a small impact on total cost saving. The negative cost saving, per patient, at 20 years changed from -£2,032 to -£1,955. The number of TKR in the AposHealth arm reduced from 71 to 70, per 100 patients, at 20 years.

Potential sub-groups would include younger patients and patients who are significantly overweight or obese, as the likelihood of TKR and subsequent outcomes will vary. At this point in time the EAG feel there is insufficient evidence to create even an exploratory scenario for these groups.

9.4 *The EAG's interpretation of the economic evidence*

The key changes made by the EAG are listed below with a fuller description found in Appendix E.

- Extension of time horizon to 20 years
- Addition of variable mortality based on ONS life tables (same risk as overall population)
- Change of costs from NHS Tariff to NHS Reference costs
- Inclusion of revisions for the duration of the model

The most important change was to extend the time horizon to 20 years from 5 years. The majority of additional changes were to adapt the model to this extended time line. The company chose the 5-year horizon based on the maximum evidence duration of 2 years, however the EAG noted that at 5 years the model was already becoming less cost saving per year, and that there is no evidence of long-term surgery avoidance.

Due to the extended time horizon it was necessary to also add a variable mortality rate, allowing for the increasing age of the modelled population.

Following discussions, the company also submitted a model with a 10 year time horizon, and this also included a variable mortality rate, inclusion of revisions and a reduction to AposHealth follow up appointments after 2 years.

The EAG and company models have some differences, but have approximately similar findings at 5 and 10 years.

The EAG extended model showed that (based on the initial model assumptions) while the standard care arm rapidly moved to TKR, there was a slower move to TKR in the AposHealth. This means that the costs of the surgical intervention are still accumulated in the AposHealth arm of the model for most patients, but over a longer time period. Over 20 years, in standard care, 97% of patients received a TKR at a median of 21 months; for AposHealth 74% at a median of 101 months. This is shown graphically in

Figure ***4*** and Figure 5.

In the submitted model there are costs accumulated for standard care prior to surgery, but no costs accumulated after year 3 post TKR surgery. This is likely to be a simplification, and both the company 10-year model and the EAG base case addressed this partially by including revision surgery post year 2.

With the extended time horizon, patients in the AposHealth arm accumulate high OA care costs prior to TKR, and patients in the standard care arm accumulate much lower costs post TKR. These costs are relatively unimportant for a short time horizon, but become more critical as the time horizon is extended. Cost evidence comes from large data sets, but is not specific to those using AposHealth, and may not reflect the actual resource use. Post primary TKR, there is a consideration for contralateral TKR and for revisions, but there may be a need for additional support prior to a contralateral procedure that would not be included. The company included evidence for costs over 1 and 2 years post-surgery only. The EAG identified alternative evidence for costs up to 5 years post-surgery, however there were limitations to the study and it is modelled as an additional scenario.

Figure 4: Movement of model cohort between states, Standard care arm

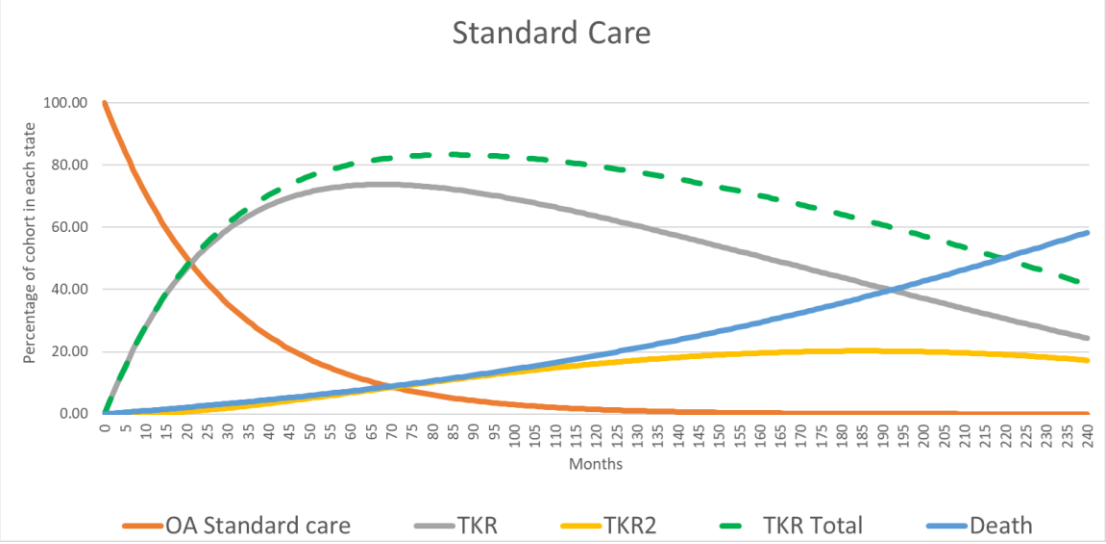
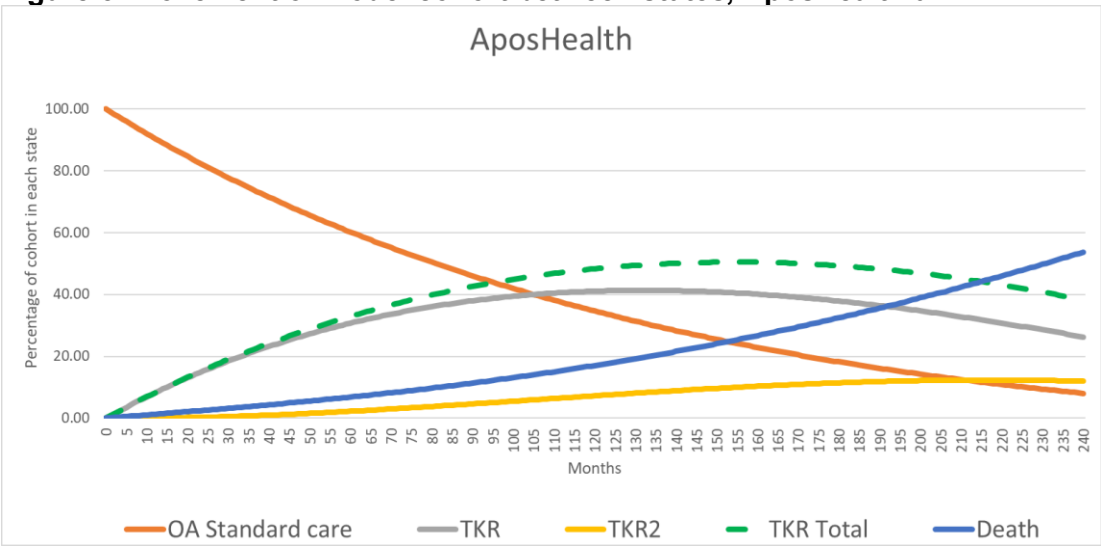


Figure 5: Movement of model cohort between states, AposHealth arm



10 Conclusions

10.1 *Conclusions from the clinical evidence*

Although primarily from non-comparative studies, results from the evidence base show a consistent decrease in pain, function limitation, and stiffness as measured by WOMAC scores after AposHealth is given as an intervention compared to baseline measurements. Improvements in mobility and quality of life were reported by the patient expert and clinical experts observed improvements for people who were using AposHealth after failing to respond to other non-surgical interventions.

The EAG notes a lack of evidence regarding rates of delay or avoidance of TKR surgery and considers this to be an important gap. There is no long-term follow-up in the published studies that extends beyond 2 years and clinical experts agreed there is insufficient long-term data for AposHealth to determine its efficacy in delaying or enabling avoidance of TKR surgery.

The position of AposHealth in the clinical pathway for knee OA management in the NHS is unclear. Clinical experts noted a lack of standardisation in the application of the current knee OA pathway, as patient preference is key in determining which patients will have surgery. The patient expert's experience supported this as they stated a desire to avoid surgery for as long as possible, and AposHealth was the only non-surgical treatment they had tried that was enabling this. The EAG acknowledges that AposHealth may provide an effective treatment for people who have a personal preference to avoid TKR surgery or a co-morbidity that means they are not suitable TKR surgery.

Overall the EAG believes there is potential for AposHealth to be an effective treatment in particular subgroups of knee OA patients, as patient-reported outcomes show high levels of satisfaction and significant symptom relief as a result of AposHealth intervention. However, the EAG is of the opinion that more research should be considered as the decision problem is inadequately addressed by the current evidence base.

10.2 *Conclusions from the economic evidence*

The submitted economic model mainly reflects the decision problem defined in the final scope. The submitted time horizon reflects the available evidence for the technology, but is not long enough to demonstrate the full consequences of the intervention and this has been addressed by the EAG additional modelling.

The model does not address the subgroup of people who do not want or cannot have surgical intervention, and the evidence used in the model does not explicitly include this group, although some patients in pragmatic studies may fall into this category. EAG exploratory analysis suggested that balancing AposHealth provision costs with reduced health care costs is plausible if clinical outcomes are sufficiently improved over the long term, but there is insufficient evidence to go beyond an initial exploration.

The model for AposHealth demonstrated a longer time to TKR procedures and a reduction in the overall number of TKRs required at both 5 and 20 years, although the difference is reduced at 20 years. With an assumption of constant OA care costs prior to TKR, the AposHealth arm accumulates large amounts of costs in this area over the duration of the model. The impact is accentuated by the assumption of no costs, or limited costs, after 2 years post TKR procedure, other than a risk of contralateral TKR.

The economic findings therefore depend on two main areas

- Changes in transition to TKR, depending on:
  - the strength of evidence for AposHealth delaying the need for TKR
  - this impact being maintained over time

- Costs of care before and after TKR, including
  - the need for, and cost of continued care for OA prior to TKR
  - the need for, and cost of continued care after 2 years post primary TKR.

The submitted company models demonstrate cost savings at 5 and 10 years, however extending the time horizon in the EAG base case results in

AposHealth being cost incurring, by £2,032. Where AposHealth is delaying TKR rather than avoiding it, the costs of surgery will eventually be incurred. There is uncertainty around changes in transition to TKR for the AposHealth arm compared to standard care, and there is no available evidence on the total avoidance of TKR due to the long follow up that would be required.

11 Summary of the combined clinical and economic sections

The clinical evidence indicates that use of AposHealth may result in improvements in symptoms of knee OA and in quality of life however there is limited evidence that this translates to avoidance or delay in surgery for people with knee OA. There may be particular sub-groups that benefit from AposHealth, such as people who wish to avoid surgery for as long as possible or people who cannot have surgery.

Potential cost savings in the economic model are from avoiding TKR surgery, however there is only limited evidence for delaying surgery available. There is no clear case for AposHealth being cost saving when compared to standard care in the long term, although there may be other system benefits in waiting list reduction. The EAG base case was cost incurring by £2,032.

The evidence indicates that AposHealth has the potential to delay or avoid surgery however there is a lack of long-term follow-up data beyond 2 years Research to identify subgroups most likely to benefit from AposHealth should be considered. This should, however be balanced against the observed improvements in symptom management and impact of patient quality of life, as well as the fact that there is a proportion of people who would prefer to avoid surgery, findings which were supported by both clinical experts and patient expert.

12 Implications for research

The EAG believes that additional research would help to support the adoption of AposHealth into the NHS. This is in alignment with the draft NICE guideline for the management of osteoarthritis (expected publication October 2022)

which recommends that further research is needed to determine any benefit from shoes (such as AposHealth) as an intervention for knee OA. The draft guideline also states that devices such as insoles, braces, tape, splints or supports should not be routinely offered to people with osteoarthritis due to a lack of evidence behind their efficacy. As noted, the draft guideline was developed prior to the publication of the study by Drew (2022) and upcoming publication of Greene (unpublished) which are included in the EAG's evidence review and company submission.

The EAG has identified the following key considerations for decision makers when considering research approaches:

- Consideration should be given to the positioning of AposHealth in knee OA treatment pathway. The potential places for AposHealth may include:
    - As a first-line intervention following diagnosis of knee OA to manage symptoms
    - As an intervention given after other non-surgical interventions for knee OA have 'failed' to delay or avoid TKR surgery
- Studies with long term follow-up periods (5 years plus) of AposHealth users would be beneficial to elucidate the full risks of adverse events, rates of surgery avoidance/delays and reductions to standard care usage. A registry or clinical audit approach could be considered.
- Comparative studies where the comparator/control group is standard care and TKR surgery delay or avoidance rates are the outcomes measured would help better understand the efficacy of AposHealth.
- Consideration should be given to the most appropriate tool for measuring outcomes to be used in any studies investigating the efficacy of AposHealth. Aspects to be considered include:
    - The validation of specific tools in the context of knee OA management in a UK setting

- What differences in scores are considered clinically significant
- Ease of use, scoring and interpretation, and accessibility

Overall, the EAG considers AposHealth to have potential as an effective management option for people with knee OA, particularly those who do not want or cannot have TKR surgery. However, there are uncertainties in the clinical and cost data that need to be addressed.

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14 Appendices

Appendix A: Clinical and economic evidence identification

Company search strategy, screening criteria and process for clinical evidence

Date search conducted:	1/6/22
Date span of search:	2004-1/6/22
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
The company tracks all peer-reviewed publications, all of them were included in this review. In additions, the company holds copies of un-published supporting evidence. Some are used in this submission. The company is aware of all on-going research activity and have disclosed them in this submission. With that, there is not additional scientific evidence that was not included in this submission.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
Enter text.	
Inclusion and exclusion criteria:	
Enter text.	
Data abstraction strategy:	
Enter text.	

Company study selection for clinical evidence

The company did not detail a selection process for the clinical evidence and state that they are aware of all on-going research activity on the device.

Company search strategy, screening criteria and process for economic evidence

The company did not detail a selection process for the economic evidence. The same number of studies were identified for the clinical and economic evidence indicating exactly the same process for searching and screening was conducted.

Company search strategy for adverse events

The company did not detail any search strategy for adverse events.

EAG search strategy and study selection for clinical and economic evidence

The EAG conducted a single search for both clinical and economic evidence as directed by the scope. Ten bibliographic databases were searched to include the period from 1st January 2004 to 21st June 2022, using a range of free text terms and, where appropriate, indexed terms. The searches were not restricted by language of publication. Two clinical trial registries were also searched for ongoing and unpublished trials; the company's website was also searched for additional literature. The MHRA's medical device alerts and field safety notices and the FDA MAUDE database were searched for adverse events.

Date	Database Name	Total Number of records retrieved	Total number of records from database after de-duplication
21/06/22	Medline ALL (includes Medline In Process & Medline Epub Ahead of Print)	133	
21/06/22	EMBASE	153	
21/06/22	Cochrane Library CDSR CENTRAL	 0 65	
21/06/22	CRD (DARE, NHS EED)	1	

Date	Database Name	Total Number of records retrieved	Total number of records from database after de-duplication
21/06/22	INAHTA	1	
21/06/22	PubMed	34	
21/06/22	Web of Science	137	
21/06/22	Scopus	173	
21/06/22	Company website	60	
22/06/22	MHRA	0	
27/06/22	FDA MAUDE	0	
21/06/22	Clinical Trials.gov	3	
22/06/22	ICTRP	7	367 records after manual deduplication

EAG Search strategies

Ovid MEDLINE(R) ALL <1946 to June 17, 2022>

1	(knee adj3 osteoarthritis).tw.	19712
2	Osteoarthritis, Knee/	24950
3	1 or 2	31966
4	(AposHealth or "AposHealth").tw.	0
5	(apostherapy or "apos therapy").tw.	16
6	pertupods.tw.	0
7	(biomechanical adj3 (device or treatment)).tw.	412
8	(biomechanical adj3 (footwear or shoe*)).tw.	64
9	"Foot Orthoses"/	1301
10	or/4-9	1759
11	3 and 10	133
12	exp animals/ not humans.sh.	5019716
13	11 not 12	133
14	limit 13 to yr="2004-Current"	133

Embase <1974 to 2022 June 20>

1	(knee adj3 osteoarthritis).tw.	29966
2	knee osteoarthritis/	39977
3	1 or 2	46126

4	(AposHealth or "AposHealth").tw.	1
5	(apostherapy or "apos therapy").tw.	46
6	pertupods.tw.	0
7	(biomechanical adj3 (device or treatment)).tw.	554
8	(biomechanical adj3 (footwear or shoe*)).tw.	83
9	foot orthosis/	1783
10	or/4-9	2412
11	3 and 10	156
12	limit 11 to yr="2004-Current"	153

Cochrane

ID	Search	Hits
#1	(knee NEAR/3 osteoarthritis):ti,ab,kw	12080
#2	MeSH descriptor: [Osteoarthritis, Knee] this term only	5094
#3	#1 or #2	12080
#4	(AposHealth or "AposHealth"):ti,ab,kw	0
#5	(apostherapy or "apos therapy"):ti,ab,kw	8
#6	(pertupods):ti,ab,kw	0
#7	(biomechanical NEAR/3 (device or treatment)):ti,ab,kw	51
#8	(biomechanical NEAR/3 (footwear or shoe*)):ti,ab,kw	23
#9	MeSH descriptor: [Foot Orthoses] this term only	231

#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	304
#11	#3 AND #10 with Cochrane Library publication date Between Jan 2004 and Dec 2022, in Cochrane Reviews	0
#12	#3 AND #10 with Publication Year from 2004 to 2022, in Trials	65

CRD

1	(knee adj3 osteoarthritis) IN DARE, NHSEED	193
2	MeSH DESCRIPTOR Osteoarthritis, Knee IN DARE,NHSEED	262
3	#1 OR #2	311
4	(AposHealth) OR ("AposHealth") IN DARE, NHSEED	183
5	(apostherapy) OR ("apos therapy") IN DARE, NHSEED	55
6	(pertupods) IN DARE, NHSEED	0
7	(biomechanical adj3 (device or treatment)) IN DARE, NHSEED	3
8	(biomechanical adj3 (footwear or shoe*)) IN DARE, NHSEED	1
9	MeSH DESCRIPTOR foot orthoses IN DARE,NHSEED	11
10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	252
11	#3 AND #10 IN DARE, NHSEED FROM 2004 TO 2022	1

INAHTA

(((AposHealth) OR ("AposHealth") OR (apostherapy) OR ("apos therapy") AND (pertupods) OR (foot orthoses)[mh]) OR ((biomechanical) AND (device

or treatment or footwear or shoe))) AND (((knee osteoarthritis)) OR (Osteoarthritis, Knee)[mh])

0 results

Pubmed

Apostherapy 33

AposHealth 1 (duplicate, included in above 33)

Web of Science

10	#1 AND #8 (2004 – 2022)	137
9	#1 AND #8	138
8	#7 OR #6 OR #5 OR #4 OR #3 OR #2	3,621
7	TS=(Foot Orthoses)	2,535
6	TS=(biomechanical NEAR/3 (footwear or shoe*))	132
5	TS=(biomechanical NEAR/3 (device or treatment))	993
4	TS=(pertupods)	0
3	TS=(apostherapy or "apos therapy")	13
2	TS=(AposHealth or "AposHealth")	1
1	TS=(knee NEAR/3 osteoarthritis)	33,612

Scopus

(TITLE-ABS-KEY (knee W/3 osteoarthritis)) AND ((TITLE-ABS-KEY (AposHealth OR "AposHealth" OR apostherapy OR "apos therapy" OR pertupods)) OR (TITLE-ABS-KEY (biomechanical W/3 (device OR treatment OR footwear OR shoe*))) OR (TITLE-ABS-KEY ("Foot Orthoses"))) AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005))

Clinicaltrials.gov

AposHealth | Knee Osteoarthritis 1 study

AposHealth | Studies With Results | Knee Osteoarthritis 1 additional study

apostherapy | Studies With Results | Knee Osteoarthritis 0 additional results

apos therapy | Knee Osteoarthritis 0 additional results

pertupods | Knee Osteoarthritis 0 additional results

foot orthoses | Knee Osteoarthritis 1 additional study

biomechanical footwear | Knee Osteoarthritis 0 additional studies

biomechanical shoe | Knee Osteoarthritis 0 additional studies

---

ICTRP

AposHealth OR “AposHealth” OR “apos therapy” OR Apostherapy OR “biomechanical footwear” = 7 results

Main ID	Public Title
NCT04732962	Biomechanical Footwear as a Non-invasive Alternative and Supplement to Total Knee Replacement
NCT03153956	Efficacy of AposTherapy® in Knee OA
NCT03171168	The Effect of AposTherapy on Knee Pain
NCT01562652	AposTherapy for Singaporean Patients With Knee Osteoarthritis (OA)
NCT01450254	Effects of Foot Center of Pressure Manipulation on Hip Osteoarthritis Patients During Gait
NCT01412814	Biomechanics of Gait Pattern Adaptation in Patients After Total Knee Arthroplasty
NCT01266382	The Effect of AposTherapy on the Level of Pain, Function and Quality of Life in Patients With Neuro-muscular and Neurological Disorders

MHRA

AposHealth, results = 0

“AposHealth”, results = 0

“apos therapy”, results = 0

Apostherapy, results = 0

“biomechanical footwear”, results = 0

“biomechanical shoe”, results = 0

FDA MAUDE

AposHealth, results = 0

“AposHealth”, results = 0

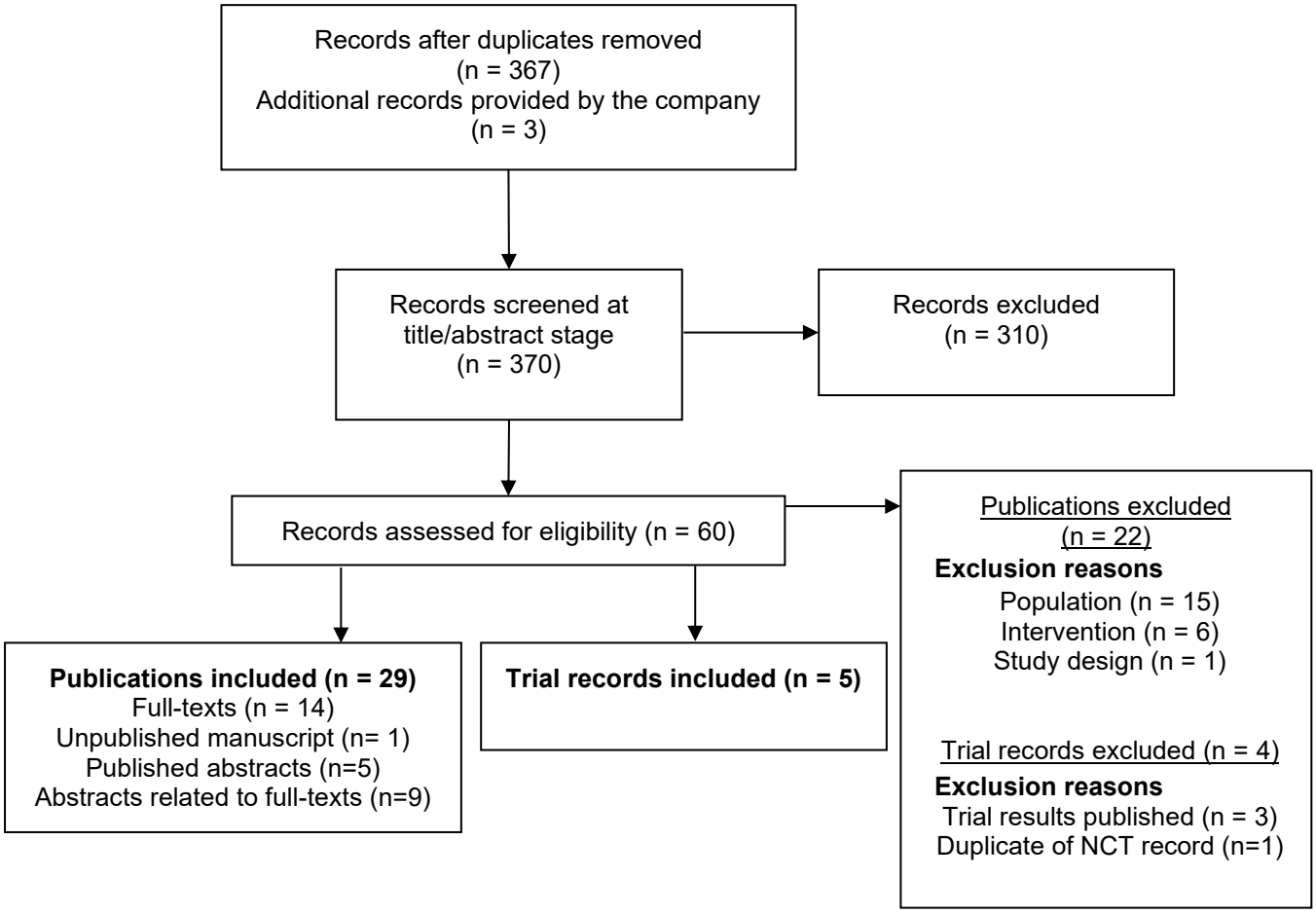
Apostherapy, results = 0

“apos therapy”, results = 0

“biomechanical footwear”, results = 0

“biomechanical shoe”, results = 0

EAG study selection



Appendix B: Critical Appraisals

JBI Critical Appraisal Checklist for randomised controlled trials

Author and Year: Reichenbach (2020) **Date**: 22/08/2022

Reviewer: Samuel Bird

Item	Yes/No/Unclear/Not applicable
1. Was true randomization used for assignment of participants to treatment groups?	**Yes**
2. Was allocation to treatment groups concealed?	**Yes**
3. Were treatment groups similar at the baseline?	**Yes**. There is no statistically significant difference between groups at baseline.
4. Were participants blind to treatment assignment?	**Yes**. The control shoe looked the same except it had the pods embedded in a transparent outer sole of the shoe. Patients were told it was a new design being tested.
5. Were those delivering treatment blind to treatment assignment?	**No**. Clinicians and researchers could not be blinded, but were told not to disclose the treatment and nature of the trial to participants.
6. Were outcomes assessors blind to treatment assignment?	**No**. See above.
7. Were treatment groups treated identically other than the intervention of interest?	**Yes**
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	**Yes**. The post-randomisation attrition was similar (98.2% active vs 95.4% control), and the reasons for attrition were similar. Although the control group had a few more discontinuing treatment.
9. Were participants analysed in the groups to which they were randomized?	**Yes**
10. Were outcomes measured in the same way for treatment groups?	**Yes**
11. Were outcomes measured in a reliable way?	**Yes**
12. Was appropriate statistical analysis used?	**Yes**. Statistical power was 90%. Appropriate tests used.
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	**Yes**

Overall appraisal comments:
Good quality trial overall. Sample size of ~200. Only single-blinded, and the control shoe did look different to the Apos shoe. The between-group differences were smaller than the within-group differences of the baseline group. The paper reports how the clinical importance of its results remain uncertain. Those with severe knee pain were also excluded from the trial, so the results are not generalisable to this population.

JBI Critical Appraisal Checklist for Quasi-Experimental Studies

Author and Year: Bar-Ziv (2010) **Date**: 18/08/2022

Reviewer: Samuel Bird

Item	Yes/No/Unclear/Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	**Yes**. Cause is the difference in footwear. One arm is Apos, the other is the sham device. The effect is on pain and function in the patient's knees.
2. Were the participants included in any comparisons similar?	**Yes**. There was no statistically significant difference between patients on; age, gender, K&L score, and BMI.
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	**Yes.** Active and control patients were given the same instructions with regards to how to use the shoe, and to not use any pain medication during treatment. Not clear if the control patients received a sham calibration of the device. It is assumed that the control shoe will act as a normal walking shoe.
4. Was there a control group?	**Yes**. The control group received a sham device that was identical to the Apos shoe, except it did not have the pertupods on the bottom and instead had a regular rubber sole.
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	**Yes**. Measurements were made before treatment began for both groups, then at 4 weeks in the middle of treatment, and finally at the end after treatment.
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	**Yes**. Follow up was completed for most patients. Three patients overall were lost to follow up. Two from the active arm and one from control. The differences between the groups after those lost to follow up is not mentioned.
7. Were the outcomes of participants included in any comparisons measured in the same way?	**Yes**. Standardised scores used for both groups.
8. Were outcomes measured in a reliable way?	**Yes**. The outcomes are standardised scores that are rated objectively.
9. Was appropriate statistical analysis used?	**Yes.** The trial has 80% statistical power. Statistical testing is appropriate.

Overall appraisal comments:
The study is only pseudo-randomised, but the patient groups used in each arm of the study are very similar. The follow up period is very short at only 8 weeks. The control arm utilises a sham shoe which may not be a valid control.

JBI Critical Appraisal Checklist for Quasi-Experimental Studies

Author and Year: Bar-Ziv (2013) **Date**: 18/08/2022

Reviewer: Samuel Bird

Item	Yes/No/Unclear/Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	**Yes**. The cause is the difference in footwear used, sham device vs Apos. And the effect is pain and functioning in the knees.
2. Were the participants included in any comparisons similar?	**Yes**. There was no significant difference found in age, gender, and K&L grade between patients of the active and control groups. However, other characteristics such as BMI and weight, that might impact the effect, were not accounted for. The active arm had over double the number of patients (N=40) compared to the control arm (N=16).
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	**Yes**. The patients were given the same instructions with regards to the exercises they need to do. Both groups could take any other medication to help with their condition. The control group were given a sham device that did not have the biomechanical elements. However, the control group were not given a sham calibration. Therefore, it is possible they knew they were given a sham device.
4. Was there a control group?	**Yes**. They were given a sham device that looked the same as the Apos shoe, except it did not have the biomechanical element (the pods).
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	**Yes**. Primary outcome was WOMAC and ALF. These were done for both groups before treatment began, and once for the control group in follow up and three times for the active group.
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	**Yes**. Follow up was completed for 38 of the 40 in the active group. And for 9 of the 16 in the control group. Differences with regards to baseline characteristics at follow up are not analysed.
7. Were the outcomes of participants included in any comparisons measured in the same way?	**Yes**. Standardised and objective tests were used in the form of patient questionnaires and a gait test. Paper does not go into much more details with regards to any differences between the groups in measuring these. The one difference is the follow up time scale. The active group was followed up at 6, 12, and 24 months, whereas the control group was followed up only at 24 months.
8. Were outcomes measured in a reliable way?	**Yes**. Standardised and objective tests were used.
9. Was appropriate statistical analysis used?	**Yes**. The study had a statistical power of >99.9%. The statistical tests used were appropriate.

Overall appraisal comments:
This study ran is a two year follow-up of the initial 8 week trial period reported by Bar-Ziv (2010). It was unblinded (or as the paper says 'unblended') as opposed to Bar-Ziv (2010).

There was also no randomisation. However as with the previous study, there was no significant difference in the baseline characteristics. There were also considerably more patients in the active arm over the control arm, which ended the study with only 9 patients. As with Bar-Ziv (2010) there are concerns regarding the validity of using the sham device as a control and if it can have any effect on patients.

JBI Critical Appraisal Checklist for case series studies

Author and Year: Drew (2022) **Date**: 03/10/2022

Reviewer: Samuel Bird

Item	Yes/No/Unclear/Not applicable
1. Were there clear criteria for inclusion in the case series?	**Yes**. Patients that met eligibility criteria for a TKR and chose to receive AposHealth.
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	**Unclear**. There are no details regarding how knee OA is diagnosed, it just states that they are 'end stage'.
3. Were valid methods used for identification of the condition for all participants included in the case series?	**Unclear**. Doesn't provide details regarding how patients were diagnosed with end-stage knee OA. Just states that patients were identified from a network.
4. Did the case series have consecutive inclusion of participants?	**Yes**. All patients identified from the network that met the criteria for TKR and received Apos between March 2018 and March 2019.
5. Did the case series have complete inclusion of participants?	**Yes**. See above.
6. Was there clear reporting of the demographics of the participants in the study?	**Yes**. Reports gender and age.
7. Was there clear reporting of clinical information of the participants?	**Yes**. Reports WOMAC, gait analysis, and SF-36 are reported.
8. Were the outcomes or follow up results of cases clearly reported?	**Yes**
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	**Unclear**. Only reports on gender and age. Doesn't mention where patients are from except that they're US patients.
10. Was statistical analysis appropriate?	**Yes**

Overall appraisal comments:
This study is based in the USA and so might not be entirely generalisable to patients with knee OA in the UK. A cohort that has elected to have surgery is utilised as a control at baseline only. The study reports the surgery outcomes of patients receiving AposHealth, in addition to their WOMAC and SF-36 scores.

JBI Critical Appraisal Checklist for case series studies

Author and Year: Debbi (2015) **Date**: 19/08/2022

Reviewer: Samuel Bird

Item	Yes/No/Unclear/Not applicable
1. Were there clear criteria for inclusion in the case series?	**Yes.** However, they are quite broad and only include women with knee OA. They do not rely on severity for inclusion.
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	**Yes.** K&L, WOMAC, SF-36, and knee alignment were all measured.
3. Were valid methods used for identification of the condition for all participants included in the case series?	**Yes.** Physician-diagnosed medial knee OA and fulfilment of the American College of Rheumatology criteria for OA of the knee are used.
4. Did the case series have consecutive inclusion of participants?	**Unclear.** 25 female patients were included. It does not state how they were found, or if they were previously being treatment with Apos. However, the study does have a somewhat quasi-experimental design to it and so this may just be the nature of this study. It is not necessary a true case series study.
5. Did the case series have complete inclusion of participants?	**See above.**
6. Was there clear reporting of the demographics of the participants in the study?	**Yes.** Gender, age, height, and weight.
7. Was there clear reporting of clinical information of the participants?	**Yes.** Reports K&L grade, WOMAC, and coronal knee alignment.
8. Were the outcomes or follow up results of cases clearly reported?	**Yes.** It clearly reports the results from the outcomes measures of WOMAC, SF-36, and the changes in knee alignment.
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	**No.** It reports that patients were female, and gives their ages. However, that is the only information provided.
10. Was statistical analysis appropriate?	**Yes.** However, no power calculations are mentioned.

Overall appraisal comments:
Unsure whether to appraise this study as quasi-experimental, cohort, or case series. It is experimental in a sense as there are clear independent and dependant variables i.e. the dependent variable of knee pain and function is measured before and after the independent variable of the Apos intervention is given to them.
Otherwise this study had quite a low sample size, and no power calculations are mentioned. It has a fairly long follow up period of nine months. There is no control group or randomisation.

JBI Critical Appraisal Checklist for case series studies

Author and Year: Drexler (2012) **Date**: 19/08/2022

Reviewer: Samuel Bird

Item	Yes/No/Unclear/Not applicable
1. Were there clear criteria for inclusion in the case series?	**Yes.**
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	**Yes.**
3. Were valid methods used for identification of the condition for all participants included in the case series?	**Yes.** Physician-diagnosed medial knee OA and fulfilment of the American College of Rheumatology criteria for OA of the knee are used.
4. Did the case series have consecutive inclusion of participants?	**Yes.** It includes all patients, within the criteria, that had treatment at the AposTherapy centre between Apr 2009 and Sep 2010.
5. Did the case series have complete inclusion of participants?	**No.** Many patients that came for Apos treatment were excluded from the sample. Of the 5,682 that began Apos, only 652 were used. The rest were excluded due to exclusion criteria, or due to the lack of baseline or follow up questionnaires.
6. Was there clear reporting of the demographics of the participants in the study?	**Yes.** Gender, age, height, and weight are all recorded.
7. Was there clear reporting of clinical information of the participants?	**Unclear.** WOMAC and SF-36 are reported. However, an objective measure of severity of knee OA is not reported through K&L or another measure.
8. Were the outcomes or follow up results of cases clearly reported?	**Yes.** OMERAC-OARSI guidelines are used to show a true benefit to the patient. However, no adverse events are reported.
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	**Yes.** Differences in BMI, gender, and age are all reported on.
10. Was statistical analysis appropriate?	**Yes.** Statistical power is reported on as 80%. Statistical tests are appropriate.

Overall appraisal comments:
Study uses a large sample size, although it does exclude much of the population. The follow up period is only three months. The assessment of OA excludes radiographic assessment and only relies upon clinician assessment.

JBI Critical Appraisal Checklist for case series studies

Author and Year: Elbaz (2010) **Date**: 19/08/2022

Reviewer: Samuel Bird

Item	Yes/No/Unclear/Not applicable
1. Were there clear criteria for inclusion in the case series?	**Yes**
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	**Yes**
3. Were valid methods used for identification of the condition for all participants included in the case series?	**Yes.** The study used radiographic assessment of knee OA in addition to ACR clinical criteria.
4. Did the case series have consecutive inclusion of participants?	**Unclear.** The sample was pulled from the APOS Therapy Centre database. However, it does not state when these patients received treatment.
5. Did the case series have complete inclusion of participants?	**Unclear.** Patient data was pulled from the APOS Therapy Centre database, and only 46 patients were included. It does not explain
6. Was there clear reporting of the demographics of the participants in the study?	**Yes.** Age, height, weight, and BMI are all reported.
7. Was there clear reporting of clinical information of the participants?	**Unclear.** It reports the exclusion criteria, and so we can work out what patients do not have. However outside of the demographic details and the study outcomes, there is little else reported on. It does report patient's OMERACT-OARSI response to treatment as well.
8. Were the outcomes or follow up results of cases clearly reported?	**Yes**
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	**Yes.** Differences due to BMI are reported upon.
10. Was statistical analysis appropriate?	**Unclear.** Statistical power is not reported.

Overall appraisal comments:
Small sample size of only 46. No control or randomisation, and much of the population are excluded. The follow up period is for only 12 weeks.

JBI Critical Appraisal Checklist for case series studies

Author and Year: Elbaz (2014) **Date**: 19/08/2022

Reviewer: Samuel Bird

Item	Yes/No/Unclear/Not applicable
1. Were there clear criteria for inclusion in the case series?	**Yes**
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	**Yes.** Measured using ACR criteria, and by being radiographically assessed.
3. Were valid methods used for identification of the condition for all participants included in the case series?	**Yes**
4. Did the case series have consecutive inclusion of participants?	**Unclear.** It does not go into detail about how patients were identified for the study. 68 patients were assessed for eligibility and 58 were included on the study.
5. Did the case series have complete inclusion of participants?	**Unclear.** See above.
6. Was there clear reporting of the demographics of the participants in the study?	**Yes.** It reports gender, age, BMI, and ethnicity/nationality.
7. Was there clear reporting of clinical information of the participants?	**Yes.** It reports K&L, gait analysis, and scores from WOMAC and SF-36.
8. Were the outcomes or follow up results of cases clearly reported?	**Yes**
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	**Unclear.** It reports demographic information; however, it does not report on any comparison in outcomes between these.
10. Was statistical analysis appropriate?	**Unclear.** No statistical power reported. Statistical tests used are appropriate.

Overall appraisal comments:
Similar to Elbaz (2010). Sample size of only 58. Has a longer follow up of 6 months. No statistical power is reported. Also lacked a control group and randomisation.

JBI Critical Appraisal Checklist for case series studies

Author and Year: Goryachev (2011) **Date**: 19/08/2022

Reviewer: Samuel Bird

Item	Yes/No/Unclear/Not applicable
1. Were there clear criteria for inclusion in the case series?	**Yes**
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	**Yes.** Measured using ACR criteria, and by being radiographically assessed.
3. Were valid methods used for identification of the condition for all participants included in the case series?	**Yes**
4. Did the case series have consecutive inclusion of participants?	**Unclear**
5. Did the case series have complete inclusion of participants?	**Unclear.** See above.
6. Was there clear reporting of the demographics of the participants in the study?	**Yes.** Gender, age, height, and weight are reported.
7. Was there clear reporting of clinical information of the participants?	**Yes.** WOMAC, SF-36, and gait analysis.
8. Were the outcomes or follow up results of cases clearly reported?	**Yes**
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	**Unclear.** It reports demographic information; however, it does not report on any comparison in outcomes between these.
10. Was statistical analysis appropriate?	**Unclear.** No statistical power reported. Statistical tests used are appropriate.

Overall appraisal comments:
Very small sample size of only 14 (all female), and only 3 months follow up. No statistical power reported. It seems the primary aim of this study is determining mechanical changes in the limbs as a result of using AposHealth, rather than the clinical outcomes patients experience from it.

JBI Critical Appraisal Checklist for case series studies

Author and Year: Greene (Unpublished) **Date**: 05/09/2022

Reviewer: Samuel Bird

Item	Yes/No/Unclear/Not applicable
1. Were there clear criteria for inclusion in the case series?	**Yes**
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	**Yes.** Oxford Knee Score and radiological evidence of knee OA.
3. Were valid methods used for identification of the condition for all participants included in the case series?	**Yes.** All patients that met the criteria for orthopaedics referral.
4. Did the case series have consecutive inclusion of participants?	**Yes.** All patients receiving AposHealth between Nov 2017 and Nov 2019.
5. Did the case series have complete inclusion of participants?	**Unclear**
6. Was there clear reporting of the demographics of the participants in the study?	**Yes**
7. Was there clear reporting of clinical information of the participants?	**Yes**
8. Were the outcomes or follow up results of cases clearly reported?	**Yes**
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	**Yes**
10. Was statistical analysis appropriate?	**Yes**

Overall appraisal comments:
A clinical audit/case series type study. Provides some evidence for how much AposHealth is able to reduce patients needing TKR after two years. No control or comparator.

JBI Critical Appraisal Checklist for case series studies

Author and Year: Herman (2018) **Date**: 22/08/2022

Reviewer: Samuel Bird

Item	Yes/No/Unclear/Not applicable
1. Were there clear criteria for inclusion in the case series?	**Yes**
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	**Yes.** Although not measured by radiographic assessment.
3. Were valid methods used for identification of the condition for all participants included in the case series?	**Yes**
4. Did the case series have consecutive inclusion of participants?	**Unclear.** 852 patients were screened and 518 included in the final data set. Various exclusion criteria excluded many.
5. Did the case series have complete inclusion of participants?	**No.** It does not report when these patients were having treatment, or any sort of timeframe.
6. Was there clear reporting of the demographics of the participants in the study?	**Yes.** However only gender and age are reported.
7. Was there clear reporting of clinical information of the participants?	**Yes.** It reports K&L.
8. Were the outcomes or follow up results of cases clearly reported?	**Yes.** WOMAC, SF-36, and K&L are reported.
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	**Unclear.** Only gender and age are reported. There is no comparison of them with the outcomes.
10. Was statistical analysis appropriate?	**Unclear.** No statistical power reported.

Overall appraisal comments:
Large sample size, and 12 months follow up. However, this is a retrospective analysis and does not involve randomisation or a control. The study's primary aim is to determine the validity of a new classification for patients with knee OA having AposHealth treatment.

JBI Critical Appraisal Checklist for case series studies

Author and Year: Haim (2012) **Date**: 19/08/2022

Reviewer: Samuel Bird

Item	Yes/No/Unclear/Not applicable
1. Were there clear criteria for inclusion in the case series?	**Yes**
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	**Yes**
3. Were valid methods used for identification of the condition for all participants included in the case series?	**Yes.** Physician and radiographic assessment.
4. Did the case series have consecutive inclusion of participants?	**Unclear.** Only 25 female patients are included and it does not explain how they were identified.
5. Did the case series have complete inclusion of participants?	**Unclear.** See above.
6. Was there clear reporting of the demographics of the participants in the study?	**Yes.** Reports gender, age, height, and weight.
7. Was there clear reporting of clinical information of the participants?	**Yes.** WOMAC, SF-36, and gait analysis.
8. Were the outcomes or follow up results of cases clearly reported?	**Yes**
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	**Unclear.** It reports demographic information; however, it does not report on any comparison in outcomes between these.
10. Was statistical analysis appropriate?	**Unclear.** No statistical power reported. Statistical tests used are appropriate.

Overall appraisal comments:
Similar to Goryachev (2011). Small sample size of only females. A longer follow up of nine months however. The aim was to show the biomechanical changes rather than the clinical outcomes.

JBI Critical Appraisal Checklist for case series studies

Author and Year: Lador (2013) **Date**: 22/08/2022

Reviewer: Samuel Bird

Item	Yes/No/Unclear/Not applicable
1. Were there clear criteria for inclusion in the case series?	**Yes**
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	**Yes.** ACR criteria and 6 months of knee OA.
3. Were valid methods used for identification of the condition for all participants included in the case series?	**Yes**
4. Did the case series have consecutive inclusion of participants?	**Unclear.** 1,410 patients on the AposTherapy centre database. 988 patients included in final analysis. Many excluded due to lack of data, or exclusion criteria.
5. Did the case series have complete inclusion of participants?	**Unclear.** See above.
6. Was there clear reporting of the demographics of the participants in the study?	**Yes.** Age, gender, height, weight, and BMI are all reported.
7. Was there clear reporting of clinical information of the participants?	**Yes.** WOMAC, gait analysis, and SF-36 are all reported.
8. Were the outcomes or follow up results of cases clearly reported?	**Yes**
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	**Yes.** It reports differences in outcomes between gender, and BMI.
10. Was statistical analysis appropriate?	**Unclear.** No statistical power reported.

Overall appraisal comments:
Large sample size, but only 4 months of follow up. No control or randomisation. A before-and-after comparison study that provides evidence for Apos but does not compare it against anything.

JBI Critical Appraisal Checklist for case series studies

Author and Year: Lubovsky (2017) **Date**: 22/08/2022

Reviewer: Samuel Bird

Item	Yes/No/Unclear/Not applicable
1. Were there clear criteria for inclusion in the case series?	**Yes**
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	**Yes**
3. Were valid methods used for identification of the condition for all participants included in the case series?	**Yes**
4. Did the case series have consecutive inclusion of participants?	**Unclear.** The dates of when patients had treatment is reported. However, it does not report how many were screened. Only that 105 met the inclusion criteria. It does not report how many were excluded due to exclusion criteria.
5. Did the case series have complete inclusion of participants?	**Unclear.** See above
6. Was there clear reporting of the demographics of the participants in the study?	**Yes.** Gender, age, height, weight, and BMI are all reported.
7. Was there clear reporting of clinical information of the participants?	**Yes**
8. Were the outcomes or follow up results of cases clearly reported?	**Unclear.** Gait analysis and SF-36 are reported in tables. But WOMAC is reported in a graph and in the text.
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	**Yes.** The differences between gender and BMI in outcome are reported.
10. Was statistical analysis appropriate?	**Unclear.** No statistical power reported.

Overall appraisal comments:
A retrospective case series study for Apos. This study focuses on obesity. It had a sample size of 105 and 12 months of follow up. No control or randomisation. A before-and-after study but unable to provide evidence for Apos against any other treatments.

JBI Critical Appraisal Checklist for case series studies

Author and Year: Miles (2020) **Date**: 22/08/2022

Reviewer: Samuel Bird

Item	Yes/No/Unclear/Not applicable
1. Were there clear criteria for inclusion in the case series?	**Yes**
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	**Yes.** Based upon primary diagnosis of KOA.
3. Were valid methods used for identification of the condition for all participants included in the case series?	**Yes**
4. Did the case series have consecutive inclusion of participants?	**Yes.** All patients having treatment for Apos in the UK between 2009 and 2017 were screened.
5. Did the case series have complete inclusion of participants?	**No.** Does not include all patients available as there are some exclusion criteria that exclude some.
6. Was there clear reporting of the demographics of the participants in the study?	**Yes.** But only reports gender and age.
7. Was there clear reporting of clinical information of the participants?	**Yes.** However, only KOFG and WOMAC are reported. There is no radiographic assessment of KOA.
8. Were the outcomes or follow up results of cases clearly reported?	**Yes.** Reports the changes in KOFG and WOMAC.
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	**Yes**
10. Was statistical analysis appropriate?	**Yes.** But no statistical power reported.

Overall appraisal comments:
Large sample size. Only six months of follow up. UK-based. However, it is not randomised nor does it have a control arm or comparison against any other treatments.

Appendix C Summary of Studies used to provide costs for economic model

Abraham 2022

This was a retrospective analysis using Salford Integrated Record for UK patients with moderate to severe OA pain (n=3,123) or severe OA pain (n=1922), compared to matched patients without OA. Matching was by age, sex and Charlson Comorbidity Index (CCI). Patients had a OA diagnosis and several episodes of pain related consolations with a GP or specialist. An initial recorded pain event was used as the index event, and all healthcare resource use recorded for the next 24 months. Within that 24 months, 13.4% of the moderate to severe OA pain group and 22.2% of the severe OA pain group had one or more total joint replacements. There is very little information on how costs are calculated.

Table 21: Abraham 2022 Costs

Mean cost, 1 year(£)	In-patients	Primary care	Out-patients	A&E	Analgesic	Total
Severe OA	£2,299.89	£174.16	£659.72	£86.60	£168.99	**£3,389**
Comparator	£828.61	£112.88	£369.88	£48.86	£36.67	**£1,397**

Leal 2022

This study analyses data for patients age ≥18 years with primary planned hip or knee replacements and osteoarthritis in England, between 2008 and 2016, using linked Clinical Practice Research Database (CPRD) and Hospital Episode Statistics (HES) data. The authors took secondary care episodes and assigned HRG codes by clinical coding and hence costs. Similar methods were used for primary care, using Personal Social Services Research Unit (PSSRU) costs, also for medication using British National Formulary (BNF) codes and then NHS digital prescription cost analysis. Complications were coded using a list that clinicians rated as being related. Revisions were classified as those notified to NJR within a year from procedure. All costs were based on 2016/17 prices. With costing based on episodes or contacts with primary care staff, there is no information available on the use of specific medical devices as part of the intervention. The costs are based on mean HRG group prices. There is very limited information available on the collection of data for the year prior to the TKR procedure. The authors noted that costs in Year 2 post intervention were greater than the year prior to intervention.

Although health care costs are reported for years preceding and post TKR, this study is used for the 1-year complication and revision rates which are 0.5% and 6% respectively. It is also used for the second year post intervention, taking the difference of cost between year 2 post intervention and the pre-intervention cost as being a proxy for costs of complications and revisions.

Table 22: Leal 2022 Costs

Mean cost (£)	In-patients	Primary care	Out-patients	Total
Pre intervention, 1 year	£1,240	£960	£576	**£2,776**
Index admission	£6,122			
Post intervention, Year 1 (including TKR)	£7,803	£1024	£656	**£9,483**
Post intervention, Year 2	£1,628	£997	£470	**£3095**

Cole 2022

Reports healthcare resource use for 5 years following TKR for cohorts with and without chronic pain 1 year after surgery. Data was from a prospective cohort study with 552 knee procedures in two NHS hospitals between 2010 and 2011. Costs are shown for one year prior to the intervention and 5 additional years. Healthcare resource use was by patient questionnaire, recalling the previous year, and was specific to their operated knee, rather than all healthcare use. These two factors may explain the much lower costs seen in this study.

Results for healthcare resource use were presented by cohort with and without chronic pain, and are available in the supplementary data published by Cole (2022). For the purposes of the assessment report the EAG have calculated total costs for the entire group, using weighted averages.

Table 23: Cole 2022 Costs

	Annual health care costs
Pre intervention	£335.75
1 year post	£665.70
2 year post	£244.28
3 year post	£152.26
4 year post	£41.43
5 year post	£73.19

Dakin, 2012

This retrospective analysis linked CPRD with HES data for 5,931 UK patients, with moderate to severe OA pain or severe OA pain. Patients had an existing OA diagnosis, and the index event was the first event within a series of pain related events. Cases were matched on age, sex, CCI, GP practice and linkage eligibility. Healthcare resource use and costs were reported for 6 months, 1 and 2 years following (and including) the index event. Costs values at 2007-2008 prices. Each admission for primary TKR cost £6,363 per patient (SD £1702) Readmissions, revisions, GP, outpatient and physiotherapy related to the knee study cost £1,095 over next 5 years (SD £3,579). Costs were greater for patients with lower OKS (more severe OA).

Lohan 2021 (abstract only)

Retrospective analysis linking CPRD with HES data for 5,931 UK patients, with moderate to severe OA pain or severe OA pain. {Patients had an existing OA diagnosis. The index event was the first event within a series of pain related events. Cases were matched on age, sex, CCI, GP practice and linkage eligibility.

Healthcare resource use and costs were reported for 6 months, 1 and 2 years following (and including) the index event

Table 24: Lohan 2022 Costs

Mean cost	In-patients	Primary care	Out-patients	A&E	Analgesic	Total
0-12 months						
Mod -Severe OA	3079	£453	£590	£44	£33	**£4,199**
Comparator	£341	£217	£161	£21	£42	**£781**
0-24 months						
Mod-Severe OA	4354	825	985	75	70	**6,309**
Comparator	683	437	319	42	52	**1531**

Appendix D Ranges used for sensitivity analysis

Variable	Input values			Results		
	Low	Model	High	Low	Model	High
SC Arm: TKR monthly rate , +/- 50% variation	1.64%	3.28%	4.92%	-£1,235	-£2,032	-£2,406
Apos Arm: TKR monthly rate, -50% low, equal to SC arm low range for high	0.36%	0.72%	1.64%	-£2,065	-£2,032	-£1,501
Transition to contralateral TKR monthly rate, +/- 50% variation	0.13%	0.26%	0.39%	-£2,420	-£2,032	-£1,726
Age at start of model, +/- 3 years	65	68	71	-£2,270	-£2,032	-£1,723
Cost of AposHealth device, +/- 20%	700	875	1050	-£1,776	-£2,032	-£2,207
Patients seen per physio, for Apos training cost, assumption	50	250	500	-£2,037	-£2,032	-£2,031
Evaluation time for AposHealth (hours), assumption	0.50	1.00	1.50	-£1,992	-£2,032	-£2,072
Follow up Yr 1 AposHealth (hours), assumption	1.00	1.50	2.00	-£1,994	-£2,032	-£2,070
Follow up Yr2+ AposHealth (hours), assumption	0.00	1.00	1.50	-£1,570	-£2,032	-£2,263
OA Standard Care monthly cost, Cole (2022) and +20%	£32.07	£101.94	£122.33	+£908	-£2,032	-£2,890
Reduction in SC cost associated with Apos, assumption	0.00%	15.00%	30.00%	-£3,267	-£2,032	-£797
TKR initial cos, t+/- 20%	£5,983	£7,479	£8,975	-£2,654	-£2,032	-£1,409
TKR year 1 monthly cost, Cole (2022) and +20%	£64	£76.75	£92.10	-£2,096	-£2,032	-£1,956
TKR Y2 monthly cost, Cole (2022) and +20%	£23	£30.67	£36.80	-£2,066	-£2,032	-£2,003
TKR Y3+ monthly cost, 0 and Cole (2022)	£0	£3.89	£5.47	-£2,190	-£2,032	-£1,962

Appendix E: Description of EAG changes, with cell reference and impact on 5 year result

Worksheet	Cell	Description	SOC	Apos	Incr
		Base Case prior to modifications			
SC_arm	Row 64:243	Added in 20 year time horizon (cumulative net cost)			
Apos arm	Row 64:243	Added in 20 year time horizon (cumulative net cost)	£13,955	£16,733	£2,779
Inputs and results		Added in 10 and 20 year net Apos cost to results table			
Inputs and results	G14:K29	Added in 10 and 20 year net Apos cost to sensitivity analysis			
Mortality	ColB:D	tab created, and life tables added from ONS, for males and females aged 65-100 years, from the 2017-2019 time range (avoiding any impact from Covid)	£13,955	£16,733	£2,779
Mortality	E2	Enter percentage of patients who are female (taken from NJR report, 2021) 56.3%			
Mortality	Col E	Calculate weighted average of annual mortality, using percentage female from cell E2			
Mortality	Col F to M	Take calcualtions from probability tab and apply to annual mortality to give monthly transitions	£13,955	£16,733	£2,779
SC_arm	Col B:C	insert new columns			
SC_arm	B2	Add a start age			
SC_arm	Col B	Fill down, giving the age (in whole years) for each month			
SC_arm	Col C	Use Vlook up to reference the mortality transitions for that age			
SC_arm	Col E:BD	Replace all references to mortality in the inputs page with the age dependant mortality transition	£13,579	£16,733	£3,154
Apos arm	Col B:C	insert new columns			
Apos arm	B2	Add a start age - reference the one in SC_arm			
Apos arm	Col B	Fill down, giving the age (in whole years) for each month			
Apos arm	Col C	Use Vlook up to reference the mortality transitions for that age			
Apos arm	Col E:BD	Replace all references to mortality in the inputs page with the age dependant mortality transition	£13,579	£15,983	£2,404
TKR costs_details	B5, Col M:O	Added in calcualtions for weighted averaged of the two TKR surgery costs. Changed TKR cost to weighted average of 2019/20 ref costs, and inflated to 2022/23 price.	£14,274	£16,080	£1,805

TKR costs_details	B7	Changed TKR rehab cost to 2019/20 ref cost inflated to 2022/23	£14,086	£16,058	£1,972
TKR costs_details	B31	Changed first orthopaedic OA to 19/20 ref cost unlifted to 22/23	£14,071	£16,056	£1,985
TKR costs_details	B32	Changed follow-up OA to 19/20 ref cost unlifted to 22/23	£14,150	£16,067	£1,917
Second TKR_detail	B7	changed from 33.5% to 33% based on our reading of the graph, very small impact	£14,108	£16,042	£1,933
Second TKR_detail	B7	changed from 33.5% to 37.8% at 10 years based on extended time horizon.			
Probability calculator	C10	changed from 5 years to 10 years (120 months)	£12,849	£15,288	£2,439
SC_arm	B2	Set start age to 68 (so median TKR age is 70 in line with NJR report)	£12,630	£14,821	£2,190
Apos_arm	Col BG	Added separated OA care costs	£12,630	£14,821	£2,190
Apos_arm	Col BH	Added separated Apos costs	£12,630	£14,821	£2,190
Apos_arm	Col BT:BW	Added in discounted separate Apos costs	£12,630	£14,821	£2,190
Apos_arm	Col CG:CI	Moved total costs columns to the end	£12,630	£14,821	£2,190
Inputs and results	Col G37:N60	Breakdown by care table updated with separated Apos cost	£12,630	£14,821	£2,190
State diagrams		New tab added with state diagram graphs	£12,630	£14,821	£2,190
Probability calculator	Row 12	Added in rate of TKR revisions from NJR	£12,630	£14,821	£2,190
TKR cost_details	Row 27	Added in monthly cost of TKR revisions	£12,630	£14,821	£2,190
Apos costs_detail	A43:B47	Added in gait analysis costs	£12,630	£14,821	£2,190
Probability calculator	B12, C12	TKR revisions revised to run from year 2 only, taking first year from Leal (0.5%)	£12,630	£14,821	£2,190
Inputs and results	D53	this revision given costs and added to year3 plus costs post TKR	£12,982	£15,010	£2,028
Inputs and results	P81:T90	Extend data table for reduction in standard care costs	£12,982	£15,010	£2,028
Inputs and results	P93:V100	Add two way data table for std care costs and % reduction, just for 20 year costs	£12,982	£15,010	£2,028
Inputs and results	AC45:AE58	Add one way table for year 3 monthly cost, include a *-1 column to be consistent for report	£12,982	£15,010	£2,028
Inputs and results	graph	create graph of table above	£12,982	£15,010	£2,028
Probability calculator	B12, C12	TKR revisions revised to run from year 2 only, taking first year from Leal (0.5%)	£12,974	£15,005	£2,032

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

AposHealth for osteoarthritis of the knee

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Group (EAG) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAG assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient experts
- Appendix D: Decision problem from the scope

1 The technology

AposHealth (AposHealth, previously AposTherapy) is a non-invasive device worn on the feet. AposHealth aims to improve the pathological walking patterns of people with knee osteoarthritis, a condition that causes the joint to become painful and stiff. The device consists of a pair of AposHealth shoes with two curved pods (pertupods) on the heel and forefoot of each shoe. The pertupods are positioned and securely attached to tracks on the bottom of the shoe with screws. Positioning of the pertupods is performed by trained healthcare professionals and can be aided by gait analysis software and/or hardware.

The AposHealth 4-step treatment plan takes place over the course of 1 year and consists of an initial patient assessment, personalisation of the device, at-home treatment, and ongoing monitoring. The at-home treatment step involves the user wearing the device for short periods of time during daily activities, for a total of up to 60 minutes per day. The company claims that the device improves biomechanics by redistributing pressure away from affected areas and re-educates the muscles to correct abnormal gait patterns, which can extend to when not actively wearing the footwear.

AposHealth received a CE mark in October 2017 as a class I medical device for knee osteoarthritis. AposHealth was erroneously marked as a class IIa device in the scope.

2 Proposed use of the technology

2.1 Disease or condition

Osteoarthritis is a condition that can affect any joint in the body and is particularly common in weight-bearing joints such as the knees. Knee osteoarthritis is the most common form of osteoarthritis. It occurs as a result of damage to the cartilage in the joint which subsequently undergoes changes as the body attempts to repair the damage. It typically presents with joint

symptoms such as pain and stiffness. Symptoms vary from mild and intermittent, to more persistent or severe.

2.2 Patient group

AposHealth is intended for use by adults aged 16 years and over with knee osteoarthritis. Knee osteoarthritis is more common in women, people living in deprived areas, people aged 45 and over and people who are obese. It is estimated that 1 in 5 people over 45 years have knee osteoarthritis in England and the prevalence of osteoarthritis is increasing. AposHealth is contraindicated for people with balance issues, people who require walking aids and people with especially severe osteoporosis.

2.3 Current management

Treatment of knee osteoarthritis depends on the severity of symptoms. Current treatment options include pharmacological and non-pharmacological treatments. NICE's guideline on the diagnosis and management of osteoarthritis in over 16s recommends tailoring information to the individual needs of people with osteoarthritis, their families, and carers, and ensuring it is in an accessible format.

Non-pharmacological core treatments for osteoarthritis are therapeutic exercise and weight loss (if appropriate), along with information and support. Other non-pharmacological treatment options include manual therapy (such as manipulation, mobilisation or soft tissue techniques), and devices (such as walking aids). NICE's guideline on the diagnosis and management of osteoarthritis in over 16s recommends that devices such as insoles, braces, tape, splints, or supports should not routinely be offered to people with knee osteoarthritis. These interventions should only be used when there is joint instability or abnormal biomechanical loading and therapeutic exercise is ineffective or unsuitable without the addition of an aid or device and the addition of an aid or device is likely to improve movement and function. Pharmacological treatment options include topical and oral non-steroidal anti-inflammatories (NSAIDs) to relieve pain and inflammation. They should be used alongside non-pharmacological treatments and to support therapeutic

exercise. Intra-articular corticosteroid injections should be considered when other pharmacological treatments are ineffective or unsuitable, or to support therapeutic exercise. However, these treatments only provide short term relief and may become less effective as the severity of knee osteoarthritis increases. NICE's interventional procedures guidance on platelet-rich plasma injections for knee osteoarthritis states that this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.

Referral for knee surgery should be considered for people who experience joint symptoms (such as pain, stiffness, reduced function or progressive joint deformity) that have a substantial impact on their quality of life, and non-surgical management is ineffective or unsuitable. Clinical assessment should be used when deciding to refer someone for joint replacement, instead of systems that numerically score severity of disease. NICE's guideline on joint replacement (primary): hip, knee and shoulder recommends offering a choice of partial or total knee replacement (TKR) to people with isolated medial compartmental osteoarthritis. Surgery may not be suitable for some people who are unable, or do not want to undergo surgery.

2.4 Proposed management with new technology

AposHealth is proposed for use by adults aged 16 years and over with knee osteoarthritis who have been offered but not sufficiently benefitted from non-surgical standard care treatment options, in addition or as an alternative to devices or intra-articular corticosteroid injections.

3 Company claimed benefits and the decision problem

Details of the company's claimed benefits and the decision problem from the scope are described in Appendix D. The company has further defined the subgroups in the decision problem table of their evidence submission. These clarifications are described in the following table.

Table 1: Variations to the decision problem proposed by the company

Decision problem	Variation proposed by company	EAG view of the variation
Subgroups	• Unicompartmental OA • Patellofemoral Joint Osteoarthritis (PFJOA) • Anyone who has not responded sufficiently to previous treatments (may not necessarily be at surgical threshold yet), or • People for who there is benefit in delaying surgery • People for who surgery is the only remaining choice.	The EAG agrees that this information provided by the company is for clarification purposes only and does not represent a variation to the scope.

Although not in the scope, the EAG noted that AposHealth functions through adjustments to gait and have included gait analysis outcomes in their evidence review. Recommendations for the use of devices for people with osteoarthritis have been updated since the publication of the scope. See NICE's draft guideline update for the assessment and management of osteoarthritis for further information.

4 The evidence

4.1 Summary of evidence of clinical benefit

The EAG included evidence from 29 publications (15 full-text publications, 9 abstracts associated with the included full texts, and 5 additional abstracts) covering a total of 19 unique studies in its evidence review. These studies comprise 1 randomised controlled trial (RCT), 1 prospective comparative study with a 2 year follow up study, 1 retrospective comparative study, 15 non-comparative studies and 1 meta-analysis which included multiple devices

and was published in poster abstract form. The rationale for the selection of these studies is in section 4.1 and 4.2 of the EAG assessment report.

Table 2: Summary of evidence base

Study	Type of publication	Type of study	Comment
Studies included by both EAG and company			
14 studies	15 full papers (covering 14 studies)	1 RCT, 1 prospective comparative study, a 2-year follow-up study of the prospective comparative study, 4 prospective cohort studies, 8 retrospective cohort studies	RCT: Reichenbach (2020) Prospective comparative study and 2-year follow up: Bar-Ziv (2010) and Bar-Ziv (2013) Prospective cohort studies: Debbi (2015), Elbaz (2014), Goryachev (2011), Haim (2012) Retrospective cohort studies: (Drew (2022), Drexler (2012), Elbaz (2010), Herman (2018), Lador (2013), Lubovsky (2017), Miles (2020), Greene (2022)
Studies in submission excluded by EAG			
2 studies	2 full papers	2 retrospective non-comparative studies	Elbaz (2013) and Haim (2013) were excluded as the populations were not relevant to the decision problem.
Studies not in submission included by EAG			
5 studies	5 poster abstracts	1 meta-analysis, 1 retrospective comparative study, 2 prospective non-comparative studies and 1	Elbaz (2009), Elbaz (2012), Hagen (2018, Van Ginckel (2021) and Veeramachaneni (2016)

		retrospective non-comparative study	

EAG critique of the clinical evidence base

The EAG critically appraised 15 full texts covering 14 studies. Abstracts were not critically appraised by the EAG due to a lack of data. Full critical appraisal of included studies is in section 5.1, 5.2 and Appendix B of the EAG assessment report.

The Biochemical Therapy for Osteoarthritis of the Knee (BIOTOK) RCT compared AposHealth to a sham device. The EAG considered the RCT to be of high quality as the groups were similar at baseline, true randomisation and concealed allocation was used, and the participants were blind to their treatment assignment. Similarly to the RCT, the prospective comparative study also compared AposHealth with a sham device. The initial 8-week study was blinded, and participants were assigned to each group depending on when they could attend the clinic. However, in the 2-year follow up period, participants were unblinded and were permitted to cross over between groups. The EAG stated that the unclear description of participant movement between groups undermined the robustness of the results. The EAG also noted that both comparative studies partially met the decision problem of the scope, as AposHealth was compared to a sham device rather than standard care.

One retrospective cohort study reported the rate of TKR surgery in a group of patients that received AposHealth. The EAG noted that the study authors also reported clinical information for a cohort of patients that elected to undergo TKR and did not receive AposHealth for comparison at baseline only. As the study only compared the groups at baseline, the EAG treated the study as a single-arm observational study.

The remaining 11 included studies were observational with no comparator. The EAG acknowledged that the outcomes reported across studies were relatively consistent, as Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores, SF-36 questionnaire results and gait outcomes were frequently reported. However, they noted that the WOMAC scores reported in the included studies were not all on the same scale and felt that caution should be taken when comparing WOMAC scores between studies and interpreting the evidence. Further detail of the WOMAC scales used in included studies is in Table 7 of the EAG assessment report.

The EAG noted a lack of evidence comparing AposHealth to non-surgical standard care treatments such as manual therapy, walking aids and intra-articular steroid injections. However, they acknowledged that this may be driven by uncertainties in the care pathway making it difficult to design and conduct comparative studies. They also noted the limited evidence relating to the outcome of TKR surgery delay or avoidance and a lack of long-term follow up data beyond 2 years.

Gait analysis

The EAG stated that the correlation between modification of gait parameters and changes in clinical outcomes, such as improvements in pain and function, is not consistently reported across the evidence base. However, 2 studies reported high correlation between changes in gait parameters and improvement in self-evaluation clinical outcome questionnaires. Further details about outcomes and the type of gait analysis equipment used in included studies is in Table 6 of the EAG assessment report.

Pain, function and stiffness

The clinical evidence showed that AposHealth consistently reduced pain, function limitation and stiffness when compared to baseline measurements. Pain, function and stiffness were primarily measured using the WOMAC score. One observational cohort study used the Oxford Knee Score (OKS) as a measure of pain and found an improvement after treatment with AposHealth

at 6 months and 2 years. However, 1 prospective comparative study used the aggregated locomotor function (ALF) score as a measure of function and found that scores did not differ between groups after 2 years. Further details of pain, stiffness and function outcomes for included studies is in section 5.3.2 and Table 8 of the EAG assessment report.

Quality of life and patient satisfaction

Quality of life outcomes were consistently reported in the evidence base, measured by the SF-36 questionnaire. The EAG noted that there was some evidence that AposHealth can improve quality of life for people with knee osteoarthritis, with stronger evidence for improvements to physical aspects and weaker evidence for improvements to emotional aspects. Further details of quality of life and patient satisfaction outcomes for included studies is in section 5.3.3 and Table 9 of the EAG assessment report.

Surgery avoidance or delay

The EAG stated that there was extremely limited, low-quality evidence that AposHealth can delay surgery for people with knee osteoarthritis. The EAG also consulted clinical experts who said that there were insufficient long-term data to determine how long AposHealth can delay TKR, or whether it can be avoided altogether. A patient expert stated they have been 'avoiding' surgery for approximately 3 years by using AposHealth to manage their symptoms. The EAG noted that this patient expert expressed personal wishes to avoid surgery and clinical experts agreed that this would be the case for a proportion of people with knee osteoarthritis.

The company emphasised the potential of AposHealth for altering and improving gait patterns of people with knee osteoarthritis and stated an assumption that this is the reason patients may be able to delay or avoid TKR. The EAG acknowledged that there is some evidence that gait is modified by AposHealth. However, only 2 studies include surgery avoidance as the primary outcome and neither explored the relationship between gait

modification and surgery avoidance or delay. Further details of surgery avoidance or delay is in section 5.3.4 of the EAG assessment report.

Reduction in the use of standard care or conventional therapies

The EAG stated that there was limited, low quality evidence that AposHealth can reduce the use of pain medication, physical therapy and other non-pharmacological interventions. Further details about reduction in standard care use are in section 5.3.5 of the EAG assessment report.

EAG summary of the clinical evidence

The EAG were satisfied that there were no safety concerns for AposHealth, and acknowledged that the clinical evidence showed improvement in outcomes such as relief of knee osteoarthritis symptoms and quality of life with AposHealth, which was supported by patient and clinical expert experiences. However, the EAG noted the lack of long-term follow up reporting regarding rates of delay or avoidance of TKR that extend beyond 2 years and considered this an important gap.

Overall, the EAG felt that AposHealth has the potential to be an effective treatment in particular subgroups of people with knee osteoarthritis, such as people who want to avoid a TKR or people who cannot have a TKR. However, the EAG also felt that the current evidence base was insufficient to address the decision problem and more research is needed before AposHealth can be integrated into clinical practice.

Table 3: Key comparative studies

Study and design	Participants/ population	Intervention & comparator	Outcome measures and follow up	Results	Withdrawals	Funding	EAG Comments
Reichenbach (2020) **Design**: Single blinded RCT **Location**: Switzerland	**Participants:** 220 adults diagnosed with symptomatic unilateral and bilateral medial compartmental knee OA. **AposHealth**: 51 females (45.9%) mean age (years) 65.3 ± 9.2 **Control**: 53 females (48.6%) mean age (years) 65 ± 9.3	**Intervention:** AposHealth daily use for 24 weeks **Comparator:** Sham device near identical to AposHealth shoe. The biomechanical elements were encased in a transparent outsole so they were visible but didn't create a convex surface. Daily use for 24 weeks	**Follow ups** at **4, 8, 12, 16, and 24 weeks** after the start of treatment. **Outcomes**: WOMAC SF-36 health survey	WOMAC scores at 24 weeks: Pain subscore between group difference -1.3 (p<0.001) Physical function subscore between group difference -1.1 (p<0.001) WOMAC stiffness sub score between group difference -1.4 (p<0.001) WOMAC global score between group difference -1.2 (p<0.001).	1 participant in the AposHealth group refused treatment. 7 participants in the AposHealth group and 13 in the control group discontinued treatment during follow-up. Primary outcome data at 24 weeks was collected for 109 participants (98.2%) in the AposHealth group and	The trial was funded by the Mäxi Foundation. Apos Medical Assets provided AposHealth and control footwear, and provided technicians trained to install and calibrate the pods without charge.	A controlled single blinded comparison of AposHealth against a sham device whereby patients were also allowed to use other physical and medical therapies. The EAG noted that this study partially meets the scope as AposHealth is compared to a sham device and not standard care. The paper notes that while results are statistically significant for the primary outcome, they cannot be certain of the clinical importance of the overall results.

				No statistically significant difference between groups in SF-36 mental and physical subscores after 24 weeks.	104 participants (95.4%) in the control group.		
Bar-Ziv (2010) **Design:** Prospective comparative study **Location**: Israel	**Participants:** 57 adults diagnosed with symptomatic bilateral medial compartmental knee OA. **AposHealth**: 23 females (74.2%) mean age (years) 64 ± 8.1 **Control**: 19 females (73.1%)	**Intervention:** AposHealth daily use for 8 weeks **Comparator:** Sham device identical to AposHealth shoe minus the biomechanical elements daily use for 8 weeks	**Follow ups** at **4 and 8 weeks** after the start of treatment. **Outcomes**: WOMAC ALF SF-36 health survey KSS	Statistically significant difference in WOMAC pain, stiffness, function and global scores (all p<0.001) in the AposHealth group compared to the sham device group at 8 weeks. Statistically significant difference in the ALF score, SF-36 and KSS (all p<0.001) for the	3 participants were lost to follow up.	The study was sponsored by Assaf-Harofeh Medical Center. Funding information was unavailable.	The EAG noted that the study partially meets the scope as AposHealth is being compared against a sham device rather than standard care. The study was not randomised as participants were assigned based on when they were able to attend the clinic. There is no mention of any other care patients might be receiving.

	mean age (years) 66 ± 7.8			AposHealth group compared to the sham device group at 8 weeks.			
Bar-Ziv (2013) **Design**: 2 year follow up of prospective comparative study (Bar-Ziv 2010) **Location**: Israel	**Participants:** 56 adults diagnosed with symptomatic bilateral medial compartmental knee OA. **AposHealth**: 30 females (75%) mean age (years) 64.1 ± 7.5 **Control**: 11 females (68.7%) mean age (years) 69 ± 8.6	**Intervention:** AposHealth daily use for 12 weeks **Comparator:** Sham device identical to AposHealth shoe minus the biomechanical elements daily use for 12 weeks	**Follow up** at **6,12, and 24 months** from the start of treatment for the AposHealth group, and at 24 months only for the control. **Outcomes**: WOMAC ALF SF-36 KSS	Statistically significant difference in WOMAC pain, stiffness and function (all p<0.001) in the AposHealth group compared to the sham device group at 2 years. Statistically significant difference for the ALF score, KSS score and the SF-36 score (all p<0.001) in the AposHealth group compared to	2 participants were lost to follow up in the AposHealth group as 1 declined to participants and 1 underwent a TKR. 7 participants were lost to follow up in the control group due to 1 death, 1 declined to participant and 5 TKRs.	The journal article states that the study was not funded in any way.	The EAG noted that the study partially meets scope as AposHealth is being compared against a sham device rather than standard care. However, patients could use standard care available to them, although this was not controlled for or reported. There was no blinding or randomisation in this phase of the trial, in contrast to the initial 8 week trial period (Bar-Ziv 2010). Additionally, participants underwent unspecified crossover between trial arms during the 2 year follow-up period. The EAG also noted that the follow up schedules for each group were different.

				the sham device group at 2 years.			
Abbreviations used: ALF – aggregated locomotor function; EAG – external assessment group; KSS – knee society score; OA - osteoarthritis; RCT – randomised controlled trial; SF-36 – short form health survey - 36; WOMAC – Western Ontario and McMaster University Osteoarthritis Index.							

4.2 Summary of economic evidence

The company conducted a combined search for clinical and economic evidence, identifying 48 records in total, however no economic evidence was identified. The EAG also undertook a combined search but did not identify any economic studies relevant to the decision problem of the scope.

Company decision model

The company submitted a Markov decision model comparing standard care to standard care with AposHealth which is illustrated in the following figure. The company model used an NHS perspective, with a 3.5% discount rate and 1-month cycles. The model is based on movement of patients from standard care for osteoarthritis (with or without AposHealth) to TKR, and subsequently to a TKR of the other knee.

The results were reported at a 2 year and 5-year time horizon, which were based on the duration of available evidence. The EAG considered the model comparator and structure appropriate for the decision problem. However, they felt that it was important to explore the longer-term impact despite the lack of evidence beyond 2 years, as osteoarthritis is a chronic condition. Further details about the model structure and assumptions are in section 9.2.1 and Table 11 of the EAG assessment report.

Revised company 10-year model

Following queries from the EAG about the time horizon, the company submitted an additional model with an extended 10-year time horizon and some altered parameters. The model structure and main assumptions remained unchanged. The key changes were a change in mortality calculations, inclusion of TKR revisions after year 2**,** and a reduction of follow up appointments with AposHealth from 2 per year to 1 per year after year 5.

Figure 1: Model structure

DIAGRAM 1. STANDARD CARE ARM

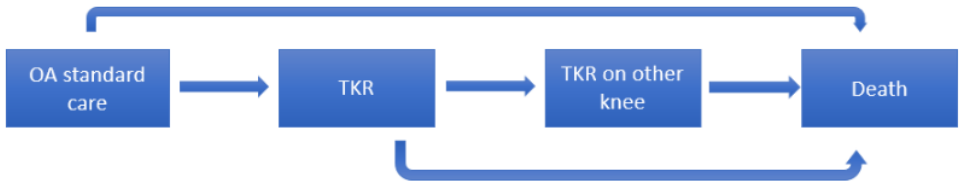
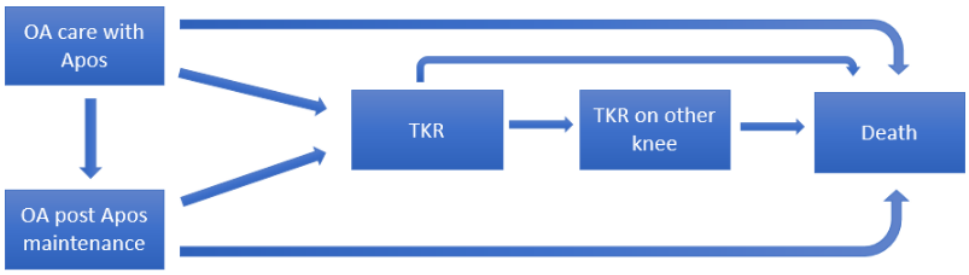


DIAGRAM 2. APOS ARM



Model parameters

Key clinical parameters included in the company model were the rate of surgery for TKR, subsequent TKR on the other knee, post-operative complications and mortality. The EAG noted that the rates of surgery for TKR are reported in only a limited number of selected papers.

The EAG considered most of the company estimates to be reasonable but made a few alterations and conducted sensitivity analyses to understand the impact of the uncertainty around the model parameters. The changes made by the EAG are in the following table, and further details can be found in section 9.2.2 and Table 14 of the EAG assessment report.

Table 4: Parameters used in the company model and changes made by the EAG

Parameter	Company value	EAG value	EAG comments and sources

Average patient starting age (years)	Not included (variable mortality added for 10-year model)	68	The EAG included a start age based on the mean age of those receiving a primary knee replacement (70 years, NJR annual report 2021), and the time for 50% of the standard care arm to have received a knee replacement (2 years).
Monthly probability of TKR (rates are constant over time, and constant during and post Apos delivery period)			
OA standard care to TKR	3.282%	No change	Taken from McHugh (2011).
OA care with Apos to TKR	0.724%	No change	Taken from Green (2022)
TKR on contralateral knee	0.500% per month (33.5% identified from a graph in Sander 2017 over 5 years)	0.395% per month	The EAG obtained a slightly lower figure of 33% from the graph in Sanders (2017) for a 5-year period. As the EAG extended the time horizon, 37.8% over 10 years was used for the EAG model.
Percent of patients who have a prior TKR	33.6%	No change	Taken from Chitnavis (2000).
Monthly probability of death			
Death	0.067% (variable rate in 10 year model) from Leal (2022)	Variable rate	The EAG used life tables from the Office for National Statistics 2017-19 (pre COVID-19) to introduce variable mortality as the cohort progresses through an extended model.
Adverse events			
Post-operative complications (of those receiving TKR)	6%	No change	Taken from Leal (2022).

Revision during year 1 (of those receiving TKR)	0.5%	No change	Taken from Leal (2022).
Adverse events during year 2			The EAG noted that these are not explicitly calculated, but costs are derived to include revisions.
Adverse events during years 3+	0.34% (10-year model only)	0.32%	The EAG calculated the monthly rate of revisions from the National Joint Registry cumulative revision rate of 6.43% at 17 years.

Costs and resource use

The company provided a cost for the AposHealth system of £875 excluding VAT. Training is provided by AposHealth free of charge. The company model assumed that each trained member of staff, typically a physiotherapist, would treat 250 patients per year, resulting in a training cost of £1.31 per patient. The EAG felt that the company justification of this volume within a year was optimistic, however, the training would last for longer than one year, so the cost was accepted by the EAG.

Gait analysis tools or equipment may be used when calibrating the AposHealth shoes or assessing a person's gait. However, the company advised that they are not necessary and have not been included in the company's modelled costs. The EAG noted that gait analysis equipment was described in the clinical evidence studies and included an extra scenario resulting in an additional £24.30 added to the initial AposHealth evaluation appointment.

The company also provided the costs of standard care for osteoarthritis before and after TKR. The EAG supported these costs, but also identified alternative published data to inform an additional scenario for standard care costs before and after TKR. Further details about standard care costs used in the EAG base case and additional scenario is in Table 17 of the EAG assessment

report. The company model assumed a 15% reduction in standard care costs based on published studies showing a reduction in pain and function limitation, and unpublished audits that reported resource use. The EAG felt that the published studies showed limited evidence of reductions in standard care. The results from one unpublished study were not used in the model, and the EAG noted that they were not able to fully critique the other unpublished study due to limited reporting of methodology.

TKR costs in the company model were taken from NHS best practice tariffs. The EAG used alternative NHS Reference Cost data from 2019/20 (to avoid the impact of COVID-19) and inflated to 2022/2023, which only had a small impact on the results. The company also identified follow up costs after TKR from a study using data from the National Joint Registry. Total costs after TKR were calculated as costs following TKR minus costs pre-TKR.

In response to company fact check comments, the EAG produced an additional scenario exploring changes in the likelihood of TKR as patients age based on the National PROMs data (NHS Digital (2019-2020), which was highlighted by the company. The EAG did not include this as part of the base case due to the uncertainties of how this may translate to the modelled population, or the different impact on the standard care and AposHealth arms of the model. Further details about costs used in the company model and EAG changes are in section 9.2.2 and Table 16 of the EAG assessment report.

Results

Both the company base case and the EAG base case were cost saving for AposHealth at 5 years, and the company 10-year model was also cost saving at 10-years. The EAG base case results show that treatment with AposHealth would lead to a cost saving of £1,958 per patient in comparison with standard care over a 5-year time horizon. However, the EAG base case results show that treatment with AposHealth would be cost incurring over a 10-year time horizon by £46 and would also be cost incurring over a 20-year time horizon

by £2,032. Further details of the company and EAG base case results are in section 9.3.1 of the EAG assessment report.

A summary of the results from the company base case and the EAG base case at different time horizons is presented in the following tables.

Table 5: Detailed summary of company and EAG base case results

	Company result						EAG result					
	5-year time horizon			10-year time horizon			5-year time horizon			20-year time horizon		
	Technology	Comparator	Cost saving per patient	Technology	Comparator	Cost saving per patient	Technology	Comparator	Cost saving per patient	Technology	Comparator	Cost saving per patient
AposHealth provision	£1,292		-£1,292	£1,355		-£1,355	£1,288	£0	-£1,288	£1,531	£0	-£1,531
Care prior to total knee replacement	£4,076	£2,584	-£1,492	£5,893	£2,805	-£3,089	£3,829	£2,432	-£1,397	£6,999	£2,710	-£4,289
Total knee replacements and 2-year follow up	£2,915	£7,557	+£4,642	£4,759	£9,449	+£4,690	£2,953	£7,596	+£4,643	£6,475	£10,264	+£3,789
Total	**£8,283**	**£10,141**	**+£1,858**	**£12,007**	**£12,254**	**+£247**	**£8,069**	**£10,027**	**+£1,958**	**£15,005**	**£12,974**	**-£2,032**

Table 6: Summary of company and EAG base case results

	Cost saving per patient		
Time horizon	**Company 5-year time horizon**	**Company 10-year extended time horizon**	**EAG Base Case**
5 years	+£1,858	+£1,886	+£1,958
10 years		+£247	-£46
15 years			-£1,396
20 years			-£2,032

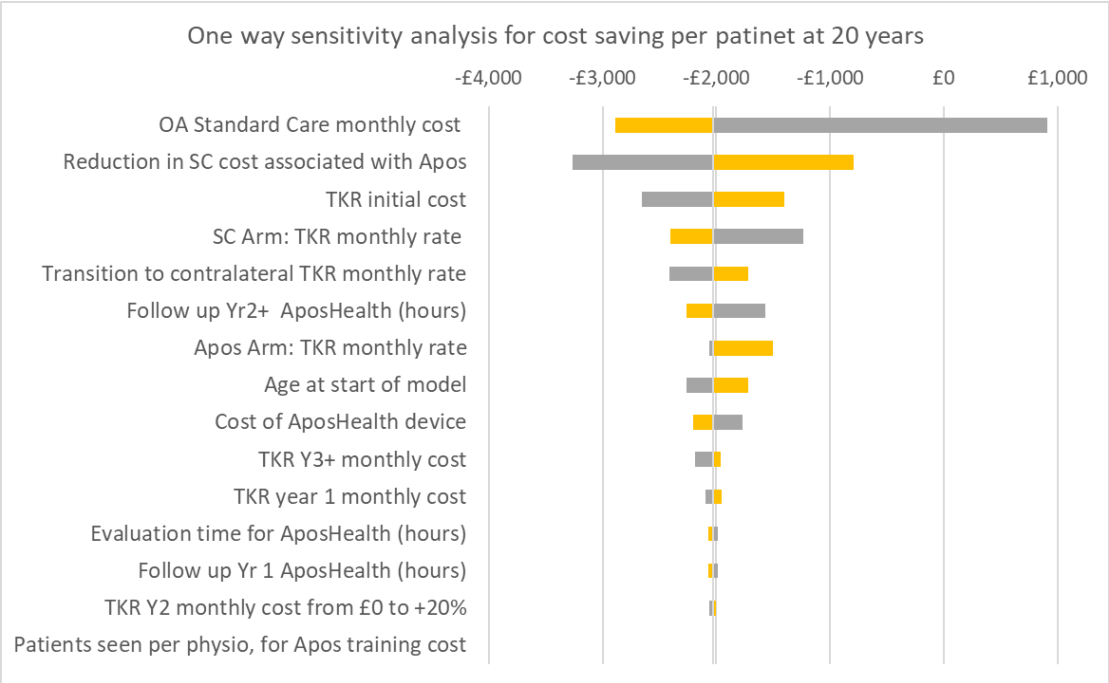
The EAG noted that cost savings primarily come from a reduction in TKR and subsequent complications and follow up. The EAG therefore felt that the results should be treated with caution as the existing evidence for delay to surgery is only over 2 years, and the model may not include all costs that could be considered over a longer duration, and the direction of impact is uncertain.

Sensitivity analysis

The company carried out deterministic sensitivity analysis with both one- and two-way tables for key parameters, which were varied by 20%. The EAG repeated this with the amended model, extended it to 20 years and added additional parameters and ranges. Further details are in Appendix D of the EAG assessment report.

For AposHealth vs. standard care the key cost drivers were standard care for osteoarthritis before TKR, reduction in standard care costs due to AposHealth and transitions to TKR. The EAG found that the cost of standard care prior to TKR was the only parameter that made the sensitivity analysis cost saving at 20 years. The tornado diagram in the following figure shows the importance of the cost of standard care prior to TKR, and standard care reduction due to AposHealth. The EAG noted that both of these parameters have considerable uncertainty attached. Further details of the EAGs sensitivity analysis results are in section 9.3.2 of the EAG assessment report.

Figure 1: Tornado diagram for EAG base case at 20 years



Additional scenario results

The EAG additional scenario that included gait analysis equipment showed a small change at 20 years and was cost incurring by £2,056 compared to £2,032 without the equipment.

The EAG additional scenario using alternative standard care cost for before and after TKR resulted in a change from cost incurring to cost saving at 20 years, with a total cost saving due to AposHealth of £879. The EAG noted that this should be considered with caution as the alternative standard care costs were lower than costs reported in other studies, relied on patient recall and were only related to the costs of a primary TKR.

The EAG also considered a scenario for people that do not want or are unable to have a TKR by setting movement of people having a TKR to 0%. Using the EAG base case with a 15% reduction in standard care costs, AposHealth was cost incurring at 5 years by £538 and was cost incurring at 20 years by £40. However, if reduction in standard care use was 20%, AposHealth becomes cost saving by £259 at 5 years and £701 at 20 years.

The EAG additional scenario exploring variation in the likelihood of TKR as patients age resulted in treatment with AposHealth being cost incurring by £1,995 at 20 years, compared to £2,032 in the EAG base case.

EAG summary of economic evidence

The EAG and company models have some differences but have approximately similar findings at 5 and 10 years. The EAG 20-year model showed that while the standard care arm rapidly moved to TKR, there was a slower move to TKR in the AposHealth arm. This means that the costs of TKR are still accumulated in the AposHealth arm of the model for most patients, but over a longer time-period.

The EAG felt that there is not a clear case for AposHealth to be cost saving when compared to standard care in the long-term, due to the limited evidence for delaying surgery. However, the EAG noted that there are potential system benefits for short-term waiting list reductions.

5 Ongoing research

The company submission identified 7 ongoing or unpublished studies, 1 of which has now been which has now been published in the Journal of Orthopaedic Experience and Innovation (Greene, 2022). One of the studies (NCT04732962) in the company submission was also identified by the EAG. The EAG identified 4 additional NCT registered trials, although they were marked as either ‘terminated’ or ‘unknown status’. Further details about these trials are in section 8.2 and Table 10 of the EAG assessment report.

The remaining 5 studies identified by the company included 2 unpublished studies that were not planned for publication. One reported research proposals relating to AposHealth, and the other is a report on a study that assessed the use of AposHealth for people with knee osteoarthritis and lower back pain. Two studies are reports of patient satisfaction or audit data, and one study is a summary of data on file evidencing surgery avoidance rates, which the EAG agreed was relevant to the economic model. The EAG

acknowledged the relevance of the 5 studies, but as they were not peer-reviewed and/or due for publication, did not consider them to be robust evidence.

6 Issues for consideration by the Committee

Clinical evidence

The clinical evidence for AposHealth comes from 1 RCT, 1 prospective comparative study and 12 observational studies. This evidence shows that users of AposHealth experience improvement in pain, function, stiffness and quality of life outcomes, which is supported by the experience from clinical and patient experts.

Outcomes reported across studies were relatively consistent, as WOMAC scores, SF-36 questionnaire results and gait outcomes were frequently reported. However, WOMAC scores reported in the included studies were not all on the same scale. The EAG felt that caution should be taken when comparing WOMAC scores between studies and interpreting the evidence.

There is a lack of evidence comparing AposHealth to non-surgical standard care treatments such as manual therapy, walking aids and intra-articular corticosteroid injections. However, it should be noted that there are inconsistencies in the NHS standard care pathway that may make it difficult to identify clear comparators.

The 2 comparative studies both compared AposHealth with a sham device, and only partially met the scope. The recently updated NICE guidelines for the assessment and management of osteoarthritis agreed that further research is needed on devices (including footwear) and recognises that the difficulty in designing an appropriate sham device is a significant limitation for studies involving shoe devices.

Additionally, there is limited evidence relating to TKR avoidance or delay, with long-term evidence up to 2 years only.

Cost evidence

No published evidence relevant to the decision problem of the scope was identified.

The company base case and EAG base case were similar at 5 and 10 years, with both models were cost saving at 5 years, and the EAG's model only slightly cost incurring at 10 years. However, the EAG's base case at 20 years was cost incurring by £2,032. Cost savings primarily come from a reduction in TKR and subsequent complications and follow up. The evidence for delay to surgery is only over 2 years, and the model may not include all costs that could be considered over a longer duration.

Key cost drivers in the sensitivity analyses included standard care for osteoarthritis before TKR and reduction in standard care costs due to AposHealth and transitions to TKR. Clinical experts have noted the inconsistencies in the NHS standard care pathway and the EAG exploratory analysis suggested that balancing AposHealth provision costs with reduced health care costs is plausible if clinical outcomes are sufficiently improved over the long term. However, there is insufficient evidence to go beyond an initial exploration.

Other considerations

The EAG noted that AposHealth may have potential system benefits for short-term waiting list reductions for people referred for TKR. In May 2022 the British Orthopaedic Association stated that a large number of patients on orthopaedic waiting lists have osteoarthritis and are waiting for surgery. Clinical experts stated that surgery waiting times should be approximately 18 weeks, but can often vary between 6 months to 2 years.

The likely position of AposHealth in the NHS care pathway is still unclear. Clinical experts noted a lack of standardisation in the application of the current knee osteoarthritis pathway, as patient preference is key in determining which patients will have surgery. Clinical experts also noted that the NHS is a single treatment pathway and were unsure if patients would need to delay referral to

surgical waiting lists to receive the treatment. The EAG did acknowledge that AposHealth may provide an effective treatment for people who have a personal preference to avoid TKR surgery or a co-morbidity that means they are not suitable TKR surgery.

7 Authors

Amy Barr, technical analyst

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Kimberley Carter, technical adviser

NICE Medical Technologies Evaluation Programme

October 2022

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- O'Connell S, et al. AposHealth for osteoarthritis (OA) of the knee (September 2022)

B Submissions from the following sponsors:

- AposHealth

C Related NICE guidance

- Osteoarthritis: care and management (update). NICE clinical guideline GID-NG10127 (Expected publication date 19 October 2022). Available from www.nice.org.uk/guidance/indevelopment/gid-ng10127
- Osteoarthritis: care and management. NICE clinical guideline CG177 (2020). Available from www.nice.org.uk/guidance/CG177
- Joint replacement (primary): hip, knee and shoulder. NICE guideline NG157 (2020). Available from https://www.nice.org.uk/guidance/ng157
- Platelet-rich plasma injections for knee osteoarthritis. NICE interventional procedure guidance IPG637 (2019). Available from www.nice.org.uk/guidance/IPG637

D References

Please see EAG assessment report for full list of references.

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Dr Toby Smith

Associate Professor in Physiotherapy, University of East Anglia

Ms. Robyn Hickey

First Contact Physiotherapist/ AposHealth Certified Senior Physiotherapist, Circle Integrated Care

Mr Chinmay Gupte

Consultant Orthopaedic Surgeon, Imperial College London

Professor Adewale Adebajo

Consultant Rheumatologist, Barnsley Hospital NHS Foundation Trust

Mr. Alistair Shaw

Clinical Director and Chartered Physiotherapist, Integrated Clinical Excellence Limited

Mr. Michael Kelly

Orthopaedic Surgeon, North Bristol NHS Trust

Michelle Phillips

Physiotherapist, Mid and South Essex Integrated Care Board

For full details, please see the expert adviser questionnaire (EAQ) responses which are included in the committee pack.

Appendix C: Comments from patient experts

Advice and information were sought from patient experts who have experience with the technology. Please see the patient expert statements included in the pack for full details.

William Oxlade

Patient expert

Susan Field

Patient expert

Appendix D: Claimed benefits and decision problem from scope

The benefits to patients claimed by the company are:

- Improved quality of life due to reduced pain and improved joint function
- Reduced need for knee replacement surgery

The benefits to the healthcare system claimed by the company are:

- Cost savings as a result of reduced need for conventional therapies and associated appointment costs for physiotherapy, knee braces, orthotic devices, joint injections, and pharmacological treatments
- Increased operating and facilities resources due to reduced need for knee replacement surgery and associated post-operative hospital stay
- Reduced waiting lists for surgical treatments
- Increased patient compliance and engagement due to ease of use of the technology

Population	Adults aged 16 years and over with knee osteoarthritis who have been offered but not sufficiently benefited from non-surgical standard care treatment options, including education and advice; exercise and manual therapy; weight loss (for people who are overweight); and pain relief (oral, topical, or transdermal).
Intervention	AposHealth alone or in addition to non-surgical standard care
Comparator(s)	Non-surgical standard care treatment options, including but not limited to: • Devices (such as supports, splints and braces) • Intra-articular corticosteroid injections

Outcomes	The outcome measures to consider include:
	• measures of treatment effectiveness
	  ○ patient reported outcome measures (for example, the Western Ontario and McMaster Universities Osteoarthritis Index and the Oxford Knee Score)
	  ○ STEADI assessment
	  ○ mobility
	  ○ avoidance of knee replacement
	  ○ avoidance of secondary care referral
	  ○ health-related quality of life (for example, measured by the SF-36)

	• measures of resource use
	  ○ health care use (for example, use of corticosteroid injections, analgesic use, number of physiotherapy sessions, and other healthcare appointments)
	  ○ surgical intervention - knee replacement
	  ○ surgical intervention - other
	• device-related adverse events	

Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	
Subgroups to be considered	• People for whom knee replacement is recommended • People who do not want, or cannot have surgical intervention	
Special considerations, including those related to equality	AposHealth is intended for people with knee osteoarthritis. The technology is contraindicated in people who have severe imbalance or vertigo issues. The technology is also not suitable for people considered at high risk of falls or those with severe osteoporosis. The technology should be worn for at least an hour a day so may not be suitable for people with very limited mobility or those who use walking aids to get around at home, depending on clinical judgment. Osteoarthritis is more common in people who are older, in women and in people with obesity. One meta-analysis conducted in North America found that pain severity and disability is higher for people with an African family background compared with people with a European family background. Age, sex, disability and race are protected characteristics.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Not applicable	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

AposHealth for knee osteoarthritis

1 Technology

1.1 Description of the technology

AposHealth device

AposHealth (AposHealth, previously AposTherapy) is a non-invasive foot-worn device which aims to improve the pathological walking patterns of people with knee osteoarthritis, a condition that causes the joint to become painful and stiff.

The device consists of a pair of AposHealth shoes with two curved pods (pertupods) on the heal and forefoot of each shoe. The pertupods are positioned and securely attached to tracks on the bottom of the shoe with screws. Pertupods are available in different sizes and levels of hardness. The height can be changed by adding spacers and weight can be increased by adding weighted discs. Gait analysis software is used by trained healthcare professionals to position the pertupods on the device.

The AposHealth shoes are available with a Velcro fastening, or with a lace fastening depending on the person's hip flexibility, finger dexterity, foot width and preference.

AposHealth treatment plan

The AposHealth treatment plan consists of 4 steps over a 1-year treatment period:

- Step 1: initial assessment. An AposHealth trained healthcare professional assesses in detail the patient's movement patterns (computerised gait analysis). The gait analysis provides parameters of gait (step lengths, velocity and single limb support) that form objective, functional outcome measures. In addition, patients usually complete the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index (a disease-specific tool used for people with knee osteroarthritis to measure physical function, pain, and stiffness in the past 48 hours), the SF-36 (a widely used generic measure of health-related quality of life), and the Stopping Elderly Accidents Deaths and Injuries (STEADI) assessment (an assessment to evaluate the risk of falls). This can be done in a clinic or remotely using a smartphone application.

- Step 2: personalised device and treatment programme. After the initial assessment, the trained healthcare professional personalises the pair of AposHealth foot-worn devices by calibrating the under sole pods to the patient's needs and prescribes a personalised programme for the patient.

- Step 3: treatment. Patients wear the device for a short period during the day (see Table 1), while carrying out usual daily activities either at home or at work.

- Step 4: ongoing monitoring. Patients will undergo up to 4 follow-up consultations over the year. This includes a retest of their computerised gait analysis and questionnaires which were done during the initial consultation. Combined, these provide a decision-supporting tool to determine whether or not to change the device’s calibration or adjust the treatment plan. Follow ups are usually done face-to-face but may be done remotely.

Table 1 – Recommended daily time to wear AposHealth

Week number	Time spent wearing the AposHealth device per day	Time spent walking or standing in the AposHealth device per day
1	30 minutes	6 minutes
2	40 minutes	8 minutes
3	50 minutes	10 minutes
4	60 minutes	12 minutes

The outcome measures from the gait analysis and questionnaires are fed into the AposHealth clinical tracking system which processes them and can be graphically presented to the patient, presented to the referring health care provider, and used for assessment of effectiveness of treatment.

The company claims that the technology is the first home-based non-invasive treatment for people with knee osteoarthritis based on 2 biomechanical principles. The device improves biomechanics by redistributing pressure away from affected areas and thus reducing knee pain. On a neuromuscular level, it re-educates the muscles and can correct abnormal gait patterns, which can extend to when not actively wearing the footwear.

AposHealth is not suitable for people who have unexplained recurrent falls, people who experience balance problems and need indoor walking aids, and people with especially severe osteoporosis.

1.2 Relevant diseases and conditions

The scope of this evaluation is for using AposHealth for treating knee osteoarthritis. Knee osteoarthritis is the most common form of osteoarthritis. It typically presents with joint symptoms such as pain and stiffness. Symptoms vary from mild and intermittent, to more persistent or severe. The company

claims the device can treat hip, lower back, and ankle pain but this is not the focus of this scope.

Knee osteoarthritis is more common in women, people living in deprived areas, people aged 45 and over and people who are obese. It is estimated that 1 in 5 people over 45 years have knee osteoarthritis in England. The prevalence of osteoarthritis is increasing. Between 1 January 2018 to 30 December 2020, The National Joint Registry for England, Wales, Northern Ireland and the Isle of Man recorded 226,350 primary total knee replacements. Osteoarthritis was given as a documented indication for surgery in 97.4% of these cases.

1.3 Current management

Treatment of knee osteoarthritis depends on the severity of symptoms. Current treatment options include pharmacological and non-pharmacological treatments. NICE's guideline on the care and management of osteoarthritis recommends assessing the effect of osteoarthritis using a holistic approach. Healthcare professionals should ensure people with knee osteoarthritis have access to accurate verbal and written information.

Non-pharmacological treatment options include prescribed exercise to improve function and mobility, interventions to achieve weight loss for people who are obese or overweight, and devices (such as supports, splints, and braces) for people with biomechanical joint pain or instability. Healthcare professionals should consider the use of transcutaneous electrical nerve stimulation (TENS) as an adjunct to core treatments for pain relief.

Pharmacological treatment options include medications and corticosteroid injections to relieve pain and inflammation. However, these treatments may become less effective as the severity of knee osteoarthritis increases. Topical non-steroidal anti-inflammatory drugs and topical capsaicin should be considered as an adjunct to core treatments for pain relief. NICE's interventional procedures guidance on platelet-rich plasma injections for knee osteoarthritis states that this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.

Referral for knee surgery should be considered for people who experience joint symptoms (pain, stiffness and reduced function) that have a substantial impact on their quality of life, and have been offered, or are refractory to, the core (non-surgical) treatment options. NICE's guideline on joint replacement (primary): hip, knee and shoulder recommends offering a choice of partial or total knee replacement to people with isolated medial compartmental osteoarthritis. Surgery may not be suitable for some people who are unable, or do not want to undergo surgery.

1.4 Regulatory status

AposHealth received a CE mark in October 2017 as a class IIa medical device for knee osteoarthritis.

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Improved quality of life due to reduced pain and improved joint function
- Reduced need for knee replacement surgery

The benefits to the healthcare system claimed by the company are:

- Cost savings as a result of reduced need for conventional therapies and associated appointment costs for physiotherapy, knee braces, orthotic devices, joint injections, and pharmacological treatments
- Increased operating and facilities resources due to reduced need for knee replacement surgery and associated post-operative hospital stay
- Reduced waiting lists for surgical treatments
- Increased patient compliance and engagement due to ease of use of the technology

2 Decision problem

Population	Adults aged 16 years and over with knee osteoarthritis who have been offered but not sufficiently benefited from non-surgical standard care treatment options, including education and advice; exercise and manual therapy; weight loss (for people who are overweight); and pain relief (oral, topical, or transdermal).
Intervention	AposHealth alone or in addition to non-surgical standard care
Comparator(s)	Non-surgical standard care treatment options, including but not limited to: • Devices (such as supports, splints and braces) • Intra-articular corticosteroid injections

Outcomes	The outcome measures to consider include:
	• measures of treatment effectiveness
	  ○ patient reported outcome measures (for example, the Western Ontario and McMaster Universities Osteoarthritis Index and the Oxford Knee Score)
	  ○ STEADI assessment
	  ○ mobility
	  ○ avoidance of knee replacement
	  ○ avoidance of secondary care referral
	  ○ health-related quality of life (for example, measured by the SF-36)
	• measures of resource use
	  ○ health care use (for example, use of corticosteroid injections, analgesic use, number of physiotherapy sessions, and other healthcare appointments)
	  ○ surgical intervention - knee replacement
	  ○ surgical intervention - other
	• device-related adverse events

Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	• People for whom knee replacement is recommended • People who do not want, or cannot have surgical intervention
Special considerations, including those related to equality	AposHealth is intended for people with knee osteoarthritis. The technology is contraindicated in people who have severe imbalance or vertigo issues. The technology is also not suitable for people considered at high risk of falls or those with severe osteoporosis. The technology should be worn for at least an

	hour a day so may not be suitable for people with very limited mobility or those who use walking aids to get around at home, depending on clinical judgment. Osteoarthritis is more common in people who are older, in women and in people with obesity. One meta-analysis conducted in North America found that pain severity and disability is higher for people with an African family background compared with people with a European family background. Age, sex, disability and race are protected characteristics.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Not applicable	

3 Related NICE guidance

Published

- Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain (2021) NICE guideline NG193.
- Joint replacement (primary): hip, knee and shoulder (2020) NICE guideline NG157.
- Platelet-rich plasma injections for knee osteoarthritis (2019) NICE interventional procedures guidance IPG637.
- Osteoarthritis: care and management (2014) NICE guideline CG177 (currently being updated, publication expected October 2022.

In development

There is no related guidance in development for this technology.

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- Bedfordshire Clinical Commissioning Group
- British Orthopaedic Association
- British Society for Rheumatology
- Chartered Society of Physiotherapists
- Mid Essex Clinical Commissioning Group
- Primary Care Rheumatology Society
- South East London Clinical Commissioning Group

4.2 Patient

NICE's Public Involvement Programme contacted the following organisations for patient commentary and asked them to comment on the draft scope:

- Arthritis Action
- Arthritis and Musculoskeletal Alliance (ARMA)
- British Orthopaedic Association Patient Liaison Group
- Dystonia Society
- Lindsay Leg Club Foundation
- Versus Arthritis

Adoption report: MTG570 AposHealth for osteoarthritis of the knee

Summary

Adoption levers identified by contributors

- Non-invasive.
- Provides an alternative treatment option where other treatments have been exhausted. Especially if surgery is unsuitable and not wanted.
- Perceived to be cost effective compared to surgery.
- Focus of treatment is on correcting biomechanics rather than pain management or support.

Adoption barriers identified by contributors

- Initial cost considered high compared to existing non-surgical treatment options.
- Perceived lack of long-term data with a range of comparators available on existing treatment pathways.
- Uncertainty about patient compliance.
- Uncertainty about where it is offered on the treatment pathway.
- Uncertainty about the level of severity of osteoarthritis the technology is suitable for.
- Storage space for the equipment.

1 Introduction

The adoption team has collated information from 7 healthcare professionals working within NHS organisations 2 of whom have experience of using AposHealth as part of a pilot and in private practice. It has been developed for the medical technologies advisory committee (MTAC) to provide context from current practice and an insight into the potential levers and barriers to adoption and includes adoption considerations for the routine NHS use of the technology. It does not represent the opinion of NICE or MTAC.

The system has been available in the UK since 2015. In February 2022 it was used in 3 NHS organisations in England. The company are in the process of transitioning to a version 4 of AposHealth.

2 Contributors

Details of contributing individuals are listed in the below table.

Site	Job title	Experience
1	**Physiotherapist**	Used on 900 knee and hip osteoarthritis patients over past 7 years. Has a contract with the NHS. Receives 5 to 10 referrals a month.
2	**Physiotherapist**	Used intermittently in approximately 100 people over past 4 years. Initially used for 2 years in NHS pilot and now in private practice, but has since moved into another job. User unsure why it was not recommissioned within the NHS, possibly pressures from COVID-19.
3	**Professor of clinical biomechanics**	Was involved in research discussions with the inventors of the product and part of the team who published the largest RCT of the treatment.
4	**Consultant Musculoskeletal (MSK) physiotherapist**	Non-user
5	**Private practitioner Chiropractor NICE Fellow**	Non-user
6	**MSK Clinical Lead Podiatrist**	Non-user
7	**Diabetes Specialist Podiatrist**	Non-user

3 Current practice in clinical area

Current practice and pathways are multifaceted and vary between contributors. One contributor explains the musculoskeletal (MSK) guidance toolkit for primary and community care (needs a FutureNHS log in to access) published in March 2022 has aspirational pathways which their service is evolving to adopt.

A contributor reports their current access pathway requires primary care to refer people with knee osteoarthritis (OA) to a secondary care MSK service. Once a referral is received, an extended scope physiotherapist triages by initial assessment.

Depending on the severity of OA contributors report that people may be offered one or a combination of treatments as follows using a holistic approach:

- Health and wellbeing coaching: individualised or group interventions. This may include a referral to exercise to increase mobility and physical activity
- Physiotherapy
- Podiatry for treatment such as customised insoles
- Orthotist for treatment such as a brace
- Pharmacological treatments such as intra-articular corticosteroid injections, analgesics, topical non-steroidal anti-inflammatory drugs or topical capsaicin
- Tailored lifestyle advice about staying active, alcohol consumption smoking cessation or weight loss. Supportive treatments such as change in footwear, insoles for shoes or transcutaneous electrical nerve stimulation (TENS) may be advised.
- Pain management service: this may include psychological therapy
- Further assessments such as MRI, Xray or ultrasound scan
- Surgery interventions which may include the following:

- Arthroscopy: to assess the knee and determine the extent of the OA or to alleviate some of the symptoms by flushing the joint and removing damaged tissue.

- Osteotomy: where some bone may be removed, and realignment allowed to correct the mechanics of the lower limb.

- Arthroplasty: where either part of or the total knee is replaced

At contributing sites surgical interventions have approximately a 1 to 2 year waiting list. Contributors explain rehabilitation prior to surgery is advised because recovery is quicker in their experience.

4 Use of AposHealth in practice

Users have offered AposHealth to people with knee OA after other treatments have been tried and prior to surgical interventions. One site piloted AposHealth on patients waiting for surgery.

Once a person agrees to try AposHealth, users report they would be led by a physiotherapist through the following steps. This is over 2, 3 or 4 years depending on the site.

- Step 1: a 90-minute initial assessment. This includes a subjective and objective physical assessment, computerised gait analysis and balance assessment. OptoGait is used for gait analysis and users either purchased this or it was loaned by the company. More recently the company have used [redacted], a digital app for gait analysis. Patient information is kept anonymous, and local NHS IT systems allow data to be copied over from the gait analysis software to the electronic NHS patient records. There are no confidentiality issues or concerns reported.

    - During the first part of this assessment, approximately 5% to 15% are considered inappropriate for AposHealth because of balance or cognitive issues or if the patient declines. One user explained that they have reduced this percentage as more appropriate referrals have been received

since the technology was introduced. This is due to increased knowledge from the referrer.

- Around 85% to 95% are deemed appropriate and receive the full 90 min assessment. Outcomes measures such as the oxford knee score and Western Ontario and McMaster Universities Arthritis Index (WOMAC) are recorded.

- Step 2: Personalised AposHealth shoes are provided with pods (pertupods). The pods are calibrated according to the patients subjective and objective findings, such as reported areas of pain and gait results. Tailored lifestyle advice such as appropriate exercises, staying active, alcohol consumption, smoking cessation, weight loss and alternative footwear when not using AposHealth may be provided.

- Step 3: Treatment period. Patients are advised to wear AposHealth initially for 20 to 30 minutes a day and gradually build wear time to 1 to 2 hours a day with a combination of sitting and standing or walking. The gradual increase is to avoid muscle fatigue and soreness.

- Step 4: ongoing monitoring

  - 3 to 4 weeks following initial consultation a 20 to 30 min remote review appointment is offered. This is to review progress and reconfirm advice

  - 6 to 12 weeks later a 45 min face to face appointment is offered often to reconfirm advice, take outcome measures and to calibrate the technology.

  - A further 5 face-to-face review appointments offered every 12 weeks. Then annual appointments thereafter

The company's recommendation for step 4 has changed for version 4 of AposHealth as follows:

- 4-6 weeks following initial consultation, a 30minute follow up appointment is offered. This is to review progress and reconfirm advice

- 8-12 weeks later, a 30minute follow up appointment to take outcome measures and to calibrate the technology.

- 24-52 weeks later, a 30minute follow up appointment to take outcome measures and to calibrate the technology.

- After the first 12months, patient initiated follow up appointment as clinically indicated (estimate 1-2 per year)

Recommendations for when to utilise online or remote consultations include:

- First follow-up appointment unless there is a clinical need for face-to-face such as calibration change. Normally the first follow-up there is no requirement for calibration change.

- When progress is as expected by health professional and the patient. The patient has not requested a face-to-face review appointment.

5 Reported benefits

The potential benefits of adopting AposHealth, as reported to the adoption team by the healthcare professionals using the technology are:

- Non-invasive.
- Provides an alternative treatment option where other treatments have been exhausted. Especially if surgery is unsuitable and not wanted.
- Perceived to be cost effective compared to surgery.
- Focus of treatment is on correcting biomechanics rather than pain management or support.

6 Insights from the NHS

Care pathway

If AposHealth avoids patients having a surgical intervention contributors found this to be a benefit. Although one contributor would invest in more surgery and shorten surgical waiting lists instead because surgery has good long-term outcomes.

One contributor explained the creation of new pathway and measuring long term success is a barrier to adoption.

Most contributors were unclear about where AposHealth is best placed on the MSK pathway. They also had uncertainty about the level of severity of OA the technology is suitable for.

Patient selection

Some contributors agree AposHealth provides an alternative treatment option for those who have a long wait for, don't want or can't have surgery where other treatments have been exhausted.

Contributors would like to ensure all other treatments have been exhausted, other than surgery, before AposHealth is considered. This is because initial costs of the technology compared to existing non-surgical treatment options is considered to be high.

Clinician confidence and acceptance

Some contributors want to see more independent long-term data with a range of comparators available on existing treatment pathways. The studies should include detail on which existing treatments have been previously tried and how candidates are selected.

AposHealth is considered to be more cost effective compared to a total knee replacement by contributors. But they want to see more long-term data on how many patients have a surgical intervention after using AposHealth. This is because they had reservations about if AposHealth is delaying surgery and whether it may correct damage already done to the knee.

Some contributors like the treatment focuses on re-educating the muscles and correcting abnormal gait patterns rather than pain management or support.

Commissioning

The company explained the cost per treatment programme includes treating both knees and includes the following.

• full mobilisation of the initial service delivery
• unlimited parts (pods) while in programme
• computerised gait analysis using specialist equipment
• standardised outcome measures completed on the AposHealth clinical tracking system
• outcomes tracking and account management
• monthly outcomes report for effective contract monitoring.

The gait analysis assessment may be completed by smart-phone technology, so no gait mat is needed. All hardware and software costs are included in the price.

Resources and storage

Users need storage space for the following equipment.

- Velcro and laced versions of AposHealth shoes. Sizes range from 35 to 51.
- Boot bags.
- Size 'A' to 'D' pertupods. The pertupods differ in size. A user explained 'A' pods are appropriate for people with less significant issues and 'D' pertupods are significantly more challenging for the user. The 'D' pertupods possibly would be used in an athletic cohort. The cohort being treated by one contributor, those who had been referred for surgical consideration, would typically start on 'A' pertupods. 4 pertupods are needed on a pair of shoes and come in bags of 10. For Apos 4 version, only one size of hardness of pertupod will be available

Users explain a 5-metre walking area, such as a corridor, is needed for the gait analysis. A stock order is completed once a month by a user and takes 45 minutes.

Training

The company offers training as follows:

- Optional but recommended pre-course online modules/resources (4 hours).
- Theory training: Virtual (2 half days) or face-to-face (1 full day).
- Practical (each trainee):

  - 10 supervised Initial Evaluations on real patients.
  - 5 supervised follow-ups.
- Assessment:
  - Theory: 45-minute multiple choice (70% pass mark).
  - Practical: 9 to 10th patient assessment (70% pass mark).

May be done over 3 practical days. Health professionals fully independent after passed assessments, with ongoing support and training as needed.
Training may be delivered remotely if the organisation chooses.

One user said there was resistance from staff on the MSK pathway as they did not have education and training about the benefits of the technology because it was a pilot. They recommend this is provided to ensure efficient implementation within NHS services.

NHS users explain in their opinion adoption of the technology requires band 6 or 7 physiotherapists or professionals with MSK experience or equivalent.

Patient experience

A podiatry (non-user) contributor experiences poor compliance when recommending their patients change footwear or wear a knee brace so assumes it to be the same for this technology.

NHS users have had no compliance issues that has caused concern. People have been supported to adopt the device into their day to day routine by users. For example, people who worked full time have the option of wearing the device at work during lunch breaks.

An NHS user reports some people experience immediate pain relief when wearing AposHealth whereas others it may take up to 12 weeks.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT570 AposHealth for osteoarthritis (OA) of the knee

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	AposHealth®
Submission date	13/6/2022
Regulatory documents attached	Please list regulatory documents submitted (e.g., CE certificate, instructions for use, etc.) • CE • NHRA • ISO • FDA

Contains confidential information	Yes: • [redacted] • [redacted] • [redacted] • [redacted] • [redacted]

Contents

1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	Adults aged 16 years and over with knee osteoarthritis who have been offered, or are refractory to, non-surgical standard of care treatment options, including education and advice; exercise and manual therapy; weight loss (for people who are overweight); and pain relief (oral, topical, or transdermal).	Enter text.	Enter text.
Intervention	AposHealth alone or in addition to non-surgical standard care	Enter text.	Enter text.
Comparator(s)	Non-surgical standard care treatment options, including but not limited to: • Devices (such as supports, splints, and braces) • Intra-articular corticosteroid injections	Enter text.	Enter text.
Outcomes	The outcome measures to consider include: 1. Measures of treatment effectiveness: • Patient-reported outcome measures (for example, the Western Ontario and McMaster Universities	Enter text.	Enter text.

	Osteoarthritis Index and the Oxford Knee Score) • STEADI assessment • Mobility • Avoidance of knee replacement • Avoidance of secondary care referral • Health-related quality of life (for example, measured by the SF-36) 2. Measures of resource use • Health care use (for example, use of corticosteroid injections, analgesic use, number of physiotherapy sessions, and other healthcare appointments) • Surgical intervention - knee replacement • Surgical intervention - other 3. Device-related adverse events		
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared.	Enter text.	Enter text.

	Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.		
Subgroups to be considered	• People for whom total knee replacement is recommended • People who don't want or can't have surgical intervention	- The company would like to suggest the following subgroups as clarifications to the type of population that might benefit from AposHealth: - Unicompartmental OA - PFJOA - Anyone who has not responded sufficiently to previous treatments (may not necessarily be at surgical threshold yet), or - People for who there is benefit in delaying surgery - People for who surgery is the only remaining choice.	Clarification purposes

Special considerations, including issues related to equality	AposHealth is intended for people with knee osteoarthritis. The technology is contraindicated in people who have severe imbalance or vertigo issues. The technology is also not suitable for people considered at high risk of falls or those with severe osteoporosis. The technology should be worn for at least an hour a day so may not be suitable for people with very limited mobility or those who use walking aids to get around at home, depending on clinical judgment. It may also not be suitable for people with neurological impairments who cannot consent to the programme or may not be safe to use the technology independently. Osteoarthritis is more common in people who are older, in women and in people with obesity. One meta-analysis conducted in North America found that pain severity and disability is higher for people with an African family background compared with people with a European family background. Age, sex, disability, and race are protected characteristics.	Enter text.	Enter text.

2 The technology

Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

Brand name	AposHealth (AposHealth, previously AposTherapy)
Approved name	AposTherapy
UKCA/ CE mark class and date of authorisation	AposHealth received a CE mark in October 2017 as a class IIa medical device for knee osteoarthritis.

Version(s)	**Launched**	**Features**
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.

What are the claimed benefits of using the technology for patients and the NHS?

In addition to the table below, the company would also like to submit some clinical opinion on claimed benefits (Supp S).

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Improved quality of life due to reduced pain and improved joint function	Multiple trials, including RCTs, single cohort prospective trials and retrospective real-world evidence, suggest a significant reduction in pain and improved function and quality of life following treatment with AposHealth. Clinical improvements meet the MCID for treating knee OA. In addition, a significant improvement is also seen in mobility, measured with objective gait metrics (increased gait velocity, longer step length and increased ability to bear loads on the affected limb/s).	The Apos device functionality enables manipulation of the centre of pressure by positioning the unique pods under the sole of the shoe and controlling the contact area of the foot with the ground. The structure of the device allows for unlimited positions which are personally calibrated to each patient based on symptoms, clinical examination and gait patterns. Changing the forces acting on the painful joint (i.e., unloading the painful area) allows the patient to exercise with diminished pain. The perturbation, induced by the unique pods' profile underneath the shoes, trains neuromuscular control and leads to a more coordinated movement pattern. Together with home-based task-specific exercise (patients are instructed to wear the device for up to an hour a day and go about their daily activities), AposHealth leads to acquiring new motor learning, better mobility, and improved symptoms.

Reduced need for knee replacement surgery	Two peer-reviewed publications support high surgery avoidance rate at 2-yrs following AposHealth. One study suggests that 97% of the patients treated with AposHealth avoided surgery compared to 70% of the controls (Bar-Ziv et al., 2013). Data on file provides a summary of a 5-yrs follow-up study that was performed on the same cohort of patients. At 5 yrs., 15% of patients that were treated with AposHealth have had a TKR (85% surgery avoidance) compared to 45% of patients that received the standard of care (55% surgery avoidance). A second study suggests that 86% of the patients treated with AposHealth avoided surgery at 2-yrs compared to 12% in the control group. Another study is currently under peer-review evaluation. A UK-based study that looked at NHS patients suffering	Patients treated with AposHealth experience a significant reduction in pain and improved function leading to better QoL. AposHealth is a home-based treatment that is easy to comply with, hence high adherence rates. Knowing the risks associated with surgery and the minimal risks associated with AposHealth, patients find it an effective intervention and an attractive one given the lack of effective treatments. Most patients report that after using Apos they think less of having a surgical intervention. Some believe they can avoid surgery altogether. With patients being able to access AposHealth as a non-surgical option, they feel less pressure to progress to the surgical waiting list because they know they will have a long wait, which in turn put further demands on the waiting lists.

	from knee OA and eligible for secondary care. Results suggest that 84% of the patients that were treated with AposHealth avoided TKR at 2-yrs. (Greene et al. 2022). Data on file: 1. UK data - 13% of patients with a primary knee condition that were treated with AposHealth have had a surgical intervention to their knee at an average follow up time of 6 yrs. Data is for a UK private payor. Furthermore, an independent member survey suggests that 87% expect to delay surgery and 63% expect to avoid it altogether. 2. US data – a 2-yrs follow-up on surgery avoidance rate amongst patients with knee OA treated with AposHealth in commercial settings suggest that 96.5%	

	of the patients avoid TKR at 1 year and 93% avoid TKR at 2 yrs. 3. IL data – 3-yrs. data on surgery avoidance amongst patients with a knee condition that were treated with AposHealth suggest a 98%, 92% and 89% avoidance at 1-yr., 2-yrs., and 3-yrs., respectively.	
System benefits		
Reduced waiting lists for surgical treatments	Two peer-reviewed publications support high surgery avoidance rate at 2-yrs following AposHealth. One study suggests that 97% of the patients treated with AposHealth avoided surgery compared to 70% of the controls (Bar-Ziv et al., 2013). Data on file provides a summary of a 5-yrs follow-up study that was performed on the same cohort of patients. At 5 yrs., 15% of patients that were treated with AposHealth have had a TKR (85% surgery avoidance) compared to	A direct impact on the waiting list is expected to significantly affect surgery rates among those treated with AposHealth (as described above). With Covid-19, there was an exponential growth in the waiting lists for TKR which the healthcare systems are trying to address, yet with limited capacities for elective surgery many patients are left untreated. Now, more than ever, there is an urgent unmet need for non-invasive interventions that will be an alternative to TKR. For this reason, delaying surgery for a reasonable period of time is likely to be helpful in the current immediate post-COVID world. In addition, with the growing aging population and prevalence of OA, there is a need to

	45% of patients that received the standard of care (55% surgery avoidance). A second study suggests that 86% of the patients treated with AposHealth avoided surgery at 2-yrs compared to 12% in the control group. Another study is currently under peer-review evaluation. A UK-based study looked at NHS patients suffering from knee OA and eligible for secondary care. Results suggest that 84% of the patients that were treated with AposHealth avoided TKR at 2-yrs. (Greene et al. 2022). Data on file: 1. UK data - 13% of patients with a primary knee condition that were treated with AposHealth have had a surgical intervention to their knee at an average follow up time of 6 yrs. Data is for a UK private payor.	find effective alternatives to manage this demand. Long waiting lists are a well-publicised problem and many patients choose to join the list for surgery, potentially earlier than expected or maybe needed. This is exacerbating the situation further. The significant improvement in patients' symptoms felt by utilising AposHealth will lead patients to reconsider a surgical intervention, hence a direct impact on waiting lists is expected and the ability to better prioritise those most at need. It will enable health systems to better prioritise the waiting lists for those in most need. Those that are unsuitable (e.g. balance problems), too severe and should not delay surgery, or do not respond to the therapy can be prioritised over those responsive and managing their symptoms in the community.

	Furthermore, an independent member survey suggests that 87% expect to delay surgery and 63% expect to avoid it altogether. 2. US data – a 2-yrs follow-up on surgery avoidance rate amongst patients with knee OA treated with AposHealth in commercial settings suggest that 96.5% of the patients avoid TKR at 1 year and 93% avoid TKR at 2 yrs. 3. IL data – 3-yrs. data on surgery avoidance amongst patients with a knee condition that were treated with AposHealth suggest a 98%, 92% and 89% avoidance at 1-yr., 2-yrs., and 3-yrs., respectively.	
Increased system capacity to treat more of this population *without* needing to increase operating facilities and associated	Two peer-reviewed publications support high surgery avoidance rate at 2-yrs following AposHealth. One study suggests that 97% of the patients treated with	The ability to treat those that would otherwise have knee surgery in an inpatient setting, at home, in the community, with little/no risks. A direct impact on the waiting list is expected to significantly affect surgery rates among

costs (inpatient stays and rehabilitation) of knee replacement surgery in order to address the growing demand.	AposHealth avoided surgery compared to 70% of the controls (Bar-Ziv et al., 2013). Data on file provides a summary of a 5-yrs follow-up study that was performed on the same cohort of patients. At 5 yrs., 15% of patients that were treated with AposHealth have had a TKR (85% surgery avoidance) compared to 45% of patients that received the standard of care (55% surgery avoidance). A second study suggests that 86% of the patients treated with AposHealth avoided surgery at 2-yrs compared to 12% in the control group. Another study is currently under peer-review evaluation. A UK-based study that looked at NHS patients suffering from knee OA and eligible for secondary care. Results suggest that 84% of the patients that were treated with AposHealth avoided TKR	those treated with AposHealth (as described above). Providing a clinically proven home-based non-invasive intervention as an alternative to TKR will enable an increased capacity to treat moderate-severe knee OA population, without increasing associated costs of surgery/hospital stays and rehabilitation. Those that are unsuitable, whose condition is too severe or who fail to respond to AposHealth treatment can be better prioritised whilst others that respond well will be able to remain in treatment or self-manage their condition with the use of the Apos® device.

	at 2-yrs. (Greene et al. 2022). Data on file: 1. UK data - 13% of patients with a primary knee condition that were treated with AposHealth have had a surgical intervention to their knee at an average follow up time of 6 yrs. Data is for a UK private payor. Furthermore, an independent member survey suggests that 87% expect to delay surgery and 63% expect to avoid it altogether. 2. US data – a 2-yrs follow-up on surgery avoidance rate amongst patients with knee OA treated with AposHealth in commercial settings suggest that 96.5% of the patients avoid TKR at 1 year and 93% avoid TKR at 2 yrs. 3. IL data – 3-yrs. data on surgery avoidance	

	amongst patients with a knee condition that were treated with AposHealth suggest a 98%, 92% and 89% avoidance at 1-yr., 2-yrs., and 3-yrs., respectively.	
Increased patient compliance and engagement due to ease of use of the technology	The company has evidence to support high adherence to the treatment with no adverse events associated with the intervention compared to controls (Reichenbach et al., 2020). The company also has data on file to present patient satisfaction in commercial settings. A NHS CCG providing AposHealth as an intervention for NHS patients suffering from severe knee OA and eligible for secondary care, evaluated patient satisfaction regularly and reported high satisfaction rates. Furthermore, an independent member survey from a private UK payor that provided AposHealth to patients	AposHealth is a home-based intervention. Patients are instructed to wear the device for about an hour a day and go about their daily activities. Patients find it very easy to perform and comply, hence the high adherence and satisfaction rates. Unlike braces that often become restrictive to wear, inhibit normal daily function, and for which exercise can often be too painful for this cohort, the Apos device enables symptom modification (reduction in pain) whilst simultaneously training muscular control, all during day to day activity. The ease of use together with a significant and impactful clinical effect leads patients to refrain from looking for other treatments, reduce reliance on pharmacological care and consider delaying surgery of even avoiding it altogether. A video of testimonials will be provided to this submission (Supp. R)

	with knee pain suggests that 92% of the patients were satisfied with the intervention. 88% report that AposHealth exceeded their expectations and 93% say they will recommend AposHealth to friends and family. Furthermore, patients reported a decrease in consumption of other knee OA interventions once they've started using Apos.	
Cost benefits		
Cost savings as a result of reduced need for conventional therapies and associated appointment costs for physiotherapy, knee braces, orthotic devices, joint injections, and pharmacological treatments	An independent report assessed claims data and costs associated with management of knee OA pre and post AposHealth. Results suggest a decrease in out-patient visits in general and visits for knee OA in particular. There was also a significant reduction in the use of opioids, physical therapy, and knee x-ray. An independent member survey conducted by a private UK payor suggested a significant	The reduction in claim data of doctor office visits, examinations, pharmacological treatments, and physical therapy supports the overall conclusion of cost savings. A detailed analysis will be provided in the economic model.

	self-reported reduction in the utilisation of different knee OA interventions including pharmacological, injections, physiotherapy, and braces. Lastly, several trials suggest surgery avoidance, an end-stage solution of knee OA which poses a huge burden on the healthcare system.	
Sustainability benefits		
A reduction in the use of conventional therapies and thus reduces the number of appointments and has an environmental impact.	An independent report assessed claims data and costs associated with management of knee OA pre and post AposHealth®. Results suggest a decrease in out-patient visits in general and for knee OA specifically. In addition, there was also a significant reduction in the use of opioids, physical therapy, and knee x-ray. In addition, an independent member survey conducted by a private UK payor suggest	The reduction in OP visits and traditional PT is expected to have a positive environmental impact. In addition, self-reported reduction in consumption of other interventions also supports a potential positive environmental impact. Less travel to and from appointments reduces patient's carbon footprint. Apos treatment requires minimal physio appointments spread across a longer period (e.g.1 year) whilst the patient is getting the daily therapy at home. This means less travelling for patients, giving them the self-efficacy to manage their condition independently/minimal support. Potential use of hybrid models of care (using phone/telehealth) when patients

	a significant self-reported reduction in the utilization of different knee OA interventions including pharmacological, Injections, physiotherapy, and braces.	are doing well and may not need face to face visits. This again means less need for travel/in clinic resources.
It also claims that increased mobility, range of movement and quality of life supports patients having physical activity and reducing their reliance on car or bus transportation.	Multiple trials, including RCTs, single cohort prospective trials and retrospective real-world evidence, suggest a significant reduction in pain and improved function and quality of life following treatment with AposHealth®. Clinical improvements meet the MCID for treating knee OA. In additions, a significant improvement is also seen in mobility, measured with objective gait metrics (increased gait velocity, longer step length and increased ability to bear loads on the affected limb/s).	The clinical evidence supports a significant improvement in patients' symptoms. This is likely to have a direct impact on the ability to use transportation. Moreover, the reduction in claims data (including OP visits, physiotherapy, and examinations), as well as the self-reported reduction in consumption of other interventions, also supports a potential decrease in the use of transportation. Improved pain and function means patients are able to rely less of other modes of transport and return to walking/cycling if they desire.

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

AposHealth Technology

For the past decade, a personalised non-invasive biomechanical treatment for patients with knee OA has been available in the UK, with over 10,000 patients treated to date. AposHealth is an FDA-cleared class I medical device for patients with knee OA and a CE mark as a class IIa medical device for knee OA. As of 2022 more than 110,000 patients were treated with AposHealth worldwide. In essence, it is a shoe-like device that provides the platform to fit two convex pods under the sole. One is located under the anterior part of the sole and the other under the posterior, both attached using special rails and screws and can be adjusted based on clinical needs (Figure 1). The AposHealth shoes (AKA Apos) are available with a Velcro fastening, or with a lace fastening depending on the person's hip flexibility, finger dexterity, foot width and preference. Adjusting the pods' location changes the ground reaction force (GRF) vector and immediately reduces pressure on the area (Haim, Rozen et al. 2010, Haim, Wolf et al. 2011). The convex nature of the elements induces a level of controlled perturbation and proprioceptive training causing muscles in the lower limb to work differently (Goryachev, Debbi et al. 2011, Debbi, Wolf et al. 2012). The combination of altered forces and moments acting on the affected joint due to the device set-up, combined with controlled perturbation, allows a neuromuscular training response and carry-over effect to usual walking without the device to occur (Haim, Rubin et al. 2012, Debbi, Wolf et al. 2015).

AposHealth is a home-based intervention. Patients are instructed to wear a personally calibrated device for 30-60 minutes a day while performing their daily activities at home or work (usage time may increase gradually, depending on progress and symptoms). The application of the treatment comprises the functional rehabilitation principle, which stresses the importance of task-specific rehabilitation with repetitive and sub-conscious activities (Levin, Weiss et al. 2015, Charlton, Eng et al. 2021). In addition, patients are also educated about the condition and ways to manage their symptoms.

Since the COVID-19 pandemic more telehealth, remote care, and home-based interventions are emerging. Furthermore, the need to postpone a huge number of elective interventions including doctor visits, physiotherapy, injections, and surgeries causes a very long waiting list and patients are left untreated. More specifically, the waiting lists for

TKR have grown exponentially, with the number of inpatient procedures rising by 73% compared to the previous year. Healthcare systems are trying to address the backlogs, but with limited capacities for elective surgery, patients are left untreated, and the recovery from the backlog is much slower than required. Therefore, it is paramount that health systems look for effective alternatives for treating these cohorts with interventions that can alleviate symptoms and significantly delay and potentially avoid the need for joint replacement surgery altogether where possible. AposHealth is a clinically proven home-based intervention that addresses those requirements and can be an alternative for those on the waiting lists.

Figure 1. Apos device

Sole platform includes two mounting rails and a positioning matrix. **Biomechanical pods** are available in different degrees of convexity and sizes.

Biomechanical pods can be configured on the sole platform with flexible positioning for **personalized biomechanical placement**.

Methodology

The AposHealth treatment plan is delivered over a 1-year period and consists of 4 key features:

Step 1: In-depth initial evaluation – The AposHealth treatment begins with an AposHealth-trained clinician (ATC) conducting an in-depth evaluation of the patient's movement patterns and the root causes of their pain. This consultation includes an interview, Patient Reported Outcome Measure (PROM) questionnaires to assess pain, function, and quality of life, a computerised gait analysis, and a physical examination.

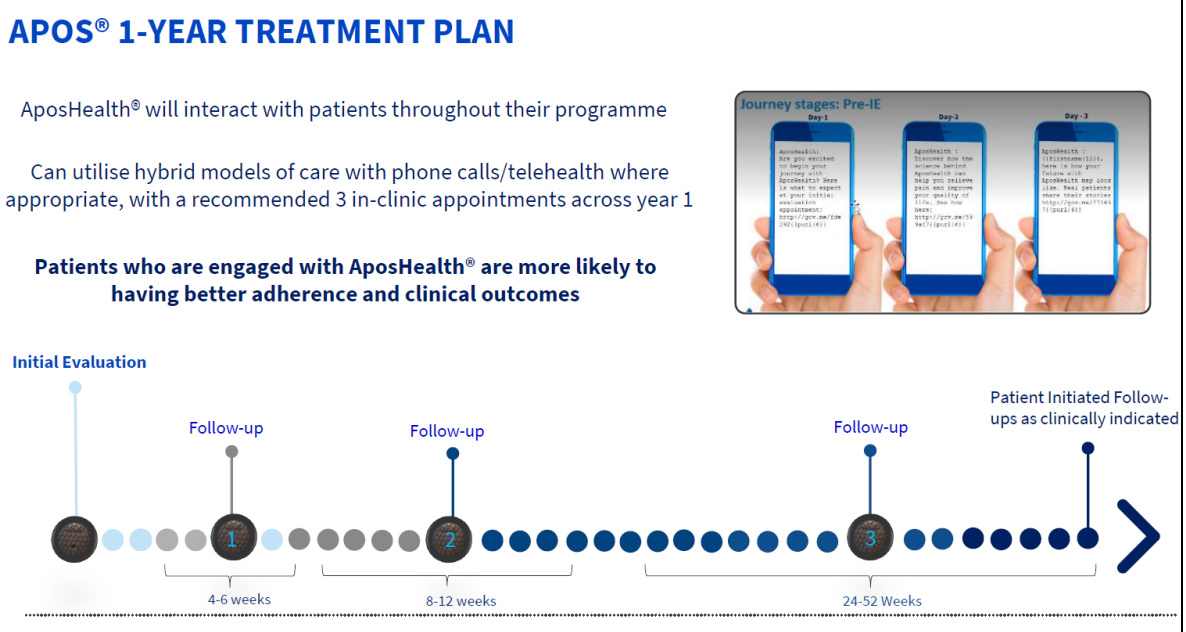
Step 2: Personalised device & treatment – Once the patient has been evaluated, the clinician personalises the Apos foot-worn device by calibrating the under-sole pods to the patient's specific needs and then prescribes a personalised programme for the patient.

Step 3: Effortless at-home treatment – Wearing the Apos device for about an hour a day, the patient can go about their daily schedule while the footwear corrects their gait and relieves the stress on the affected area(s). Patients who wish to wear the device for longer period of time and/or walk outdoors are encouraged to do so, after consulting with their Apos clinician.

Step 4: Ongoing monitoring for optimised outcomes – The treatment plan includes follow-up consultations and check-ups to assess the patient's pain relief and functional improvement. Follow-up meetings include many of the evaluations performed during the initial consultation and allow careful monitoring of progress. Whenever necessary, the device is recalibrated, and the personalised treatment plan is updated. After their initial treatment plan, patients are discharged to self-manage or seen on an adhoc basis as clinical indicated.

The Treatment Programme is summarised in Figure 2.

Figure 2. Apos initial treatment plan



Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

Environmental impact & Sustainability consideration

Using AposHealth is expected to reduce the use of conventional therapies and thus reduce the number of appointments, which has an environmental impact. In addition, the positive clinical effect which includes increased mobility, range of movement and quality of life supports patients having physical activity and reducing their reliance on car or bus transportation.

In addition, the company included the clinical opinion of some of AposHealth providers on claimed benefits (Supp S).

3 Clinical context

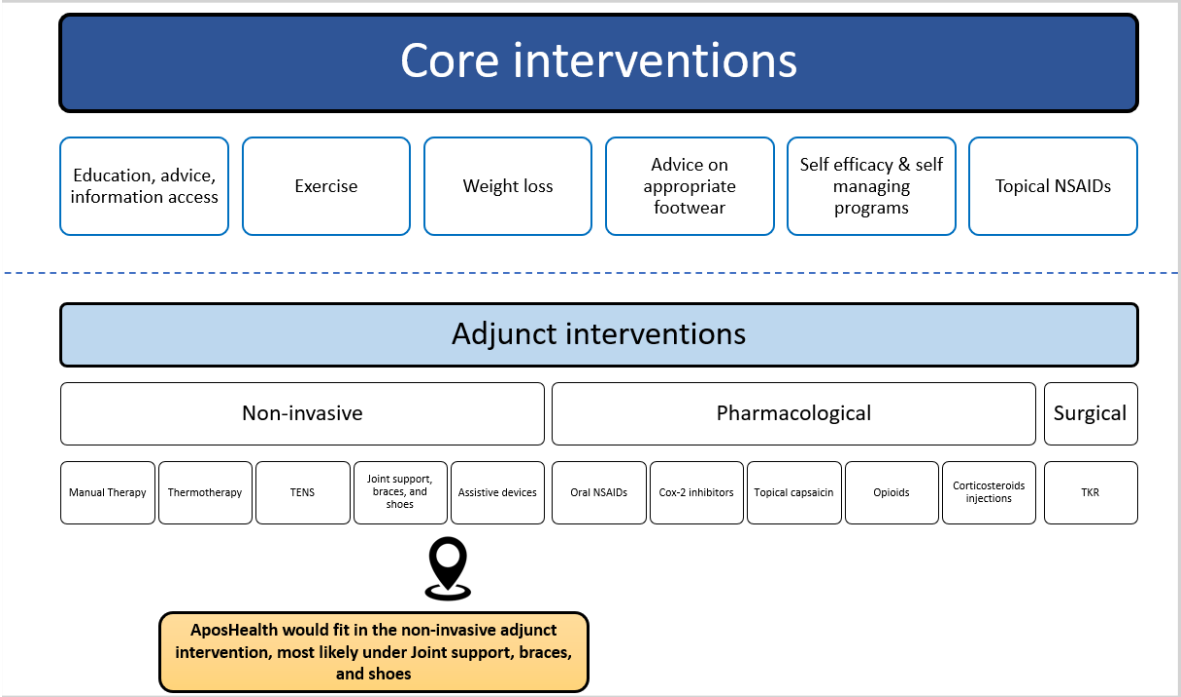
Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant

pathways.

According to NICE all patients should receive the core interventions. Adjunct interventions recommendation depends on the severity of symptoms, patient characteristics, and preference. For this reason, the current literature review will not focus on core treatments as they are not questionable or replaceable. Those will come as the first line of treatment, followed by adjunct interventions. We believe AposHealth should be positioned alongside aids and devices and pharmacological management, namely intra-articular corticosteroid knee injections. Surgical intervention might also be considered as a comparator (Figure 4).

That being said, it is important to stress that the effectiveness of core interventions is limited and short-termed. We reviewed the updates for NICE's guidance for arthritis, which will be published in October 2022 and used them in our review, as recommended in NICE Medical Technologies Guidance.

Figure 4. AposHealth in the care pathway



Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

The technology is used by clinicians (Allied Health Professionals; physiotherapists, orthotists,podiatrists) that are trained in AposHealth. The company provides comprehensive training on how to calibrate the device, appropriate patient selection and technology workshops to ensure safe and effective use. Clinicians would attend a 1-day theory course, followed by supervised assessments (between 5-10 patients) by AposHealth Trainers before becoming certified. The company provides ongoing support on an ad hoc basis with clinical experts based on clinical need and access to additional online learning materials. All training costs are included in the purchase price.

AposHealth can be utilised in primary care, secondary and community settings delivered in face-to-face clinics, home care or digital care (remote care). It should be utilised as an adjunct within existing pathways, therefore limited changes to the system. The flexibility of delivery options means it can be easily integrated into various points in the system depending on need. Additional training for admin staff, referrers, and wider MDT, all delivered as part of service implementation as required.

Attached to this submission is a copy of the company's training materials and supplementary materials (**all confidential**) including the following:

[redacted]

4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		48
Number of studies identified as being relevant to the decision problem.		24
Of the relevant studies identified:	Number of published studies (included in table 1).	17
	Number of abstracts (included in table 2).	0
	Number of ongoing studies (included in table 3).	7

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.
- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant published studies

In addition to the summary below, which captures all peer-reviewed publications associated with the mechanism of action of the device and its clinical outcomes for patients with knee OA, the company would like to submit Supp E, which summarises all publications, including clinical outcomes for other MSK conditions, some might be associated with knee OA (i.e., low back pain). AposHealth uses gait modifications and neuromuscular training to alleviate symptoms and improve function using a foot-worn device. This device can address multiple lower back and lower extremity MSK conditions. For many patients this is an advantage as patients with knee OA frequently suffer from other pains (lower back, hip). Furthermore, this also applies to patients suffering from a bilateral condition. While for some interventions there is a need to treat each knee separately (braces, injections), with AposHealth one can treat a bilateral condition simultaneously, and it is even recommended as the body constantly compensating for symptoms. The device's versatility allows to account for those compensations. All publications underwent peer-review evaluation.

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Link to source	Reichenbach et al., 2020. Switzerland	Double blind, randomised controlled trial	Two hundred and twenty (n=220) men and nonpregnant women aged 40 years or older who had symptomatic, radiologically confirmed knee OA according to criteria from the American College of Rheumatology. At the screening visit, participants had knee pain lasting six months or longer and a score of 3 or greater on the WOMAC pain subscale standardised to range from 0-10). Between April 20, 2015, and January 10, 2017, 220 participants were randomised. There were 111 participants randomised to the biomechanical footwear group and 109 participants randomised to the control footwear group. One participant in the biomechanical footwear group refused treatment and did not receive the intervention. Seven participants in the biomechanical footwear group and 13 participants in the control footwear group discontinued treatment during follow-up. The last participant visit occurred on August 15, 2017. There were complete data for the primary outcome at 24 weeks of follow-up for 109 participants (98.2%) in the biomechanical footwear group and 104 participants (95.4%) in the control footwear group.	AposHealth	Sham device	The primary outcome measure was pain. The biomechanical footwear group had a larger decrease in standardised WOMAC pain subscore at 24 weeks of follow-up than the control footwear group (mean score, 1.3 vs 2.6, respectively; between-group difference, −1.3 [95% CI, −1.8 to −0.9]; *P* < .001) 83% of patients in the biomechanical group had a 50% reduction in WOMAC pain, 92% with a 30% reduction compared to 42% and 58%, respectively in the control group (P< 0.001) Secondary outcome measures included WOMAC scores, SF-36, Spatio-temporal gait analysis. There were no significant adverse events associated with the treatment compared to controls.

						Gait velocity improved by 37% (p<0.05)
Link to source	Drew et al., 2022. US	Retrospective, matched controlled	Five hundred and thirty-one (n=531) patients with knee OA eligible for TKR. The eligibility criteria for TKR comprised a combination of the following: 2 professional claims related to knee pain, radiological confirmation of knee OA, subjective knee pain >3 months impacting the QoL, no reliance on assistive devices to walk indoors, and <2 falls in the past year. Of 237 patients that were enrolled to the study, 27 patients (11%) termed their insurance coverage and were disenrolled from HPN, and five patients (2%) were deceased. All other patients completed a 2-yrs follow-up.	AposHealth	Standard of care	Over the 24-month study period, 34 patients who received the intervention (14%, 95% CI 82%–91%) progressed to a TKR. The average time to progress to TKR was 324 days (ranging from 31 to 671 days). Sixty-four percent of those who underwent TKR had their surgery within 12 months after the initiation of the intervention. Of the 294 patients in the control group who chose TKR surgery, 259 (88%) received a knee replacement. With respect to the clinical outcomes' measurements, for the 172 patients who chose the biomechanical intervention and who completed the program, 138 (88%) had clinical data at three months, 111 (65%) patients had clinical data at 6 months, and 52 (30%) patients had clinical data at 12 months.

						The General Mixed Model which includes repeated measures from 4 visits showed a significant reduction in WOMAC pain (P < 0.001) and WOMAC function (P < 0.001) after 12 months of treatment. It is estimated that pain decreased by 19.6 points (36%) at the end of year 1, and functional disability decreased by 16.4 points (34%). There was a significant increase in the SF-36 overall score by 5.4 points (10%) at one year (P < 0.001). Likewise, the PCS increased significantly by 5.6 points (13%) after 12 months of treatment (P < 0.001). No significant changes in MCS were noted. Gait velocity improved by 11% (p<0.05)
Link to source	Bar-Ziv et al., 2010. Israel	Prospective controlled trial	Fifty-seven (n=57) patients with symptomatic bilateral knee OA of the medial compartment for at least six months. All patients fulfilled the American College of Rheumatology clinical criteria for OA of the knee and had radiographically assessed	AposHealth	Sham device	At the 8-week endpoint the WOMAC pain score and function score revealed significant differences between the groups over time (Time by treatment

			osteoarthritis of the knee according to the Kellgren & Lawrence (K&L) scale. All patients had a varus knee alignment. Exclusion criteria were acute septic arthritis, inflammatory arthritis, patients with a history of increased tendency to fall, patients with a history of knee buckling, lack of physical or mental ability to perform or comply with the treatment procedure, diabetes mellitus, and patients with a history of pathological osteoporotic fracture. Fifty-seven patients were enrolled into the study. Thirty-one patients received AposHealth and 26 patients received a shame device. Twenty-nine patients that were treated with AposHealth and 25 patients treated with a sham device completed the study (8 weeks)			interaction, p < 0.001). The active group reported significant pain relief after eight weeks of treatment with a mean difference of 3.5 cm (64.8%) and a 95% confidence interval ranging between 2.7-4.4. In contrast, the control group reported no pain relief, having a mean increase of 0.4 cm (8%) with a 95% confidence interval ranging between -1.7-0.8. On the WOMAC function scale, the active group reported significant improvement with a mean decrease of 3.2 cm (62.7%) after eight weeks and a 95% confidence interval ranging between 2.5-4.1. The control group reported no function improvement, having a mean increase of 0.5 cm (9.8%) with a 95% confidence interval ranging between -1.4-0.5. QoL: Physical component summary increased by 50% at two months in the AposHealth group

						compared to an 11% deterioration in the control group. Mental component summary increased by 58% at two months in the AposHealth group compared to a 21% decrease in the control group Patients also demonstrated a significant improvement in ALF – a functional test, and in the Knee Society Score questionnaires. Unmarked acetaminophen - Patients from the control group used more of the rescue medication given to them at the start of the study than did the active group. After four weeks, the active group as a whole consumed 145 rescue pills whereas the control group consumed 281 pills. After eight weeks, the active group consumed 128 pills and the control group consumed 366 pills. Overall, the active group consumed 273 pills and the control group consumed 647 pills.

						No side effects were reported by any of the patients.
Link to source	Haim et al., 2011. Israel	Prospective, single cohort study	Twenty-five (n=25) female patients with symptomatic bilateral medial compartment knee OA. Inclusion criteria: symptomatic physician-diagnosed medial knee OA for at least six months, fulfilling the ACR (American College of Rheumatology) criteria for OA of the knee. All 25 patients enrolled in the study completed the treatment program with satisfactory compliance (i.e., Adherence of >75% to the proposed treatment protocol). Two patients had brief (3–4 weeks) treatment intermissions, one due to plantar fasciitis and the other due to trochanteric bursitis, both of which resolved spontaneously.	AposHealth	N/A	Post-treatment testing demonstrated a reduction of the KAM magnitude during the stance phase. The knee adduction impulse and the 1st and the 2nd KAM peaks were reduced by 0.54N-m/kg/sec, 0.06 N-m/kg, and 0.07N-m/kg, respectively. A reduction of 15%, 18%, and 17%, respectively, from the pre-training values. Velocity improved by 10% ($p<0.05$). Patient self-reported WOMAC pain scores and function scores as well as SF-36 revealed a significantly favourable outcome at the 3-month follow-up and the 9-month endpoint ($p<0.001$). Overall pain reduced by 61%, and function and QoL have improved by 63% and 32%, respectively.
Link to source	Debbi et al., 2015 Israel	Prospective, single cohort study	Twenty-five (n=25) female patients with symptomatic bilateral medial compartment knee OA. Inclusion criteria: symptomatic physician-	AposHealth	N/A	Peak knee flexion moment (KFM) at loading response decreased significantly with therapy (p =

			diagnosed medial knee OA for at least six months, fulfilling the ACR (American College of Rheumatology) criteria for OA of the knee. All 25 patients enrolled in the study completed the treatment program with satisfactory compliance (i.e., Adherence of >75% to the proposed treatment protocol). Two patients had brief (3–4 weeks) treatment intermissions, one due to plantar fasciitis and the other due to trochanteric bursitis, both of which resolved spontaneously.			0.001). Duration of KFM and impulse of knee flexion also decreased significantly (p = 0.024 and p = 0.029, respectively). These changes were accompanied by increased walking velocity, significant pain reduction, and increased functional activity. Post-training kinetic evaluation demonstrated profound alterations of knee sagittal moments at the loading response KFM. - A 49% reduction in knee flexion moment during loading response - A 40% reduction in peak knee flexion moment during loading response Velocity improved by 10% (p<0.05) Patient self-reported WOMAC pain scores and function scores as well as SF-36 revealed a significantly favourable outcome at the 3-month follow-up and the 9-month endpoint (p<0.001).

						Overall pain reduced by 61% and function and QoL have improved by 63% and 32%, respectively.
Link to source	Bar-Ziv et al., 2013. Israel	Prospective, controlled study	Fifty-six patients with knee OA participated in the study. Forty patients were treated with AposHealth, and 16 patients served as controls. Inclusion criteria were (1) symptomatic bilateral knee OA of the medial knee compartment for at least six months; (2) qualification of OA of the knee according to the American College of Rheumatology clinical criteria for OA of the knee, which include knee pain with at least 3 of the following: age > 50 years, stiffness < 30 minutes, crepitus, bony tenderness, bony enlargement, no palpable warmth; (3) radiographically assessed OA of the knee according to the Kellgren & Lawrence (K&L) scale. Only patients of grade II or above were included in the study. At the two-year endpoint, thirty-eight patients and nine patients completed the trial. AposHealth group: One patient has had a TKR, and one patient declined to participate. Control group: One patient was deceased, one declined to participate, and five patients have had a TKR.	AposHealth	Traditional care	A significant difference was found between the active and control groups in all three WOMAC categories (pain, stiffness, and function) at the two-year endpoint. There was also a significant difference in improvement over time between groups in all three categories (for interaction =16.8, 21.7 and 18.1 for pain, stiffness, and function, respectively). At two years, patients treated with AposHealth improved by 62% compared to an increase of 24% in the control group. Patients also reported a 61% improvement in function compared to a deterioration of 12% in the control group. A significant difference between the active and control groups was also found in the ALF score at the two-year endpoint (P<0.001). The two groups did not differ

						significantly in their improvement over time (F for interaction =0.67). At the two-year endpoint, a significant difference was found between groups in all categories of the SF-36 except for the category of emotional well-being. This is reflected in the two summary indices of the SF-36: the SF-36 PCS and SF-36 MCS (P<0.001). There was a significant difference in improvement over time between groups in the SF-36 PCS (F for interaction =5.8) but not in the SF-36 MCS (for interaction =0.032). At the two-year endpoint, a significant difference was found between groups in the KSS-K and the KSS-F (P<0.001). The two groups also differed significantly in their improvement over time in the KSS-K (F for interaction =4.3) and the KSS-F (F for interaction =6.5). The groups also differed in the number of total knee replacements (TKRs) performed

						at two years. One patient from the active group required a TKR during the study period (2.6%), while five patients (31%) of the control group required a TKR during the two-year study period.
Link to source	Lador et al., 2013 Israel	A retrospective single cohort study in commercial setting	Nine hundred and eighty-eight (n=988) patients diagnosed with knee OA were treated with AposHealth for four months. Inclusion criteria were patients suffering from symptomatic bilateral knee OA at the medial compartment for at least six months, fulfilling the American College of Rheumatology clinical criteria for OA of the Knee. Patients are referred to this treatment by general practice and orthopedic doctors from the general community medical care.	AposHealth	N/A	Pain significantly decreased by 31% (p<0.001). Function significantly improved by 28% (p<0.001). SF-36: PCS significantly improved by 21% (p<0.001). MCS significantly improved by 12% (p<0.001). Gait velocity improved by 10% (p<0.05)
Link to source	Drexler et al., 2012. Israel	A retrospective single cohort study in commercial setting	Six hundred and fifty-four (n=654) patients with medial compartment knee OA were examined before and after 12 weeks of AposHealth	AposHealth	N/A	Pain significantly decreased by 30% (p<0.001). Function significantly improved by 29% (p<0.001). SF-36: PCS significantly improved by 28% (p<0.001). MCS significantly improved by 20% (p<0.001).

Link to source	Lubovsky et al., 2015. Israel	A retrospective single cohort study in commercial setting	One hundred and five (n=105) obese patients diagnosed with knee OA participated in the study and were treated with AposHealth for 12 months. Inclusion criteria were diagnosis of symptomatic bilateral knee OA of the medial compartment for at least six months, fulfilling the American College of Rheumatology clinical criteria for OA of the knee,17 a body mass index (BMI) > 30 kg/m2, having undergone a gait test and having completed questionnaires at baseline and after 3 and 12 months of therapy.	AposHealth	N/A	Pain significantly decreased by 46% (p<0.001). Function significantly improved by 45% (p<0.001). SF-36: PCS significantly improved by 27% (p<0.001). MCS significantly improved by 15% (p<0.001). Gait velocity improved by 16.5% (p<0.05)
Link to source	Elbaz et al., 2010 Israel	A retrospective single cohort study in commercial setting	Forty-six (n=46) patients with knee OA were included in the study. Eligibility to the study was defined as follows: 1. Patients suffering from symptomatic bilateral knee OA at the medial compartment for at least six months, fulfilling the ACR clinical criteria for OA of the knee, and having radiographically assessed OA of the knee according to Kellgren and Lawrence scale. Patients that have completed a gait test, WOMAC questionnaire and SF-36 Health Survey at baseline and after 12 weeks of treatments. All patients complied completely with the treatment protocol. Compliance was verified at several points	AposHealth	N/A	Pain significantly decreased by 26% (p<0.001). Function significantly improved by 34% (p<0.001). SF-36 significantly improved by 14% (p<0.001). Gait velocity improved by 10% (p<0.05) There were no reports of imbalance, tripping or other physical problems during the study period.

			during the study. After the first week and second week of treatment all patients received a telephone call to verify compliance. In addition, when they arrived at the therapy centre the physiotherapist also verified the patient's compliance with the treatment			
Link to source	Haim et al., 2012 Israel	A retrospective single cohort study in commercial setting	Forty-eight (n=48) patients with anterior knee pain participated in the study. Patients were treated with AposHealth for 6sixmonths. Anterior knee or retro-patellar pain for over three months diagnosed by a physician; reproducible pain upon carrying out at least two of the following functional activities: stair ascent or descent, squatting, kneeling, prolonged sitting or isometric quadriceps contraction; tenderness on palpation of the patella, or pain with stepping down or double leg squatting. There were no reports of imbalance, tripping or other physical problems during the study period. All patients completed the treatment program with satisfactory compliance (i.e., adherence of >75% of the proposed treatment protocol).	AposHealth	N/A	Pain significantly decreased by 49% (p<0.001). Function significantly improved by 42% (p<0.001). SF-36: PCS significantly improved by 14% (p<0.001). MCS significantly improved by 8% (p<0.001). Gait velocity improved by 8% (p<0.05) There were no reports of imbalance, tripping or other physical problems during the study period.
Link to source	Elbaz et al., 2014 Israel	A retrospective single cohort study in	Thirty-four (n=34) patients (18 women) diagnosed with medial compartment knee OA by their physician who has had a low-energy indirect injury to the knee, causing pain and functional limitation were included in the study. Patients were diagnosed with a large complex medial meniscal tear related to	AposHealth	N/A	All patients complied with the study protocol, and none reported any adverse events that disqualified them from the study. One patient chose to undergo knee arthroscopy and was

		commercial setting	the injury accompanied with bone bruise of the knee via magnetic resonance imaging (MRI). Symptomatically, patients reported a sudden increase in their knee pain and limitation in function following the injury. Patients were monitored for 12 months. All patients complied with the study protocol.			considered as a failure of treatment. Pain significantly decreased by 73% (p<0.001). Function significantly improved by 64% (p<0.001). SF-36: PCS significantly improved by 35% (p<0.001). MCS significantly improved by 16% (p<0.001). Gait velocity improved by 15% (p<0.05)
Link to source	Herman et al., 2018 Israel	A retrospective single cohort study in commercial setting	The study population included 518 patients, of which 336 (64.8%) patients were females and 182 (35.1%) patients were males. Patients had bilateral knee OA diagnosed by the referring physician (as defined by the American College of Rheumatology), patients that completed one-year follow-up and had a complete set of clinical questionnaires and spatiotemporal gait analysis.	AposHealth	N/A	Pain significantly decreased by 41% (p<0.001). Function significantly improved by 35% (p<0.001). SF-36 significantly improved by 16% (p<0.001). At baseline, the KOFG distribution has a symmetric bell-shaped with 17.6%, 36.9%, 32.5% and 13.1% in grades 1-4, respectively. This however changed with time to a distribution with a right tail as

						more patients have lower KOFG (better functional condition). At one year of follow-up this trend towards better KOFG was further improved with distribution of 32.9%, 43.3%, 18.9% and 5.0% for grades 1-4, respectively. The results of the current study validate the knee OA functional grade classification scheme as a tool to assess time-dependent changes in KOA as well as its sensitivity to assess treatment effect. The KOFG can offer a more robust mode of reporting clinical results in describing the natural history and time-dependent treatment results of patients suffering from knee OA and should be considered as an additional outcome measure in future studies.
Link to source	Miles et al., 2020 UK	A retrospective single cohort study in	Four hundred and fifty-five patients (n=457), 247 females (54%) and 208 males (46%) with symptomatic knee OA participated in this study. Patients were followed up for six months.	AposHealth	N/A	All spatial-temporal gait parameters significantly improved following three months of treatment (all less than $p < 0.01$).

		commercial setting				There were also further significant improvements in all parameters between 3 and 6 months of treatment (All less than $p < 0.01$), except SLS on both sides ($p = 0.554$ and 0.452). Specifically, gait velocity, step length and SLS of the more symptomatic knee improved by 13, 7.8 and 3% respectively ($p < 0.01$). There was a significant improvement in KOFG between baseline and three months follow-up ($p < 0.001$), with retained improvements at 6 months. More specifically, at baseline two thirds (71%) of the patients were classified with grade 1 and 2 (i.e., mild-moderate functional limitation) and a third of the patients (29%) were classified with grade 3 and 4 (i.e., moderate-severe functional severity). After six months of treatment 86% of the patients had a functional classification grade 1

						& 2 and 14% with grade 3 and 4, respectively. Following six months of treatment, all patients' self-evaluation questionnaires improved significantly. All WOMAC subscales significantly improved following three months of treatment, with further improvements at six months ($p < 0.001$). WOMAC Total, along with pain, function and stiffness subscales improved by 46.2, 48.6, 45.7 and 43.4% respectively ($p < 0.001$ for all). 67% of the patients met the OMERACT-OARSI criteria. All SF-36 subscales also significantly improved following three months of treatment ($p < 0.001$). After six months of treatment all subscales had significantly improved ($p < 0.001$). Specifically, SF-36 Total, PCS and MCS improved by 11.73, 15.7, and 9.62 points, or 22, 34 and 15% respectively compared to baseline. These improvements

						also met the minimal clinically important differences (MCID) for clinical significance of 7.8 points. A sub-group analysis revealed no baseline differences between those who were recommended joint replacement and those who were not. Both groups improved significantly over time ($p < 0.05$ for all).
Link to source	Elbaz et al., 2014 Singapore	Prospective, multi-centre single cohort study	Fifty-eight (n=58) patients (39 females and 19 males) diagnosed with primary medial compartment knee OA participated in this study, and 54 patients completed it (93%). Four patients did not complete the study: two patients did not comply with the treatment; one patient relocated and could not continue with therapy and one patient chose to undergo a total knee replacement. All remaining patients complied with the treatment, and there were no reports of any adverse events during the treatment period. Ninety-five percent of the patients (49 patients) had bilateral knee OA. The mean (standard deviation (SD)) age was 59.7 (6.1) years and mean (SD) body mass index (BMI) was 30.7 (14.6) kg/m2. Forty-four patients (82%) were Chinese, five	AposHealth	N/A	After 6 months of therapy, all parameters improved significantly compared to baseline. Pain significantly decreased by 68% ($p<0.001$). Function significantly improved by 76% ($p<0.001$). SF-36: PCS significantly improved by 46% ($p<0.001$). MCS significantly improved by 22% ($p<0.001$). Gait velocity improved by 16% ($p<0.05$)

			patients (9%) were Indian, and five patients (9%) were Malay. Patients' structural OA severity was determined by the Kellgren and Lawrence (KL) score. Twenty patients (37.0%) were graded 2, 21 patients (38.9%) were graded 3 and 13 patients (24.1%) were graded 4.			
Link to source	Goryachev et al., 2011 Israel	Prospective single cohort study	Fourteen (n=14) females with symptomatic bilateral medial compartment knee OA for at least 6 months, fulfillment of the American College of Rheumatology (ACR) criteria for OA of the knee and radiographic signs of OA in the medial compartment of the knee of grade two or greater on the Kellgren & Lawrence (K&L) scale. Patients were treated with AposHealth for 3 months.	AposHealth	N/A	The average EMG varied significantly with COP changes in at least one phase of stance in all examined muscles of the less symptomatic leg and in three muscles of the more symptomatic leg. After training, a significant increase in average EMG was observed in most muscles. Most muscles of the less symptomatic leg showed significantly increased peak EMG. Activity duration was shorter for all muscles of the less symptomatic leg (significant in the lateral gastrocnemius) and three muscles of the more symptomatic leg (significant in the biceps femoris). These results were associated with a significant reduction in pain (64%), increased function (51%) and improved spatiotemporal parameters (an

						increase of 8% in gait velocity). P<0.05 for all.
Link to source	Haim et al, 2011 Israel	Prospective, cross-sectional study	Twenty-two (n=22) female patients with symptomatic bilateral medial compartment knee OA participated in this trial. All patients had symptomatic knee OA for ≥6 months, fulfilled the ACR criteria for knee OA, had definite radiographic signs of OA in the medial compartment with KL grades from 1 to 4, and had no signs of lateral compartment joint space narrowing	AposHealth	N/A	Functional assessment was performed prior to testing by a single physician. Calibration of the biomechanical device was performed by a single trained physiotherapist. First, position of the elements for the "functional neutral sagittal axis" was determined and documented. The functional neutral axis was defined as the position in which the apparatus caused the least valgus or varus torque at the ankle. Medial and lateral axes were then defined as 0.8 cm medial and 1.5 cm lateral deviation of the biomechanical elements from the neutral sagittal axis, respectively. Successive testing, each with singular calibration of the apparatus, was conducted in four conditions: foot-worn platform with no elements attached (control condition); biomechanical elements placed at neutral axis;

						elements placed at lateral sagittal axis; and elements placed at medial sagittal axis. Modulation of the COP coronal trajectory from medial to lateral offset resulted in a significant reduction of the KAM. On average, translation of the elements from the neutral to the lateral configuration reduced 1st and 2nd peaks by 0.1 and 0.07 mN-m/kg, a reduction of 10% ($p < 0.001$) and 14% ($p < 0.001$), respectively, and reduced the knee adduction impulse by 0.54 N-m/kg/s, a reduction of 14% ($p < 0.001$). Translation of the elements from neutral to medial increased the 1st and 2nd peaks by 0.06 mN-m/kg ($p < 0.001$) and 0.04 mN-m/kg ($p < 0.06$), an increase of 8.4% and 8%, respectively, and increased the knee adduction impulse by 0.41 Nm/kg/sec, an increase of 10.8% ($p < 0.001$).

Table 2 Summary of all relevant abstracts

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text

Table 3 Summary of all relevant ongoing or unpublished studies

Data source	Author, year (expected completion) and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Outcomes
Supp. F	Greene et al., 2022, UK.* *Currently in peer-review. Expecting publication	Retrospective	Patient with knee OA eligible for Orthopaedic referral	AposHealth	NA	Surgery avoidance • Pain • Function • QoL • Gait • OKS Significant improvements were seen in WOMAC pain and function subscales of 34% and 31% respectively at 3 months, increasing to 42% and 39% at 6 months. These continued to improve to 49% and 54% respectively over the 2 years. 67% of patients met the OMERACT-OARSI criteria for clinically significant improvement. OKS improved by 7.6 points

						in the first 6 months of treatment, and further to 10.6 points at 2 years, meeting the minimally important change of 7 points
Link to source	Suk et al. Q2 2024, Geisinger Medical Center, PA, USA.	RCT comparing AposHealth as a non-invasive intervention compared to pos-TKR rehab with/without AposHealth. A RCT.	1. Patients with severe knee OA 2. Patient post primary TKR	Group 1 – Patients with severe knee OA treated with AposHealth Group 2 – Patients post TKR with traditional PT rehab Group 3 – Patients post TKR with traditional PT rehab and AposHealth	TKR/standard of care	Primary outcome measure: • Pain at 12 months Secondary outcome measures: • Function • Gait • QoL • Surgery avoidance • AE
Supp. G	Hillstrom H. 2022 Hospital for Special Surgery (HSS), NY, US.	A prospective single cohort study	Thirty adults (15 male, 15 female) with bilateral knee OA will be recruited for participation in this study. Inclusion criteria will be male or female, symptomatic bilateral medial compartment knee OA for at least 6	AposHealth	N/A	Outcome measures: • 3D gait analysis combined with EMG • PROMS

			months, KL 2-4, and visual analog scale pain (VAS) pain ≥ 30mm on both knees while walking 50' on the level or descending stairs.			
Supp. H	Truven Health Analytics, an IBM Company	Retrospective, longitudinal, pre-post cohort study	A total of 369 patients with 6 months and 214 patients with 12 months of pre- and post-index data with a claim for AposHealth were included in the study. Among the patients with 12 months pre- and post-index, 88 patients had a primary diagnosis of knee OA and 126 had a primary diagnosis of LBP.	AposHealth	Pre-AposHealth medical claims	The proportion of all patients using opioids dropped significantly after receipt of AposHealth (34.1% to 21.0%, p<0.001), and the use of oxycodone specifically fell by 40% (24.8% to 15.0%, p=0.002). LBP patients saw a larger drop than knee OA patients. The LBP cohort filled significantly fewer pain medications in the post- vs. pre-index period (7.3 +8.0 vs. 8.3 +8.4, p=0.03), and there was a 20 percentage-point drop in the proportion of LBP patients with an opioid prescription (pre:

						42.1% vs. post: 22.2%; p<0.001). The proportion of knee OA patients with a knee x-ray was reduced by more than half from 12 months pre- to 12 months post-index (54.5% to 23.9%; p<0.0001). The proportion of patients with a physical therapy visit for knee OA decreased significantly from pre- (28.8%) to post-index (10.3%; p<0.0001). The proportion of patients having a knee OA- or LBP-related OP office visit decreased from pre- to post-index in the knee OA cohort (79.5% to 52.3%; p<0.001) and LBP cohort (81.7% to 52.4%; p<0.001).

Supp J	Surgery avoidance rate	Data on file	Patients with knee OA	AposHealth	N/A	Two peer-reviewed publications support high surgery avoidance rate at 2-yrs following AposHealth. One study suggests that 97% of the patients treated with AposHealth avoided surgery compared to 70% of the controls (Bar-Ziv et al., 2013). Data on file provides a summary of a 5-yrs follow-up that was performed on the same cohort of patients. At 5 yrs., 15% of patients that were treated with AposHealth have had a TKR (85% surgery avoidance) compared to 45% of patients that received the standard of care (55% surgery avoidance). A second study suggests that 86% of the patients treated with

						AposHealth avoided surgery at 2-yrs compared to 12% in the control group. Another study is currently under peer-review evaluation. A UK-based study looked at NHS patients suffering from knee OA and eligible for secondary care. Results suggest that 84% of the patients that were treated with AposHealth avoided TKR at 2-yrs. (Greene et al. 2022). Data on file: 1. UK data - 13% of patients with a primary knee condition have had a surgical intervention to the knee at an average FU of 6 yrs. Data is for a UK private

						payor. Furthermore, an independent member survey suggests that 87% expect to delay surgery and 63% expect to avoid it altogether. 2. US data – a 2-yrs follow-up on surgery avoidance rate amongst patients with knee OA treated with AposHealth in commercial settings suggest that 96.5% of the patients avoid TKR at 1 year and 93% avoid TKR at 2 yrs. 3. IL data – 3-yrs. data on surgery avoidance suggest a 98%, 92% and 89% avoidance at 1-yr., 2-yrs., and 3-yrs., respectively.

Supp K	UK Private payor report	Independent report by a private UK payer	Patients with knee pain	AposHealth	N/A	• 92% of the patients are satisfied with AposHealth. • 93% are likely to recommend Apos to friends or family • 72% have fewer consultant visits • 87% expect to delay surgery • 63% expect to avoid surgery • Reduction in utilization – 82% stopped/reduces OTC, 80% stopped/ use less prescribed medication, 78% stopped/use less NSAIDs, 86% stopped/use less injections, 83% stopped/use less Physiotherapy, 78% stopped/use less braces, 51% stopped/use less orthotics.

Supp L	NHS CCG	Commercial audit	Patients eligible for TKR	AposHealth	N/A	98% of the patients treated with AposHealth are extremely likely / likely to recommend AposHealth to friends or family. Very high satisfaction rate concerning aspects associates with the delivery of care including waiting time, courtesy of physiotherapist, appointments are on time, and customer service

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Results of all clinical trials are summarised in Appendix I

Study	Results	Company comments
Reichenbach et al., 2020. Switzerland	• Primary outcome measure was pain. • The biomechanical footwear group had a larger decrease in standardized WOMAC pain subscore at 24 weeks of follow-up than the control footwear group (mean score, 1.3 vs 2.6, respectively; between-group difference, −1.3	This is a pivotal study for the company. A Level I double blind RCT on 220 patients demonstrated statistical and clinically significant outcomes for patients with knee OA. The results of this this study are supported with additional scientific evidence, both prospective clinical trials and real-life evidence, that will be described in detail below. The reduction in pain is associated with improved function and ultimately higher quality of life as reported by the patients. In addition, the

	[95% CI, −1.8 to −0.9]; *P* < .001). SMD for pain at 6 months was 0.67 with a NNT of 3. • 83% of patients in the biomechanical group had a 50% reduction in WOMAC pain, 92% with a 30% reduction compared to 42% and 58%, respectively in the control group (P< 0.001) • Secondary outcome measures included WOMAC scores, SF-36, and spatio-temporal gait analysis. • There were no significant adverse events associated with the treatment compared to controls. • Gait velocity improved by 37% (p<0.05) • Treatment is safe - no SAE associates with the device	improvements are also quantified objectively demonstrating a significant increase in walking speed (an indicator for longevity), longer step length and increased ability to bear single loads on the affected limbs. There are no other non-surgical interventions with such a high SMD and low NNT. In addition, the treatment is highly safe, with no serious adverse events associates with the interventions. Patients that have failed the first line of treatment and are still in pain can benefit from using AposHealth. It can be a non-invasive alternative for other non-surgical interventions (pharmacological, devices, injections) and will help delay surgery.
Drew et al., 2022. US	Over the 24-month study period, 34 patients who received the intervention (14%, 95% CI 82%–91%) progressed to a TKR. The average time to progress to TKR was 324 days (ranging from 31 to 671 days). Sixty-four percent (64%) of those who underwent TKR had their surgery within 12 months from baseline (treatment initiation). Of the 294 patients in the control group who chose TKR surgery, 259 (88%) received a knee replacement. With respect to the clinical outcomes measurements, for the 172 patients who chose the biomechanical intervention and who completed the program, 138 (88%) had clinical data at three months, 111 (65%) patients had clinical data at six months, and 52 (30%) patients had clinical data at 12 months.	The results of this study suggests that patients with severe knee OA who are eligible for a TKR can benefit from AposHealth clinically. It is assumed that the positive clinical effect (reduction in pain and improvement in functions) led most patients to reconsider surgery. It is reasonable to assume that patients that are on the waiting list, even if they have joined early knowing that the waiting times are long, may also benefit from this intervention as most likely they have failed the core interventions. Additional information on surgery avoidance will be provided below, however in short, the rates of surgery avoidance mirror in different populations (UK, US, IL)

	The General Mixed Model which includes repeated measures from 4 visits showed a significant reduction in WOMAC pain (P < 0.001) and WOMAC function (P < 0.001) after 12 months of treatment. It is estimated that pain decreased by 19.6 points (36%) at the end of year 1, and functional disability decreased by 16.4 points (34%). There was a significant increase in the SF-36 overall score by 5.4 points (10%) at 1 year (P < 0.001). Likewise, the PCS increased significantly by 5.6 points (13%) after 12 months of treatment (P < 0.001). No significant changes in MCS were noted. Gait velocity improved by 11% (p<0.05)	
Bar-Ziv et al., 2010. Israel	At the 8-week endpoint the WOMAC pain score and function score revealed significant differences between the groups over time (Time by treatment interaction, p < 0.001). The active group reported significant pain relief after 8 weeks of treatment with a mean difference of 3.5 cm (64.8%) and a 95% confidence interval ranging between 2.7-4.4. In contrast, the control group reported no pain relief, having a mean increase of 0.4 cm (8%) with a 95% confidence interval ranging between -1.7-0.8. The active group reported significant improvement on the WOMAC function scale with a mean decrease of 3.2 cm (62.7%) after 8 weeks and a 95% confidence interval ranging between 2.5-4.1. The control group reported no function improvement, having a mean	Text

	increase of 0.5 cm (9.8%) with a 95% confidence interval ranging between -1.4-0.5. QoL: PCS - An increase of 50% at 2 months in the AposHealth group compared to a 11% deterioration in the control group. MCS - An increase of 58% at 2 months in the AposHealth group compared to a 21% decrease in the control group Patients also demonstrated a significant improvement in ALF – a functional test, and in the Knee Society Score questionnaires Unmarked acetaminophen - Patients from the control group use more of the rescue medication given to them at the start of the study than did the active group. After 4 weeks, the active group as a whole consumed 145 rescue pills whereas the control group consumed 281 pills. After 8 weeks, the active group consumed 128 pills and the control group consumed 366 pills. Overall, the active group consumed 273 pills and the control group consumed 647 pills. No side effects were reported by any of the patients.	
Haim et al., 2011. Israel	Post-treatment testing demonstrated a reduction of the KAM magnitude during the stance phase. The knee adduction impulse and the 1st and the 2nd KAM peaks were reduced by 0.54N-m/kg/sec, 0.06 N-m/kg, and 0.07N-m/kg, respectively. A reduction of 15%, 18%, and 17%, respectively, from the pre-training values. Velocity improved by 10% ($p<0.05$).	The results of this study and the study below (Debbi et al) are an indication of biomechanical changes and gait adaptations that occur following AposHealth. In addition to the significant clinical improvement, which is in accordance with other studies, these two studies suggest a reduction in the knee adduction moment and knee flection moment – both are strong biomechanical indicators for disease severity and progression. The knee adduction moment also correlates with likelihood of TKR.

	Patient self-reported WOMAC pain scores and function scores and SF-36 revealed a significantly favourable outcome at the 3-month follow-up and the 9-month endpoint (p<0.001). Overall pain was reduced by 61%, and function and QoL have improved by 63% and 32%, respectively.	Based on these results, it can be assumed that an inherent change occurs in the pathomechanics of the disease which might provide insight on the mechanism of action of AposHealth and how it treated knee OA.
Debbi et al., 2015 Israel	Peak knee flexion moment (KFM) at loading response decreased significantly with therapy (p = 0.001). Duration of KFM and impulse of knee flexion also decreased significantly (p = 0.024 and p = 0.029, respectively). These changes were accompanied by increased walking velocity, significant pain reduction, and increased functional activity. Post-training kinetic evaluation demonstrated profound alterations of knee sagittal moments at the loading response KFM. - A 49% reduction in knee flexion moment during loading response - A 40% reduction in peak knee flexion moment during loading response Velocity improved by 10% (p<0.05) Patient self-reported WOMAC pain scores and function scores as well as SF-36 revealed a significantly favourable outcome at the 3-month follow-up and the 9-month endpoint (p<0.001). Overall pain reduced by 61% and function and QoL have improved by 63% and 32%, respectively.	Text
Bar-Ziv et al., 2013. Israel	A significant difference was found between the active and control groups in all three WOMAC categories (pain, stiffness, and function) at the two-year endpoint. There was also a significant difference in improvement over time	Text

	between groups in all three categories (for interaction =16.8, 21.7 and 18.1 for pain, stiffness, and function, respectively). At 2 years, patients treated with AposHealth improved by 62% compared to an increase of 24% in the control group. Patients also reported a 61% improvement in function compared to a deterioration of 12% in the control group. A significant difference between the active and control groups was also found in ALF score at the two-year endpoint (P<0.001). The two groups did not differ significantly in their improvement over time (F for interaction =0.67). At the two-year endpoint, a significant difference was found between groups in all categories of the SF-36 except for the category of emotional well-being. This is reflected in the two summary indices of the SF-36: the SF-36 PCS and SF-36 MCS (P<0.001). There was a significant difference in improvement over time between groups in the SF-36 PCS (F for interaction =5.8) but not in the SF-36 MCS (for interaction =0.032). At the two-year endpoint, a significant difference was found between groups in the KSS-K and the KSS-F (P<0.001). The two groups also differed significantly in their improvement over time in the KSS-K (F for interaction =4.3) and the KSS-F (F for interaction =6.5). The groups also differed in the number of total knee replacements (TKRs) performed at two years. One patient from the active group required a TKR during the study period	

	(2.6%), while 5 patients (31%) of the control group required a TKR during the two-year study period.	
Lador et al., 2013 Israel	Pain significantly decreased by 31% (p<0.001). Function significantly improved by 28% (p<0.001). SF-36: PCS significantly improved by 21% (p<0.001). MCS significantly improved by 12% (p<0.001). Gait velocity improved by 10% (p<0.05)	Text
Drexler et al., 2012. Israel	Pain significantly decreased by 30% (p<0.001). Function significantly improved by 29% (p<0.001). SF-36: PCS significantly improved by 28% (p<0.001). MCS significantly improved by 20% (p<0.001).	A sub-group analysis of age (above and below 66 yrs.), BMI (above and below 28 m^2/kg) and gender was conducted. Both age groups improved significantly following treatment. Based on the results of this study, age, gender and BMI should not affect patient eligibility to the treatment, assuming all suffer from knee OA.
Lubovsky et al., 2015. Israel	Pain significantly decreased by 46% (p<0.001). Function significantly improved by 45% (p<0.001). SF-36: PCS significantly improved by 27% (p<0.001). MCS significantly improved by 15% (p<0.001). Gait velocity improved by 16.5% (p<0.05)	This study looked at a sub-group of knee OA patients, obese patients (BMI>35 m^2/kg). The results suggest that the clinical effect of the treatment for obese patients with knee OA is similar non-obese patients. Obesity should not be a contraindication for the treatment.
Elbaz et al., 2010 Israel	Pain significantly decreased by 26% (p<0.001). Function significantly improved by 34% (p<0.001). SF-36 significantly improved by 14% (p<0.001). Gait velocity improved by 10% (p<0.05)	Text

	There were no reports of imbalance, tripping or other physical problems during the study period	
Haim et al., 2012 Israel	Pain significantly decreased by 49% (p<0.001). Function significantly improved by 42% (p<0.001). SF-36: PCS significantly improved by 14% (p<0.001). MCS significantly improved by 8% (p<0.001). Gait velocity improved by 8% (p<0.05) There were no reports of imbalance, tripping or other physical problems during the study period.	Anterior knee pain is a limiting condition with no effective interventions. Being able to manipulate the centre of pressure and reduce loads form the anterior aspect of the knee while training neuromuscular control helps alleviate pain. Anterior knee pain is more common in the younger population and given that there are no effective interventions to treat anterior knee pain, providing AposHealth will help with this patient population.
Elbaz et al., 2014 Israel	All patients complied with the study protocol, and none reported any adverse events that disqualified them from the study. One patient chose to undergo knee arthroscopy and was considered as a failure to treatment. Pain significantly decreased by 73% (p<0.001). Function significantly improved by 64% (p<0.001). SF-36: PCS significantly improved by 35% (p<0.001). MCS significantly improved by 16% (p<0.001). Gait velocity improved by 15% (p<0.05)	
Herman et al., 2018 Israel	Pain significantly decreased by 41% (p<0.001). Function significantly improved by 35% (p<0.001). SF-36 significantly improved by 16% (p<0.001).	Text

	At baseline, the KOFG distribution has a symmetric bell-shaped with 17.6%, 36.9%, 32.5% and 13.1% in grades 1-4, respectively. This however changed with time to a distribution with a right tail as more patients have lower KOFG (better functional condition). At one year of follow-up this trend towards better KOFG was further improved with a distribution of 32.9%, 43.3%, 18.9% and 5.0% for grades 1-4, respectively. The results of the current study validate the knee OA functional grade classification scheme as a tool to assess time-dependent changes in KOA as well as its sensitivity to assess treatment effect. The KOFG can offer more robust reporting clinical results in describing the natural history and time-dependent treatment results of patients suffering from knee OA and should be considered an additional outcome measure in future studies.	
Miles et al., 2020 UK	All spatial-temporal gait parameters significantly improved following three months of treatment (all less than $p < 0.01$). There were also further significant improvements in all parameters between 3 and 6 months of treatment (All less than $p < 0.01$), except SLS on both sides ($p = 0.554$ and 0.452). Specifically, gait velocity, step length and SLS of the more symptomatic knee improved by 13, 7.8 and 3%, respectively ($p < 0.01$). There was a significant improvement in KOFG between baseline and three months follow-up ($p < 0.001$), with	Text

	retained improvements at six months. More specifically, at baseline two thirds (71%) of the patients were classified with grade 1 and 2 (i.e., mild-moderate functional limitation) and a third of the patients (29%) were classified with grade 3 and 4 (i.e., moderate-severe functional severity). After six months of treatment 86% of the patients were with a functional classification grade 1 & 2 and 14% with grade 3 and 4, respectively. Following six months of treatment, all patients' self-evaluation questionnaires improved significantly. All WOMAC subscales significantly improved following three months of treatment, with further improvements at six months ($p < 0.001$). WOMAC Total, along with pain, function and stiffness subscales improved by 46.2, 48.6, 45.7 and 43.4% respectively ($p < 0.001$ for all). 67% of the patients met the OMERACT-OARSI criteria. All SF-36 subscales also significantly improved following 3 months of treatment ($p < 0.001$). After 6 months of treatment all subscales had significantly improved ($p < 0.001$). Specifically, SF-36 Total, PCS and MCS improved by 11.73, 15.7, and 9.62 points, or 22, 34 and 15% respectively compared to baseline (See Table Table4).4). These improvements also met minimal clinical important differences (MCID) for clinical significance of 7.8 points. A sub-group analysis revealed no baseline differences between those who were recommended joint replacement	

	and those who were not. Both groups improved significantly over time ($p < 0.05$ for all).	
Elbaz et al., 2014 Singapore	After six months of therapy, all parameters improved significantly compared to baseline. Pain significantly decreased by 68% ($p<0.001$). Function significantly improved by 76% ($p<0.001$). SF-36: PCS significantly improved by 46% ($p<0.001$). MCS significantly improved by 22% ($p<0.001$). Gait velocity improved by 16% ($p<0.05$)	Study suggests similar clinical effect in an Asian population
Goryachev et al., 2011 Israel	The average EMG varied significantly with COP changes in at least one phase of stance in all examined muscles of the less symptomatic leg and in three muscles of the more symptomatic leg. After training, a significant increase in average EMG was observed in most muscles. Most muscles of the less symptomatic leg showed significantly increased peak EMG. Activity duration was shorter for all muscles of the less symptomatic leg (significant in the lateral gastrocnemius) and three muscles of the more symptomatic leg (significant in the biceps femoris). These results were associated with a significant reduction in pain (64%), increased function (51%) and improved spatiotemporal parameters (an increase of 8% in gait velocity). $P<0.05$ for all.	Text

Haim et al., 2011 Israel	Functional assessment was performed prior to testing by a single physician. Calibration of the biomechanical device was performed by a single trained physiotherapist. First, position of the elements for the “functional neutral sagittal axis” was determined and documented. The functional neutral axis was defined as the position in which the apparatus caused the least valgus or varus torque at the ankle. Medial and lateral axes were then defined as 0.8 cm medial and 1.5 cm lateral deviation of the biomechanical elements from the neutral sagittal axis, respectively. Successive testing, each with singular calibration of the apparatus, was conducted in four conditions: foot-worn platform with no elements attached (control condition); biomechanical elements placed at neutral axis; elements placed at lateral sagittal axis; and elements placed at medial sagittal axis. Modulation of the COP coronal trajectory from medial to lateral offset resulted in a significant reduction of the KAM. On average, translation of the elements from the neutral to the lateral configuration reduced 1st and 2nd peaks by 0.1 and 0.07 mN-m/kg, a reduction of 10% ($p < 0.001$) and 14% ($p < 0.001$), respectively, and reduced the knee adduction impulse by 0.54 N-m/kg/s, a reduction of 14% ($p < 0.001$). Translation of the elements from neutral to medial increased the 1st and 2nd peaks by 0.06 mN-m/kg ($p < 0.001$) and 0.04 mN-m/kg ($p < 0.06$), an increase of 8.4% and 8%,	Text

	respectively, and increased the knee adduction impulse by 0.41 Nm/kg/sec, an increase of 10.8% ($p < 0.001$).	

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

Effect of Biomechanical Footwear on Knee in People With Knee Osteoarthritis. The BIOTOK Randomized Clinical Trial **Reichenbach et al., 2020.**	
How are the findings relevant to the decision problem?	Level I large scale RCT comparing AposHealth to a sham device in 220 patients with knee OA. The study was conducted by KOL in knee OA and was published in JAMA. Results suggest a superiority effect to AposHealth with respect to pain reduction, with a high effect size (ES = 0.72), low NNT (NNT = 3), minimal adverse events (not more than controls) and no serious adverse events. The authors concluded that the treatment is safe and effective. This was the pivot trial in the company's FDA submission that led to approve AposHealth as a Class I Medical device for patients with knee OA
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	• The control group was comprised of a sham device with similar treatment plan. In essence this group can also be referred as 'active controls as they were asked to follow a walking protocol. However, AposHealth was found superior even in this scenario (actively walking = type of exercise), hence it can be assumed that group differences would have been higher if no activity was done at all.

	• Analgesic treatment for pain was allowed during the trial; however, the rates of analgesic use did not differ between groups.
How was the study funded?	The trial was sponsored by Bern University Hospital and coordinated by CTU Bern, the University of Bern's clinical trials unit. The trial was funded by the Mäxi Foundation. Dr Jüni is a tier 1 Canadian research chair in clinical epidemiology of chronic diseases; this research was completed, in part, with funding from the Canada Research Chairs Programme. Apos Medical Assets provided the biomechanical footwear system and the control footwear, and provided the technicians trained to install and calibrate the external pods on the biomechanical footwear without charge.

Avoidance of total knee replacement in a population health setting. Introducing a non-invasive biomechanical intervention for patients with knee osteoarthritis **Drew et al., 2022.**	
How are the findings relevant to the decision problem?	Results suggest that 86% of TKR candidates treated with AposHealth avoided TKR at a 2-yrs compared to 12% in the controls. These results were associated with significant clinical improvement. This is an indication that patients with severe knee OA who are eligible for a TKR can benefit from AposHealth clinically. It is assumed that the positive clinical effect (reduction in pain and improvement in functions) led most patients to reconsider surgery. It is reasonable to assume that patients that are on the waiting list, even if they have joined early knowing that the waiting times

	are long, may also benefit from this intervention as most likely they have failed the core interventions. The results of this study are also supported with additional information on surgery avoidance in different populations (UK, US, IL)
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function • Reduced need for knee replacement surgery
Will any information from this study be used in the economic model?	Yes. Surgery avoidance rates will be used in the economic model
What are the limitations of this evidence?	Patients chose their group allocation hence the possibility of a selection bias cannot be ruled out. However, it is noteworthy that randomising patients against their choice was not possible and such a study methodology is impossible.
How was the study funded?	No external funding was received for this article

A treatment applying a biomechanical device to the feet of patients with knee osteoarthritis results in reduced pain and improved function: a prospective controlled study **Bar-Ziv et al., 2010.**	
How are the findings relevant to the decision problem?	The results support a superiority effect for AposHealth compared to a sham device with a significant reduction in pain and improvement in function as well as an increase in QoL. In additions, patients who were treated with AposHealth consumed less rescue medicine (paracetamol) compared to controls.

Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	This study lacked randomization in the assignment of the patients to control and active groups. However, both groups were similar in their characteristics.
How was the study funded?	No external funding was received for this study

Reduction in knee adduction moment via non-invasive biomechanical training: A longitudinal gait analysis study **Haim et al., 2011.**	
How are the findings relevant to the decision problem?	This study provides evidence that biomechanical indicators for disease severity and progression are positively impacted following AposHealth. More specifically, the knee adduction moment, which is a primary biomechanical indicator for disease severity and progression, decreased significantly following nine months of AposHealth. These results were accompanied by a significant reduction in pain and improvement in function and QoL. The results of this study provides indication of the mechanism of actions and the biomechanical effect of AposHealth on the underlying biomechanical causes for knee OA.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function

Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	This involved a relatively small cohort with no control group. However, the primary outcome of this study was changes in the knee adduction moment using 3D gait analysis. Tests and objective and done in laboratory settings, hence the changes in kinetics and kinematics are accurate and valid, with minimal external (subject) bias.
How was the study funded?	No external funding was received for this study

Alterations in Sagittal Plane Knee Kinetics in Knee Osteoarthritis Using a Biomechanical Therapy Device **Debbi et al., 2015**	
How are the findings relevant to the decision problem?	The results of this study provide evidence that biomechanical indicators for disease severity and progression are positively impacted following AposHealth. More specifically, the knee flexion moment, which is a primary biomechanical indicator for disease severity and progression, decreased significantly following nine months of AposHealth. These results were accompanied by a significant reduction in pain and improvement in function and QoL.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No

What are the limitations of this evidence?	This study comprises a relatively small cohort with no control group. However, the primary outcome of this study was changes in the knee adduction moment using 3D gait analysis. Tests ~~and objective and done~~ were undertaken in laboratory settings, hence the changes in kinetics and kinematics are accurate and valid, with minimal external (subject) bias.
How was the study funded?	No external funding was received for this study

Long-Term Effects of AposTherapy in Patients with Osteoarthritis of the Knee: A Two-Year Follow-up **Bar-Ziv et al., 2013**	
How are the findings relevant to the decision problem?	The results of this study provide long-term evidence on the clinical effectiveness of AposHealth in reducing pain and improving function relative to a cohort of patients that was treated with the standard of care. At 2-yrs patients maintain the significant clinical outcomes with a large effect size of 1.44. In comparison, patients that were in the control group that were treated with the standard of care and reported a slight deterioration in symptoms at 2-yrs. This is not surprising given that knee OA is a chronic condition that often progresses with time. In addition, the results also support a reduction in decay rates to TKR at 2-yrs in patients that were treated with AposHealth compared to controls. Only 2.5% of the patients that were treated with AposHealth have had a TKR withing 2-yrs compared to 30% in the control group.

Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function • Reduced need for knee replacement surgery
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	• This was not a randomised trial. Nevertheless, the two groups were equal at the baseline in terms of patient characteristics and clinical outcomes. In additions, the sample size is relatively small. We consider the results of this study to be supportive to our pivotal RCT.
How was the study funded?	No external funding was received for this study

Non-invasive biomechanical therapy improves objective and subjective measurements of pain and function in patients with knee osteoarthritis: a retrospective analysis **Lador et al., 2013.**	
How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. Real-life evidence are as equally important as clinical trials as it better reflects reality. The results support a significant reduction in pain and improvement in function and QoL. In addition, a significant improvement was also seen in objective gait patterns.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit:

	• Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	A retrospective analysis was undertaken with no control group. Nevertheless, the primary measurements of this study were objective gait parameters of these patients. These measurements were found to correlate with the patient's subjective assessments, thus validating, to a certain extent, the success of this suggested therapy.
How was the study funded?	No external funding was received for this study

Effects of a customized biomechanical therapy on patients with medial compartment knee osteoarthritis **Drexler et al., 2012.**	
How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. Real-life evidence are as equally important as clinical trials as it better reflects reality. The results support a significant reduction in pain and improvement in function and QoL. Sub-group analysis of the data suggest that the treatment is not sensitive to age, gender, or BMI and that there should not be a limitation receiving this intervention in those sub-groups.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function

Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	The study involved a retrospective analysis with no controls group.
How was the study funded?	No external funding was received for this study

A novel self-care biomechanical treatment for obese patients with knee osteoarthritis. Lubovsky et al., 2015	
How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. The results of this study provide more information on the effect of treatment in a subgroup of patients – obese patients with knee OA. Obesity is one of the reasons for knee OA and helping this specific population be more active is positive not just for treating their knee pain, but also to help with other health issues. The results support a significant reduction in pain and improvement in function and QoL. In addition, a significant improvement was also seen in objective gait patterns.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	A retrospective analysis was undertaken with no control group. In addition, weight change was not monitored over time. It cannot be determined whether (or to what extent) the improvements in gait pattern, pain and

	function are due to weight reduction or the intervention itself. However, we anticipate that the reduction in pain while using Apos would enable patients to be more active, leading to improvement over time. It is similar to the chicken and egg syndrome, but the positive effect is what matters.
How was the study funded?	No external funding was received for this study

APOS therapy improves clinical measurements and gait in patients with knee osteoarthritis **Elbaz et al., 2010**	
How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. The results support a significant reduction in pain and improvement in function and QoL. In addition, a significant improvement was also seen in objective gait patterns.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	This was a retrospective study with no control group. Nevertheless, the primary measurements of this study were objective gait parameters of these patients that are not commonly used in knee OA studies.
How was the study funded?	No external funding was received for this study

The outcome of a novel biomechanical therapy for patients suffering from anterior knee pain **Haim et al., 2013**	
How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. The results of this study provide more information on the effect of treatment in a subgroup of patients that suffer from anterior knee pain. Anterior knee pain is a limiting condition with no effective interventions. Being able to manipulate the centre of pressure and reduce loads form the anterior aspect of the knee while training neuromuscular control helps alleviate pain. The results support a significant reduction in pain and improvement in function and QoL. In addition, a significant improvement was also seen in objective gait patterns. Anterior knee pain is more common in the younger population and given that there are no effective interventions to treat anterior knee pain, providing AposHealth will help with this patient population
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	This comprised a retrospective analysis with no control group. In addition, only spatiotemporal gait data were gathered. A three-dimensional gait analysis would offer far greater information regarding the kinematics and kinetics of the lower limb in this unique group of patients.
How was the study funded?	No external funding was received for this study

A unique foot-worn device for patients with degenerative meniscal tear **Elbaz et al., 2012**	
How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. The results of this study provide more information on the effect of treatment in a subgroup of patients – patients with knee OA and a degenerative meniscal tear. Although, arthroscopic intervention is clearly not recommended in the management of knee OA (except for specific cases of joint locking), some are still recommending it as a treatment option. The results provide a strong indication that patients with degenerative meniscal tear can benefit from a non-surgical intervention. Following AposHealth there was a significant reduction in pain and improvement in function and QoL. In addition, a significant improvement was also seen in objective gait patterns. Furthermore, only one patient (3%) had a knee arthroscopy at 12 months.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No

What are the limitations of this evidence?	This was a retrospective analysis with no control group. In addition, the interventions did not commence immediately following the injury but within a 3-month time window.
How was the study funded?	No external funding was received for this study

Knee Osteoarthritis functional classification scheme – validation of time dependant treatment effect. One year follow-up of 518 patients **Herman et al., 2018**	
How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. This study used an objective functional classification for patients with knee OA to help assess their limitations pre-interventions and assess the changes in classification as an objective measure post-intervention (any intervention). Gait is a vital sign with great importance and may help objectively assess patients. We believe that improved functionality is an important outcome measure when assessing interventions to treat knee OA. The results support a significant reduction in pain and improvement in function and QoL. In addition, a significant improvement was also seen in objective gait patterns. Patients shifted from a severe gait classification group to a less severe one, indicating better movement patterns.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function

Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	A retrospective analysis with no control group was undertaken. Previous studies have reported a placebo effect in knee OA studies, especially for pain, stiffness, and self-reported function. Without a control group we cannot estimate the placebo effect, however we believe that the effect of treatment is beyond the placebo effect as the effect size of the treatment was larger than the effect size that was reported for the placebo effect.
How was the study funded?	No external funding was received for this study

Patients with knee osteoarthritis demonstrate improved gait pattern and reduced pain following a non-invasive biomechanical therapy: a prospective multi-centre study on Singaporean population Elbaz et al., 2014	
How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. The results provide more information on the clinical effect of the intervention in an Asian population providing evidence that the treatment is no sensitive to race. The results support a significant reduction in pain and improvement in function and QoL. In addition, a significant improvement was also seen in objective gait patterns.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function

Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	There was no control group.
How was the study funded?	No external funding was received for this study

Foot centre of pressure manipulation and gait therapy influence lower limb muscle activation in patients with osteoarthritis of the knee **Goryachev et al., 2011**	
How are the findings relevant to the decision problem?	This study provides evidence of changes in muscle activation patterns following treatment with AposHealth. A change in muscle activations was seen after three months of treatment, indicating that induced perturbation for neuromuscular training led to improved muscle activation. These results were also supported with an improvement in clinical outcomes including a significant reduction in pain and improvement in function and QoL.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	First, the study cohort was relatively small. Second, since no normalisation procedure on the data was performed, the ARV and peak EMG values are valid for this study only and cannot be compared to

	other studies. However, there was a consistent increase of ARV and peak EMG after training for almost all examined muscles, so it is reasonable to assume that it was induced by the training and not by the varying factors of signal acquisition.
How was the study funded?	No external funding was received for this study

Surgery avoidance rates among total knee replacement candidates following a non-invasive biomechanical intervention: A retrospective cohort study **Greene et al., 2012 (In peer-review)**	
How are the findings relevant to the decision problem?	Results suggest that 84% of TKR candidates treated with AposHealth avoided TKR at a 2-yrs. These results were associated with a significant clinical improvement. OKS has improved by 7.6 points in the first 6 months of treatment, and further to 10.6 points at 2 years, meeting the minimally important change of 7 points. This study is currently under peer-review evaluation in the Journal of Orthopaedic Experience & Innovation. The manuscript was submitted for review on June 1st and we expect to receive a decision in about 2 months.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function • Reduced need for knee replacement surgery
Will any information from this study be used in the economic model?	No

What are the limitations of this evidence?	This was a commercial audit with no control group. However, studies have reported that 33% of the patients that are referred to secondary consultation by a general practitioner will undergo surgery within 12 months. This is over 5-times more than the 6% seen in the present study.
How was the study funded?	No external funding was received for this study

6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

N/A

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

One RCT thoroughly assess the safety of the treatment in a RCT comparing AposHealth to a sham device in 220 patients diagnosed with knee OA. In summary, the authors have reported the treatment to be safe and effective (Reichenbach et al 2020).

Twenty-six participants (23.4%) in the biomechanical footwear group and 38 participants (34.9%) in the control footwear group experienced an adverse event and 3 (2.7%) and 9 (8.3%), respectively, experienced serious adverse events (Table 3). None were considered to be related to treatment. Of the serious adverse events, there were 0 in the biomechanical footwear group vs 4 in the control footwear group that were musculoskeletal, 1 vs 3, respectively, that were circulatory, and 2 vs 2 that were in other categories (eTable 12 in Supplement 3). One or more falls occurred in 2 participants (1.8%) in the biomechanical footwear group and in 4 participants (3.7%) in the control footwear group. One participant in the control group fell while wearing the control footwear.

Table 3. Adverse Events[a]

	No. (%)	
	Biomechanical Footwear (n = 111)	Control Footwear (n = 109)
Any adverse events	26 (23.4)	38 (34.9)
Minor adverse events	23 (20.7)	30 (27.5)
Musculoskeletal	15 (13.5)	21 (19.3)
Knee pain or swelling[b]	2 (1.8)	3 (2.8)
Low back pain	5 (4.5)	5 (4.5)
Hip pain	5 (4.5)	3 (2.8)
Foot pain	2 (1.8)	3 (2.8)
Other	3 (2.7)	8 (7.3)
Injury	6 (5.4)	9 (8.3)
Ankle sprain	2 (1.8)	1 (0.9)
Fall[c]	2 (1.8)	4 (3.7)
Other	2 (1.8)	4 (3.7)
Genitourinary	2 (1.8)	2 (1.8)
Circulatory	1 (0.9)	1 (0.9)
Nervous system	0	2 (1.8)
Eye	0	1 (0.9)
Respiratory system	1 (0.9)	0
Digestive system	1 (0.9)	0
Serious adverse events[d]	3 (2.7)	9 (8.3)
Musculoskeletal	0	4 (3.7)
Total hip or knee replacement surgery	0	3 (2.8)
Low back pain[e]	0	1 (0.9)
Circulatory	1 (0.9)	3 (2.8)
Coronary heart disease[f]	1 (0.9)	2 (1.8)
Other	0	1 (0.9)
Genitourinary	1 (0.9)	0
Eye	0	1 (0.9)
Digestive system	1 (0.9)	1 (0.9)

[a] Adverse event categories correspond to chapters in the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision,* and are summarized as clinical subcategories if at least 3 participants experienced a specific type of event.

[b] Corresponds to local adverse events as prespecified in the protocol.

[c] Prespecified in the statistical analysis plan. One participant in the control footwear group experienced a fall while wearing the study footwear.

[d] Defined as events resulting in hospitalization, prolongation of hospitalization, persistent or significant disability, congenital abnormality or birth defects of offspring, life-threatening events, or death.

[e] One participant in the control footwear group underwent lumbar disc herniation surgery.

[f] One participant in the biomechanical footwear group had an acute myocardial infarction.

eTable 12. Serious adverse events and relationship to intervention

SAE category	Clinical description	Treatment group	Relationship to treatment*
Musculoskeletal	Lumbar spine disc herniation surgery	Control	Unlikely
Musculoskeletal	Total hip replacement surgery	Control	Unlikely
Musculoskeletal	Total knee replacement surgery	Control	Unlikely
Musculoskeletal	Total knee replacement surgery	Control	Unlikely
Circulatory	Acute myocardial infarction with angiography	Experimental	Unlikely
Circulatory	Atrial fibrillation with angiography	Control	Unlikely
Circulatory	Coronary heart disease with angiography	Control	Unlikely
Circulatory	Varicose vein surgery	Control	Unlikely
Digestive	Acute appendicitis with appendectomy	Experimental	Unlikely
Digestive	Inguinal hernia repair surgery	Control	Unlikely
Eye	Central retinal artery occlusion	Control	Unlikely
Genitourinary	Renal colic due to kidney stones	Experimental	Unlikely

* This table lists all serious adverse events that occurred during the trial and their deemed causal relationship to the intervention (classified as certain, probable, possible, unlikely, and unclassifiable). Serious adverse events were defined as events resulting in hospitalization, prolongation of hospitalization, persistent or significant disability, congenital abnormality or birth defects of offspring, life-threatening events, or death.

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

N/A

Report all relevant results, including diagrams if appropriate.

Enter text.

Explain the main findings and conclusions drawn from the evidence synthesis.

Enter text.

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

Osteoarthritis (OA) is a major cause of pain and disability, with 18.8 million people being affected across the UK. In England, one in five people over the age of 45 has knee OA and the rates are constantly increasing due to an aging population and a rise in obesity (Arden and Nevitt 2006, Arthritis 2019). Knee OA leads to major social, psychological, and economical burdens with a substantial financial burden to the individual and society. Overall annual costs of OA to the healthcare system are estimated to be £10.2 billion (Woolf 2018).

The care management of knee OA is a stepped programme aiming to alleviate symptoms, provide joint stability, and postpone disease progression (Wallis, Taylor et al. 2019). The National Institute of Clinical Excellence (NICE) guidelines (Conaghan, Dickson et al. 2008) outline core treatments such as education and exercise as first-line care, progressing to more advanced modalities such as biomechanical interventions, including valgus knee braces and orthotics, alongside with pharmacological interventions and knee injections (Figure 3) (NICE). Total knee replacement (TKR) is considered the most common treatment for end-stage knee OA and appears to be increasing over time (Carr, Robertsson et al. 2012). It is estimated that the rates of TKA will reach 119,000 procedures per year by 2035 and 226,000 procedures per year by 2050 (Culliford, Maskell et al. 2015, Klug, Gramlich et al. 2021). At the same time, because the average age for a TKR is falling, the

prevalence of revision knee surgery is also expected to rise even more rapidly by almost 90%, reaching nearly 47,500 procedures per year by 2050 (Klug, Gramlich et al. 2021). Despite the favourable surgical outcomes, approximately 20% of post-TKR patients continue to experience chronic pain and an equal number report that their expectations for a full recovery are unmet (Tilbury, Haanstra et al. 2016, Wylde, Beswick et al. 2018). These projections show that the steep increase in TKR and revision surgeries will place an immense burden on the cost of health care, highlighting the urgent need for new non-surgical approaches that more effectively manage OA symptoms of the knee (Klug, Gramlich et al. 2021).

Figure 3. NICE Treatment Guidelines for knee OA

NICE treatment guidelines for knee OA			
	Strongly recommended	**Adjunct to core treatment**	**Recommended against use**
Non-invasive treatments	Education, advice, information access	Manual therapy (manipulation and stretching)	Nutraceuticals
	Strengthening exercise, aerobic fitness training	Thermotherapy	Acupuncture
	Self efficacy and self managing programs	Electrotherapy (TENS) (2020 update questions this recommendation)	
	Weight loss for overweight/obese	Joint support and braces (2020 update questions this recommendation)	
	Advice on appropriate footwear	Shock absorbing shoes or insoles (2020 update questions this recommendation)	
		Assistive devices (walking stick, tap turners)	
Pharmacological treatment	Paracetamol (2020 update questions the effectiveness of paracetamol)	Oral NSAIDs including COX-2 inhibitors	Rubefacients
	Topical NSAID's	Cyclo-oxygenase (Cox-2)	Intra-articular hyaluronic injections
		Topical Capsaicin	
		Opioids	
		Corticosteroid injections	
Surgical treatments		TKR	Arthroscopic lavage or debridement

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

AposHealth (AposHealth, previously AposTherapy) is a non-invasive foot-worn device which aims to improve the pathological walking patterns of people with knee osteoarthritis, a condition that causes the joint to become painful and stiff. The device consists of a pair of AposHealth shoes with two curved pods (pertupods) on the heal and forefoot of each shoe. The pertupods are positioned and securely attached to tracks on the bottom of the shoe with screws. Pertupods are available in different sizes and levels of hardness. The height can be changed by adding spacers and weight can be increased by adding weighted discs. Gait analysis software is used by trained healthcare professionals to position the pertupods on the device.

Clinically, there is growing evidence of the effectiveness of AposHealth in several musculoskeletal conditions, including knee OA (Bar-Ziv, Beer et al. 2010, Elbaz, Mor et al. 2010, Elbaz, Mor et al. 2011, Goryachev, Debbi et al. 2011, Drexler, Elbaz et al. 2012, Haim, Rubin et al. 2012, Bar-Ziv, Debbi et al. 2013, Lador, Segal et al. 2013, Elbaz, Mor et al. 2014, Debbi, Wolf et al. 2015, Lubovsky, Mor et al. 2015, A, A et al. 2018, Miles and Greene 2020, Reichenbach, Felson et al. 2020), low back pain (Elbaz, Mirovsky et al. 2009, Barzilay, Segal et al. 2015, Lee, Veeramachaneni et al. 2018), degenerative meniscal tear (Elbaz, Beer et al. 2013), anterior knee pain (Haim, Segal et al. 2013), spontaneous osteonecrosis of the knee (Atoun, Mor et al. 2016), total knee arthroplasty (Elbaz, Debbi et al. 2014, Yaari, Kosashvili et al. 2015, Debbi, Bernfeld et al. 2019), hip OA (Drexler, Segal et al. 2013, Solomonow-Avnon, Herman et al. 2017), total hip arthroplasty (Segal, Bar-Ziv et al. 2013), and recurrent ankle sprain (Tenenbaum, Chechik et al. 2017). In summary, patients report a significant reduction in pain and improved function and quality of life. In addition, a significant improvement is also seen in objective gait metrics, including spatiotemporal, kinetic, and kinematic parameters. Lastly, there are no serious adverse events related to the treatment, and patients report high compliance with the treatment program (Elbaz, Beer et al. 2013). A summary of AposHealth peer-reviewed publications on the mechanism of action and clinical efficacy is provided in Supp E.

We classified the evidence into two main areas: prospective clinical trials, RCT, or single cohort 3D motion analysis, undertaken in a controlled environment with a pre-defined, relatively homogeneous patient population. The second one, equally important, is real-life evidence demonstrating the effectiveness in a heterogenic population suffering from multiple MSK conditions, frequently with severe comorbidities. Both methodologies complement each other and address different aspects, yet the effectiveness of the treatment on patients' symptoms was significant in both routes. Whether in a controlled environment or real-life clinical practice, the clinical outcomes following treatment meet the gold-standard clinical significance threshold (Pham, van der Heijde et al. 2004, Copay, Eyberg et al. 2018).

Alongside a statistical and clinically significant reduction in pain and improvement in functions, there is a significant improvement in function measure via objective gait metrics (i.e., higher walking speed with longer step length and an increased ability to bear loads in the painful limb). This positive impact is thought to be the main reason for patients avoiding surgery. On average, 85% of TKR candidates that were treated with AposHealth avoided surgery at two years. Furthermore, there is data to support a

reduction in healthcare utilization and costs following AposHealth reflected in less doctor visits, examinations, and interventions (pharmacological, injections and physiotherapy).

With Covid-19, there was an exponential growth in the waiting lists for TKR which the healthcare systems are trying to address, yet with limited capacities for elective surgery many patients are left untreated. Now, more than ever, there is an urgent unmet need for non-invasive interventions that will be an alternative to TKR. For this reason, delaying surgery for a reasonable period of time is likely to be helpful in the current immediate post-COVID world. In addition, with the growing aging population and prevalence of osteoarthritis, there is a need to find effective alternatives to manage this demand. Currently, there is no effective treatment once patients have failed to respond to core therapies and therefore patients feel they need to join the list for surgery, potentially earlier than expected now as they are aware of the long waits.

Clinical effect of Knee OA

With respect to knee OA, studies show an improvement in biomechanical parameters and indicators of knee OA while walking with and without the device including a reduction in KAM (Haim, Rubin et al. 2012), a reduction in knee flexion moment (Debbi, Wolf et al. 2015), improvement in muscle activation (Goryachev, Debbi et al. 2011), and improvement in spatiotemporal gait patterns (Elbaz, Mor et al. 2010, Lador, Segal et al. 2013, Elbaz, Mor et al. 2014, Lubovsky, Mor et al. 2015, A, A et al. 2018). The improvement in biomechanical indicators was associated with improved PROMs, i.e., pain, functional disability, and quality of life (Bar-Ziv, Beer et al. 2010, Bar-Ziv, Debbi et al. 2013, Reichenbach, Felson et al. 2020). Recently, a double-blind RCT was published in The Journal of the American Medical Association (JAMA) (Reichenbach, Felson et al. 2020). Two hundred twenty (n=220) patients with knee OA were enrolled in a double-blind RCT that compared AposHealth to a sham device. Patients were assigned to one of two groups and were treated for six months. The primary outcome measure was a change in pain and the secondary outcomes were function, QoL, gait patterns, and adverse events. A significant reduction in pain and improvement in function and quality of life was seen in the Apos group with an average reduction in pain of 69%. 92% of the patients treated with Apos reported more than 30% reduction in pain, well above the minimal clinical important difference, and 83% of them reported more than 50% reduction in pain, a strong indication of the high efficacy with the number needed to treat (NNT) equal to three (Reichenbach, Felson et al. 2020). Another study evaluated KAM changes and symptoms of pain and functional disability in a sub-group analysis of disease severity measured by Kellgren and Lawrence (KL 2, KL 3-4) and found both groups to improve significantly. A trend towards increased improvement was seen in the more severe group (Haim, Rubin et al. 2012). The treatment also seems to have a similar effect on sub-group analysis of age, BMI, and gender (Drexler, Elbaz et al. 2012, Lubovsky, Mor et al. 2015). One UK-based study assessed 455 patients with knee OA that were treated with AposHealth for six months and reported a significant reduction in pain (49%) and improvement in function (46%), quality of life (22%) and gait velocity (13%) (Miles and Greene 2020). Another study,

currently in peer-review assessed surgery avoidance at 2-yrs among patients with knee OA. In additional to that, the authors also reported on clinical outcomes suggesting a significant reduction in pain and improvement in function. In this study the Oxford Knee Score (OKS) was also captured. OKS has improved by 7.6 points in the first 6 months of treatment, and further to 10.6 points at 2 years, meeting the minimally important change of 7 points.

With respect to long-term data, a two-year follow-up study of patients with knee OA reported maintenance of clinical efficacy seen after eight weeks over a 2-yrs timespan (Bar-Ziv, Beer et al. 2010, Bar-Ziv, Debbi et al. 2013). Patients reported a 62% reduction in pain and a 61% improved function with a significant time-by-treatment interaction. Another retrospective study evaluated pain, function, and gait patterns at 12 months and reported a significant increase of 16% in gait velocity alongside a significant reduction of 46% in pain and 45% in functional disability (Lubovsky, Mor et al. 2015). Interestingly, AposHealth was shown to have a superiority effect as a rehabilitation regimen for patients post-TKR compared to traditional PT – an important fact given the statistics that suggest that 20%-30% of the post-TKR patients are with consistent pain (Wylde, Hewlett et al. 2011, Yaari, Kosashvili et al. 2015, Wylde, Beswick et al. 2018, Debbi, Bernfeld et al. 2019).

Unpublished data suggest similar surgery avoidance amongst different knee OA populations in commercial settings including IL, UK, and the US. Figure 4 summarized surgery avoidance across the different data sets.

Figure 4.

AposHealth: Percent failure necessitating eventual TKR

AposHealth failure rate All results are cumulative	1 Year	2 Years	3 Years	4 Years	5 Years	6 Years
Benchmark data set: Surgical Candidates		~85-90%				
Drew et al. 2022 (Heritage IPA)[1]	9%	14% (cumulative result) (88% in the control group)				
CCG, an NHS Provider[2]		16% (all patients referred to TKR wait list)				
Benchmark data set: Moderate-severe knee OA patients[3]	12.9%	20.6%	27.3%	33.5%		
Montefiore group	3.5%	7%				
Bar-Ziv et al. 2013[4] (Israel)		2.6% (30% in the control group)			15% (45% in the control group, white paper)	
UK Private payor						13.3%
Israel data on file	2%	8%	11%			

1. Drew I et al: https://www.liebertpub.com/doi/10.1089/pop.2021.0336
2. Publication under review- Clinics in Orthopedic Surgery
3. Millman Report, January 2020
4. Bar-Ziv et al: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3603601/

AposHealth

Pain medication and utilization of other non-surgical interventions

One study showed a significant reduction of 58% in rescue medicine during a 2-month trial comparing the therapy to controls (Bar-Ziv, Beer et al. 2010).

Unpublished data supports these findings. In one independent analysis the proportion of patients using non-NSAID, non-opioid pain medications decreased by 33% (37.5% to 25.0%, p=0.029) (Supp H). Another independent member survey conducted by a private UK payer suggest a reduction in pharmacological treatment including OTC and prescribed pain killers, self-reported utilization of pharmacological interventions suggest that 82% of the patients treated with AposHealth stopped using / are using less OTC pain killers and 80% stopped using / are using less prescribed pain killers. 78% of the patients stopped using / are using less NSAIDs (Supp K).

In the same independent member survey (Supp K), a potential decrease in the utilization of intra-articular injections (86% stopped / reduced use), physiotherapy (83% stopped / reduced use), and braces (78% stopped / reduced use) is also reported. The reduction in physical therapy visits is also supported by a second independent utilization study done on US population (Supp H).

Surgery avoidance

One double-blind study looked at 2-yrs surgery avoidance rates among patients that were treated with AposHealth compared to controls. At 2-yrs, 2.6% of patients treated with Apos required a TKR compared to 31% of patients in the control group, an absolute risk reduction of 28.4% (relative risk reduction of 92%), and a NNT of 3.5 (Bar-Ziv, Debbi et al. 2013). Data on file provides a summary of a 5-yrs follow-up that was performed on the same cohort of patients. At 5 yrs. 15% of patients that were treated with AposHealth have had a TKR (85% surgery avoidance) compared to 45% of patients that received the standard of care (55% surgery avoidance).

A more recent publication on 2-yrs surgery avoidance was published in Population Health Management. The study was conducted by Heritage Provider Network and looked at 2-yrs surgery avoidance outcomes amongst TKR candidates treated with Apos (n=237) compared to controls (n=294). Primary outcomes suggest that 86% of the patients that were treated with AposHealth avoided surgery compared to 12% in the control group (Drew, Hoffing et al. 2022). Lastly, a UK-based clinical trial evaluating surgery avoidance at 2-yrs is currently in peer review. Three hundred sixty-five patients diagnosed with knee OA the have met the criteria for secondary care were treated with AposHealth for 2-yrs. The primary outcomes measure was surgery avoidance and secondary measures were pain and function. 84% of the patients avoided surgery at 2-yrs, demonstrating a significant reduction in pain (42%) and improvement in function (39%), meeting the MCID.

There is additional internal evidence to support the above-mentioned clinical trials. All are based on the company's commercial activity in different territories. In all cohorts, rates of surgery avoidance were the same, indicating consistency of outcomes and clinical effect.

- **UK data** - 13% of patients with a primary knee condition have had a surgical intervention to the knee at an average FU of 6 yrs. Data is for a UK private payor. Furthermore, an independent member survey suggests that 87% expect to delay surgery and 63% expect to avoid it altogether.
- **US data** – a 2-yrs follow-up on surgery avoidance rate amongst patients with knee OA treated with AposHealth in commercial settings suggest that 96.5% of the patients avoid TKR at 1 year and 93% avoid TKR at 2 yrs.
- **IL data** – 3-yrs. data on surgery avoidance suggest a 98%, 92% and 89% avoidance at 1-yr., 2-yrs., and 3-yrs., respectively.

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

The NICE guideline was published in 2014, with the most recent update done in December 2020, providing care and management recommendations for knee OA. NICE encourages a comprehensive approach, highlighting that core treatment should be provided for all people with clinical OA.

Core treatments

- Education and self-management (including advice on appropriate footwear)
- Exercise
- Weight loss when appropriate
- Topical NSAIDs

Adjuncts to core treatments

Adjuncts to core treatment should be tailored to the patient in a shared decision process and include the following:

Non-pharmacological	- Thermotherapy - Manual therapy - Electrotherapy - Braces/joint support/ insoles

	- Assistive devices
Pharmacological	- Topical capsaicin - Oral NSAIDs - Cyclo-oxygenase 2 (COX-2) inhibitors - Opioids
Injections	- Intra-articular corticosteroid injections
Joint surgery	Referral for secondary care should be a shared decision between the GP and the patient (or patient representatives). However, clinicians with responsibility for referring a person with knee OA for consideration of joint surgery should ensure that the person has been offered at least the core (non-surgical) treatment options.

NICE Updates to knee OA care and management guidelines for adjunct interventions

Supported by a recent update by the American College of Rheumatology and Arthritis Foundation knee OA guidelines (Kolasinski, Neogi et al. 2020) and OARSI guidelines for non-surgical management of knee OA (McAlindon, Bannuru et al. 2014)

The summary below provides knee OA management guidelines by three leading organizations (NICE, ACR and OARSI) after thoroughly evaluating and assessing the scientific information associated with each intervention. Some interventions are recommended against use, other receive conditionally endorsement and some receive strong recommendation. Having said that, when looking at the clinical effectiveness, none of the interventions presents a compelling effect size. All interventions have an SMD<0.5 for pain, except for intra-articular corticosteroid injection (0.72). with respect to IA corticosteroid injections, there are some concerns about the contribution of injections to cartilage loss, but the results are still not clear.

Manual therapy

NICE update – There is insufficient evidence to indicate a benefit from manual therapy alone. However, there was evidence of benefits for manual therapy when combined with exercise. In addition, most of the evidence was at less than three months. Given this, NICE committee agreed that manual therapy should be provided in the short term to help people start exercise if they found this difficult without additional intervention. Manual therapy could be considered for people with OA. However, people should be informed that there is insufficient evidence for manual therapy alone

ACR recommendations – small number of studies evaluated manual therapy added to exercise versus exercise alone in knee OA. Limited data show little additional benefit over exercise alone for managing OA symptoms. Therefore, the committee conditionally recommends **against** the use of manual therapy.

Electrotherapy (interferential therapy, laser therapy, shockwave therapy, neuromuscular electrical stimulation, TENS, US)

NICE update - Although there are many studies on electrotherapy, most of them are low quality, with a very low sample size and inconsistent findings, mostly showing the little benefit of electrotherapy. Due to this being present throughout NICE's update, they recommended not routinely using electrotherapy and advised that more high-quality research is required in this area. The committee noted that people with OA more commonly used electrotherapy outside of formal medical care. Devices can be purchased and used by patients independent of health care professional involvement.

ACR recommendations – Studies examining the use of TENS have been of low quality with small size and variable controls, making comparisons across trials difficult. Studies have demonstrated a lack of benefit for knee OA and therefore the committee recommends **against** their use.

The **OARSI review** suggest a very low effect size of 0.07 for pain.

Devices

NICE update

- Walking aids – The committee recommends considering walking aids for people with knee OA. Walking aids, specifically cane is also strongly recommended by the ACR.
- Joint support and bracing - The committee concluded that there was not enough evidence to support the use of insoles, braces, tape, splints or supports. They also noted that there is a potential risk that some of these devices could cause significant adverse events, such as blistering and other pressure damage.

  In addition to NICE update, in 2015 Cochran database systematic reviews published an update to their evaluation of braces and orthoses for the management of knee OA (Duivenvoorden, Brouwer et al. 2015). Authors could not reach a conclusion due to low-quality evidence. However, the data shows lack of an effect on improvement in pain, stiffness and function when using lateral wedge insoles, or valgus knee braces.

  However, the ACR strongly recommends the use of tibiofemoral knee braces and conditionally recommends the use of patellofemoral knee braces.
- Shoes - for the comparison of shoes (variable stiffness walking shoes) and sham devices (constant stiffness shoes) in knee OA, no clinically important difference was seen in quality of life, pain, and physical function at less than and more than three months and adverse events at more than three months only (although for the latter the effect was bordering on a clinically important harm). Based on limited information, the committee concluded that there was insufficient

evidence of benefit from shoes in knee and toe OA. On discussion the committee agreed that they had seen benefits from using and providing people with OA with the correct footwear. They acknowledged that there was evidence of benefit from observational studies that were not included in this protocol.

According to the ACR' while optimal footwear is likely to be of considerable importance for those with knee OA, the available studies do not define the best type of footwear to improve specific outcomes for knee and therefore conditionally recommend against it.

Topical, oral, and transdermal medicine

Pharmacological treatments may be useful for reducing symptoms and supporting people to start other more effective treatments, such as therapeutic exercise. However, they noted that the risks of pharmacological treatments should be understood and that treatments should not be overused or used when they are not needed. In general, treatments should use the lowest effective dose for the shortest possible time.

- Paracetamol - has no benefit in reducing pain and improving quality of life and physical function compared with placebo. The ACR conditionally recommends topical NSAIDs for the management of knee OA.

  The OARSI guidelines suggest a small effect size of 0.18 for pain reduction.
- Topical NSAIDs - clinically effective in reducing pain and generally the most cost-effective medicine for OA. The ACR strongly recommends topical NSAIDs for the management of knee OA.
- Topical capsaicin - There is some evidence showing that topical capsaicin reduces knee pain and has minimal adverse events. However, capsaicin is more expensive and topical NSAIDs are considered a better option. The ACR conditionally recommends topical NSAIDs for the management of knee OA.
- Oral NSAIDs - evidence shows they slightly reduce pain and improve physical function. Due to a potential harm for gastrointestinal, cardiovascular, and liver and kidney adverse events, it should be used for as short a time as possible. These results are also supported by a Cochran database systematic review published in 2017 (Puljak, Marin et al. 2017). The ACR strongly recommends oral NSAIDs for the management of knee OA.

  The OARSI guidelines suggest a small effect size of 0.37 for pain reduction.
- Opioids - Evidence showed that opioids also have the potential for harm, including gastrointestinal and central nervous system adverse events, physical dependence, opioid-induced hyperalgesia, and tolerance. The committee recommends against the use of strong opioids. Weak opioids should be considered for short-term pain relief and if two all other pharmacological treatments are contraindicated, not tolerated or ineffective.

  According to the ACR, there are circumstances in which tramadol or other opioids may be appropriate in the treatment of OA, including when patients may have contraindications to

NSAIDs, find other therapies ineffective, or have no available surgical options. If an opioid is being considered, tramadol is conditionally recommended over non- tramadol opioids which is conditionally recommended against use. There are concerns regarding potential adverse effects and addiction potential.

The OARSI guidelines suggest a low-medium effect size of 0.36 for pain reduction.

Injections

NICE update

- **Hyaluronic acid -** There is limited evidence on the effect of hyaluronan-acid injection for patients with knee OA. Results suggest inconsistent benefits and some potential harms. Based on their expert opinion, the committee agreed that hyaluronan injections should not be offered.

  The ACR conditionally recommends against the use of HA injections. The conditional recommendation against is consistent with the use of hyaluronic acid injections, in the context of shared decision- making that recognizes the limited evidence of benefit of this treatment, when other alternatives have been exhausted or failed to provide satisfactory benefit.
- **Corticosteroids -** In general, the quality of the research is low-moderate and often downgraded due to a risk of bias. Very low-quality evidence of short-term benefit for pain and no clinically important difference in physical function or quality of life. No evidence to support long-term (>3 months) benefit. Given the potential benefits and committee expert opinion, they agreed that intra-articular corticosteroids could be considered if other treatments had not worked, provided the person was aware that the injection would only provide short-term relief.

  The ACR strongly recommends glucocorticoid injections, however acknowledge that its effect is short termed.

  There is some evidence that raises the possibility that specific steroid preparations or a certain frequency of steroid injections may contribute to cartilage loss, but the clinical significance of this finding is still not clear (McAlindon, LaValley et al. 2017). Effect size for corticosteroid injection is 0.72 (McAlindon, LaValley et al. 2017).

TKR

TKR has revolutionised the care of patients with knee OA and is considered an effective intervention for treating chronic knee pain and disability (7). However, some patients experience chronic knee pain, functional disability, and poor quality of life after TKR (8). It is suggested that approximately 18% of patients report the outcomes of their surgery as only fair or poor, with a small proportion of these experiencing complications (9). One plausible explanation is related to a poor patient selection process. Although the NHS is trying to optimize the selection criteria for TKR, ultimately it is a shared decision between the physician and the patient.

Comparative analysis

Appendix I summarises the clinical evidence of knee OA interventions. The following metrics were included, when available:

- TKR avoidance at 2-yrs.
- Number needed to treat (NNT) - The number of patients you need to treat to prevent one additional bad outcome.
- Effect size - a quantitative measure of the magnitude of the experimental effect. The larger the effect size the stronger the relationship between two variables. It is a way to standardize the clinical effect when interventions are not compared in RCTs.

In most cases we used the research work of McAlindon et al. (McAlindon, Bannuru et al. 2014) who published the OARSI guidelines for the non-surgical management of knee OA. In other cases, we used meta-analysis, literature reviews or Cochran database systematic reviews.

In summary, AposHealth is a non-invasive intervention with very low risk and good clinical outcomes. Relative to other interventions, when comparing the effect size, AposHealth is ranked 2nd after opioids with the NNT. Most interventions do not assess surgery delay or avoidance as an outcomes measure. We found one trial looking at braces that reported 70% surgery avoidance at two years amongst surgical candidates. 90% of the patients that were treated with Apos avoided surgery at 2-yrs. Lee et al. have suggested that if patients' symptoms are tolerable at 24 months, the chances of undergoing subsequent surgery decline significantly (Lee, Winfield et al. 2016). Data on file indicate that 85% of patients treated with AposHealth avoid surgery at 5 yrs.

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

There are no expected differences between the patients in the submitted studies and patients having routine care in the UK NHS. Moreover, some of the evidence presented in this submission is based on a UK population and suggest similar results to those from the rest of the world.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

Patients with knee OA that have failed the core interventions (i.e., exercise, education, self-manage and weight loss when applicable)

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

The submission summarises the clinical evidence of AposHealth as a non-invasive intervention for patients with knee OA. Forty-eight (48) research reports/studies were identified, half of them are relevant for the current target population (i.e. patients with knee OA). There is strong evidence to support that the treatment is safe and effective for patients with knee OA. Moreover, some evidence suggest that AposHealth reduces the utilisations of other non-surgical interventions and that it helps delay surgery amongst severe patients who were recommended a TKR. In the presence of an exponential growth in the waiting lists for TKR, a constant increase in the prevalence of knee OA and the lack of effective non-surgical interventions for knee OA there is an urgent need for non-surgical, effective, interventions, otherwise many patients will be left untreated while experiencing severe symptoms. We believe that utilising AposHealth with patients who failed the core interventions (i.e., exercise, education, self-manage and weight loss when applicable) will provide an effective alternative to all other adjunct interventions helping to delay, or even avoid altogether a TKR.

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10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	1/6/22
Date span of search:	2004-1/6/22
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
The company tracks all peer-reviewed publications, all of them were included in this review. In additions, the company holds copies of un-published supporting evidence. Some are used in this submission. The company is aware of all on-going research activity and have disclosed them in this submission. With that, there is not additional scientific evidence that was not included in this submission.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
Enter text.	
Inclusion and exclusion criteria:	
Enter text.	
Data abstraction strategy:	
Enter text.	

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full-text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Link	Double blind RCT. AposHealth compared to traditional PT	Non knee OA populations (Post TKR rehab)	Text
link	Case study AposHealth	Post ACL injury	Text
link	Retrospective AposHealth	Non knee OA population. Patients with spontaneous osteonecrosis of the knee	Text
link	Prospective, single cohort. AposHealth	Non knee OA populations (Post TKR rehab)	Text
link	Prospective, single cohort. AposHealth	Non knee OA populations (Post TKR rehab)	Text
link	Retrospective study AposHealth	Non knee OA population Patients with chronic non-specific LBP	Text
link	Retrospective study AposHealth	Non knee OA population Patients with chronic non-specific LBP	Text

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
link	Retrospective study AposHealth	Non knee OA population Patients with chronic non-specific LBP	
link	Prospective single cohort study AposHealth	Non knee OA population Patients with hip OA	
link	Retrospective study AposHealth	Non knee OA population Patients post THR	
link	Retrospective study AposHealth	Non knee OA population Patients with hip OA	
link	Retrospective study AposHealth	Non knee OA population Patients with chronic ankle instability	

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Enter text.

Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Search strategy for adverse events

Date search conducted:	Enter text.
Date span of search:	Enter text.
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
Enter text.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
Enter text.	
Inclusion and exclusion criteria:	
Enter text.	
Data abstraction strategy:	
Enter text.	

Adverse events evidence

List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

Study	**Design and intervention(s)**	**Details of adverse events**	**Company comments**
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Study	Design and intervention(s)	Details of adverse events	Company comments
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Enter text.

Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☐ If no, please proceed to declaration (below)

Yes ☒ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
[redacted]	☒ Commercial in confidence ☐ Academic in confidence	We provided a copy of the training program for the committee to get better understanding of the methodology and training. However, this is the company's IP and we would like to keep it confidential.	Unlimited. Confidentiality should be maintained.
Details	Enter text.		
Supp F	☐ Commercial in confidence ☒ Academic in confidence	We have included a clinical trial that is currently under peer-review assessment.	Confidentiality should be maintained until publication

		The company believes that the outcomes of this research are important for this evaluation yet, requests to keep it confidential.	
[redacted]	☒ Commercial in confidence ☐ Academic in confidence	We provide a copy of Apos user guide for the committee to get better understanding of the product. However, this is the company's IP and we would like to keep it confidential.	
[redacted]	☒ Commercial in confidence ☐ Academic in confidence	We provide a copy of the forms used while delivering AposHealth for the committee to get better understanding of the delivery of care. However, this is the company's IP and we would like to keep it confidential.	
[redacted]	☒ Commercial in confidence ☐ Academic in confidence	We provide a copy of the safety precautions disclaimer for the committee to get better understanding of the delivery of care. However, this is the company's IP and we would like to keep it confidential.	
[redacted]	☒ Commercial in confidence ☐ Academic in confidence	We provide a copy of the patient progress pack for the committee to get better understanding of the delivery of care. However, this is the company's IP and we would like to keep it confidential.	

[redacted]	☒ Commercial in confidence ☐ Academic in confidence	We provide a copy of the [redacted] user guide. [redacted] is an off the shelf technology used to evaluate computerised gait analysis.	
Details	Enter text.		

Confidential information declaration

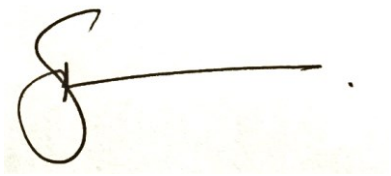
I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for disclosing confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: **Date:** 13/6/2022

** Must be Medical Director or equivalent*



Print: Sachin Gohil, MRPharmS

Role / organisation: Senior Vice President, Chief Commercial Officer AposHealth UK

Contact email:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT570 AposHealth for osteoarthritis (OA) of the knee

Company evidence submission

Part 2: Economic evidence

Company name	Apos Medical UK Ltd (AposHealth)
Submission date	27 July 2022
Contains confidential information	No

Contents

1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		48
Number of studies identified as being relevant to the decision problem.		24
Of the relevant studies identified:	Number of published studies.	16
	Number of abstracts.	0
	Number of ongoing studies.	7

List of relevant studies

In table 1, provide brief details of any published or unpublished economic studies or abstracts identified as being relevant to the decision problem.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data provided.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant studies (published and unpublished)

AposHealth uses gait modifications and neuromuscular training to alleviate symptoms and improve function using a foot-worn device. It is a non-invasive, home-based, intervention that was found to be safe and effective for multiple MSK conditions. Specifically, for patients with knee OA, which is a chronic, disabling, progressive disease, that negatively affects quality of life, using AposHealth as a non-invasive treatment helps alleviate pain, restore functionality and as a result improve quality of life. For many patients with knee OA, total knee replacement (TKR) is the end-stage solution, when other non-surgical interventions have failed to help. Despite the favourable surgical outcomes, approximately 20% of post-TKR patients continue to experience chronic pain and an equal number report that their expectations for a full recovery are unmet. There is an on-going increase in surgery rates and it is estimated that the rates of TKR will reach 119,000 procedures per year by 2035 and 226,000 procedures per year by 2050 (Culliford, Maskell et al. 2015, Klug, Gramlich et al. 2021). It is expected that this will place an immense burden on the cost of health care, highlighting the urgent need for new non-surgical approaches that more effectively manage OA symptoms of the knee (Klug, Gramlich et al. 2021). AposHealth has significant evidence to support a reduction in TKR in patients with knee OA that were found eligible for surgery. This has significant implications on the healthcare system, primarily providing an additional non-surgical intervention that is clinically effective, safe, and cost-effective.

The Apos device can address multiple lower back and lower extremity MSK conditions. For many patients this is an advantage as patients with knee OA frequently suffer from other pain (lower back, hip). Furthermore, this also applies to patients suffering from a bilateral condition. While for some interventions there is a need to treat each knee separately (braces, injections), with AposHealth one can treat a bilateral condition simultaneously, and it is even recommended as the body is constantly compensating for symptoms. The device's versatility enables these compensations.

All publications that are presented in Table 1 below underwent peer-review evaluation. AposHealth scientific evidence indicates a significant clinical effect expressed by reduction in pain, and improvement in function, quality of life, gait patterns, and 3D biomechanical indicators of knee OA. These clinical outcomes have an impact on the likelihood of patients requiring joint replacement surgery. Evidence indicates that most patients that are treated with AposHealth will avoid TKR for at least 2 yrs. A recent publication reports on surgery avoidance in patients with knee OA under NHS settings. These results have broader implications on other areas of disease management, for example the indirect impact associated with improved mobility, social care costs, comorbidities, and work absenteeism.

Data source	Author, year and location	Patient population and setting	Intervention and comparator	Unit costs	Outcomes and results	Sensitivity analysis and conclusion
Link to source	Reichenbach et al., 2020. Switzerland	Two hundred and twenty (n=220) men and nonpregnant women aged 40 years or older who had symptomatic, radiologically confirmed knee OA according to criteria from the American College of Rheumatology. At the screening visit, participants had knee pain lasting six months or longer and a score of 3 or greater on the WOMAC pain subscale standardised to range from 0-10). Between April 20, 2015, and January 10, 2017, 220 participants were randomised. There were 111 participants randomised to the biomechanical footwear group and 109 participants randomised to the control footwear group. One participant in the biomechanical footwear group refused treatment and	AposHealth vs. Sham device	Text	The primary outcome measure was pain. The biomechanical footwear group had a larger decrease in standardised WOMAC pain subscore at 24 weeks of follow-up than the control footwear group (mean score, 1.3 vs 2.6, respectively; between-group difference, −1.3 [95% CI, −1.8 to −0.9]; $P < .001$) 83% of patients in the biomechanical group had a 50% reduction in WOMAC pain, 92% with a 30% reduction compared to 42% and 58%, respectively in the control group (P< 0.001) Secondary outcome measures included WOMAC scores, SF-36, Spatio-temporal gait analysis. There were no significant adverse events associated with the treatment compared to controls.	Text

		did not receive the intervention. Seven participants in the biomechanical footwear group and 13 participants in the control footwear group discontinued treatment during follow-up. The last participant visit occurred on August 15, 2017. There were complete data for the primary outcome at 24 weeks of follow-up for 109 participants (98.2%) in the biomechanical footwear group and 104 participants (95.4%) in the control footwear group.			Gait velocity improved by 37% ($p<0.05$)	
Link to source	Drew et al., 2022. US	Five hundred and thirty-one (n=531) patients with knee OA eligible for TKR. The eligibility criteria for TKR comprised a combination of the following: 2 professional claims related to knee pain, radiological confirmation of knee OA, subjective knee pain >3 months impacting the QoL, no	AposHealth Vs. Standard of care	Text	Over the 24-month study period, 34 patients who received the intervention (14%, 95% CI 82%–91%) progressed to a TKR. The average time to progress to TKR was 324 days (ranging from 31 to 671 days). Sixty-four percent of those who underwent TKR had their surgery within 12 months after	Text

		reliance on assistive devices to walk indoors, and <2 falls in the past year. Of 237 patients that were enrolled to the study, 27 patients (11%) termed their insurance coverage and were disenrolled from HPN, and five patients (2%) were deceased. All other patients completed a 2-yrs follow-up.			the initiation of the intervention. Of the 294 patients in the control group who chose TKR surgery, 259 (88%) received a knee replacement. With respect to the clinical outcomes' measurements, for the 172 patients who chose the biomechanical intervention and who completed the program, 138 (88%) had clinical data at three months, 111 (65%) patients had clinical data at 6 months, and 52 (30%) patients had clinical data at 12 months. The General Mixed Model which includes repeated measures from 4 visits showed a significant reduction in WOMAC pain ($P < 0.001$) and WOMAC function ($P < 0.001$) after 12 months of treatment. It is estimated that pain decreased by 19.6 points (36%) at the end of year 1, and functional disability	

					decreased by 16.4 points (34%). There was a significant increase in the SF-36 overall score by 5.4 points (10%) at one year (P < 0.001). Likewise, the PCS increased significantly by 5.6 points (13%) after 12 months of treatment (P < 0.001). No significant changes in MCS were noted. Gait velocity improved by 11% (p<0.05)	
Link to source	Bar-Ziv et al., 2010. Israel	Fifty-seven (n=57) patients with symptomatic bilateral knee OA of the medial compartment for at least six months. All patients fulfilled the American College of Rheumatology clinical criteria for OA of the knee and had radiographically assessed osteoarthritis of the knee according to the Kellgren & Lawrence (K&L) scale. All patients had a varus knee alignment.	AposHealth vs Sham device	Text	At the 8-week endpoint the WOMAC pain score and function score revealed significant differences between the groups over time (Time by treatment interaction, p < 0.001). The active group reported significant pain relief after eight weeks of treatment with a mean difference of 3.5 cm (64.8%) and a 95% confidence interval ranging between 2.7-4.4. In contrast, the	Text

		Exclusion criteria were acute septic arthritis, inflammatory arthritis, patients with a history of increased tendency to fall, patients with a history of knee buckling, lack of physical or mental ability to perform or comply with the treatment procedure, diabetes mellitus, and patients with a history of pathological osteoporotic fracture. Fifty-seven patients were enrolled into the study. Thirty-one patients received AposHealth and 26 patients received a shame device. Twenty-nine patients that were treated with AposHealth and 25 patients treated with a sham device completed the study (8 weeks)			control group reported no pain relief, having a mean increase of 0.4 cm (8%) with a 95% confidence interval ranging between -1.7-0.8. On the WOMAC function scale, the active group reported significant improvement with a mean decrease of 3.2 cm (62.7%) after eight weeks and a 95% confidence interval ranging between 2.5-4.1. The control group reported no function improvement, having a mean increase of 0.5 cm (9.8%) with a 95% confidence interval ranging between -1.4-0.5. QoL: Physical component summary increased by 50% at two months in the AposHealth group compared to an 11% deterioration in the control group. Mental component summary increased by 58% at two months in the AposHealth group compared to a	

					21% decrease in the control group Patients also demonstrated a significant improvement in ALF – a functional test, and in the Knee Society Score questionnaires. Unmarked acetaminophen - Patients from the control group used more of the rescue medication given to them at the start of the study than did the active group. After four weeks, the active group as a whole consumed 145 rescue pills whereas the control group consumed 281 pills. After eight weeks, the active group consumed 128 pills and the control group consumed 366 pills. Overall, the active group consumed 273 pills and the control group consumed 647 pills. No side effects were reported by any of the patients.	

Link to source	Haim et al., 2011. Israel	Twenty-five (n=25) female patients with symptomatic bilateral medial compartment knee OA. Inclusion criteria: symptomatic physician-diagnosed medial knee OA for at least six months, fulfilling the ACR (American College of Rheumatology) criteria for OA of the knee. All 25 patients enrolled in the study completed the treatment program with satisfactory compliance (i.e., Adherence of >75% to the proposed treatment protocol). Two patients had brief (3–4 weeks) treatment intermissions, one due to plantar fasciitis and the other due to trochanteric bursitis, both of which resolved spontaneously.	AposHealth	Text	Post-treatment testing demonstrated a reduction of the KAM magnitude during the stance phase. The knee adduction impulse and the 1st and the 2nd KAM peaks were reduced by 0.54N-m/kg/sec, 0.06 N-m/kg, and 0.07N-m/kg, respectively. A reduction of 15%, 18%, and 17%, respectively, from the pre-training values. Velocity improved by 10% ($p<0.05$). Patient self-reported WOMAC pain scores and function scores as well as SF-36 revealed a significantly favourable outcome at the 3-month follow-up and the 9-month endpoint ($p<0.001$). Overall pain reduced by 61%, and function and QoL have improved by 63% and 32%, respectively.	Text
Link to source	Debbi et al., 2015 Israel	Twenty-five (n=25) female patients with symptomatic bilateral medial compartment	AposHealth	Text	Peak knee flexion moment (KFM) at loading response decreased	Text

		knee OA. Inclusion criteria: symptomatic physician-diagnosed medial knee OA for at least six months, fulfilling the ACR (American College of Rheumatology) criteria for OA of the knee. All 25 patients enrolled in the study completed the treatment program with satisfactory compliance (i.e., Adherence of >75% to the proposed treatment protocol). Two patients had brief (3–4 weeks) treatment intermissions, one due to plantar fasciitis and the other due to trochanteric bursitis, both of which resolved spontaneously.			significantly with therapy (p = 0.001). Duration of KFM and impulse of knee flexion also decreased significantly (p = 0.024 and p = 0.029, respectively). These changes were accompanied by increased walking velocity, significant pain reduction, and increased functional activity. Post-training kinetic evaluation demonstrated profound alterations of knee sagittal moments at the loading response KFM. - A 49% reduction in knee flexion moment during loading response - A 40% reduction in peak knee flexion moment during loading response Velocity improved by 10% (p<0.05) Patient self-reported WOMAC pain scores and function scores as well as SF-36 revealed a significantly	

					favourable outcome at the 3-month follow-up and the 9-month endpoint (p<0.001). Overall pain reduced by 61% and function and QoL have improved by 63% and 32%, respectively.	
Link to source	Bar-Ziv et al., 2013. Israel	Fifty-six patients with knee OA participated in the study. Forty patients were treated with AposHealth, and 16 patients served as controls. Inclusion criteria were (1) symptomatic bilateral knee OA of the medial knee compartment for at least six months; (2) qualification of OA of the knee according to the American College of Rheumatology clinical criteria for OA of the knee, which include knee pain with at least 3 of the following: age > 50 years, stiffness < 30 minutes, crepitus, bony tenderness, bony enlargement, no palpable warmth; (3) radiographically assessed OA of the	AposHealth Vs. Standard care	Text	A significant difference was found between the active and control groups in all three WOMAC categories (pain, stiffness, and function) at the two-year endpoint. There was also a significant difference in improvement over time between groups in all three categories (for interaction =16.8, 21.7 and 18.1 for pain, stiffness, and function, respectively). At two years, patients treated with AposHealth improved by 62% compared to an increase of 24% in the control group. Patients also reported a 61% improvement in function compared to a deterioration of 12% in the control group.	Text

		knee according to the Kellgren & Lawrence (K&L) scale. Only patients of grade II or above were included in the study. At the two-year endpoint, thirty-eight patients and nine patients completed the trial. AposHealth group: One patient has had a TKR, and one patient declined to participate. Control group: One patient was deceased, one declined to participate, and five patients have had a TKR.			A significant difference between the active and control groups was also found in the ALF score at the two-year endpoint (P<0.001). The two groups did not differ significantly in their improvement over time (F for interaction =0.67). At the two-year endpoint, a significant difference was found between groups in all categories of the SF-36 except for the category of emotional well-being. This is reflected in the two summary indices of the SF-36: the SF-36 PCS and SF-36 MCS (P<0.001). There was a significant difference in improvement over time between groups in the SF-36 PCS (F for interaction =5.8) but not in the SF-36 MCS (for interaction =0.032). At the two-year endpoint, a significant difference was found between groups in the KSS-K and the KSS-F	

					(P<0.001). The two groups also differed significantly in their improvement over time in the KSS-K (F for interaction =4.3) and the KSS-F (F for interaction =6.5). The groups also differed in the number of total knee replacements (TKRs) performed at two years. One patient from the active group required a TKR during the study period (2.6%), while five patients (31%) of the control group required a TKR during the two-year study period.	
Link to source	Lador et al., 2013 Israel	Nine hundred and eighty-eight (n=988) patients diagnosed with knee OA were treated with AposHealth for four months. Inclusion criteria were patients suffering from symptomatic bilateral knee OA at the medial compartment for at least six months, fulfilling the American College of Rheumatology clinical	AposHealth	Text	Pain significantly decreased by 31% (p<0.001). Function significantly improved by 28% (p<0.001). SF-36: PCS significantly improved by 21% (p<0.001). MCS significantly improved by 12% (p<0.001). Gait velocity improved by 10% (p<0.05)	Text

		criteria for OA of the Knee. Patients are referred to this treatment by general practice and orthopedic doctors from the general community medical care.				
Link to source	Drexler et al., 2012. Israel	Six hundred and fifty-four (n=654) patients with medial compartment knee OA were examined before and after 12 weeks of AposHealth	AposHealth	Text	Pain significantly decreased by 30% (p<0.001). Function significantly improved by 29% (p<0.001). SF-36: PCS significantly improved by 28% (p<0.001). MCS significantly improved by 20% (p<0.001).	Text
Link to source	Lubovsky et al., 2015. Israel	One hundred and five (n=105) obese patients diagnosed with knee OA participated in the study and were treated with AposHealth for 12 months. Inclusion criteria were diagnosis of symptomatic bilateral knee OA of the medial compartment for at	AposHealth	Text	Pain significantly decreased by 46% (p<0.001). Function significantly improved by 45% (p<0.001). SF-36: PCS significantly improved by 27% (p<0.001). MCS significantly improved by 15% (p<0.001).	Text

		least six months, fulfilling the American College of Rheumatology clinical criteria for OA of the knee,17 a body mass index (BMI) > 30 kg/m2, having undergone a gait test and having completed questionnaires at baseline and after 3 and 12 months of therapy.			Gait velocity improved by 16.5% (p<0.05)	
Link to source	Elbaz et al., 2010 Israel	Forty-six (n=46) patients with knee OA were included in the study. Eligibility to the study was defined as follows: 1. Patients suffering from symptomatic bilateral knee OA at the medial compartment for at least six months, fulfilling the ACR clinical criteria for OA of the knee, and having radiographically assessed OA of the knee according to Kellgren and Lawrence scale. Patients that have completed a gait test,	AposHealth		Pain significantly decreased by 26% (p<0.001). Function significantly improved by 34% (p<0.001). SF-36 significantly improved by 14% (p<0.001). Gait velocity improved by 10% (p<0.05) There were no reports of imbalance, tripping or other physical problems during the study period.	

		WOMAC questionnaire and SF-36 Health Survey at baseline and after 12 weeks of treatments. All patients complied completely with the treatment protocol. Compliance was verified at several points during the study. After the first week and second week of treatment all patients received a telephone call to verify compliance. In addition, when they arrived at the therapy centre the physiotherapist also verified the patient's compliance with the treatment				
Link to source	Haim et al., 2012 Israel	Forty-eight (n=48) patients with anterior knee pain participated in the study. Patients were treated with AposHealth for 6sixmonths. Anterior knee or retro-patellar pain for over three months diagnosed by a physician; reproducible pain	AposHealth		Pain significantly decreased by 49% (p<0.001). Function significantly improved by 42% (p<0.001). SF-36: PCS significantly improved by 14% (p<0.001). MCS significantly improved by 8% (p<0.001).	

		upon carrying out at least two of the following functional activities: stair ascent or descent, squatting, kneeling, prolonged sitting or isometric quadriceps contraction; tenderness on palpation of the patella, or pain with stepping down or double leg squatting. There were no reports of imbalance, tripping or other physical problems during the study period. All patients completed the treatment program with satisfactory compliance (i.e., adherence of >75% of the proposed treatment protocol).			Gait velocity improved by 8% ($p<0.05$) There were no reports of imbalance, tripping or other physical problems during the study period.	
Link to source	Elbaz et al., 2014 Israel	Thirty-four (n=34) patients (18 women) diagnosed with medial compartment knee OA by their physician who has had a low-energy indirect injury to the knee, causing pain and functional limitation were included in the study. Patients were	AposHealth		All patients complied with the study protocol, and none reported any adverse events that disqualified them from the study. One patient chose to undergo knee arthroscopy and was considered as a failure of treatment.	

		diagnosed with a large complex medial meniscal tear related to the injury accompanied with bone bruise of the knee via magnetic resonance imaging (MRI). Symptomatically, patients reported a sudden increase in their knee pain and limitation in function following the injury. Patients were monitored for 12 months. All patients complied with the study protocol.			Pain significantly decreased by 73% (p<0.001). Function significantly improved by 64% (p<0.001). SF-36: PCS significantly improved by 35% (p<0.001). MCS significantly improved by 16% (p<0.001). Gait velocity improved by 15% (p<0.05)	
Link to source	Herman et al., 2018 Israel	The study population included 518 patients, of which 336 (64.8%) patients were females and 182 (35.1%) patients were males. Patients had bilateral knee OA diagnosed by the referring physician (as defined by the American College of Rheumatology), patients that completed one-year follow-up and had a complete set of clinical	AposHealth		Pain significantly decreased by 41% (p<0.001). Function significantly improved by 35% (p<0.001). SF-36 significantly improved by 16% (p<0.001). At baseline, the KOFG distribution has a symmetric bell-shaped with 17.6%, 36.9%, 32.5% and 13.1% in grades 1-4, respectively. This however changed with	

		questionnaires and spatiotemporal gait analysis.			time to a distribution with a right tail as more patients have lower KOFG (better functional condition). At one year of follow-up this trend towards better KOFG was further improved with distribution of 32.9%, 43.3%, 18.9% and 5.0% for grades 1-4, respectively. The results of the current study validate the knee OA functional grade classification scheme as a tool to assess time-dependent changes in KOA as well as its sensitivity to assess treatment effect. The KOFG can offer a more robust mode of reporting clinical results in describing the natural history and time-dependent treatment results of patients suffering from knee OA and should be considered as an additional outcome measure in future studies.	

Link to source	Miles et al., 2020 UK	Four hundred and fifty-five patients (n=457), 247 females (54%) and 208 males (46%) with symptomatic knee OA participated in this study. Patients were followed up for six months.	AposHealth		All spatial-temporal gait parameters significantly improved following three months of treatment (all less than $p < 0.01$). There were also further significant improvements in all parameters between 3 and 6 months of treatment (All less than $p < 0.01$), except SLS on both sides ($p = 0.554$ and 0.452). Specifically, gait velocity, step length and SLS of the more symptomatic knee improved by 13, 7.8 and 3% respectively ($p < 0.01$). There was a significant improvement in KOFG between baseline and three months follow-up ($p < 0.001$), with retained improvements at 6 months. More specifically, at baseline two thirds (71%) of the patients were classified with grade 1 and 2 (i.e., mild-moderate functional limitation) and a third of the	

					patients (29%) were classified with grade 3 and 4 (i.e., moderate-severe functional severity). After six months of treatment 86% of the patients had a functional classification grade 1 & 2 and 14% with grade 3 and 4, respectively. Following six months of treatment, all patients' self-evaluation questionnaires improved significantly. All WOMAC subscales significantly improved following three months of treatment, with further improvements at six months ($p < 0.001$). WOMAC Total, along with pain, function and stiffness subscales improved by 46.2, 48.6, 45.7 and 43.4% respectively ($p < 0.001$ for all). 67% of the patients met the OMERACT-OARSI criteria. All SF-36 subscales also significantly improved following	

					three months of treatment ($p < 0.001$). After six months of treatment all subscales had significantly improved ($p < 0.001$). Specifically, SF-36 Total, PCS and MCS improved by 11.73, 15.7, and 9.62 points, or 22, 34 and 15% respectively compared to baseline. These improvements also met the minimal clinically important differences (MCID) for clinical significance of 7.8 points. A sub-group analysis revealed no baseline differences between those who were recommended joint replacement and those who were not. Both groups improved significantly over time ($p < 0.05$ for all).	
Link to source	Elbaz et al., 2014 Singapore	Fifty-eight (n=58) patients (39 females and 19 males) diagnosed with primary medial compartment knee OA participated in this	AposHealth		After 6 months of therapy, all parameters improved significantly compared to baseline.	

		study, and 54 patients completed it (93%). Four patients did not complete the study: two patients did not comply with the treatment; one patient relocated and could not continue with therapy and one patient chose to undergo a total knee replacement. All remaining patients complied with the treatment, and there were no reports of any adverse events during the treatment period. Ninety-five percent of the patients (49 patients) had bilateral knee OA. The mean (standard deviation (SD)) age was 59.7 (6.1) years and mean (SD) body mass index (BMI) was 30.7 (14.6) kg/m2. Forty-four patients (82%) were Chinese, five patients (9%) were Indian, and five patients (9%) were Malay. Patients' structural OA severity was determined by the Kellgren and			Pain significantly decreased by 68% (p<0.001). Function significantly improved by 76% (p<0.001). SF-36: PCS significantly improved by 46% (p<0.001). MCS significantly improved by 22% (p<0.001). Gait velocity improved by 16% (p<0.05)	

		Lawrence (KL) score. Twenty patients (37.0%) were graded 2, 21 patients (38.9%) were graded 3 and 13 patients (24.1%) were graded 4.				
Link to source	Goryachev et al., 2011 Israel	Fourteen (n=14) females with symptomatic bilateral medial compartment knee OA for at least 6 months, fulfillment of the American College of Rheumatology (ACR) criteria for OA of the knee and radiographic signs of OA in the medial compartment of the knee of grade two or greater on the Kellgren & Lawrence (K&L) scale. Patients were treated with AposHealth for 3 months.	AposHealth		The average EMG varied significantly with COP changes in at least one phase of stance in all examined muscles of the less symptomatic leg and in three muscles of the more symptomatic leg. After training, a significant increase in average EMG was observed in most muscles. Most muscles of the less symptomatic leg showed significantly increased peak EMG. Activity duration was shorter for all muscles of the less symptomatic leg (significant in the lateral gastrocnemius) and three muscles of the more symptomatic leg (significant in the biceps femoris). These results were associated with a significant reduction in	

					pain (64%), increased function (51%) and improved spatiotemporal parameters (an increase of 8% in gait velocity). P<0.05 for all.	
Link to source	Haim et al, 2011 Israel	Twenty-two (n=22) female patients with symptomatic bilateral medial compartment knee OA participated in this trial. All patients had symptomatic knee OA for ≥6 months, fulfilled the ACR criteria for knee OA, had definite radiographic signs of OA in the medial compartment with KL grades from 1 to 4, and had no signs of lateral compartment joint space narrowing	AposHealth		Functional assessment was performed prior to testing by a single physician. Calibration of the biomechanical device was performed by a single trained physiotherapist. First, position of the elements for the "functional neutral sagittal axis" was determined and documented. The functional neutral axis was defined as the position in which the apparatus caused the least valgus or varus torque at the ankle. Medial and lateral axes were then defined as 0.8 cm medial and 1.5 cm lateral deviation of the biomechanical elements from the neutral sagittal axis, respectively.	

					Successive testing, each with singular calibration of the apparatus, was conducted in four conditions: foot-worn platform with no elements attached (control condition); biomechanical elements placed at neutral axis; elements placed at lateral sagittal axis; and elements placed at medial sagittal axis. Modulation of the COP coronal trajectory from medial to lateral offset resulted in a significant reduction of the KAM. On average, translation of the elements from the neutral to the lateral configuration reduced 1st and 2nd peaks by 0.1 and 0.07 mN-m/kg, a reduction of 10% ($p < 0.001$) and 14% ($p < 0.001$), respectively, and reduced the knee adduction impulse by 0.54 N-m/kg/s, a reduction of 14% ($p < 0.001$). Translation of	

					the elements from neutral to medial increased the 1st and 2nd peaks by 0.06 mN-m/kg ($p < 0.001$) and 0.04 mN-m/kg ($p < 0.06$), an increase of 8.4% and 8%, respectively, and increased the knee adduction impulse by 0.41 Nm/kg/sec, an increase of 10.8% ($p < 0.001$).	
Accepted for publication in Journal of Orthopaedic Experience & Innovation Attached as Supp F, as waiting for final vesion form journal.	Greene et al., 2022, UK	365 NHS patients with end-stage knee OA. All patients had met the criteria for orthopaedics referral as set out in the CCG's Value-Based Commissioning Policy and been screened by the CCG's clinical triage team to ensure appropriate candidate selection	AposHealth		Surgery avoidance Pain Function QoL Gait OKS Significant improvements were seen in WOMAC pain and function subscales of 34% and 31% respectively at 3 months, increasing to 42% and 39% at 6 months. These continued to improve to 49% and 54% respectively over the 2 years. 67% of patients met the OMERACT-OARSI criteria for clinically significant improvement. OKS improved by 7.6	

					points in the first 6 months of treatment, and further to 10.6 points at 2 years, meeting the minimally important change of 7 points Results suggest that 84% of TKR candidates treated with AposHealth avoided TKR at a 2-yrs	
Un-published data. On-going clinical trial Link to source	Suk et al. Q2 2024, Geisinger Medical Center, PA, USA.	1. Patients with severe knee OA 2. Patient post primary TKR	Group 1 – Patients with severe knee OA treated with AposHealth Group 2 – Patients post TKR with traditional PT rehab Group 3 – Patients post TKR with traditional PT rehab and AposHealth		Primary outcome measure: • Pain at 12 months Secondary outcome measures: • Function • Gait • QoL • Surgery avoidance AE	
Un-published data. On-going clinical trial. Supp. G	Hillstrom H. 2022 Hospital for Special Surgery (HSS), NY, US.	Thirty adults (15 male, 15 female) with bilateral knee OA will be recruited for participation in this study. Inclusion criteria will be male or female, symptomatic bilateral medial compartment knee OA for at least 6 months,	AposHealth		Outcome measures: • 3D gait analysis combined with EMG PROMS	

		KL 2-4, and visual analog scale pain (VAS) pain ≥ 30mm on both knees while walking 50' on the level or descending stairs.				
Un-published data Supp. H	[redacted]	A total of 369 patients with 6 months and 214 patients with 12 months of pre- and post-index data with a claim for AposHealth were included in the study. Among the patients with 12 months pre- and post-index, 88 patients had a primary diagnosis of knee OA and 126 had a primary diagnosis of LBP.	Pre/post index knee (AposHealth) medical costs		The proportion of all patients using opioids dropped significantly after receipt of AposHealth (34.1% to 21.0%, p<0.001), and the use of oxycodone specifically fell by 40% (24.8% to 15.0%, p=0.002). LBP patients saw a larger drop than knee OA patients. The LBP cohort filled significantly fewer pain medications in the post- vs. pre-index period (7.3 +8.0 vs. 8.3 +8.4, p=0.03), and there was a 20 percentage-point drop in the proportion of LBP patients with an opioid prescription (pre: 42.1% vs. post: 22.2%; p<0.001). The proportion of knee OA patients with a knee x-ray was reduced by more than half from 12 months	

					pre- to 12 months post-index (54.5% to 23.9%; p<0.0001). The proportion of patients with a physical therapy visit for knee OA decreased significantly from pre- (28.8%) to post-index (10.3%; p<0.0001). The proportion of patients having a knee OA- or LBP-related OP office visit decreased from pre- to post-index in the knee OA cohort (79.5% to 52.3%; p<0.001) and LBP cohort (81.7% to 52.4%; p<0.001).	
Un-published data Supp K	UK Private payor report	Patients with knee pain	AposHealth		• 92% of the patients are satisfied with AposHealth. • 93% are likely to recommend Apos to friends or family • 72% have fewer consultant visits • 87% expect to delay surgery • 63% expect to avoid surgery Reduction in utilization – 82%	

					stopped/reduces OTC, 80% stopped/ use less prescribed medication, 78% stopped/use less NSAIDs, 86% stopped/use less injections, 83% stopped/use less Physiotherapy, 78% stopped/use less braces, 51% stopped/use less orthotics.	
Un-published data Supp L	NHS CCG	Patients eligible for TKR	AposHealth		98% of the patients treated with AposHealth are extremely likely / likely to recommend AposHealth to friends or family. Very high satisfaction rate concerning aspects associates with the delivery of care including waiting time, courtesy of physiotherapist, appointments are on time, and customer service	

2 Details of relevant studies

Please give details of all relevant studies (all studies in table 1). Copy and paste a new table into the document for each study. Please use 1 table per study.

Surgery avoidance rates among total knee replacement candidates following a non-invasive biomechanical intervention: A retrospective cohort study **Greene et al., 2022 (Accepted for publication in Journal of Orthopaedic Experience & Innovation)**	
What are main differences in resource use and clinical outcomes between the technologies?	NA
How are the findings relevant to the decision problem?	Results suggest that 84% of TKR candidates treated with AposHealth avoided TKR at a 2-yrs. These results were associated with a significant clinical improvement. OKS has improved by 7.6 points in the first 6 months of treatment, and further to 10.6 points at 2 years, meeting the minimally important change of 7 points. Note: This study has been **accepted for publication** in the Journal of Orthopaedic Experience & Innovation (Acceptance confirmation, July 25th). We are waiting for the final online version
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function Reduced need for knee replacement surgery
Will any information from this study be used in the economic model?	Yes
What cost analysis was done in the study? Please explain the results.	This study did not do cost analysis. We will use the outcomes of this study to model surgery avoidance rate and compare them to the standard care to calculate potential cost savings
What are the limitations of this evidence?	This was a commercial audit with no control group. However, the NHS Service Restriction Policy within the NHS locality meant all patients had failed core therapies and met the strict criteria for secondary care referral. Studies have also reported that 33% of the patients that

	are referred to secondary consultation by a general practitioner will undergo surgery within 12 months. This is over 5-times more than the 6% seen in the present study.
How was the study funded?	Study was not funded

Effect of Biomechanical Footwear on Knee in People With Knee Osteoarthritis. The BIOTOK Randomized Clinical Trial **Reichenbach et al., 2020.**	
What are main differences in resource use and clinical outcomes between the technologies?	The primary outcome measure was pain. The biomechanical footwear group had a larger decrease in standardised WOMAC pain subscore at 24 weeks of follow-up than the control footwear group (mean score, 1.3 vs 2.6, respectively; between-group difference, −1.3 [95% CI, −1.8 to −0.9]; *P* < .001) 83% of patients in the biomechanical group had a 50% reduction in WOMAC pain, 92% with a 30% reduction compared to 42% and 58%, respectively in the control group (P< 0.001) Secondary outcome measures included WOMAC scores, SF-36, Spatio-temporal gait analysis. There were no significant adverse events associated with the treatment compared to controls. Gait velocity improved by 37% (p<0.05)
How are the findings relevant to the decision problem?	Level I large scale RCT comparing AposHealth to a sham device in 220 patients with knee OA. The study was conducted by KOL in knee OA and was published in JAMA. Results suggest a superiority effect to AposHealth with respect to pain reduction, with a high effect size (ES = 0.72), low NNT (NNT = 3), minimal adverse events (not more than controls) and no serious adverse events.

	The authors concluded that the treatment is safe and effective. This was the pivotal trial in the company's FDA submission that led to approve AposHealth as a Class I Medical device for patients with knee OA
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	NA
What are the limitations of this evidence?	• The control group was comprised of a sham device with similar treatment plan. In essence this group can also be referred as 'active controls as they were asked to follow a walking protocol. However, AposHealth was found superior even in this scenario (actively walking = type of exercise), hence it can be assumed that group differences would have been higher if no activity was done at all. Analgesic treatment for pain was allowed during the trial; however, the rates of analgesic use did not differ between groups.
How was the study funded?	The trial was sponsored by Bern University Hospital and coordinated by CTU Bern, the University of Bern's clinical trials unit. The trial was funded by the Mäxi Foundation. Dr Jüni is a tier 1 Canadian research chair in clinical epidemiology of chronic diseases; this research was completed, in part, with funding from the Canada Research Chairs Programme. Apos Medical Assets provided the biomechanical footwear system and the control footwear, and provided the technicians trained to install and calibrate the external pods on the biomechanical footwear without charge.

Avoidance of total knee replacement in a population health setting. Introducing a non-invasive biomechanical intervention for patients with knee osteoarthritis **Drew et al., 2022.**	
What are main differences in resource use and clinical outcomes between the technologies?	Results suggest that 86% of TKR candidates treated with AposHealth avoided TKR at a 2-yrs compared to 12% in the controls. These results were associated with significant clinical improvement in patient treated with AposHealth. Patients reported a significant reduction in pain and improvement in function.
How are the findings relevant to the decision problem?	Results suggest that 86% of TKR candidates treated with AposHealth avoided TKR at a 2-yrs compared to 12% in the controls. These results were associated with significant clinical improvement. This is an indication that patients with severe knee OA who are eligible for a TKR can benefit from AposHealth clinically. It is assumed that the positive clinical effect (reduction in pain and improvement in functions) led most patients to reconsider surgery. It is reasonable to assume that patients that are on the waiting list, even if they have joined early knowing that the waiting times are long, may also benefit from this intervention as most likely they have failed the core interventions. The results of this study are also supported with additional information on surgery avoidance in different populations (UK, US, IL)
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function Reduced need for knee replacement surgery
Will any information from this study be used in the economic model?	Partially. Surgery avoidance rates will be used to **support** the pivotal study. It provides additional validation for the primary outcome (TKR rates) on a different cohort.

What cost analysis was done in the study? Please explain the results.	Cost savings as a result of surgery avoidance at 2-yrs
What are the limitations of this evidence?	Patients chose their group allocation hence the possibility of a selection bias cannot be ruled out. However, it is noteworthy that randomising patients against their choice was not possible and such a study methodology is impossible.
How was the study funded?	Study was not funded

A treatment applying a biomechanical device to the feet of patients with knee osteoarthritis results in reduced pain and improved function: a prospective controlled study **Bar-Ziv et al., 2010.**	
What are main differences in resource use and clinical outcomes between the technologies?	The results support a superiority effect for AposHealth compared to a sham device with a significant reduction in pain and improvement in function as well as an increase in QoL. In additions, patients who were treated with AposHealth consumed less rescue medicine (paracetamol) compared to controls. There were no additional monitoring of claims data.
How are the findings relevant to the decision problem?	The results support a superiority effect for AposHealth compared to a sham device with a significant reduction in pain and improvement in function as well as an increase in QoL. In additions, patients who were treated with AposHealth consumed less rescue medicine (paracetamol) compared to controls.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit:

	Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	NA
What are the limitations of this evidence?	This study lacked randomisation in the assignment of the patients to control and active groups. However, both groups were similar in their characteristics.
How was the study funded?	Study was not funded

Reduction in knee adduction moment via non-invasive biomechanical training: A longitudinal gait analysis study **Haim et al., 2011.**	
What are main differences in resource use and clinical outcomes between the technologies?	NA
How are the findings relevant to the decision problem?	This study provides evidence that biomechanical indicators for disease severity and progression are positively impacted following AposHealth. More specifically, the knee adduction moment, which is a primary biomechanical indicator for disease severity and progression, decreased significantly following nine months of AposHealth. These results were accompanied by a significant reduction in pain and improvement in function and QoL. The results of this study provides indication of the mechanism of actions and the biomechanical effect of AposHealth on the underlying biomechanical causes for knee OA.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No

What cost analysis was done in the study? Please explain the results.	NA
What are the limitations of this evidence?	This involved a relatively small cohort with no control group. However, the primary outcome of this study was changes in the knee adduction moment using 3D gait analysis. Tests and objective and done in laboratory settings, hence the changes in kinetics and kinematics are accurate and valid, with minimal external (subject) bias.
How was the study funded?	Study was not funded

Alterations in Sagittal Plane Knee Kinetics in Knee Osteoarthritis Using a Biomechanical Therapy Device **Debbi et al., 2015**	
What are main differences in resource use and clinical outcomes between the technologies?	NA
How are the findings relevant to the decision problem?	The results of this study provide evidence that biomechanical indicators for disease severity and progression are positively impacted following AposHealth. More specifically, the knee flexion moment, which is a primary biomechanical indicator for disease severity and progression, decreased significantly following nine months of AposHealth. These results were accompanied by a significant reduction in pain and improvement in function and QoL.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	NA
What are the limitations of this evidence?	This study comprises a relatively small cohort with no control group. However, the primary outcome of this study was changes in the knee adduction moment using

	3D gait analysis. Tests were undertaken in laboratory settings, hence the changes in kinetics and kinematics are accurate and valid, with minimal external (subject) bias.
How was the study funded?	Study was not funded

Long-Term Effects of AposTherapy in Patients with Osteoarthritis of the Knee: A Two-Year Follow-up **Bar-Ziv et al., 2013**	
What are main differences in resource use and clinical outcomes between the technologies?	The results of this study provide long-term evidence on the clinical effectiveness of AposHealth in reducing pain and improving function relative to a cohort of patients that was treated with the standard of care. In addition, the results also support a reduction in surgery rates to TKR at 2-yrs in patients that were treated with AposHealth compared to controls. Only 2.5% of the patients that were treated with AposHealth have had a TKR withing 2-yrs compared to 30% in the control group.
How are the findings relevant to the decision problem?	The results of this study provide long-term evidence on the clinical effectiveness of AposHealth in reducing pain and improving function relative to a cohort of patients that was treated with the standard of care. At 2-yrs patients maintain the significant clinical outcomes with a large effect size of 1.44. In comparison, patients that were in the control group that were treated with the standard of care and reported a slight deterioration in symptoms at 2-yrs. This is not surprising given that knee OA is a chronic condition that often progresses with time. In addition, the results also support a reduction in surgery rates to TKR at 2-yrs in patients that were treated with AposHealth compared to controls. Only 2.5% of the patients that were treated with AposHealth have had a TKR withing 2-yrs compared to 30% in the control group.

Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function Reduced need for knee replacement surgery
Will any information from this study be used in the economic model?	No. although the study report surgery avoidance at 2-yrs, the population is different than the targeted one (moderate-severe instead of severe patients)
What cost analysis was done in the study? Please explain the results.	NA
What are the limitations of this evidence?	This was not a randomised trial. Nevertheless, the two groups were equal at the baseline in terms of patient characteristics and clinical outcomes. In additions, the sample size is relatively small.
How was the study funded?	Study was not funded

Non-invasive biomechanical therapy improves objective and subjective measurements of pain and function in patients with knee osteoarthritis: a retrospective analysis **Lador et al., 2013.**	
What are main differences in resource use and clinical outcomes between the technologies?	NA
How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. Real-life evidence are as equally important as clinical trials as it better reflects reality. The results support a significant reduction in pain and improvement in function and QoL. In addition, a significant improvement was also seen in objective gait patterns.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: Improved quality of life due to reduced pain and improved joint function

Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	NA
What are the limitations of this evidence?	A retrospective analysis was undertaken with no control group. Nevertheless, the primary measurements of this study were objective gait parameters of these patients. These measurements were found to correlate with the patient's subjective assessments, thus validating, to a certain extent, the success of this suggested therapy.
How was the study funded?	Study was not funded

Effects of a customized biomechanical therapy on patients with medial compartment knee osteoarthritis Drexler et al., 2012.	
What are main differences in resource use and clinical outcomes between the technologies?	NA
How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. Real-life evidence are as equally important as clinical trials as it better reflects reality. The results support a significant reduction in pain and improvement in function and QoL. Sub-group analysis of the data suggest that the treatment is not sensitive to age, gender, or BMI and that there should not be a limitation receiving this intervention in those sub-groups.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No

What cost analysis was done in the study? Please explain the results.	NA
What are the limitations of this evidence?	The study involved a retrospective analysis with no controls group.
How was the study funded?	Study was not funded

A novel self-care biomechanical treatment for obese patients with knee osteoarthritis. **Lubovsky et al., 2015**	
What are main differences in resource use and clinical outcomes between the technologies?	NA
How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. The results of this study provide more information on the effect of treatment in a subgroup of patients – obese patients with knee OA. Obesity is one of the reasons for knee OA and helping this specific population be more active is positive not just for treating their knee pain, but also to help with other health issues. The results support a significant reduction in pain and improvement in function and QoL. In addition, a significant improvement was also seen in objective gait patterns.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	NA

What are the limitations of this evidence?	A retrospective analysis was undertaken with no control group. In addition, weight change was not monitored over time. It cannot be determined whether (or to what extent) the improvements in gait pattern, pain and function are due to weight reduction or the intervention itself. However, we anticipate that the reduction in pain while using Apos would enable patients to be more active, leading to improvement over time. It is similar to the chicken and egg syndrome, but the positive effect is what matters.
How was the study funded?	Study was not funded

APOS therapy improves clinical measurements and gait in patients with knee osteoarthritis **Elbaz et al., 2010**	
What are main differences in resource use and clinical outcomes between the technologies?	NA
How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. The results support a significant reduction in pain and improvement in function and QoL. In addition, a significant improvement was also seen in objective gait patterns.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	NA

What are the limitations of this evidence?	This was a retrospective study with no control group. Nevertheless, the primary measurements of this study were objective gait parameters of these patients that are not commonly used in knee OA studies.
How was the study funded?	Study was not funded

The outcome of a novel biomechanical therapy for patients suffering from anterior knee pain **Haim et al., 2013**	
What are main differences in resource use and clinical outcomes between the technologies?	NA
How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. The results of this study provide more information on the effect of treatment in a subgroup of patients that suffer from anterior knee pain. Anterior knee pain is a limiting condition with no effective interventions. Being able to manipulate the centre of pressure and reduce loads form the anterior aspect of the knee while training neuromuscular control helps alleviate pain. The results support a significant reduction in pain and improvement in function and QoL. In addition, a significant improvement was also seen in objective gait patterns. Anterior knee pain is more common in the younger population and given that there are no effective interventions to treat anterior knee pain, providing AposHealth will help with this patient population
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: Improved quality of life due to reduced pain and improved joint function

Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	NA
What are the limitations of this evidence?	This comprised a retrospective analysis with no control group. In addition, only spatiotemporal gait data were gathered. A three-dimensional gait analysis would offer far greater information regarding the kinematics and kinetics of the lower limb in this unique group of patients.
How was the study funded?	Study was not funded

A unique foot-worn device for patients with degenerative meniscal tear **Elbaz et al., 2012**	
What are main differences in resource use and clinical outcomes between the technologies?	NA
How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. The results of this study provide more information on the effect of treatment in a subgroup of patients – patients with knee OA and a degenerative meniscal tear. Although, arthroscopic intervention is clearly not recommended in the management of knee OA (except for specific cases of joint locking), some are still recommending it as a treatment option. The results provide a strong indication that patients with degenerative meniscal tear can benefit from a non-surgical intervention. Following AposHealth there was a significant reduction in pain and improvement in function and QoL. In addition, a significant improvement was also seen in objective gait patterns.

	Furthermore, only one patient (3%) had a knee arthroscopy at 12 months.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: • Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	NA
What are the limitations of this evidence?	This was a retrospective analysis with no control group. In addition, the interventions did not commence immediately following the injury but within a 3-month time window.
How was the study funded?	Study was not funded

Knee Osteoarthritis functional classification scheme – validation of time dependant treatment effect. One year follow-up of 518 patients **Herman et al., 2018**	
What are main differences in resource use and clinical outcomes between the technologies?	NA
How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. This study used an objective functional classification for patients with knee OA to help assess their limitations pre-interventions and assess the changes in classification as an objective measure post-intervention (any intervention). Gait is a vital sign with great importance and may help objectively assess patients. We believe that improved

	functionality is an important outcome measure when assessing interventions to treat knee OA. The results support a significant reduction in pain and improvement in function and QoL. In addition, a significant improvement was also seen in objective gait patterns. Patients shifted from a severe gait classification group to a less severe one, indicating better movement patterns.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	NA
What are the limitations of this evidence?	A retrospective analysis with no control group was undertaken. Previous studies have reported a placebo effect in knee OA studies, especially for pain, stiffness, and self-reported function. Without a control group we cannot estimate the placebo effect, however we believe that the effect of treatment is beyond the placebo effect as the effect size of the treatment was larger than the effect size that was reported for the placebo effect.
How was the study funded?	Study was not funded

Patients with knee osteoarthritis demonstrate improved gait pattern and reduced pain following a non-invasive biomechanical therapy: a prospective multi-centre study on Singaporean population **Elbaz et al., 2014**	
What are main differences in resource use and clinical outcomes between the technologies?	NA

How are the findings relevant to the decision problem?	The results of this study provide evidence on the clinical effect of AposHealth in commercial settings. The results provide more information on the clinical effect of the intervention in an Asian population providing evidence that the treatment is no sensitive to race. The results support a significant reduction in pain and improvement in function and QoL. In addition, a significant improvement was also seen in objective gait patterns.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	NA
What are the limitations of this evidence?	There was no control group.
How was the study funded?	Study was not funded

Foot centre of pressure manipulation and gait therapy influence lower limb muscle activation in patients with osteoarthritis of the knee **Goryachev et al., 2011**	
What are main differences in resource use and clinical outcomes between the technologies?	NA
How are the findings relevant to the decision problem?	This study provides evidence of changes in muscle activation patterns following treatment with AposHealth. A change in muscle activations was seen after three months of treatment, indicating that induced perturbation

	for neuromuscular training led to improved muscle activation. These results were also supported with an improvement in clinical outcomes including a significant reduction in pain and improvement in function and QoL.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Patients benefit: Improved quality of life due to reduced pain and improved joint function
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	NA
What are the limitations of this evidence?	First, the study cohort was relatively small. Second, since no normalisation procedure on the data was performed, the ARV and peak EMG values are valid for this study only and cannot be compared to other studies. However, there was a consistent increase of ARV and peak EMG after training for almost all examined muscles, so it is reasonable to assume that it was induced by the training and not by the varying factors of signal acquisition.
How was the study funded?	Study was not funded

3 Economic model

This section refers to the de novo economic model that you have submitted.

Description

Patients

Describe which patient groups are included in the model.

Patients with end-stage knee OA who meet the clinical criteria for referral for elective primary total knee replacement surgery (TKR). This is the population to which Apos was offered in Mid-Essex, as reported in Greene et al.

Note on terminology:
In this submission we use the term primary to indicate a first knee replacement on a given knee (i.e., not a revision). Some patients having primary knee surgery may have previously had TKR on the contralateral knee.

In England, one in five people over the age of 45 has knee OA and the rates are constantly increasing due to an ageing population and a rise in obesity. There were 85,933 NHS-funded elective knee replacements in England in 2018-2019 (pre-covid rates). Of these, we estimate based on analysis of Hospital Episode Statistics data that 94% (81,050) were primary knee replacements and the remainder were revisions (NHS PROMs data derived from Hospital Episode Statistics **NHS Digital**). According to McHugh et al., 33% of the patients with a confirmed diagnosis of OA that are referred to an orthopaedic consultant and considered potentially suitable for TKR will undergo surgery within 12 months. This implies that approximately 245,600 patients with end-stage knee OA are referred yearly to secondary care and are eligible for TKR.

The care management of knee OA is a stepped programme aiming to alleviate symptoms, provide joint stability, and postpone disease progression (Wallis, Taylor et al. 2019). The National Institute of Clinical Excellence (NICE) guidelines (Conaghan, Dickson et al. 2008) outline core treatments such as education and exercise as first-line care, progressing to more advanced modalities such as biomechanical interventions, including valgus knee braces and orthotics, alongside with pharmacological interventions and knee injections (NICE). Total knee replacement is considered the most common treatment for end-stage knee OA and appears to be increasing over time (Carr, Robertsson et al. 2012). It is estimated that the rates of TKR will reach 119,000 procedures per year by 2035 and 226,000 procedures per year by 2050 (Culliford, Maskell et al. 2015, Klug, Gramlich et al. 2021). At the same time, because the average age for a TKR is falling, the prevalence of revision knee surgery is also expected to rise even more rapidly by almost 90%, reaching nearly 47,500 procedures per year by 2050 (Klug, Gramlich et al. 2021). Despite the favourable surgical outcomes, approximately 20% of post-TKR patients continue to experience chronic pain and an equal number report that their expectations for a full recovery are unmet (Tilbury, Haanstra et al. 2016, Wylde, Beswick et al. 2018). These projections show that the steep increase in TKR and revision surgeries will

place an immense burden on the cost of health care, highlighting the urgent need for new non-surgical approaches that more effectively manage OA symptoms of the knee (Klug, Gramlich et al. 2021).

A recent study looked at the healthcare resource utilisation and costs in UK population with moderate to severe knee OA. In general, patients with moderate-severe knee OA had significant higher annual costs compared to matched controls without knee OA. Moreover, a sub-group analysis demonstrate that the healthcare resources utilisation and costs are higher in the severe population compared to controls (Abraham et al., 2022). We assume that early-stage disease management include lower costs and as disease progresses costs increase. We also believe that the first line of treatment (i.e., exercise, weight loss programmes, education, topical NSAIDs) should be maintained and maximised. If patients continue to deteriorate and present severe symptoms, other interventions should be considered. Based on our experience AposHealth should be positioned in later stages of the disease when the patients are with severe symptoms and have tried and failed first line of treatment. In this population, when symptoms are high, costs increase, and surgery becomes an option, AposHealth will provide the best value to the patient and the healthcare system. Therefore, the focus of the economic model will be on severe patients with knee OA that have tried and failed the first line of treatment.

It is also important to clarify that having a TKR will not end the costs associated with the disease – there are post-operative costs associated with surgery (complications, rehabilitation, revisions) (Leal et al., 2022) and even increased likelihood for a contralateral TKR (Sanders et al 2017). There is evidence to support the rates of post-op complications and extensive evidence of bilateral OA progression in knees and a higher likelihood of TKR after an initial TKR in the other knee, which should also be accounted for.

For these reasons, our model will focus on a specific group of knee OA population: Patients with end-stage knee OA who meet the clinical criteria for referral for elective primary total knee replacement surgery (TKR).

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

Technology: AposHealth (in conjunction with good standard care)

Comparator: Non-surgical standard care treatment options, including but not limited to:

- Devices (such as supports, splints and braces)
- Intra-articular corticosteroid injections

AposHealth

For the past decade, a personalised non-invasive biomechanical treatment for patients with knee OA has been available in the UK, with over 10,000 patients treated to date. AposHealth is an FDA-cleared class I medical device for patients with knee OA and has a CE mark as a class IIa medical device for knee OA. As of 2022 more than 110,000 patients were treated with AposHealth worldwide. In essence, it is a shoe-like device that provides the platform to fit two convex pods under the sole. One is located under the anterior part of the sole and the other under the posterior, both attached using special rails and screws and can be adjusted based on clinical needs (Figure 1). The AposHealth shoes (AKA Apos) are available with a Velcro fastening, or with a lace fastening depending on the person's hip flexibility, finger dexterity, foot width and preference. Adjusting the pods' location changes the ground reaction force (GRF) vector and immediately reduces pressure on the area (Haim, Rozen et al. 2010, Haim, Wolf et al. 2011). The convex nature of the elements induces a level of controlled perturbation and proprioceptive training causing muscles in the lower limb to work differently (Goryachev, Debbi et al. 2011, Debbi, Wolf et al. 2012). The combination of altered forces and moments acting on the affected joint due to the device set-up, combined with controlled perturbation, allows a neuromuscular training response and carry-over effect to usual walking without the device to occur (Haim, Rubin et al. 2012, Debbi, Wolf et al. 2015).

AposHealth is a home-based intervention. Patients are instructed to wear a personally calibrated device for 30-60 minutes a day while performing their daily activities at home or work. Usage time is not limited and may increase gradually, depending on progress and symptoms. The application of the treatment comprises the functional rehabilitation principle, which stresses the importance of task-specific rehabilitation with repetitive and sub-conscious activities (Levin, Weiss et al. 2015, Charlton, Eng et al. 2021). In addition, patients are also educated about the condition and ways to manage their symptoms. AposHealth aligns with core recommendations already suggested within the NICE guidelines for the management of knee OA (2008), enabling education, self-management, muscular retraining, graded exposure to activity, along with the ability to address biomechanical joint pain in a single treatment modality.

Since the COVID-19 pandemic more telehealth, remote care, and home-based interventions are emerging. Furthermore, the need to postpone a huge number of elective interventions including doctor visits, physiotherapy, injections, and surgeries causes a very long waiting list and patients are left untreated. More specifically, the waiting lists for TKR have grown exponentially, with the number of inpatient procedures rising by 73% compared to the previous year (Hampton et al., 2021). Healthcare systems are trying to address the backlogs, but with limited capacities for elective surgery, patients are left untreated, and the recovery from the backlog is much slower than required. Therefore, it is paramount that health systems look for effective alternatives for treating these cohorts with interventions that can alleviate symptoms and significantly delay and potentially avoid the need for joint replacement surgery altogether where possible. AposHealth is a clinically proven home-based intervention that addresses those requirements and can be an alternative for those on the elective surgery waiting list.

Figure 1. Apos device

Sole platform includes two mounting rails and a positioning matrix. **Biomechanical pods** are available in different degrees of convexity and sizes.

Biomechanical pods can be configured on the sole platform with flexible positioning for **personalized biomechanical placement**.

Model structure

Provide a diagram of the model structure you have chosen in Appendix B.

Justify the chosen structure of the model by referring to the clinical care pathway outlined in part 1, section 3 (Clinical context) of your submission.

The model is a Markov model which estimates the likelihood of TKR and death over 5 years, for patients with end-stage knee OA who meet the clinical criteria for referral for elective primary total knee replacement surgery (TKR). We believe that this group will include most patients who fall into the subgroups identified in the scope. However, we have not undertaken separate subgroup analysis as it was not possible to identify robust data at this level.

In one arm of the model, patients receive OA standard care plus Apos, and in the other arm patients receive OA standard care. Standard care for these patients includes all NICE-recommended therapies for severe OA, including core therapies and adjunct therapies such as joint support, bracing, and injections as appropriate for each individual.

The model is informed by the Apos studies listed above, in particular by Greene et al. which is a recent study in an NHS setting, focusing on a group of patients identical to the population in the model. It is aligned with the clinical care pathway set out in part 1, section 3 of the submission, which states that Apos should be considered an adjunct therapy for patients with relatively severe disease. Adjunct interventions are classified as non-invasive, pharmacological, and surgical. Apos is a non-invasive intervention aimed at avoiding the need for surgery.

The model cycle length is one month. The health states in the model are:

- OA care with Apos
- OA standard care
- OA post-Apos maintenance
- TKR
- Second TKR (on the contralateral knee)
- Death

In each health state (apart from death), patients have a monthly probability of remaining in that state or moving to a different state. These transitions are shown in diagrams 1 and 2 in Appendix B. Costs are assigned to each health state and applied to the proportion of patients in that state each month. These are summed at the end of the model to provide an estimate of total cost impacts in each arm.

Model inputs are derived from Greene et al., supplemented by additional NHS data and evidence from peer reviewed literature and expert opinion where necessary (Supp S). Overall, the model is based on hundreds of patients that were treated with AposHealth and demonstrated significant clinical improvements and very high surgery avoidance rates at two years, with preliminary data to support longer term outcomes (3.5 yrs.) to strengthen the 5-yrs assumptions.

A number of sensitivity analyses are provided, to explore the impact of key variables on model outputs.

Table 2 Assumptions in the model

In this table, list the main assumptions in the model and justify why each has been used.

Assumption	Assumption rate	Justification	Source
Two-year TKR rate - AposHealth	16% (monthly: 0.72%)	Greene et al. report a 2-year TKR probability of 16% in a cohort of patients with end-stage knee OA who meet the clinical criteria for referral for elective primary TKR, and this cohort matches the cohort in our model.	Greene et al., 2022 Supported by Drew et al 2022.
Yearly TKR rate – standard care	33% (monthly: 3.28%)	McHugh et al., reports a 1-year TKR probability of 33% in a cohort of patients with OA newly referred by GPs to an orthopaedic surgeon for consideration for TKR	McHugh et al., 2011
Mortality	0.8% (0.07% monthly)	Leal et al., reports an annual mortality rate of 0.8% for patients eligible for TKR/underwent TKR	Leal et al., 2022
Post-operative complications (Of those receiving TKR)	6%	Leal et al., reports a 6% post-operative complication rates associated with TKR	Leal et al., 2022
Revision during year 1 (Of those receiving TKR)	0.5%	Leal et al., reports a 0.5% of patient will require revision post primary TKR during the first year of surgery	Leal et al., 2022
Utilisation of other interventions – AposHealth	15% savings relative to standard care costs	Patients treated with AposHealth will continue to consume standard care interventions. However, the Apos interventions is associated with a significant reduction in pain and improvement in function that affect the utilisation of other health resources. Multiple data sets	[redacted]

		suggest an average saving of 15% in healthcare utilisation while using AposHealth. In one independent analysis the proportion of patients using non-NSAID, non-opioid pain medications decreased by 33% (37.5% to 25.0%, p=0.029) (` Health Analytics). Another independent member survey conducted by a private UK medical insurer suggest a reduction in pharmacological treatment including OTC and prescribed pain killers, self-reported utilisation of pharmacological interventions suggest that 82% of the patients treated with AposHealth stopped using / are using less OTC pain killers and 80% stopped using / are using less prescribed pain killers. 78% of the patients stopped using / are using less NSAIDs. In the same independent member survey, a potential decrease in the utilisation of intra-articular injections (86% stopped / reduced use), physiotherapy (83% stopped / reduced use), and braces (78% stopped / reduced use) is also reported. The reduction in physical therapy visits is also supported by a second independent utilisation study done on US population [redacted]	

Five-year rate of 2nd TKR (Probability is applied 6 months after having the first TKR)	33.5% (monthly: 0.8%)	Patients that have had a primary TKR are likely to have a secondary TKR in the contralateral knee.	Sanders et al., 2017
Percent of patients in cohort who have a prior TKR	33.6%	The probability of a patient undergoing a TKR in their other knee is scaled down by 33.6% when applied to patients who have undergone a first TKR in the model.	Chitnavis et al., 2000

Table 3 Clinical parameters, patient and carer outcomes and system outcomes used in the model

In this table, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Parameter/outcomes	Source	Relevant results	Range or distribution	How are these values used in the model?
Yearly TKR rate - AposHealth	Greene et al., 2022	16% of the patients with AposHealth will progress to TKR at 2-yrs, 0.72% monthly.	95% CI 12% to 20%	We will use this rate for TKR probabilities in patients treated with AposHealth. Greene et al., surgery avoidance rates are supported with another 2-yrs study published by Drew et al., 2022.
Yearly TKR rate – Standard care	McHugh et al., 2011	33% of the patients with a confirmed diagnosis of OA that are referred to an orthopaedic consultant and considered potentially suitable for TKR will undergo surgery within 12 months	Text	We will use this as a reference for the standard care TKR rate
Standard care costs - AposHealth	[redacted]	15% savings annually		We will use the results from the [redacted] report as a reference for knee OA healthcare utilisation savings

Mortality	Leal et al., 2022	0.8% annually	Text	Leal et al., reports mortality within 1 year of TKR
Revision	Leal et al., 2022	0.5% annually	Text	Leal et al., reports revision rates within 1 year of TKR
Second TKR	Sanders et al., 2017	0.8% monthly		Sanders reports that 33.5% of patients will have a secondary TKR in the contralateral knee within 5 years. We apply the monthly probability from month 7 after first TKR, on the assumption that a second TKR would not be performed until at least 6 months after the first.

If any outcomes listed in table 4 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

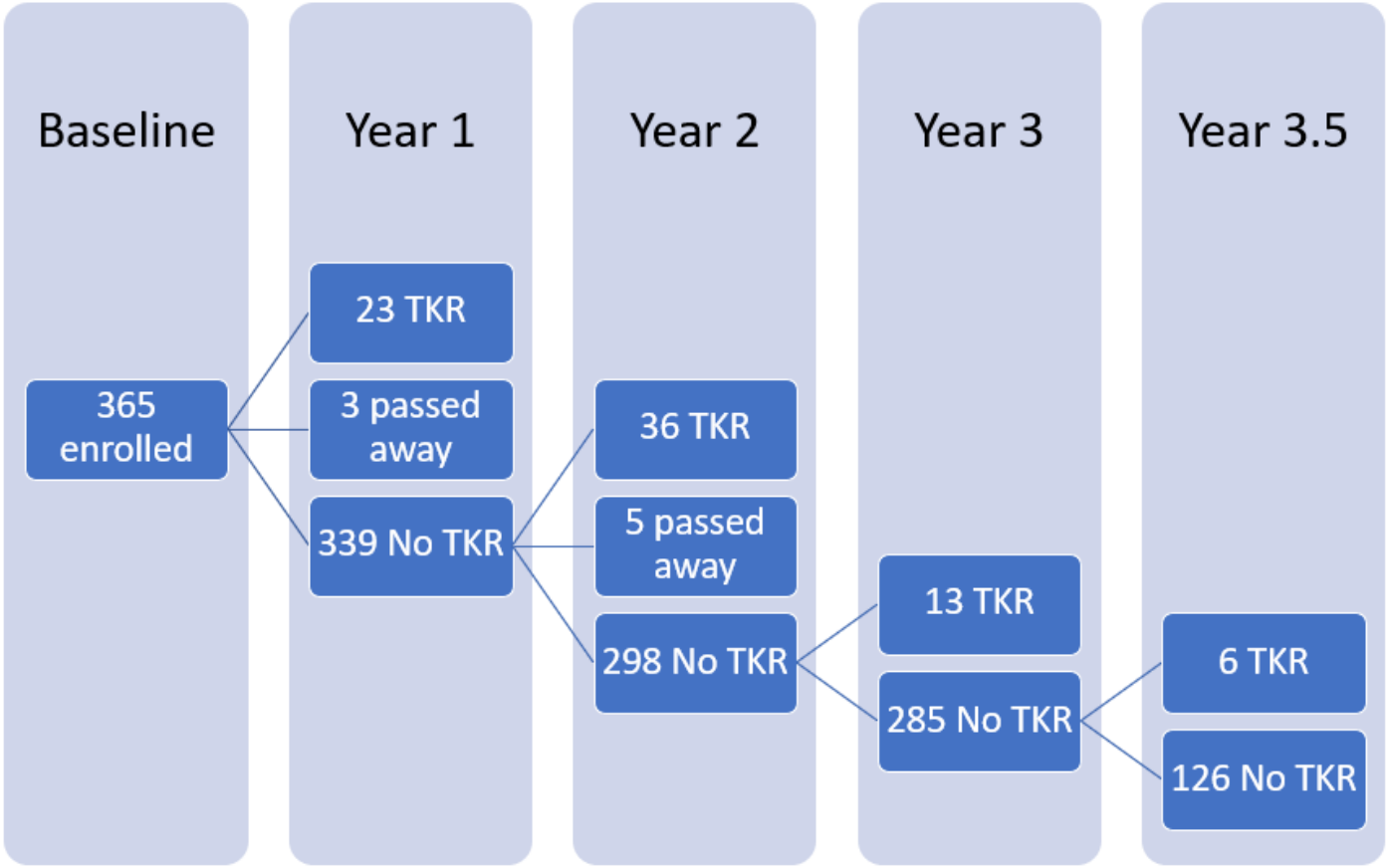
We present a 5-yrs model that looks at the knee OA costs of patients with severe knee OA in two cohorts. First cohort are patients treated with AposHealth and the second cohort are patients treated with the standard care. For years 1-2 there is evidence to support the model.

Years 3-5

There is no published data on >3 years surgery avoidance. However, the model assumptions are based on extrapolation of the probabilities based on years 1-2. This approach is supported by unpublished long-term follow-up data for the Greene et al. cohort, which shows lower TKR probabilities beyond year 2 which are lower than those used in the model. Sensitivity analysis was performed to accommodate for the uncertainties.

Long-term analysis of Greene's cohort data suggests a TKR rate of 6.3%, 9.9%, 6.1%, 4.5% for year 1, year 2, year 3 and year 3.5, respectively (Figure 2).
Longer term results from this NHS setting show a reduction in TKR rates each year after year 2 (6.1 and 4.5% respectively). This is reflective of those who responded well to treatment and either self-managing or remain actively attending follow-ups appointments to maintain results.
It is acknowledged that COVID-19 would have had an effect on surgery rates, but in the pre-covid cohort analysis, TKR rates were comparable up to 2 years. It is also likely that most patients that stopped treatment during the study time period (Nov 2017 – Nov 2019) and wished to access TKR surgery would have had enough time elapsed to access surgery prior to the analysis by Greene et al. (November 2021).

Figure 2. Long-term surgery avoidance in an NHS population (preliminary analysis)



Inclusion of second TKR

AposHealth uses gait modifications and neuromuscular training to alleviate symptoms and improve function using a foot-worn device. This device can address multiple lower back and lower extremity MSK conditions. For many patients this is an advantage as patients with knee OA frequently suffer from other pains (lower back, hip). Furthermore, this also applies to patients suffering from a bilateral condition. While for some interventions there is a need to treat each knee separately (braces, injections), with AposHealth one can treat a bilateral condition simultaneously, and it is even recommended as the body constantly compensates for symptoms. The versatility of the AposHealth device accounts for these compensations.

There is extensive evidence of bilateral OA progression in knees and a higher likelihood of TKR after an initial TKR in the other knee (Shakoor, Cooper, Chitnavis, Sanders). In a survey of 125 patients having TKR surgery in the UK, Chitnavis et al found that 33.6% of the cohort had undergone a previous TKR in the other knee (Chitnavis et al., 2000). No UK studies were identified providing probabilities of second TKR in the contralateral knee for those who have had a first. In the US, Sanders et al examined the medical records of 2,139 patients who underwent a first TKR and identified subsequent contralateral TKR in 33.5% of patients at 5 years, 38.7% at 10 years and 45.2% at 20 years (Sanders et al., 2017). In the UK general population, the estimated mortality-adjusted lifetime risk of TKR at age 50 is 10.8% for men and 8.1% for women (Culliford et al., 2012). The prevalence of TKR at age 80 in the US has been reported as 10.4% in 2010 (Kremers et al., 2015), suggesting not dissimilar risk levels.

On this evidence, it was considered important to include the dynamics of a possible second TKR in the economic model.

The Sanders probability of 33.5% over 5 years is used to generate a monthly probability for TKR on the other knee following a first TKR. However, it is assumed that 33.6% of the model cohort have undergone a TKR in the other knee prior to the model period (Chitnavis et al.,2000) and that these patients can therefore not undergo a second TKR in the model run. The probability of a patient undergoing a TKR in their other knee is therefore scaled down by 33.6% when applied to patients who have undergone a first TKR in the model. This is considered a conservative approach as it is likely that the proportion of patients with a prior TKR would be lower in the population modelled (i.e. those who meet the clinical criteria for referral for surgery) than in those actually undergoing TKR.

The model assumes that patients cannot undergo a second TKR in the model in the first 6 months after receiving a first TKR. The 5-year probability from Sanders is therefore converted to a monthly probability over 4.5 years and this is applied in the model from month 7 after a first TKR. (It is noted that in Sanders, a large number of patients received bilateral TKR surgery (both knees at once). This was not modelled as in the UK, bilateral surgery accounts for only 1% of TKRs (National Joint Registry).

The same probability for a second TKR is applied in both arms of the model. Again, this could be considered a conservative position, as it assumes there is no further benefit from AposHealth on the other knee once a patient has undergone a first TKR.

Table 4 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table. You can adapt the parameters as needed.

Parameter	Description	Justification	Source
Time horizon	5 years	The company has evidence to support 2-yrs outcomes. However, we believe a 5-yrs time horizon is more relevant in a chronic condition such as knee OA and will provide long-term cost-saving modelling. We are not convinced a longer model will provide accurate insight as there are many uncertainties in such a long follow up duration. In addition, we are not aware of long-term (> 5-yrs) data on other non-surgical interventions for knee OA and consequently have used this to guide our decision.	Text
Discount rate	3.5%	NICE recommendation	Text
Perspective (NHS/PSS)	NHS	No source identified for PSS costs	Text

<table>
<tr><td>Cycle length</td><td>Monthly</td><td>We believe monthly transitions more accurately reflect the knee OA pathway as costs for OA care and Apos follow-up appointments are incurred on a rolling basis throughout the year. An annual model would attribute the full year state cost to the entire population in a given state at the beginning of the year, and then the full costs of TKR for those who transition during the year (i.e. double counting costs for some patients).</td><td>Text</td></tr>
<tr><td>Transition probabilities</td><td colspan="3">Standard care arm
<table>
<tr><th>From</th><th>To</th><th>Monthly probability</th><th>Source</th></tr>
<tr><td>OA standard care</td><td>TKR (years 1-2)</td><td>3.282%</td><td>McHugh et al., 2011</td></tr>
<tr><td>OA standard care</td><td>TKR (years 3-5)</td><td>3.282%</td><td>McHugh et al., 2011</td></tr>
<tr><td>OA standard care</td><td>Death</td><td>0.067%</td><td>Leal et al., 2022</td></tr>
<tr><td>TKR</td><td>TKR on other knee</td><td>0.500%</td><td>Sanders et al., 2017
Chitnavis et al., 2000</td></tr>
<tr><td>TKR</td><td>Death</td><td>0.067%</td><td>Leal et al., 2022</td></tr>
</table>
Apos arm
<table>
<tr><th>From</th><th>To</th><th>Monthly probability</th><th>Source</th></tr>
<tr><td>OA care with Apos</td><td>TKR (year 1)</td><td>0.724%</td><td>Greene et al., 2022</td></tr>
<tr><td>OA post-Apos maintenance</td><td>TKR (year 2)</td><td>0.724%</td><td>Greene et al., 2022</td></tr>
<tr><td>OA post-Apos maintenance</td><td>TKR (years 3-5)</td><td>0.724%</td><td>Greene et al., 2022</td></tr>
<tr><td>OA care with Apos</td><td>Death</td><td>0.067%</td><td>Leal et al., 2022</td></tr>
</table></td></tr>
</table>

	OA post-Apos maintenance	Death	0.067%	Leal et al., 2022
	TKR	TKR on other knee	0.500%	Sanders et al., 2017 Chitnavis et al., 2000
	TKR	Death	0.067%	Leal et al., 2022

Note: All patients remaining on Apos at the end of year 1 move to OA post Apos maintenance (transition occurs at beginning of month 13).

Health states	The health states in the model are: • OA care with Apos • OA standard care • OA post-Apos maintenance • TKR • Second TKR (on the contralateral knee) • Death	Text	Text

Sources of unit costs

Cost

OA standard care	Initial cost	£0	Abraham et al., 2022
	Monthly cost	£107.22	
OA care with Apos	Initial cost of Apos	£956.13	Internal data ([redacted])
	Y1 monthly cost of Apos	£9.98	
	Y1 monthly other OA care cost		
	- reduction to standard care cost	15%	
	- resulting cost	£91.14	
	Y2+ monthly cost of Apos	£6.65	

	OA post-Apos maintenance	Y2+ monthly other OA care cost	£91.14	Internal data [redacted])
	TKR	Initial cost	£6,755.47	Leal et al., 2022
		Y1 monthly cost	£92.29	https://www.england.nhs.uk/pay-syst/national-tariff/
		Y2 monthly cost	£30.67	HCHS inflators
		Y3+ monthly cost	£0.00	
	[redacted]Text			

Explain the transition matrix used in the model and the transformation of clinical outcomes, health states or other details.

All patients start with end-stage knee OA and meet the clinical criteria for referral for elective primary total knee replacement surgery (TKR).

The initial health states are **OA care with Apos** (Apos arm) and **OA standard care** (standard care arm).

In the standard care arm, patients continue to receive good standard care including appropriate adjunct therapies recommended by NICE including and not limited to biomechanical devices such as insoles, walking aids (i.e., cane) and braces, pharmacological interventions for pain relief (Topical/Oral NSAIDS, capsaicin, opioids, and intra-articular corticosteroid injections). In the Apos arm, patients receive Apos plus good standard care.

In both initial health states, patients have a probability in each monthly cycle of staying in the same state or transitioning to one of the following states: **TKR, Death**. Patients in the **OA care with Apos** state at 12 months all transition to the **OA post-Apos maintenance state**. In the **TKR** state, patients have a probability of staying in the same state or transitioning to one of the following states: **Second TKR, Death.** The transition probability from **OA care with Apos** to **TKR** is derived from Greene et al., which reports that 16% of patients receiving Apos had TKR over 24 months. The transition probability from **OA Standard Care** to **TKR** is taken from McHugh et al. We consider the population in the McHugh study to be a close match for that in Greene et al. The patient cohort is those with a confirmed diagnosis of OA who are referred to an orthopaedic surgeon in the NHS in England. McHugh reports that 33% had a TKR within 12 months.

The transition probability from **TKR** to **second TKR** (after month 6) is derived from Sanders et al. which reports that 33.5% of people have TKR on the other knee within 5 years following a first TKR. This figure is scaled down by 33.6% to allow for estimated prior TKR in the other knee at model outset (Chitnavis et al., 2000).

Transitions from all states to **Death** are taken from Leal et al., which reported mortality of 0.8% over 12 months in TKR patients.

For **OA care with Apos** and the transition probability to **TKR** - Pivotal study is the one of Greene et al. that published a UK-based 2-year surgery avoidance rate amongst NHS patients with end-stage knee OA who meet the clinical criteria for referral for elective TKR. The results suggest that 84% of the patients avoid surgery at 2-yrs. It might be argued that COVID-19 had an effect on the results of Greene et al. For this reason, we performed a sub-group analysis and looked at patients that were enrolled until April 2018 to allow completion of 2-yrs (free of Covid-19 effect). 86 patients were included in this analysis to present pre-covid 2-yrs surgery avoidance (9.3% in year 1 and 11.6% in year 2). This is accounted for in the sensitivity analysis

The transitions are presented diagrammatically in Appendix B.

Transition probabilities estimated for time periods of multiple months were converted into rates and then monthly transition probabilities using the following method:

Monthly rate (r) = [-ln(1-P)]/t

Monthly probability = 1 – exp {-rt}

Where:

P = probability, t = number of months

Resource identification, measurement and valuation

Technology costs

Provide the list price for the technology (excluding VAT).

Device/technology costs	
Per device	£875

Per patient costs	
Device/Technology	£875
Training	£1.31
Initial patient evaluation	£79.82
Monthly follow-up cost	£9.98

Breakdown of costs

Apos patient care	
Initial Evaluation duration (hours)	1
Follow-up hours per patient in first year	1.5
Evaluation cost per patient	£79.82
Follow-up cost per patient	£119.72
Monthly follow-up cost	£9.98
Year 2+ average care time (hours)	1
Year 2+ average cost	£79.82
Monthly year 2+ average cost	£6.65

If the list price is not used in the model, provide the price used and a justification for the difference.

The price list above is the one included in the model

NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

National tariffs are used in the NHS in England for elective TKR, post-discharge rehabilitation for knee replacement, and trauma and orthopaedics outpatient attendances. These are shown below and are used in the economic model.

Code/identifier	HRG name	2022-23 tariff
HRG HN22D (elective TKR best practice tariff)	Very Major Knee Procedures for Non-Trauma with CC Score 2-3	£6,624
HTG HN22E (elective TKR best practice tariff)	Very Major Knee Procedures for Non-Trauma with CC Score 0-1	£6,313
Complexity Resource Group (Tariff section 5)	Rehabilitation post-discharge, Knee replacement	£620
HRG WF01B, Treatment Code 110	Consultant-led First Attendance - Single Professional, Trauma and Orthopaedics Service	£169
HRG WF01A, Treatment Code 110	Consultant-led Follow Up Attendance - Single Professional, Trauma and Orthopaedics Service	£67

Costs for GP consultations are estimated from PSSRU Unit Costs 2021 (PSSRU Unit Costs)

PSSRU unit costs		2019-20 unit cost	Inflation-adjusted to 2022-23 prices
GP consultation	Patient contact lasting 9.22 minutes	£39	£42.26
PSSRU unit costs		**2020-21 unit cost**	**Inflation-adjusted to 2022-23 prices**
Band 6 Physiotherapist	Cost per hour	£52	£54.67
	Cost per patient-facing hour (uplifted by 1.46 - ratio of direct to indirect time, PSSRU Unit Costs 2010)	£75.92	£79.82

OPCS-4 codes for primary elective TKR are provided in Appendix D.

Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix A.

All costs are presented in 2022-23 values, using inflation adjustment derived from PSSRU Unit Costs (PSSRU Unit Costs) of Health and Social care NHS Cost Inflation Pay and Prices Index (Unit Costs of Health and Social Care 2020).

Standard care costs

Five papers were identified that provide estimates of the cost of care for OA.

These are:

1. McCarthy C, Mills P, Pullen R, Richardson G, Hawkins N. Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis. *Health Technol Assess* 2004;8(46)
2. Richardson G, Hawkins N, McCarthy CJ, Mills PM, Pullen R, Roberts C, Silman A, Oldham JA. Cost-effectiveness of a supplementary class-based exercise program in the treatment of knee osteoarthritis. Int J Technol Assess Health Care. 2006 Winter;22(1):84-9. doi: 10.1017/s0266462306050872. PMID: 16673684.
3. Patel A, Buszewicz M, Beecham J, et al. Economic evaluation of arthritis self-management in primary care. BMJ. 2009;339:b3532. Published 2009 Sep 22. doi:10.1136/bmj.b3532.
4. Oxford Economics, The economic costs of arthritis for the UK economy Final Report, 2010, https://www.oxfordeconomics.com/publication/download/222531.

5. Abraham L, Halsby K, Stein N, Wrona B, Emir B, Stevenson H. An Observational Retrospective Matched Cohort Study of Healthcare Resource Utilisation and Costs in UK Patients with Moderate to Severe Osteoarthritis Pain. Rheumatol Ther. 2022;9(3):851-874. doi:10.1007/s40744-022-00431-2

These papers were examined in detail to determine their quality, relevance to current NHS knee OA care and costs, and relevance to the target population for Apos.

Papers 1 and 2 describe the same cost effectiveness study of an exercise intervention in the context of an RCT. The resource use estimates are from the 1990s. It is considered unlikely that this is reflective of current NHS resource use. The focus is on total NHS resource use during a 12-month period, not specifically resource use associated with OA. The difference between control and intervention groups is used to assess cost effectiveness of the exercise programme. (The control group has OA but does not receive the exercise intervention.) It is not possible to derive a cost of OA care from these estimates. The population is "intended to represent the heterogeneous population of patients with knee OA who are typically referred to physiotherapists for exercise treatment". This is therefore a more heterogeneous population than the target population for Apos. It is considered likely that many of the cohort will have less severe OA than the target population. Resource use associated with OA is not measured discretely.

Paper 3 assesses the cost effectiveness of a self-management programme for arthritis compared with usual care within a large randomised trial based in UK primary care in 2000-04. The focus is on knee and/or hip OA. Estimates of arthritis-specific resource use are presented for both health and social care. However, people who had been recommended surgery for arthritis or who had poor mobility were excluded. It is therefore considered likely that the cohort in this study had less severe OA than the target population for Apos.

Paper 4 summarises the findings of papers 2 and 3, plus an Australian study. It does not contain any additional data on NHS resource use.

Paper 5 estimates resource use associated with OA in a large-scale NHS study between 2010 and 2017. It provides discrete cost estimates for severe OA. Costs are calculated for all healthcare resource use, and OA-specific costs are estimated by comparison with a control group that does not have OA. It does not focus specifically on knee OA. However, evidence from other studies (e.g., Leal et al.) suggests that resource use is similar for knee and hip OA.

We consider paper 5 to be the most appropriate source as it is a relatively recent large scale NHS study with a control, it provides estimates of OA-specific costs rather than all healthcare costs and provides costs for a severe OA sub-group that is likely to be a reasonable match for the severe target population for Apos.

The Abraham paper is used to derive an estimate of the cost of OA standard care for the economic model. Abraham estimates a marginal annual cost for patients with severe OA of £2,258 (inflation-adjusted to 2022-23

prices using inflation adjustment factors derived from the PSSRU NHSCII pay and prices index). The components of this cost are set out in table B.

Table B Severe OA annual cost estimates, Source: Abraham et al. 2022

	2017-18 prices	Inflation-adjusted to 2022-23 prices
GP encounters	£61	£69
Inpatient admissions	£1,471	£1,667
Outpatient visits	£290	£328
A&E attendances	£38	£43
Analgesic drugs	£132	£150
Total	£1,992	£2,258

These costs include surgery. As TKR is a separate state in our model, we have adjusted the cost estimates to remove costs related to TKR. 22.2% of the severe cohort in Abraham et al. have surgery during the 24-month study period (11.8% annualised probability). Deducting the estimated year-1 and year-2 costs of TKR used in our model (£7,862.94 and £367.98 see below) for 11.8% of the cohort gives an estimated annual OA care cost for the severe cohort of £1,286.63. This estimate is used for OA standard care in our base case.

OA care with Apos costs

The Apos device and supporting technology cost is £875. The device includes a pair of shoes and 4 pods. Additional components (spacers, weights) are included in the price and should be used as clinically necessary (based on patient's characteristics). Components will be replaces as needed with no additional costs. Smartphone technology that will host the gait analysis application will also be provided as part of this cost (1 per operational clinic).

Total initial costs for Apos are £956.13 and include the cost of the device as well as training (£1.31 per patient, which is based on an estimate of 250 patients treated per clinician trained) and initial patient evaluation (£79.82, which reflects 1 hour of Band 6 time uplifted for indirect costs). Monthly follow-up costs for Apos are £9.98 per patient during year 1, reflecting **three** 30-minute follow-up appointments over the course of 12 months at an hourly rate of £79.82. Monthly follow-up costs for Apos fall to £6.65 in year 2 and beyond (reflecting **two** 30-min follow-ups at an hourly rate of £79.82).

In addition, we expect a 15% reduction in standard care costs excluding TKR (i.e. £1,286.63 for the standard care arm annually falling by 15% to £1,093.64).

Clinically, there is evidence to support the effectiveness of AposHealth in knee OA. Patients report a significant reduction in pain and improved function and quality of life. In one large double blind RCT published in JAMA (Reichenbach et al., 2020), two hundred twenty (n=220) patients with knee OA were assigned to one of two groups (Apos vs sham device) and were treated for six months. The primary outcome measure was a change in pain and

the secondary outcomes were function, QoL, gait patterns, and adverse events. A significant reduction in pain and improvement in function and quality of life was seen in the Apos group with an average reduction in pain of 69%. 92% of the patients treated with Apos reported more than 30% reduction in pain, well above the minimal clinical important difference, and 83% of them reported more than **50**% reduction in pain, a strong indication of the high efficacy with the number needed to treat (NNT) equal to three. One UK-based study assessed 455 patients with knee OA that were treated with AposHealth for six months and reported a significant reduction in pain (49%) and improvement in function (46%), quality of life (22%) and gait velocity (13%) (Miles et al., 2020).

Significant improvements are also seen in objective gait metrics (i.e., higher walking speed with longer step length and an increased ability to bear loads in the painful limb), 3-Dimentional knee loading during gait (reduction in the knee adduction moment) and improved muscle activation patterns (Haim et al., 2012, Debbi et al., 2015 Goryachev et al., 2011, Elbaz et al., 2014, Lador et al., 2013, Lubovsky et al., 2015).

These changes are thought to be the main reason for a reduction in utilisation of other healthcare resources reflected in less doctor visits, examinations, non-surgical interventions (pharmacological, injections and physiotherapy), and surgical interventions ([redacted], internal UK private insurer customer survey). One study showed a significant reduction of 58% in rescue medicine during a 2-month trial comparing the therapy to controls (Bar-Ziv, Beer et al. 2010). Unpublished data supports these findings. In one independent analysis the proportion of patients using non-NSAID, non-opioid pain medications decreased by 33% (37.5% to 25.0%, p=0.029) ([redacted], Supp H). Another independent member survey conducted by a private UK medical insurer suggest a reduction in pharmacological treatment including OTC and prescribed pain killers, self-reported utilisation of pharmacological interventions suggest that 82% of the patients treated with AposHealth stopped using / are using less OTC pain killers and 80% stopped using / are using less prescribed pain killers. 78% of the patients stopped using / are using less NSAIDs (Supp K). In the same independent member survey (Supp K), a potential decrease in the utilization of intra-articular injections (86% stopped / reduced use), physiotherapy (83% stopped / reduced use), and braces (78% stopped / reduced use) is also reported. The reduction in physical therapy visits is also supported by a second independent utilization study done on US population ([redacted], Supp H).
Lastly, the treatment is non-invasive and safe. There are no serious adverse events related to the treatment (Reichenbach et al., 2020).

TKR costs

The cost of TKR is estimated using PbR tariff prices, PSSRU unit costs, and evidence from the literature.

The relevant tariffs, codes and PSSRU unit costs are set out in the **NHS and Unit Cost** section above.

The 2022-23 best practice national tariff for primary TKR surgery is £6,313-£6,624, depending on complications and comorbidities (the mean value, £6,469, is used in the model). The tariff for rehabilitation post-TKR discharge is £620. The tariff for a first outpatient consultation with an orthopaedic consultant is £169. The tariff for follow-up

attendances is £67. We have not identified any sources detailing the number of attendances. We assume 1 consultation pre-surgery and 1 post-surgery on average for all patients. We also assume 1 GP consultation for referral to orthopaedics for all patients at a cost of £42.26, based on PSSRU average consultation cost, inflation adjusted.

No tariffs were identified that provide discrete costs for post-operative complications and revisions related to TKR. We therefore examined the literature for evidence on the costs and incidence of these.

One study was identified which examines the cost of primary knee replacements in people with OA over 24 months post-surgery in the NHS in England (Leal et al. 2022) This paper was examined in detail to determine its quality, and relevance to current NHS care and costs.

Leal et al. identifies 457,747 patients who had primary knee replacements in England between 2008 and 2016. It provides data on the incidence of post-operative complications and revisions, and estimates resource use based on linked National Joint Registry, Hospital Episode Statistics and primary care data. The inpatient costs of both post-operative complications and post-operative revisions in year 1 are directly estimated. The costs associated with post-surgical complications and revisions in year 2 are estimated indirectly, by comparing resource use in each care setting in year 2 with costs in the year before surgery.

We consider this paper to be of high quality, and highly relevant to current NHS care and costs (with appropriate inflation adjustment). For our model, we use evidence from Leal et al. to estimate the incidence of post-operative complications and revisions and associated inpatient costs in year 1, and the cost of such complications in year 2.

Leal et al. reports that in the first year after surgery 6% of patients had post-operative complications (unit cost of inpatient care, £6,220) and 0.5% of patients had revisions (unit cost of inpatient care, £10,406).

Uplifting these costs for inflation and apportioning across all patients produces a per patient cost of £487. We assume 2 follow-up outpatient consultations for each patient with a complication or revision (£8.71 apportioned across all patients).

These elements produce a total year-1 estimated cost of £7,863.

Table C. Estimated year 1 TKR costs

Activity	**Cost**
Inpatient surgery	£6,468.50
Rehabilitation	£620.00
First outpatient consultation	£169.00
Follow-up outpatient consultation	£67.00
GP consultation	£42.26
Outpatient consultations for complications and revisions	£8.71
Inpatient care for complications and revisions	£487.47
Total	**£7,862.94**

The table below sets out the estimated costs used in the model for the second year after TKR, derived from Leal et al. calculation of the difference between Year 2 and Year minus 1 costs in each care setting, and adjusted for inflation.

Table D. Estimated year 2 TKR costs

Difference between year 2 and year minus 1 cost		
	2016-17 cost	**Inflation-adjusted to 2022-23 prices**
Inpatient care	£389	£445.94
Primary care	£37	£42.42
Outpatient care	-£105	-£120.37
Total	**£321**	**£367.98**

The cost of a second TKR is the same as the cost of a first TKR.

Describe the resources needed to implement the technology in the NHS. Please provide sources and rationale.

The AposHealth innovation is delivered by Allied Health Professionals (Physiotherapists, Orthotists or Podiatrists) that have been trained and accredited in the assessment, prescribing, calibration and ongoing monitoring of patients receiving Apos treatment. There is no cost to the organisation to receive training, the only cost is that to release resource to achieve necessary competence to administer the treatment programme.

Training

Training for clinicians consists of two components: theory and practical application of knowledge. The theory element is delivered as either an online or face to face course which covers the principles of biomechanical gait alternation, measurement, and interpretation of gait parameters together with how to calibrate the Apos device based on several patient case studies. The practical element consists of an observed calibration with several patients delivered as part of routine service provision and is captured as part of service delivery cost. Dependent on the competence of the individual, the number of patients observed can vary from 5 – 10 patients.

Theory training costs are based on a Band 6 (PSSRU) clinician (physiotherapist) at a cost per hour of £54.67 (2022-23 Band 6 cost per hour)

The online/in-person theory course is delivered over 6 hours. For context, as stated in the Joint Statement on CPD for Health and Social Care Practitioners, 2007: the *minimum* time granted by employers for continuing professional development (CPD) should be 45 hours (6 days) per year. This is in addition to mandatory training and formal study leave arrangements. The time required for Apos training is similar to other OA treatment modes for example, ESCAPE-pain. Apos does not charge for training. The economic model is based on resource release costs only. The training course is flexible and can be delivered across multiple sessions (for example 1x6 hr or 2 x 3hr sessions) to accommodate service delivery requirements

Our estimate for the number of healthcare professionals needed to deliver AposHealth to the cohort identified, is based upon service delivery experience across three NHS organisations and 12 non-NHS clinic providers across the UK.

To maximise efficiencies when training clinicians, we propose a phased approach to training in addition to cohorts of clinical teams being trained in one go utlising our network of Apos trained clinicians. We acknowledge that geography and spread of clinicians will vary as Apos is adopted, however the training model is flexible to cope with variability in demand.

The cost of training per patient is calculated as follows:

6 hours of training x £54.67 = £328.01 / 250 patients per clinician = £1.31 per patient

The cost of training per patient reflect only resource release, there is no charge for the training programme.

Service Delivery

Each patient that receives AposHealth requires the following clinic time:

Year 1

Activity	Time (hr)
Initial evaluation appointment by clinician	1
Follow up appointment at 4-6 weeks	0.5
Follow up appointment at 8-12 weeks	0.5
Follow up appointment at 24-52 weeks – 30mins	0.5
Total clinic time	**2.5**

Years 2-5

Activity	Time (hr)
Ad-hoc follow up appointment 1	0.5
Ad-hoc follow up appointment 2	0.5
Total clinic time	**1.0**

The service delivery is based upon a Band 6 (PSSRU) clinician at a cost per hour of £54.67 (2022-23 Band 6 cost per hour) * 1.46 (PSSRU 2010 uplift for indirect time) = £79.82 per hour.

It is expected that after 12 months of treatment patients are moved to ad-hoc appointments as clinically indicated. Typically, patients will require a further 1-2 follow up appointments in Years 2-5. Within the economic model, it is assumed all patients in years 2-5 with have 2 follow-ups to be conservative, but it is acknowledged many will not utilise all their appointment allowance due to those self-managing independently, meaning lower service delivery costs.

Based on the clinician cost identified above, the total cost of service delivery is calculated as follows:

Year 1 = £199.54

Year 2-5 = £79.82 pa

Describe the resources needed to manage the change in patient outcomes after implementing the technology. Please provide sources and rationale.

AposHealth is a home-based intervention. After the initial evaluation and calibration of the Apos device, patients are instructed to wear the device for 30-60 minutes a day while performing their daily activities at home or work (usage time may increase gradually, depending on progress and symptoms). The treatment consists of 4 key features:

Step 1: In-depth initial evaluation – The AposHealth treatment begins with an AposHealth-trained clinician (ATC) conducting an in-depth evaluation of the patient's movement patterns and the root causes of their pain. This

consultation includes an interview, Patient Reported Outcome Measure (PROM) questionnaires to assess pain, function, and quality of life, a computerised gait analysis, and a physical examination.

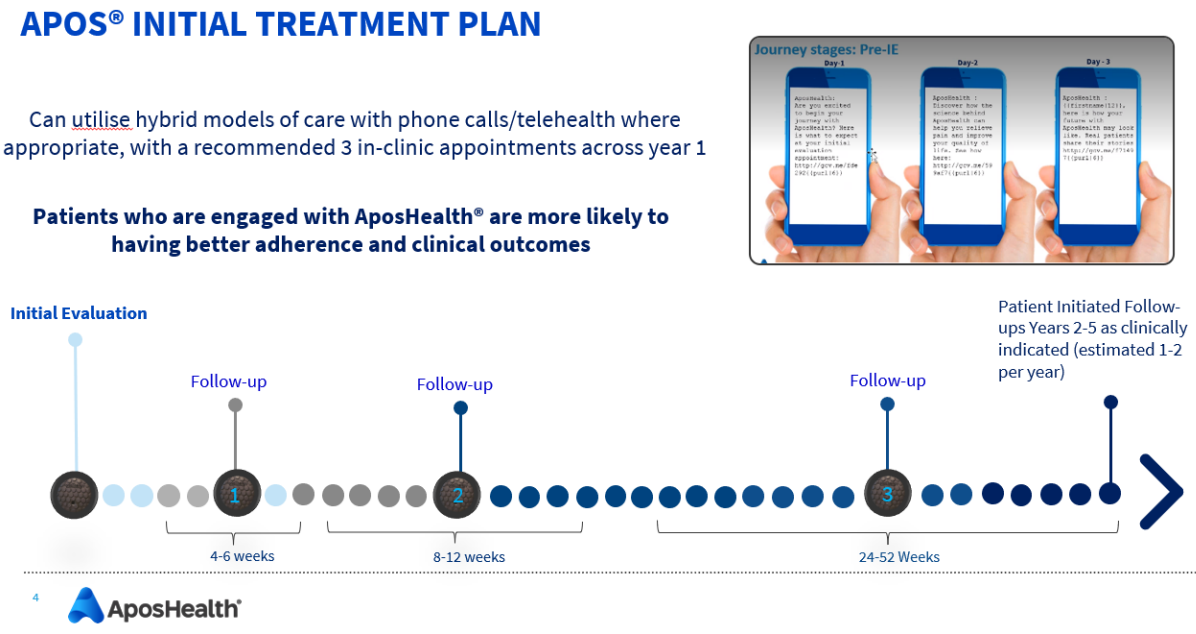
Step 2: Personalised device & treatment – Once the patient has been evaluated, the clinician personalises the Apos foot-worn device by calibrating the under-sole pods to the patient's specific needs and then prescribes a personalised programme for the patient.

Step 3: Effortless at-home treatment – Wearing the Apos device for about an hour a day, the patient can go about their daily schedule while the footwear corrects their gait and relieves the stress on the affected area(s). Patients who wish to wear the device for longer period of time and/or walk outdoors are encouraged to do so, after consulting with their Apos clinician.

Step 4: Ongoing monitoring for optimised outcomes – The treatment plan includes follow-up consultations and check-ups to assess the patient's pain relief and functional improvement. Follow-up meetings include many of the evaluations performed during the initial consultation and allow careful monitoring of progress. Whenever necessary, the device is recalibrated, and the personalised treatment plan is updated. After their initial treatment plan (1 year coverage), patients are discharged to self-manage or seen on an adhoc basis as clinically indicated.

The Treatment Programme is summarised in Figure 3.

Figure 3. Apos initial treatment plan



These are estimated to be between 1-2 follow-ups per year and were included in the model (2 FUs per year starting year 2). Based on data from our NHS projects, we envisage follow-up requirements will diminish after the first year

in the therapy and are dependent on clinical need. Many patients will be able to be discharged to self-manage their condition, whilst some continue to require the infrequent follow-up appointments as outlined above.

There is strong evidence to support that the treatment is safe and effective for patients with knee OA leading to a significant reduction in pain and improvement in function as well as quality of life in general. Moreover, evidence suggest changes in biomechanical patterns during walking following treatment which suggest reduced loads (knee adduction moment) from the knee and improved muscle activation. Some evidence suggest that AposHealth reduces the utilisations of other non-surgical interventions and that it helps delay surgery amongst severe patients who were recommended a TKR.

There are no additional resources required after implementing the treatment in order to manage the change in patient outcomes (surgery avoidance). It is envisaged that the reduction in TKR surgery demand will allow healthcare system to better prioritise those patients most at need of surgery sooner, enabling Getting it Right First Time (GIRFT). Those not progressing to surgery will need minimal therapy input spread across a year to maintain and manage their conditions in the community (one to two 30 mins appointments yearly). This is based on data from Green et al (2022), which indicates that patients can maintain these outcomes with this level of support as required. This additional therapy time will come from redirected services, away from other, largely ineffective treatments for this cohort of patients (severe knee OA) towards this more effective treatment modality.

Describe the resources needed to manage the change in system outcomes after implementing the technology. Please provide sources and rationale.

There are no additional resources required after implementing the treatment. It is envisaged that the reduction in TKR surgery demand will allow healthcare system to better prioritise those patients most at need of surgery sooner, enabling Right Care, Right Time. Those not progressing to surgery will need minimal therapy input spread across a year to maintain and manage their condition (one to two, 30 mins appointments yearly). This is based on data from Greene et al (2022), which indicates that patients can maintain these outcomes with this level of support as required. This additional therapy time will come from redirected services, away from other, largely ineffective treatments for this cohort of patients (severe knee OA) towards this more effective treatment modality.

Table 5 Resource use costs

In this table, summarise how the model calculates the results of these changes in resource use. Please adapt the table as necessary.

Please see below resources use costs (instead of template 5):

AposHealth Costs

Per patient costs	
Device/technology	£875
Training	£1.31
Patient evaluation	£79.82
Monthly follow-up cost	£9.98

Breakdown of AposHealth costs

Apos patient care	
Evaluation duration (hours)	1
Follow-up hours per patient in first year	1.5
Evaluation cost per pt	£79.82
Follow-up cost per pt	£119.72
Monthly follow-up cost	£9.98
Year 2+ average care time (hours)	1
Year 2+ average cost	£79.82
Monthly year 2+ average cost	£6.65
Training model	
Patients per staff member	250
Test for reasonableness	
Hours of care per patient per annum	*2.5*
Hours per annum per staff member	*625*
Hours per week per staff member	*13.0*
Hours of training	6
Training cost (resource release)	£328.01
Per patient	£1.31

STANDARD CARE OA COSTS		
Summary of Costs	**Value**	**Source**
OA cost annual	£1,286.63	Rates reflect costs from Abraham et al. adjusted to remove costs of surgery and uplifted for inflation, as described in resource use section above
OA cost monthly	£107.22	

TKR COSTS		
Summary of Year 1 costs	**Value**	**Source**
Surgery	£6,468.50	Costs are taken from Tariff 2022/23 referred to appendix D. Surgery complications and revisions are based on Leal et al., 2022
Revision and complication	£487	
Rehab	£620	
Outpatient care	£245	
Primary care	£42	
Total	**£7,862.94**	
Year 2 cost	**Value**	**Source**
Annual	**£367.98**	Costs reflect post-op complications reported by Leal et al.
Monthly	**£30.67**	

Adverse event costs

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

No adverse events considerations are required in the model.

AposHealth is a safe treatment with no serious adverse events. One RCT thoroughly assess the safety of the treatment in a RCT comparing AposHealth to a sham device in 220 patients diagnosed with knee OA (Reichenbach et al 2020). Twenty-six participants (23.4%) in the Apos arm and 38 participants (34.9%) in the control footwear group experienced an adverse event and 3 (2.7%) and 9 (8.3%), respectively, experienced serious adverse events). None were considered to be related to treatment. Of the serious adverse events, there were 0 in the Apos group vs 4 in the control footwear group that were musculoskeletal, 1 vs 3, respectively, that were circulatory, and 2 vs 2 that were in other categories. One or more falls occurred in 2 participants (1.8%) in the Apos group and in 4 participants (3.7%) in the control footwear group. One participant in the control group fell while wearing the control footwear.

Table 6 Adverse events and costs in the model

In this table, summarise the costs associated with each adverse event included in the model. Include all adverse events and complication costs, both during and after long-term use of the technology. Please explain whether costs are provided per patient or per event.

NA

Adverse event	Items	Cost	Source
Adverse event 1	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	Text	Text
	[Other items]	Text	Text
	Total	Text	Text
Adverse event 2	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	Text	Text
	[Other items]	Text	Text
	Total	Text	Text
[Add more rows as needed]			

Miscellaneous costs

Describe any additional costs or resource considerations that have not been included elsewhere (for example, PSS costs, and patient and carer costs). If none, please state.

NA

Are there any other opportunities for resource savings or redirection of resources that have not been possible to quantify?

It has not been possible to quantify social care resource use impacts, costs borne by patients, or impacts on tax and welfare systems. It was also not possible to determine indirect costs associated with knee OA such as work absenteeism and broader effect on comorbidities and other healthcare resources use. It is considered likely that reduced pain, increased mobility and functioning as well as overall quality of life, as observed with Apos in multiple studies, will lead to additional private and public savings in these areas.

There are some environmental impact & sustainability considerations that should be acknowledged. Using AposHealth is expected to reduce the use of conventional therapies and thus reduce the number of appointments, which has an environmental impact. In addition, the positive clinical effect which includes increased mobility, range

of movement and quality of life supports patients having physical activity and reducing their reliance on car or bus transportation.

It is expected that clinic resource will be released due to a reduced need for current treatments, and for post-operative rehabilitation appointment time. These have not been costed but will positively impact the resource capacity within this pathway. Once current elective backlogs have been addressed, it is envisaged healthcare systems will have a reduced demand for elective TKR surgery, allowing re-allocation of theatre space and resources for other procedures or allowing those most at need to access TKR surgery sooner.

Total costs

In the following tables, summarise the total costs:

- Summarise total costs for the technology in table 7.
- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7 Total costs for the technology in the model

Costs are set up above.

Table 8 Total costs for the comparator in the model

Costs are set up above.

Results

Table 9 Base-case results

In this table, report the results of the base-case analysis. Specify whether costs are provided per treatment or per year. Adapt the table as necessary to suit the cost model. If appropriate, describe costs by health state.

5-Year outcomes

The overall expected 5-yrs costs per patient in the standard care arm is £10,141. For patients that will receive the AposHealth interventions, the expected 5-yrs cost per patient is £8,283. The net cost of the Apos intervention at 5 years is -£1,858.

More specifically, in the standard care arm, the attributed costs for non-surgical interventions and surgical interventions (i.e., TKR) at 5-years are £2,584 and £7,557, respectively. In the AposHealth arm the attributed costs for non-surgical interventions and surgical interventions (i.e., TKR) at 5-years are £5,368 and £2,915, respectively. The net cost of the Apos intervention at 5 years for non-surgical interventions and surgical interventions are £2,784 and -£4,642, respectively. Combining net costs from the two categories brings total net costs of the Apos intervention at 5 years to -£1,858,

2-Year outcomes

The expected 2-yrs costs per patient in the standard care arm is £6,065. For patients that will receive the AposHealth intervention in addition to standard care, the expected 2-year cost per patient is £4,334. The net cost at 2-yrs -£1,731.

More specifically, in the standard care arm, the attributed costs for non-surgical interventions and surgical interventions (i.e., TKR) at 2-years are £1,705 and £4,360, respectively. In the AposHealth arm the attributed costs for non-surgical interventions and surgical interventions (i.e., TKR) at 2-years are £3,088 and £1,245, respectively. The net cost of the Apos intervention at 2 years for non-surgical interventions and surgical interventions are £1,383 and -£3,115, respectively. Combining net costs from the two categories brings total costs of the Apos intervention at 2 years to -£1,731,

Results are summarized in Tables E and F

Table E. Cost summary

COST SUMMARY

	SC arm cost	Apos arm cost	Net cost of Apos	**Cumulative net cost**
Year 1	£3,490	£2,726	-£764	**-£764**
Year 2	£2,575	£1,607	-£967	**-£1,731**
Year 3	£1,831	£1,457	-£373	**-£2,105**
Year 4	£1,299	£1,312	£12	**-£2,093**
Year 5	£946	£1,180	£235	**-£1,858**
Total	**£10,141**	**£8,283**	**-£1,858**	
2 year net cost	-£1,731			
5 year net cost	-£1,858			

Table F. Cost breakdown by care type i.e., non-surgical interventions, surgical interventions (TKR)

BREAKDOWN BY CARE TYPE

	OA care costs			TKR costs		
	SC arm cost	Apos arm cost	Net cost of Apos OA care	SC arm cost	Apos arm cost	Net cost of Apos TKR
Year 1	£1,038	£2,109	**£1,071**	£2,452	£617	**-£1,835**
Year 2	£667	£979	**£313**	£1,908	£628	**-£1,280**
Year 3	£428	£860	**£432**	£1,403	£597	**-£806**
Year 4	£275	£756	**£481**	£1,024	£556	**-£468**
Year 5	£176	£664	**£487**	£769	£517	**-£253**
Total	**£2,584**	**£5,368**	**£2,784**	**£7,557**	**£2,915**	**-£4,642**

Table G summarizes the percent of patients that will undergo TKR and a second TKR at each year in the two arms.

For example, for patients in the standard care arm: 54.7% will have a primary TKR at 2 years and 2.2% will have a second TKR. At 5 years rates are 85.3% for primary TKR and 13.0% for a second TKR. For patients in the AposHealth arm 15.9% will have a primary TKR at 2 years and 0.6% will have a second TKR. At 5 years rates are 34.7% for primary TKR and 4.2% for a second TKR.

Table G: % of patients that will have a TKR and a second TKR in the contralateral knee over 5-yrs

% OF COHORT THAT HAVE TKR

	SC arm	Apos arm	Impact of Apos	**Cumulative impact of Apos**
Year 1	32.9%	8.3%	-24.6%	**-24.6%**
Year 2	21.8%	7.6%	-14.3%	**-38.9%**
Year 3	14.5%	6.9%	-7.6%	**-46.5%**
Year 4	9.6%	6.3%	-3.4%	**-49.9%**
Year 5	6.4%	5.7%	-0.7%	**-50.6%**
Total	**85.3%**	**34.7%**	**-50.6%**	

% OF COHORT THAT HAVE A SECOND TKR

	SC arm	Apos arm	Impact of Apos	**Cumulative impact of Apos**
Year 1	0.3%	0.1%	-0.2%	**-0.2%**
Year 2	1.9%	0.5%	-1.4%	**-1.7%**
Year 3	3.1%	0.9%	-2.2%	**-3.8%**
Year 4	3.7%	1.2%	-2.4%	**-6.3%**
Year 5	4.0%	1.5%	-2.5%	**-8.8%**
Total	**13.0%**	**4.2%**	**-8.8%**	

The percentage of patients that are alive and without new TKR at the end of each year in the standard care arm are: year 1, 66.4%; year 2, 44.2%; year 3, 29.3%; year 4, 19.5%; and year 5, 13.0%. For patients in the AposHealth arm the percentages are year 1, 90.9%; year 2, 82.7%; year 3, 75.1%; year 4, 68.3%; and year, 5 62.1% (Table H).

Table H. Patients without TKR over 5-yrs

% OF COHORT THAT ARE ALIVE AND WITHOUT NEW TKR AT THE END OF EACH YEAR

	SC arm	Apos arm	Impact of Apos
Year 1	66.4%	90.9%	24.5%
Year 2	44.2%	82.7%	38.5%
Year 3	29.3%	75.1%	45.8%
Year 4	19.5%	68.3%	48.8%
Year 5	13.0%	62.1%	49.2%

Scenario analysis

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

NA

Describe the differences between the base case and each scenario analysis.

NA

Describe how the scenario analyses were included in the cost analysis.

NA

Describe the evidence that justifies including any scenario analyses.

NA

Table 10 Scenario analyses results

In this table, describe the results of any scenario analyse that were done. Adapt the table as necessary.

Scenario analyses was not performed

	Mean discounted cost per patient using the technology (£)	**Mean discounted cost per patient using the comparator (£)**	**Difference in cost per patient (£)***
Scenario 1 (total costs)	Text	Text	Text
Scenario 2 (total costs)	Text	Text	Text

* Negative values indicate a cost saving.

Adapt this table as necessary.

Sensitivity analysis

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

Our sensitivity analyses span +/- 20% key modelling inputs including: TKR rates for both arms, OA standard care costs, and non-tariff TKR costs. In addition, we include a range of Apos impact on standard OA care costs, with the low end showing no impact (which we believe overly conservative, given Apos' strong clinical evidence); the midpoint in-line with Apos utilisation impact on a low severity population ([redacted]); and the high-end showing Apos' 30% impact on standard OA care costs. Another sensitivity used a subgroup analysis of Greene et al., cohort looking at surgery rates in a group of patients that completed 2-yrs of treatment pre-covid (20.9% at two years).

We also include a sensitivity around Year 2 TKR costs, which we believe captures continued revision in year 2; with the low end of the range at £0 (likely overly conservative) and the high end 20% above our base case. Lastly sensitivity analysis was also applied to second TKR after a first one; with the low end of the range at 0% (likely conservative given the strong and consistent literature on the prevalence of second TKR after the first one) and the high end at 1% monthly (above our base case of 0.5% monthly).

Results of our analysis are shown in Table I below.

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

Table I. Sensitivity analysis assumption

Sensitivity analysis assumptions (+/- 20% of base cost)			
Variable	**High**	**Model**	**Low**
SC Arm: TKR monthly rate +/- 20% in years 1-2	2.6%	3.3%	3.9%
Apos Arm: TKR monthly rate +/-20% in years 1-2	0.58%	0.72%	0.87%
Apos Arm: TKR monthly rate +/- 20% in years 3-5	0.58%	0.72%	0.87%
OA Standard Care monthly cost +/- 20%	£85.78	£107.22	£128.66
TKR initial cost: non-tariff items +/-20%	£6,697	£6,755	£6,812
Reduction in SC cost associated with Apos	0%	15%	30%
TKR Y2 monthly cost	£0.00	£30.67	£36.80
Second TKR	0.0%	0.5%	1.0%

If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

NA

Sensitivity analyses results

Present the results of any sensitivity analyses using tornado plots when appropriate.

The tables below summarize cost savings in different one-way and two-way sensitivity models. Conditional formatting was applied, with color scales demonstrating which variables drove the greatest change to net 5-year savings.

Net 5 year costs of Apos across a range of sensitivities			
Variable	**Low**	**Model**	**High**
SC Arm: TKR monthly rate +/- 20% in years 1-2	2.6%	3.3%	3.9%
Apos 5 year net costs	-£1,573	-£1,858	-£2,029
Apos Arm: TKR monthly rate +/-20% in years 1-2	0.58%	0.72%	0.77%
Apos 5 year net costs	-£2,175	-£1,858	-£1,756
Apos Arm: TKR monthly rate +/- 20% in years 3-5	0.58%	0.72%	0.87%
Apos 5 year net costs	-£2,057	-£1,858	-£1,669
OA Standard Care monthly cost +/- 20%	£85.78	£107.22	£128.66
Apos 5 year net costs	-£2,156	-£1,858	-£1,559
TKR initial cost: non-tariff items +/-20%	£6,698	£6,755	£6,813
Apos 5 year net costs	-£1,825	-£1,858	-£1,891
Reduction in SC cost associated with Apos	0.00%	15.00%	30.00%
Apos 5 year net costs	-£1,139	-£1,858	-£2,577
TKR Y2 monthly cost from £0 to +20%	£0.00	£30.67	£36.80
Apos 5 year net costs	-£1,687	-£1,858	-£1,892
Second TKR monthly rate 0% to 1%	0.0%	0.5%	1.0%
Apos 5 year net costs	-£1,238	-£1,858	-£2,365

The table below summarises the cost-saving in 2 different two-way sensitivity models: 1. Different probabilities of a first TKR in the standard care arm and the Apos arm; 2. Different probabilities of a 2-yrs costs post TKR and second TKR.

Standard care arm monthly probability of TKR in years 1-2

Apos arm monthly probability of TKR in years 1-2

5 year net cost of Apos	Apos			
	-£1,858	0.58%	0.72%	0.87%
Standard care	2.63%	-£1,889	-£1,573	-£1,283
	3.28%	-£2,175	-£1,858	-£1,569
	3.94%	-£2,346	-£2,029	-£1,740

Second Year TKR Costs

Second (Contralateral) TKR Rate

5 year net cost of Apos	2nd (Contralateral) TKR Rate			
	-£1,858	0.00%	0.50%	1.00%
2nd Year Monthly TKR Cost	£0.00	-£1,074	-£1,687	-£2,188
	£30.67	-£1,238	-£1,858	-£2,365
	£36.80	-£1,271	-£1,892	-£2,400

What were the main findings of each of the sensitivity analyses?

For all sensitivity analyses, the net 2- and 5-year costs of Apos were negative, implying net savings across a +/-20% band around all key inputs. Specific impacts at 5 years are shown in the Table. This was also true for two-way sensitivity analysis.

For example, in a scenario where the rates of TKR for the standard care arm are -20% lower than our base case AND the rates of TKR for the Apos arm are +20% higher, the net costs at 5-yrs are -£1,283 (compared to -£1,858 in the base case).

The sensitivity analysis also includes Apos arm 2-year TKR rate of 20.9%, derived from the Greene subgroup analysis where 18 of 86 patients enrolled at least two years prior to the onset of COVID had a TKR; net costs at 5 years are -£1,374 (compared to -£1,858 in the base case).

In a scenario where there are no contralateral TKRs AND there are no additional costs in year 2 post TKR the net cost savings is -£1,074 (compared to -£1,858 in the base case).

If Apos has no effect on standard care cost (0% instead of our base assumption of a 15% reduction in healthcare resources), the net cost savings at 5-yrs is -£1,139 (compared to -£1,858 in the base case).

What are the main sources of uncertainty about the model's conclusion

Some uncertainty with long-term surgery avoidance (years 3-5) due to lack of published evidence. We believe, however, that the internal data on file and the preliminary results of the Greene et al., population provide support to our assumption and that most likely, the sensitivity analysis will account for this uncertainty.

Miscellaneous results

Include any other relevant results here.

Waiting list pressures, inequality impacts and the potential contribution of Apos

During the Covid period, the number of TKRs performed annually fell to around a third of the previous level (31,133 in 2020-21, source: PROMs data), of which we estimate 25,966 were elective primary TKRs based on analysis of HES data to exclude emergency admissions, revisions and partial knee replacements. Clinical codes used to identify relevant activity are set out in Appendix D). As a result, there was an exponential growth in the waiting lists for TKR which the healthcare systems are trying to address. Yet, with limited capacities for elective surgery, many patients are left untreated. Now, more than ever, there is an urgent unmet need for non-invasive interventions that will be an alternative to TKR.

NHS data indicate that more than 6.6 million people in England are currently waiting for treatment (May 2022). There are more people waiting in orthopaedics than in any other specialty (750,334, 11% of the total). The waiting list for orthopaedic care has grown by almost 50% since February 2020 and is continuing to grow at a rate of 1.5% a month (link to source). HES data on admitted patient care indicates that the mean waiting time for orthopaedic admitted patient care has risen more than 50%, from 92 days in 2018-19 (the last complete year pre-Covid) to 150 days in 2020-21 (link to source). For knee replacement, the mean waiting time is substantially longer than for other types of orthopaedic care and it has almost doubled during the Covid period (211 days in 2020-21, compared with 120 days in 2018-19). (Calculations based on published HES data on admissions identified by primary procedure. See appendix D for procedure codes, activity counts and mean waiting times).

In 2018-19, 10.70% of elective admissions in orthopaedics were for knee replacement (8.81% in 2020-21). If the 2018-19 proportion is applied to the orthopedics' waiting list, this would suggest that at least 80,000 people are waiting for knee replacement. However, this number does not take account of the longer waiting times for TKR. Adjusting for these we estimate that 14.42% of the current orthopedics' waiting list is for TKR, around 108,226 people.

Formula: (211/150 * 0.107) / (1 + (211/150 - 1) * 0.107)

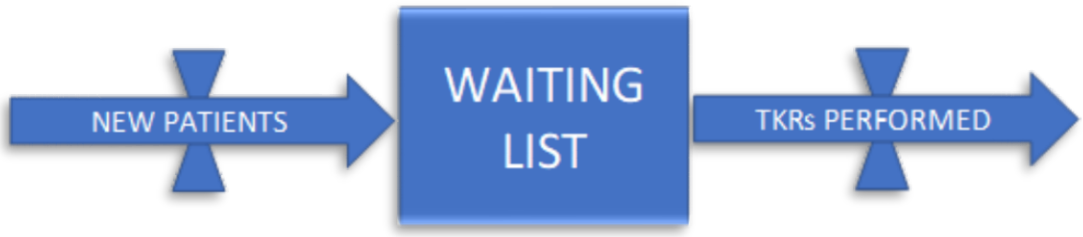
Increases in waiting lists and waiting times disproportionately impact those who live in deprived areas, exacerbating inequalities. Recent analysis by the King's Fund indicates that during the Covid period, waiting lists increased by more than half (55%) in the most deprived areas, compared with a third (36%) in the least deprived areas (link to source). People who live in deprived areas are almost twice as likely as those in the least deprived areas to wait more than a year for treatment (link to source).

Reducing waiting lists and waiting times is a key priority for the NHS in England. NHS England's 2022-23 priorities and operational planning guidance requires every local NHS system to develop an elective care recovery plan and establishes targets to reduce long waits for elective treatment (link to source).

In order to reduce the TKR waiting list to meet the targets set out by NHS England, the NHS either needs to increase surgical capacity substantially over the short to medium-term, or to find alternative therapies that enable people on the waiting list to avoid surgery. Increasing surgical capacity substantially to reduce a large and growing waiting list is a major challenge at any time and more so given the ongoing impact of Covid on workforce.

AposHealth has the potential to reduce both the waiting list for TKR and waiting times for those who do require surgery.

The challenge can be illustrated with a simple model of the waiting list dynamics.



In steady state, when the rate of TKRs activity matches the number of new patients joining the waiting list (minus those who subsequently drop out of the list), the size of the list does not change. In the 6 months prior to Covid, the orthopaedics waiting list was fairly steady at around 520,000 patients. Applying the method above, we get an estimate for the size of the pre-Covid TKR waiting list of 70,285.

At this time, approximately 81,000 TKRs were performed annually (HES data for 2018-19), equivalent to 6,750 per month. We can therefore postulate that there were roughly 6,750 new patients joining the list each month (who would go on to receive a TKR i.e., this figure is net of drop-outs). As described above, the reduction in activity during Covid resulted in an increase in the TKR waiting list to an estimated current figure of 108,226.
The size of the waiting list can be reduced by increasing TKR activity or reducing the rate at which patients join the list, or both. The rate at which the waiting list is reduced will depend on the difference between the number of TKRs performed and the number of patients joining the list. In general, in this simplified model:

Change in number on waiting list in a given period	=	Number of patients joining the list	-	Number of TKRs performed

We can estimate how long it will take to reduce the size of the list by a given amount for a given increase in TKR activity, with the following calculation:

$$\text{Time in months taken to reduce waiting list} = \frac{\text{Target reduction in list size}}{(\text{Base TKRs per month} * \text{Capacity uplift} - \text{Patients joining list per month})}$$

Assuming the pre-Covid steady state described above, the table below shows the time it would take to reduce the TKR list size from the current 108,226 back to the pre-Covid 70,285 (a reduction of 37,941 patients) if the TKR activity was increased above pre-Covid levels by different amounts. However, it should be acknowledged that the public knowledge of surgical waiting times means that some patients are "joining the queue" in response to the long waits, adding further burden into the system.

Increase in TKR activity	Time in months to reduce waiting list to pre-Covid size
10%	56.2
25%	22.5
50%	11.2
75%	7.5

If AposHealth was to be provided to all suitable patients who are referred to a consultant for possible TKR surgery, as in the economic model presented in this submission, the evidence suggests that AposHealth could reduce the number of new patients joining the waiting list by up to 75% (annual probability of TKR with Apos of 8% (converted from 16% over 2 years observed in Greene et al.), compared with annual probability of TKR for a similar cohort under standard care of 33% (McHugh et al.). This would have an effect on the waiting list equivalent to increasing the capacity by up to 75%. (It is acknowledged that not all patients joining the list would be eligible for Apos or would choose Apos. This analysis should therefore be treated as illustrative.)

It is also important to note that in order to increase surgical capacity to reduce the waiting list, it is likely that the NHS will need to ask staff to work overtime and/or to purchase extra capacity from the private sector. Each of these is likely to have an inflationary effect on the cost of TKR. The tariff used in the economic model is derived from historic NHS Reference Costs. If costs rise owing to the need to expand capacity, this tariff is likely to be an underestimate of the true cost of TKR. If so, the economic model is likely to underestimate the cost savings arising from Apos.

The additional pressures on the service arising from Covid-19 impacts, the inequalities arising from these, and the national focus on reducing waiting lists strengthen the case for an alternative therapy that could be offered to patients who might otherwise be on the waiting list for surgery. Lowering the demand for surgery through provision

of Apos would reduce both the number of patients on the waiting list and, as a result, waiting times for those who do require surgery.

Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model. Provide sources and cross-reference to evidence when appropriate.

Tests of descriptive, technical, face and predictive validity were conducted. The key questions addressed in each were:

- Descriptive validity – does the model provide a simplified but adequate picture of reality? Does it consider all relevant aspects?
- Technical validity – does the model function correctly?
- Face validity – does the model produce outputs that are consistent with the theoretical basis of the disease and the medical intervention?

Descriptive validity

Key model inputs are derived from a recent high quality NHS study, and key assumptions in the model were tested with experts. Other model inputs were validated by reference to peer reviewed literature, NHS data and expert opinion.

Where there were uncertainties over resource use inputs expert opinion was sought. Uncertainties are also examined in sensitivity analyses.

Probabilities in the model were sourced from the recent NHS Apos study and from peer reviewed literature.

Technical validity

The technical functioning of the model was tested by means of an extensive sensitivity analysis. Extreme values of input variables were used, to test the impact on model outcomes. Model inputs and outputs were checked and verified independently by two researchers. Outputs by stage were checked against expected behaviour. Discrepancies were investigated and resolved. Calibration was performed by comparing model outputs with expected outcomes from the literature.

Face validity

Face validity was assessed by comparison of model outputs with evidence from the literature and expert opinion.

It was not possible to perform convergent validity tests as no suitable models were identified for corroboration.

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

Prof. Philip Conaghan

Professor of Musculoskeletal Medicine
Director, Leeds Institute of Rheumatic and Musculoskeletal Medicine,
University of Leeds
Deputy Director, NIHR Leeds Biomedical Research Centre,
Leeds Teaching Hospitals NHS Trust

Prof. Michael Callaghan

Professor of Clinical Physiotherapy, Manchester Metropolitan University
Clinical Specialist Physiotherapist, Manchester Royal Infirmary
Honorary Senior Lecturer, University of Manchester
Head of Research & Innovation, Manchester United FC

Clinical experts provided advising guidance on NICE care pathway and common practice which informed the model formation (selection of Markov model), assumptions around standard care and Apos arm.

4 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

The economic model demonstrates that cost savings from avoided TKR surgeries were more than sufficient to offset costs of providing AposHealth in addition to ongoing standard OA care over a two- and five-year time period in patients that have met the criteria for orthopaedic referral. This target population should be relatively easy to identify since they can be identified in a defined point within the care pathway at which point patients are assessed for surgery.

The overall expected 5-yrs costs per patient in the standard care arm is £10,141. For patients that will receive the AposHealth interventions, the expected 5-yrs cost per patient is £8,283. The net cost of the Apos intervention at 5 years is -£1,858. More specifically, in the standard care arm, the attributed costs for non-surgical interventions and surgical interventions (i.e., TKR) at 5-years are £2,584 and £7,557, respectively. In the AposHealth arm the attributed costs for non-surgical interventions and surgical interventions (i.e., TKR) at 5-years are £5,368 and £2,915, respectively. The net cost of the Apos intervention at 5 years for non-surgical interventions and surgical interventions are £2,784 and -£4,642, respectively. Combining net costs from the two categories brings total costs of the Apos intervention at 5 years to -£1,858 per patient.

Sensitivity analyses was performed to account for uncertainties. Our sensitivity analyses span +/- 20% key modelling inputs including: TKR rates for both arms, OA standard care costs, and non-tariff TKR costs. In addition, we include a range of Apos impact on standard OA care costs, with the low end showing no impact (which we believe overly conservative, given Apos' strong clinical evidence); the midpoint in-line with Apos utilisation impact on a low severity population ([redacted]); and the high-end showing Apos' 30% impact on standard OA care costs. We also include a sensitivity around Year 2 TKR costs, which we believe captures continued revision in year 2; with the low end of the range at £0 (likely overly conservative) and the high end 20% above our base case. Lastly sensitivity analysis was also applied to second TKR after a first one; with the low end of the range at 0% (likely conservative given the strong and consistent literature on the prevalence of second TKR after the first one) and the high end at 1% monthly (above our base case of 0.5% monthly).

For all sensitivity analyses, the net 2- and 5-year costs of Apos were negative, implying net savings across a +/- 20% band around all key inputs. Specific impacts at 5 years are shown in the Table. This was also true for two-way sensitivity analysis. For example, in a scenario where the rates of TKR for the standard care arm are -20% lower than our base case AND the rates of TKR for the AposHealth arm are +20% higher, the net cost at 5-yrs is -£1,283 (compared to -£1,858 in the base case). In a scenario where there are no contralateral TKRs **and** there are no additional costs in year 2 post TKR that net cost is -£1,074 (compared to -£1,858 in the base case). Lastly, in a scenario where Apos has no effect on standard care cost (0% instead of our base assumption of a 15% reduction in healthcare resources), the net cost at 5-yrs is -£1,139 (compared to -£1,858 in the base case).

It has not been possible to quantify social care resource use impacts, costs borne by patients, or impacts on tax and welfare systems. It was also not possible to determine indirect costs associated with knee OA such as work absenteeism and broader effect on comorbidities and other healthcare resources use. It is considered likely that reduced pain, increased mobility and functioning as well as overall quality of life, as observed with Apos in multiple studies, will lead to additional private and public savings in these areas.

During the Covid period, the number of TKRs performed annually fell to around a third of the previous level. As a result, there was an exponential growth in the waiting lists for TKR which the healthcare systems are trying to address. Yet, with limited capacities for elective surgery, many patients are left untreated. Increases in waiting lists and waiting times disproportionately impact those who live in deprived areas, exacerbating inequalities. People who live in deprived areas are almost twice as likely as those in the least deprived areas to wait more than a year for treatment. Now, more than ever, there is an urgent unmet need for non-invasive interventions that will be an alternative to TKR. AposHealth has the potential to reduce both the waiting list for TKR and waiting times for those who do require surgery.

Briefly discuss the relevance of the evidence base to the scope.

In the presence of an unprecedented growth in the waiting lists for TKR, a constant increase in the prevalence of knee OA and the lack of effective non-surgical interventions for knee OA there is an urgent need for non-surgical, effective, interventions, otherwise many patients will be left untreated while experiencing severe symptoms.

AposHealth uses gait modifications and neuromuscular training to alleviate symptoms and improve function using a foot-worn device. For patients with knee OA, which is a chronic, disabling, progressive disease, that negatively affects quality of life, using AposHealth as a non-invasive treatment helps alleviate pain, restore functionality and as a result improve quality of life. For many patients with knee OA, TKR is the end-stage solution, when other non-surgical interventions have failed to help. The ongoing increase in TKR procedures is expected to place an immense burden on the cost of health care, highlighting the urgent need for new non-surgical approaches that more effectively manage OA symptoms of the knee (Klug, Gramlich et al. 2021). AposHealth has significant evidence to support a reduction in TKR in patients with knee OA that were found eligible for surgery as well as other healthcare resource utilisation. This has significant implications on the healthcare system, primarily providing an additional non-surgical intervention that is clinically effective, safe, and cost-effective.

The economic model demonstrates that cost savings from avoided TKR surgeries were sufficient to more than offset costs of providing AposHealth in addition to ongoing standard OA care over a five-year time period. Therefore, we believe that utilising AposHealth with patients who failed the core interventions (i.e., exercise, education, self-manage

and weight loss when applicable) will provide an effective alternative to all other adjunct interventions helping avoid a TKR entirely.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

The model results are consistent with the published literature in terms of the predicted number of TKRs in both the standard care and Apos arms.

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

The cost analysis is relevant to patients with end-stage knee OA who meet the clinical criteria for referral for elective primary TKR. The pivotal study used for the model assumptions was an NHS cohort of this specification and therefore highly relevant for the identified target population.

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

Strengths include a sufficient time horizon to demonstrate the favourable trade-off between reducing TKR surgery while maintaining standard OA care costs in the Apos arm over a five-year horizon. The published literature strongly supports cost savings over 2-yrs.

	SC arm cost	Apos arm cost	Net cost of Apos	**Cumulative net cost**
Year 1	£3,490	£2,726	-£764	**-£764**
Year 2	£2,575	£1,607	-£967	**-£1,732**
Year 3	£1,831	£1,457	-£373	**-£2,105**
Year 4	£1,299	£1,312	£12	**-£2,093**
Year 5	£946	£1,180	£235	**-£1,858**
Total	**£10,141**	**£8,283**	**-£1,858**	
2 year net cost	-£1,732			
5 year net cost	-£1,858			

Limitations include a lack of published, peer-reviewed evidence of Apos impact on TKR rates over a 3 to 5-year horizon. As a result, the model assumes a sustained 16% 2-year surgery rate, supported by the Greene sub-group analysis that include 3.5 years' outcomes as a reference for long-term TKR rate. Sensitivity analysis accommodates uncertainty around the 3–5-year rate.

Similarly, for the standard care arm, we could not find long-term data on healthcare utilisation and used the published data to guide our assumptions to years 3-5. Here too, sensitivity analysis was applied to accommodate uncertainty around the 3–5-year rate.

Detail any further analyses that could be done to improve the reliability of the results.

NA

5 References

Please include all references below using NICE's standard referencing style.

Enter text.

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6 Appendices

Appendix A: Search strategy for economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology being evaluated. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	Enter text.
Date span of search:	Enter text.

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Enter text.

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Enter text.

Inclusion and exclusion criteria:

Enter text.

Data abstraction strategy:

Enter text.

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Enter text.

Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Model structure

Please provide a diagram of the structure of your economic model.

DIAGRAM 1. STANDARD CARE ARM

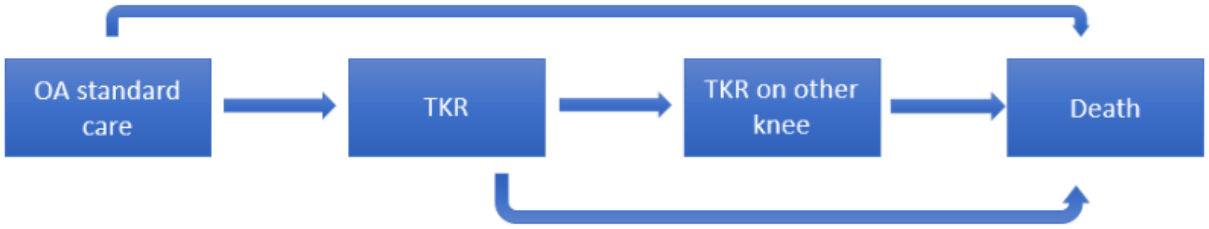
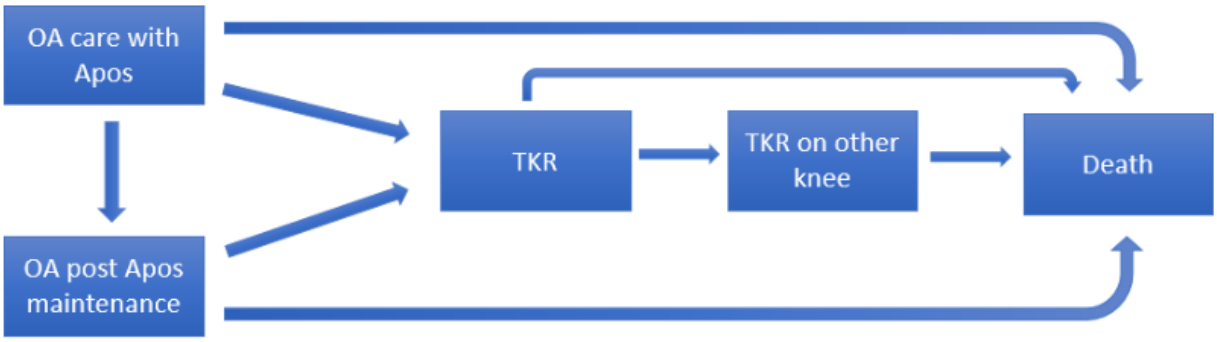


DIAGRAM 2. APOS ARM



Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No	☒	If no, please proceed to declaration (below)
Yes	☐	If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	27 July 2022
Print:	**Sachin Gohil**	**Role / organisation:**	Senior Vice President, Chief Commercial Officer, AposHealth UK

Contact email: [redacted]

Appendix D Clinical codes used to identify knee replacements in HES data

The primary procedure codes shown below for total knee replacement were used to identify knee replacement admissions for our analysis of mean waiting times. It was not possible for us to identify partial knee replacement activity as this requires a combination of codes, and published summary data do not provide sufficient detail. We have assumed that mean waiting times for partial knee replacements (estimated at 8.5% of the total) are the same as for total knee replacements.

These codes are based on those used for NHS PROMs data on knee replacements.[i]

Description	OPCS-4
Total knee replacement, primary	W40.1
	W40.8
	W40.9
	W41.1
	W41.8
	W41.9
	W42.1
	W42.8
	W42.9
Hybrid knee replacement, primary	O18.1
	O18.8
	O18.9
Total knee replacement, revision	W40.0
	W40.2
	W40.3

	W40.4
	W41.0
	W41.2
	W41.3
	W41.4
	W42.0
	W42.2
	W42.3
	W42.4
	W42.5
	W42.6
Hybrid knee replacement, revision	O18.0
	O18.2
	O18.3

National Institute for Health and Care Excellence

Medtech Innovation Briefing

Collated comments table

Expert contact details and declarations of interest:

Expert #1	Mr Alistair Shaw, Clinic Director and Chartered Physiotherapist, ICE Integrated Clinical Excellence Limited, [redacted]
	Nominated by: Company
	DOI: Yes. We are paid to deliver AposHealth for the NHS in Bedfordshire and charge for private delivery of Aposhealth largely to patients who live outside of Bedfordshire.
Expert #2	Mr Michael B Kelly, Orthopaedic Surgeon, North Bristol NHS Trust, [redacted]
	Nominated by: NICE
	DOI: None
Expert #3	Mr Chinmay M Gupte, Consultant Orthopaedic Surgeon, Imperial College London, [redacted]
	Nominated by: NICE
	DOI: None
Expert4	Robyn Hickey, First Contact Physiotherapist / Apos Certified Senior Physiotherapist, Circle Integrated Care, [redacted]
	Nominated by: Company
	DOI: NONE
Expert 5	Michelle Phillips, None (Private physiotherapy contractor) Physiotherapist, [redacted]
	Nominated by: Company
	DOI: Yes, I previously contracted with AposHealth as a Physiotherapist to provide Apos therapy to patients. This work was concluded at the time of completing this questionnaire. August 2018 31.3.2022
Expert 6	Professor Adewale Adebajo, Consultant Rheumatologist, Barnsley Hospital NHS Foundation Trust, [redacted]
	Nominated by: NICE
	DOI: NONE
Expert 7	Dr Toby Smith, Associate Professor in Physiotherapy, University of East Anglia, [redacted]

	Nominated by: NICE
	DOI: NONE

		Response
1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? Is this procedure/technology performed/used by clinicians in specialities other than your own? − If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	Expert #1: I have been using AposHealth/Apos Therapy within my clinical practice for approximately 6 years and use it on an almost daily basis for the treatment of Chronic lower back, hip and knee conditions. As a result I would consider myself very familiar with the procedure/technology. I currently use it both privately and within the NHS Musculoskeletal service in Bedfordshire. It has been used within the NHS, in Bedfordshire for approximately 6 years specifically for the treatment/management of patients with arthritic hip and knee conditions. I am confident that if this therapy was more widely available within the NHS the speed of uptake would be high as it can provide very effective pain relief and greatly increased function for patients with osteoarthritis of lower limb joints and Lumbar Spine conditions. As far as I am aware AposHealth is normally undertaken by Chartered Physiotherapists who have been specifically trained to deliver this treatment.
		Expert #2 No experience with this specific technology. Over 12 years consultant level experience in the management of knee arthritis Not widely used. There are many pain and arthroplasty avoiding strategies currently being trialled. This falls into that category. Unknown. It has potential to be used in any patient where there is potential for a limp or antalgic gait.

		If recommended it would involve a physiotherapist service.
		Expert #3 As an orthopaedic surgeon who treats knee osteoarthritis, I have experience in Apos Thearpy as well as other knee interventions. I have used this treatment occasionally in my patients. Yes. Have treated my patients with this. Approximately one per 3 months It is used occasionally in the NHS, by GP's rheumatologists, sports physicians and orthopaedic surgeons.
		Expert #4: I have four years' experience with the technology. I was trained as an Apos Certified Physiotherapist in 2018 when I also began to use the technology in practice. I continue to use this technology today. - Physiotherapists are involved in patient selection. At Circle Integrated Care MSK service in Greenwich, London, physiotherapists triage all secondary care referrals to orthopaedics for patients who are candidates for knee replacement surgery. They conduct shared decision-making telephone calls with the patients where they offer patients an option for surgical alternatives, such as Apos. Patient's who do not want surgery or are not a safe candidate for surgery can choose to do Apos as an alternative option. -Our specialty has an Apos Certified Physiotherapist in hub that can see patients for a 3-year NHS programme funded by our local commissioning group. Therefore, patients do not need to be referred onward. Following the 3-year programme, if they require further assistance with their Apos device, they can choose a private Apos provider. However, this is usually unnecessary as the device is calibrated appropriately prior to discharge. -It is utilised in a few localities now and with the growing evidence both from trials and real-world outcomes, there is huge potential to treat this growing cohort of patients. It is now also available via orthotists trained in the treatment.

		Expert # 5 I am familiar with the AposHealth biomedical device (boots). I was trained in using the AposHealth device in April 2018. I used the device with patients between October 2018 to February 2020, and again between the period November 2021 – March 2022. I am not aware of the usage nationally of the device across the NHS. I am aware the device was commissioned locally for a period of time, by Mid Essex CCG. This device is not used by clinicians outside of physiotherapy, although I believe some Orthotists are currently undergoing training. My specific role has been in assessing patients for their suitability to join the AposHealth programme and following them up through their treatment programmes. This includes making modifications to the device depending on how a patient is progressing.
		Expert #6 I am aware of the technology and I manage patients for whom the technology is indicated, but I have not as yet used this technology for any of my own patients.
		Expert #7 I treat and research patients with hip and knee osteoarthritis. I am familiar with this patient group and their interventions. I have a clear understanding of UK care pathways for this patient group and particularly in relation to NICE guidance for their management. I have not used this technology and am not currently familiar with this technology (prior to reading). I am currently unclear on how this technology is used in the NHS but could make a judgement once I understand the technology to be able to make reasoned statements on potential translation. As far as I am aware, this technology is not widely used in practice but we would be a key professional group (physiotherapy) who would potentially use this technology.

2	Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1: I have had no involvement in research on this procedure.
		Expert #2 I have had no involvement in research on this procedure.
		Expert #3 I have done bibliographic research on this procedure.
		Expert # 4 I have was not involved in research on this procedure.
		Expert # 5 I have had no involvement in research on this procedure.
		Expert # 6 I have had no involvement in research on this procedure/ technology.
		Expert # 7 I have done bibliographic research on this procedure. – In this respect I have done a brief literature review and internet search to understand the procedure and evidence-base a little more as was previously unaware.

Curent management

3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Expert #1: The first in a new class of procedure.
		Expert #2 It is innovative in that it combines gait analysis with gait re-education in a patient setting for the treatment of pain/antalgic gait using wearable technology. The concept of gait re-education is not new and there are many modalities looking at this. Definitely novel and of uncertain safety and efficacy.

		Expert #3 Novel approach. There are other gait analysis tools not dissimilar to APOS. Also orthotic fitting is inside the shoe, whereas APOS is outside, but the principles of alteration of biomechanics are the same. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.
		Expert # 4 Established practice and no longer new.
		Expert # 5 "Definitely novel and of uncertain safety and efficacy."
		Expert # 6 I accept that this is an innovative technology. Definitely novel and of uncertain safety and efficacy.
		Expert # 7 This is a novel approach/concept in mainstream knee osteoarthritis management in the NHS. Definitely novel and of uncertain safety and efficacy. – I would suggest there is uncertain efficacy for the NHS and there is uncertain cost-effectiveness data in the mainstream. There are other devices which may do something akin but not directly related.
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Expert #1: I believe this procedure can be used in addition to current standard care for the management of arthritic lower limb joints, and is likely to provide much greater and positive results for patients with these conditions.
		Expert #2 The standards of care in the literature provided are not appropriate. It needs to be compared to the various 'escape pain' initiatives already in use or being trialled to demonstrate efficacy and cost-effectiveness. It is not appropriate to include the cost of knee arthroplasty in the assessment unless there is long term data showing that this was completely avoided.

		Expert #3 No
		Expert # 4 This technology should not replace exercise-based physiotherapy management of knee osteoarthritis but instead as an addition to existing care. Patients may use this technology in replacement of having a surgical joint arthroplasty as it is non-invasive and poses less safety risk.
		Expert # 5 The device does not have the potential to replace current standard care – it would be an adjunct to existing care.
		Expert # 6 Although this technology has the unproven potential to replace current standard care, it is much more likely to be used as an addition to existing standard care.
		Expert #7 I would suggest that this intervention has the potential to augment treatment pathways.

Potential patient benefits

5	Please describe the current standard of care that is used in the NHS.	Expert #1: Typically the current standard of care for osteoarthritis of lower limb joints is a combination of pharmacological treatment and exercise based therapy with lifestyle modification.
		Expert #2

		Non-operative approaches include patient education, walking poles to correct gait or walking aids to improve pain and physiotherapy/self directed exercise programmes.
		Expert #3 Currently these patients would undergo one or a combination of: Physiotherapy, orthotics, injection of steroid or lubrication gel, bracing and analgesic treatment.
		Expert # 4 This technology is used in the NHS only for hip and knee osteoarthritis as an alternative to surgery. Therefore, patients must meet surgical criteria for NHS funding (moderate to severe degeneration on imaging, previously trialled conservative management, and oxford score <20).
		Expert # 5 The device is used for people with Osteoarthritis of the Knee. The NHS current standard of care is in line with the NICE Osteoarthritis: care and management guidance, which includes physiotherapy and potential onward referral to Orthopaedics should the subjective and objective assessment indicate that a surgical intervention may be warranted.
		Expert # 6 The current standard of care that is used in the NHS consists of simple analgesics such as paracetamol or NSAIDs together with a home exercise program, followed if required by formal physiotherapy and/ or local corticosteroid joint injection and ultimately followed by joint replacement surgery.
		Expert # 7 Current standard of care is the provision of education and advice on osteoarthritis, behaviour modification to pain management, weight management where appropriate, simple analgesics and exercise for hip and knee function to improve knee biomechanics and muscle control/strength. Foot/shoe orthoses are supplementary treatment and not core NICE recommended treatments.

6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Expert #1: I am unaware of any other competing or alternative procedure/technology that will have a similar function or provide further benefit to patients
		Expert #2 Yes. There are various app based or therapy based approaches to improve gait patterns, exercise and pain. This differs in that it uses a wearable technology to provide feedback to the patient.
		Expert #3 Orthotics Orthotics are inside the shoe, APOS is outside on the sole.
		Expert # 4 Ossur braces offer a unilateral offload for knee osteoarthritis. However, Ossur braces does not provide perturbation challenges for the muscles. Patients do not often comply with Ossur braces due to the bulkiness of the device and inability to wear over clothing. Additionally, it is not suitable for offloading more than one joint compartment whereas an Apos device can provide an offload to all three joint compartments of the knee.
		Expert # 5 I am not aware of any similar product to this.
		Expert # 6 I am not aware of any competing or alternative technology available to the NHS.
		Expert # 7 Not specifically to those claimed through this device.
7		Expert #1:

	What do you consider to be the potential benefits to patients from using this procedure/technology?	Reduction in pain levels, improved lower limb biomechanics, improved function and better quality of life.
		Expert #2 If it can establish that it is efficacious, then there is the potential to manage arthritic joints non-operatively through gait re-education. It does not remove the need for sustained therapist or trainer input to maintain the gains in the longer term.
		Expert #3 Improved pain
		Expert # 4 A non-invasive technology that can be used during activities of daily living to help improve patients' pain, function, and stiffness of the knee to help improve their quality of life.
		Expert # 5 Whilst many patients are referred to Orthopaedics and go on to undergo replacement surgery, there are many patients who do not convert to surgery, for many reasons. The Apos device (boots) is a non invasive option for managing the symptoms of knee osteoarthritis. Patients may benefit, therefore, from either ing a surgical intervention altogether, or delaying the surgery until an appropriate time.
		Expert # 6 I consider that the potential benefits to patients from using this technology include reduction in knee pain, reduction in associated potential side effects of pain relief medication and improvement in muscle strength of the knee joint related musculature with reduced knee joint pain, as well as improvement in gait and function.
		Expert # 7

		Knee osteoarthritis is a major health challenge. With an ageing population, the prevalence is expected to increase. Managing this population with non-surgical interventions is needed. This may be a intervention to offer promise to this population.

Potential system impact

8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Expert #1: Patients with chronic, degenerative low back pain, Knee, hip and ankle degenerative conditions such as Osteoarthrits.
		Expert #2 Trauma recovery, knee and hip arthritis, back pain.
		Expert #3 Early OA knee and those not suitable for or not wanting surgery.
		Expert # 4 Patients who have a high BMI or other comorbidities that make for a greater risk for surgical complications can particularly benefit from using this technology. Patients who are unable to have surgery due to socioeconomic factors (for example, inability to afford to take time off self-employed work or inability to take time from caring for a family member) benefit from this alternative option to help improve their symptoms.
		Expert # 5 This device is suitable for patients with moderate or moderate to severe knee osteoarthritis. In my personal experience, I have found patients experiencing predominantly medial knee OA have had the most noticeable improvements in symptoms.
		Expert # 6 Patients with mild to moderate osteoarthritis.

		Expert # 7 All patients who have knee osteoarthritis.
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Expert #1: Since beginning to use AposTherapy/AposHealth in Bedfordshire 6 years ago I believe, as a result, fewer patients have required surgical intervention for the management of their hip and knee arthritis, ie fewer total hip and/or knee replacement surgeries are required. I also believe that if the scope of usage was increased to allow referrals for patients with chronic Lumbar spine conditions it would reduce the medical intervention for these patients ie, fewer hospital and GP appointments required, and reduced medication required. Furthermore by increasing patients functional ability and reducing pain the impact that this could have on patients' general health and mental well-being could be significant.
		Expert #2 Rather than change it coincides with the current move to a more proactive non-operative strategy, Yes
		Expert #3 Possibly Only for a limited amount of time eg 1 yr.
		Expert # 4 Yes, this technology can lead to less invasive treatment for knee osteoarthritis and fewer secondary care / hospital visits and surgical procedures.
		Expert # 5 This technology could lead to the reduction in the number of patients advancing to knee replacement surgery, assuming the patients are appropriate for the therapy.

		This technology also encourages patients to increase their physical activity levels, which we know is beneficial with knee osteoarthritis.
		Expert # 6 This technology has the potential to lead to improved outcomes, fewer hospital visits and less invasive treatment.
		Expert # 7 This intervention has the potential to be augmented into the care pathway to improve patient outcomes. If has efficacy, some patients may not necessarily need surgical interventions to manage their symptoms which would be a major benefit to them and the NHS.
10	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Expert #1: Whilst the initial cost can be higher compared to a standard physiotherapy referral, I believe, and I understand has been proven in Bedfordshire, this technology is likely to reduce the overall cost of care compared to the current standard care pathway as reduces the need for surgical intervention and pharmacological management. There is an initial outlay in terms of purchasing gait analysis equipment and training Physiotherapy staff but the longer term cost will be more cost effective for managing these patients.
		Expert #2 Yes
		Expert #3 more
		Expert # 4 The technology costs significantly less compared to surgery (+ days in hospital and outpatient appointments with a consultant) Within the NHS 3-year programme, they receive one initial assessment where they are given the device and 4 follow up appointments per year (12 in total)

		with a physiotherapist. Following the completion of the programme, the device is theirs to keep.
		Expert # 5 Considering the care pathway as a whole, this technology is highly likely to cost more than standard care in terms of staff, equipment, care setting etc. I am not familiar with the costings of the device/therapy packages or the costs of current care to be able to answer this question.
		Expert # 6 Considering the care pathway as a whole, this technology is highly likely to cost more than standard care in terms of staff, equipment, care setting etc.
		Expert # 7 If shown to impact on the surgical need, this intervention may be cost-saving for the NHS.
11	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Expert #1: There will be a small additional cost in purchasing suitable equipment and the on-going cost of the devices and their parts which is likely higher compared to a standard cost of a physiotherapy referral. However the overall cost compared to the care pathway as a whole will be less.
		Expert #2 Yes because of the cost of the technology. It has yet to provide long term evidence that arthroplasty is avoided. If this data is provided then there are potential cost savings.
		Expert #3 more
		Expert # 4

		Resource impact includes one physiotherapist per 100 patient caseloads, a clinical setting and receptionist. This would cost less than a hospital setting for a surgical procedure.
		Expert # 5 I am not familiar with the costings of the device/therapy packages or the costs of current care to be able to answer this question.
		Expert # 6 I consider the resource impact to be significantly more than standard care in terms of staff, equipment and care setting.
		Expert # 7 There is limited resource impact of this intervention if shown to be beneficial in improving patient symptoms, particularly if negating the need for surgery.
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Expert #1: Purchase of a gait analysis device and computer equipment. Adequate space required to conduct gait analysis. Storage space for devices and components required.
		Expert #2 This could mean that conditions are managed away from hospitals in primary care setting with the involvement of therapists.
		Expert #3 Analysis centres, rooms, fitting centres
		Expert # 4 A clinical room large enough to fit an Optogait track, computer desk, and plinth.
		Expert # 5 A clinic room in order to assess patients.

		Access to a length of 5 metres to measure a patients gait (this could potentially be a corridor if a big enough room were not available).
		Expert # 6 There will be an additional space requirement for this technology to be administered safely.
		Expert # 7 I would need more information on the intervention to be able to answer this question.

General advice

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1: Yes, Clinicians need to undertake AposHealth specific training to deliver this service.
		Expert #2 Yes. Patient and therapist training.
		Expert #3 Yes
		Expert # 4 Yes, there is theory and practical learning involved. Online course followed by an in-person course following by clinical supervision, and examination. Following this completion, the clinician is accredited as an Apos Certified Physiotherapist.
		Expert # 5 Yes. The practicing clinician must be a qualified therapist by background and must undergo a specific training programme to be able to use this device with patients.

		Expert # 6 Specific training of the appropriate health care personnel as well as of the patients and their carers will be needed in order to use the technology with respect to both efficacy and safety.
		Expert # 7 I would need more information on the intervention to be able to answer this question.

Other considerations

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Expert #1: In some rare cases if the treatment programme is not strictly adhered to sometimes additional muscular aches/discomfort can occur due to the demand placed on the neuromuscular system. This can, for a short period of time, exacerbate some symptoms patients may have as a result of their hip and knee arthritis. This procedure is very unlikely to make the structural issues of arthritic hips and knees and worse. There is a small risk of patients tripping and falling whilst wearing the devices, however this risk should be mitigated during their assessment, whereby suitability tests are conducted and if a patient looks as though they would be at risk of falling then they would not be deemed suitable to commence treatment. In very rare incidents (I have known 2 patients within approximately 800) some dizziness can be provoked after wearing the Apos Health devices.
		Expert #2 Footwear issues, continued pain and progression to arthroplasty despite the intervention. These are likely to be uncommon and related to the comfort of the footwear.
		Expert #3

		Risk of falls Deterioration of knee, hip or back pain. Non compliance Patient not happy with appearance of device.
		Expert # 4 Potential harm of the technology is the risk of falling, especially in patients with osteoporosis. However, balance and past medical history is screened on initial consultation to ensure that the patient is able to safely walk in the device which has a convex bottom. This is done using the STEADi balance questionnaire. For patients who score 4 or over, they must pass 2 out of the 3 following tests: Timed Up and Go, 30 second Sit to Stand, and 4 Point Balance testing.
		Expert # 5 A potential harm risk of falls due to the convexity of the pods on the bottom of the device (boots). This is mitigated by all patients undergoing a balance screening test prior to commencing the programme. Should the patient not pass the balance test, or should the clinician sense that the patient may not be safe/stable, then a patient should not be enrolled into the programme.
		Expert # 6 There is a potential for harm if the technology is administered incorrectly.
		Expert # 7 I would need more information on the intervention to be able to answer this question
15	Please list the key efficacy outcomes for this procedure/technology?	Expert #1: Reduced pain levels (Monitored by WOMAC outcome measure), improved function and quality of life, reduced need for pharmacological and surgical intervention
		Expert #2

		Avoidance of arthroplasty at 10 years for patients referred for consideration Avoidance of the need for secondary care referrals
		Expert #3 Pain, mobility
		Expert # 4 WOMAC, EQ5D, Oxford Knee Score, and KOOS
		Expert # 5 A reduction in the symptoms of knee OA.
		Expert # 6 The key efficacy outcomes include pain scales, walking distance, walking speed and the WOMAC outcome scale.
		Expert # 7 Pain Physical function Health economic outcomes i.e. work status, health utilisation, requirement for surgery
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Expert #1: Patients ideally need to referred for AposHealth before their symptoms are too severe. As fantastic as this treatment is, it obviously has its limitations. The earlier a patient is referred the more successful their outcome is likely to be and the greater the benefit to the patient and to the NHS.
		Expert #2 As above
		Expert #3

		Risk of falls and increased strain on other joints eg hip, back.
		Expert # 4 None, as long as patients are screened for balance.
		Expert # 5 Nil known
		Expert # 6 There is insufficient knowledge of and experience with the technology to be certain about its efficacy and safety.
		Expert # 7 Is it cost-effective?
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Expert #1: None that I am aware of
		Expert #2 No
		Expert #3 Blank
		Expert # 4 No, because it is using evidence-based scientific methods (biomechanical physics and physiotherapy methods).
		Expert # 5 Nil known
		Expert # 6

		The long-term efficacy and harms of the technology are not yet fully established.
		Expert # 7 I would need to see more data before being able to answer this.
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Expert #1: Most or all district general hospitals.
		Expert #2 Most or all district general hospitals*. If efficacious, no referral to hospital would be required.
		Expert #3 Most or all district general hospitals.
		Expert # 4 Cannot predict at present.
		Expert # 5 I would envisage this device being used in community settings (out of hospital) across the UK.
		Expert # 6 Cannot predict at present.
		Expert # 7 Cannot predict at present.
19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented /	Expert #1: May 2020 independent double-blind RCT study published in the Journal of the American Medical Association.

	published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Expert #2 None
		Expert #3 Blank
		Expert # 4 Research: Two clinical trials looked at 2-yrs surgery avoidance in patients with knee OA. One study was done in the US and was recently accepted for publication in Population Health Management. The second one was done in the UK, on an NHS population and is currently under peer-review in Clinic in Orthopaedic Surgery. Both studies report >84% surgery avoidance at 2-yrs. Sources: Miles, C., Greene A. (2021). The effect of treatment with a non-invasive foot worn biomechanical devce on subjective and objective measures in knee osteoarthritis patients. *Physiotherapy Journal, 047; volume 114, supplement 1, E38* https://doi.org/10.1016/j.physio.2021.12.287 Miles, C., Greene, A. (2020). The effect of treatment with a non-invasive foot worn biomechanical device on subjective and objective measures in patients with knee osteoarthritis- a retrospective analysis on a UK population. *BMC Musculoskeletal Disorders, 21; 386.* https://doi.org/10.1186/s12891-020-03382-3
		Expert # 5 Physiotherapy UK conference – Abstract published Peer reviewed paper for the NHS cohort seen in mid Essex.
		Expert # 6 None known.
		Expert # 7 None

20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Expert #1: I am unaware of any current trials in progress but am not generally involved in the research and development programme of AposHealth
		Expert #2 Escape pain
		Expert #3 https://clinicaltrials.gov/ct2/show/NCT03171168

		Expert # 4
		• **Innovate UK**
		  ○ Government National Innovation Agency
		  ○ Awarded Apos £160k funding to develop telemedicine model of care
		• **NHS Supply Chain**
		  ○ NHS Supply Chain manages the sourcing, delivery and supply of healthcare products, for NHS trusts and healthcare organisations across England and Wales.
		  ○ Apos will be available to purchase via the NHS supply chain from March ’22
		• **Mid Essex Clinical Commissioning Group (NHS)**
		  ○ Group of 44 community physician surgeries covering a population of 392k patients
		  ○ Apos has been a partner since 2017
		  ○ Currently providing follow-up appointment activity for patients
		  ○ Strategic importance in providing use case studies and real world evidence for implementation across the NHS
		• **Partnership with Talarmade**

		○ Experienced distributor of orthotic devices across the NHS ○ Network of established NHS clinics and services ○ Gain share agreement to distribute Apos ○ Significant potential for Apos growth • **China** ○ Training physiotherapists remotely across China to run their own Apos service ○ 55% of the Chinese population >65yrs old with OA ○ Expected that 400million people will suffer from OA by 2030 ○ 8.1% of the Chinese population >45 yrs. old experience symptomatic knee OA. ○ Partnership with Grand Fortune Beijing to act as distributor for Apos across China
		Expert # 5 I am aware of 2 clinical trials that have looked at surgery avoidance in patients with knee OA over 2 years. 1. One done in America and due to be published in Population Health Management. 2. One done in the UK, on an NHS cohort (under peer-review in Clinic in Orthopaedic Surgery).
		Expert # 6 None known.
		Expert # 7 None aware of
21		Expert #1:

	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	I would expect 75%-80% of patients diagnosed with Osteoarthitis of the knee and 60% of patients diagnosed with Osteoarthitis of the hip would be eligible, which considering the current state of NHS waiting lists for surgery and the large number of patients diagnosed with these conditions, if it were used widely within the NHS, then There are likely to be hundreds of thousands/millions of patients who would benefit from this treatment. Also if this treatment was opened up for the use/management of degenerative Lumbar spine conditions the number would be even greater.
		Expert #2 Everyone referred for consideration of primary arthroplasty
		Expert #3 2000
		Expert # 4 In the UK, approximately 20% of the population over the age of 45 years suffer from knee OA, with 20% of these considered “severe”. It is also utilised effectively for hip OA within 2 CCG’s as an alternative to surgery.
		Expert # 5 Moderate to severe OA patients (unsure of numbers).
		Expert # 6 Possibly 20% of the knee osteoarthritis population/
		Expert # 7 Unsure – would need more information on the intervention
22	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert#1 As previously alluded to, there is a suitability criteria that patients need to satisfy to be considered suitable for Apos Health
		Expert#2

		Footwear considerations
		Expert#3 Yes compliance and longer term efficacy
		Expert # 4 The patient needs to be able to put on a pair of shoes or have someone assist them in donning and doffing the shoes.
		Expert # 5 The device has convex pods on the bottom, making it unsafe for any patients with balance issues. If a patient has issues with their feet (i.e. in growing toe nail/skin issues) then they would be unlikely to be able to use the device.
		Expert # 6 The usability and practical aspects of the technology are challenging and require researching into/
		Expert # 7 As comment above
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Expert #1 In theory there are no specific issues other than cost and the opinion of other medical professionals that should prevent this procedure being adopted widely by the NHS
		Expert#2 No
		Expert#3: Cost

		Expert # 4 No.
		Expert #5 In my personal opinion, I believe in order to become adopted within the NHS, this needs support from all clinicians from across the knee OA pathway. The only way to achieve this is with a bigger body of evidence to support the intervention. I also imagine that any upfront cost may be a blocker to adoption.
		Expert # 6 The technology is yet to demonstrate long term safety, feasibility, efficacy and cost-effectiveness.
		Expert # 7 None to my knowledge.
24	Is there any research that you feel would be needed to address uncertainties in the evidence base	Expert#1 More RCT trials to cement the anecdotal knowledge of the effectiveness of Aposhealth for the management of low back pain and lower limb conditions
		Expert#2 Long term effectiveness showing avoidance of secondary care referral and removing the need for arthroplasty.
		Expert#3 Yes but his trial may provide this. https://clinicaltrials.gov/ct2/show/NCT03171168
		Expert # 4 No.

		Expert # 5 In my personal opinion, I believe there needs to be data captured on a bigger cohort of patients, to prove the efficacy on a larger scale across multiple locations.
		Expert # 6 The technology needs to demonstrate and provide an evidence base for long term safety, feasibility, efficacy and cost-effectiveness.
		Expert # 7 None to my knowledge.
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured	Expert#1 Beneficial outcome measures: As standard practice we use WOMAC scale, Oxford hip and Oxford knee scores to monitor effectiveness and clinical outcomes. Outcome measure taken either every 3 or 6 months. We also use SF-36 and EQ-5D measures for Quality of life outcome measures. Adverse outcome measures: None
		Expert#2 Beneficial outcome measures: Hours worn Compliance beyond 6 months Referrals for management Unscheduled care requirement Progression to arthroplasty Adverse outcome measures: Footwear issues

		Expert#3 Beneficial outcome measures: WOMAC score, SF36 Tegner activity score Adverse outcome measures: Falls Pain in hip and knee Progression of OA in knee
		Expert # 4 Beneficial outcome measures: We measure WOMAC scores for pain, function, and stiffness at each follow up session to ensure a linear improvement is being made. Oxford knee scores are complete at baseline (0 months), 6 months, and 12 months. We also track objective improvements in barefoot walking (without the device) for each follow up. These are walking velocity, single leg stance %, and step length. Adverse outcome measures: None.
		Expert # 5 Beneficial outcome measures: WOMAC Oxford Knee Score Pain scores Gait results

		Expert # 6 Beneficial outcome measures: Pain reduction using pain VAS scales, walking distance in kilometres and walking speed in minutes both in the short term (6 weeks) and the long term (5 years). Use of the WOMAC as primary outcome both in the short term (6 weeks) and the long term (5 years). Adverse outcome measures: Injury due to administration of the technology as both early as well as late complications.
		Expert # 7 Beneficial outcome measures: Pain – frequency and intensity Physical function Occupational status Health utilisation including need for surgery Health-related quality of life Adverse outcome measures: Increase in pain at knee or other joints Falls
26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Expert#1 Since using AposHealth as part of my every day practice I feel the people of Bedfordshire are fortunate to have this innovative and generally hugely effective treatment modality available to them on the NHS. I feel that it is a safe and effective treatment modality that has the potential to great improve the standard of care available to a huge number of patients across the country and has the potential to save the NHS a large amount of money.

		Expert#2 Included above
		Expert#3 This is a therapy that has been used for over a decade. The main issue is with compliance and medium to long term efficacy and an unproven risk of falls.
		Expert # 4 My experience of the technology has been excellent. I enjoy offering Apos to patients as it significantly improves their quality of life. Most patients leave with a smile on their face knowing that their pain can be offloaded successfully without having to have surgery.
		Expert # 5
		Expert # 6 In my view, this technology is not sufficiently proven to justify adoption by NICE for use in the NHS.
		Expert # 7 Nothing further

NICE National Institute for Health and Care Excellence

Patient expert statement

GID-MT570 AposHealth for osteoarthritis (OA) of the knee

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Susan Field**

2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	APOS
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**In this statement I will inform you of my experience of living with osteoarthritis over the past 15 years.** **I started having knee problems in 2003 when I damaged my medial ligament in my right knee when playing hockey. I had a brace on my knee and follow up physiotherapy to get me back on my feet and took Naproxen for several days to get through the days and nights. This injury led to me relying on my left knee all the time. I did go back to hockey after 12 months rehab and a neoprene brace on my knee and always led a very active life.** **My job as an infant teacher meant that I spent all of my working life kneeling or crouching to work with very young children and sitting at tables and chairs that are the correct size for 4 year olds. I was also the PE lead in school so led lots of clubs and after school matches.**

	Over the next few years I had pain on and off in my right knee and eventually in my left knee as well. This often caused me to resort to pain killers and ice packs on my knees. **After a paticularly bad time with intense pain in my knees I went to the GP for stronger pain relief. I was asked to have an x-ray on my knees and was told that due to osteoarthritis in both knees I was a potential candidate for 2 total knee replacements. This was not an option that I wanted to explore at 50.(My Mother had 2 knee replacements in her 70's and, although she was pain free ,they were not that successful.) I wanted a different option. I started having acupuncture once a month. This really helped but after 2 weeks the effect had worn off and I needed it fortnightly. This was not a finacially viable situation for me.** **My knee pain became increasingly difficult both at night and during the day . It is a difficult pain to describe but it is unrelenting and just feels like toothache in the knee and no amount of massaging or ice or heat could stem it.** **Some mornings when I was walking the dog before work, I had to use a stick over uneven ground because my right knee would suddenly give way. Work became more difficult because a lot of teaching Early Years children is done on the floor.** **So in 2015 I was referred to OT at Essex County Council to see if there was anything that could be done to help me in the classroom. The only advice I as given was to reduce the number of days I worked. This was not an option I could take. I approached Teachers Pension but osteoarthritis is not a good enough reason for early retirement. After a lot of soul searching and discussion with family I decided that I really had no option but to take early retirement from teaching.**
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	At the current date there is no other treatment other than knee replacement surgery.

10. Is there an unmet need for patients with this condition?	
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	**In 2017 I retired at nearly 56 years old. I joined the gym and tried to exercise regularly, but this was difficult due to the pain. There were only specific exercises I could do. Whilst I was there I was working on my program when a friend told me about APOS. I immediately went home and researched it. It appealed to me because I really don't like having to take tablets to be able to continue with the active life style that I was used to. I was very fortunate that Mid Essex were using APOS as it would have been difficult for me to pay. I went to the doctors and she did all the paperwork for me and I had to fill in The Oxford Knee Survey. She also talked about me needing a cortsone injection in my knees as another option but said these often provide only short term relief. I decided to try the APOS treatment before resorting to injections.** **I was accepted into the treatment and started at Braintree Hospital in September 2019. I went for my first appointment and ,after computer analysis of my gait, I was amazed to be told that I was limping slightly. I was fitted with my boots and followed the program carefully increasing the use of the boots over time and doing the exercises I was also given. My knees very quickly became less swollen and stiff and I could walk the dogs without a stick again. My knees no longer give way on me and I can walk down stairs with much less pain then I did before the treatment. I now very rarely take any pain killers and I am sure I am a long way from knee surgery.** **I even managed to do a little bit of supply teaching as I felt confident that I wouldn't have pain in my knees when crawling on the floor to teach. The Covid pandemic stopped this and now I am 60 I have fully retired.** **I have been so pleased with the results and now, at the end of my 3 year trial, my knees feel completely different. I rarely have severe pain and I know if I do overdo it I can wear my boots and my knees recover. I am no longer kept awake at night and last week I played 18 holes of golf 2 days in a row.**

	My knees were tired but I put my boots on afterwards and they recovered quickly.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	**I am sad that my 3 year trial is over but I know I can pay to go and see the APOS team for any adjustments and consultations but this may not be financially viable for me. I am lucky that I still have the boots and I do wear them at least 3 times a week and more if needed. The only drawbacks to the boots are that the laces are very long and mud gets caught in the pods when out in the garden!**
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	I think any person with hip or knee pain could benefit from the programme because they make you walk in a different way and strengthen the joint.
Equality	
14. Are there any potential equality issues that should be taken into account when	**None**

considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	No
Topic-specific questions	
16. What is the wearability of the AposHealth shoes? (For example, comfort, look, ease of use for required time)	I got used to wearing them very quickly but I did follow the timetable to increase usage very rigidly to avoid muscle pain. I can now wear the for long periods but sometimes build up the time after I have had adjustments to the pods or more convex pods fitted. I still wear the shoes and will continue to do so whenever they are needed to relieve pain or just to maintain my correct walking posture.
Did you continue to use the shoes after the treatment programme had completed? If so, how often?	There is nothing in my life that would make them difficult to use at the present time.

Is there anything that makes it easy or difficult to use the technology?	

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

- Lack of pain
- Strengthened knee joints
- No need for painkillers everyday
- Ability to maintain an active life style
- Easy timetable to follow and regular check ups at the beginning give you confidence

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, confidentiality form, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

NICE National Institute for Health and Care Excellence

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

MT570 AposHealth

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
1.	03/08/2022	Company start-up meeting to discuss clinical submission.	The EAG sent a list of questions in advance of the meeting. The company responded with answers in time for the company start-up meeting on 03/08/2022.	Written responses were provided by the company and are reported in Appendix A. Verified notes from the company start-up meeting are reported in Appendix B.
2.	09/08/2022	Clinical expert engagement meeting.	The EAG sent a list of questions in advance of the meeting to the clinical experts. Responses were not provided prior to the meeting.	Questions sent to the Clinical experts prior to the meeting are reported in Appendix C. Verified notes from the clinical expert engagement meeting are reported in Appendix D.

		After the clinical expert engagement meeting, the questions were also sent to the clinical experts who were invited to, but did not attend, the meeting seeking written responses.	Email sent from EAG to clinical experts who did not attend the engagement meeting to gather responses to the initial list of questions (Appendix C).	Written responses to the questions from clinical experts who were not in attendance at the engagement meeting are reported in Appendix E.
3.	31/08/2022	Second company engagement meeting.	The EAG sent a list of questions in advance of the meeting. The company responded with answers in time for the second company meeting on 31/08/2022.	Written responses were provided by the company and are reported in Appendix F. The verified notes from the second company meeting are reported in Appendix G.

Appendix A: Company start-up meeting

Company answers to EAG questions:

No.	EAG Question	Company response
The technology		
1.	For clarity, can you confirm any different names for the technology which might come up in the literature?	Alternative names: *AposTherapy* *AposHealth* *Apos*
2.	Is the [redacted] included in the Apos Health system and are there any additional charges?	[redacted] is included in the cost of the device. There are no additional charges for the use of this technology. It is expected one application is needed per clinic.
3.	Does the App require a specific device to run? If yes, is this device provided by the company or is this sourced by the user?	There are several mobile phone models that are compatible to support [redacted] and Apos clinician application.
4.	Where is data collected on the app held, and who is able to access it?	The data is collected locally on the device and is processed and stored on the cloud. The clinician will be able to access this information via a designated clinician Application. AposHealth will have access to this information and will be responsible to support the users
5.	Is the [redacted] a CE marked medical device?	Currently, [redacted] do not have a CE mark. This can be further explored if needed.
6.	Can other gait analysis software/hardware be used alongside the AposHealth shoes? If yes, what are the requirements needed to be able calibrate the shoes?	Other gait monitoring technologies are available, for example Optogait, GaitUp, Zenomat. It is the clinic choice if they wish to use these systems. We would recommend one system is used to maintain consistency between measurements and calibration of the device. The requirements for calibration are: Spatiotemporal gait metrics (specifically, velocity, step length and single limb support) for patients walking barefoot and with the Apos device
Use of the technology		

No.	EAG Question	Company response
7.	Could you clarify what computerised gait analysis is required during set up? Is this limited to the Apos Health [redacted] analysis using a mobile phone, or is there a requirement for a Gait lab and system? (If there is a need for a Gait lab, then does the NHS have capacity to meet this need?)	There is no requirement for a gait lab to be used to undertake a computerised gait analysis. To support the calibration process we use spatiotemporal parameters. This can be measured with any validated gait system. Note: A gait labs can also be used, however test and analysis are significantly longer and is unnecessary for to support calibration.
8.	Are services expected to keep a stock of all the different sizes of shoes available?	Clinics have a choice: 1. Keeping a stock of commonly used sizes and pods that is replenished regularly based on number of patients accessing treatment 2. Employing a home delivery model where a small stock of all sizes to allow for calibration then having a calibrated device sent to the patient after the appointment – this may be a preferable option for those organisations with limited space (or homecare visits).
9.	I understand that the typical duration of treatment is one year. Is there an expectation that patients will retain the shoe at the end of that year and continue to use it? Do they normally receive follow up past this point?	Patients retain the device at the end of their 'course' of treatment. Typically patients will self-manage and access ad-hoc appointments to recalibrate or ensure progress is maintained. Following the first year of treatment, we expect patients will access 1-2 follow up appointments from Year 2 onwards. Longer term patients (3+ years) tend to use Apos as and when their symptoms flare.
10.	Are providers expected to have existing training in gait analysis at all?	No. All training on gait, measurement and interpretation is provided by Apos.
11.	Is there an expectation around the amount of activity needed during the daily session using Apos Health device?	No. Patients are advised to continue their normal daily activities whilst wearing the device. For example, a patient prescribed a 1hr a day wear time, approximately 40% of this would be spent sitting down. As a result of no specific activity expectations from patients, compliance is very high.
12.	Is there any follow up training or assurance provided (after the initial 10 procedures) to ensure devices are being set up correctly?	Yes. Our Apos clinical experts are available during regular business hours for advice in addition to regular CPD sessions run by the clinical team to share best practice.

No.	EAG Question	Company response
13.	Although the indications exclude those people who have existing or documented history of falls or balance problems, is it possible that use of AposHealth may cause problems for people who have minor problems with balance, where this has not yet been identified?	Unlikely. During the initial evaluation the patient undergoes a clinical evaluation including balance assessments with and without the device. Clinicians are trained to assess for balance issues and in case those exist the patient will be unsuitable for treatment. A large double blind RCT published in JAMA concluded that the treatment is safe and that there are adverse events associated with the device (including balance issues)
14.	Is AposHealth only suitable for bilateral osteoarthritis?	No.
Evidence and Benefits		
15.	How widespread is the use of AposHealth currently both within the NHS and private practice?	AposHealth is currently employed in three NHS organisations: • NHS Mid Essex CCG • NHS Bedfordshire CCG • NHS Greenwich CCG We also have a network of twelve private physiotherapy providers that serve the self-pay and medical insurance population.
16.	Is there evidence around acceptability, compliance with daily use sessions and continued use over the one year period?	Two supplementary materials were included in the clinical outcome submission. The first, a member survey from a private UK insurer. The second is form NHS medium size CCG. Results suggest very high satisfaction rate with treatment. Most patients are using the device 4-7 days a week. Typically patients will self-manage and access ad-hoc appointments to recalibrate or ensure progress is maintained. Following the first year of treatment, we expect patients will access 1-2 follow up appointments from Year 2 onwards. Longer term patients (3+ years) tend to use Apos as and when their symptoms flare.

Appendix B Company start-up meeting notes

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Company Start-up Meeting
MTG570 AposHealth for osteoarthritis (OA) of the knee

This document summarises the discussions that took place at the company post clinical submission meeting for MTG570, which took place on Wednesday 3rd August 2022,14:00 to 15:00pm.

It also includes a follow-up clarification document that was shared by the company following the meeting (Appendix 1)

Attendees:

NICE

- Amy Barr
- Kimberley Carter

EAG (EAC)

- Susan O'Connell
- Ayesha Rahim
- Samuel Bird
- Simone Willis

Company

- Ganit Segal
- Sachin Gohil
- Cliff Bleustein

1. Welcome and introductions

The EAC and NICE had provided the list of queries to the company and the company provided detailed responses in advance of the meeting and these are reported in Table 1. The questions provided to the company centred around some key themes including:

- The technology
- Use of the technology
- Evidence and Benefits

The Technology (Table 1, questions 1-6)

Question 1) For clarity, can you confirm any different names for the technology which might come up in the literature?

> **NICE**: NICE checked whether the EAG needed any further information from the company regarding this query.
>
> **EAG**: The EAG were happy with names that may come up in the literature based on the information provided by the company prior to the meeting.

Question 2) Is the [redacted] included in the AposHealth system and are there any additional charges?

> **Company:** The company reiterated that the company currently includes a gait assessment tool in the proposed purchase price to be used by providers. The company has multiple partners of which [redacted] is just one example of a tool that may be provided by the company.

Question 3) Does the App require a specific device to run? If yes, is this device provided by the company or is this sourced by the user?

> **Company:** Stated that typically clinics use their own existing devices to run the app. The company emphasised that the [redacted] app, or gait analysis tool in general, is not necessary to use Apos and Apos can be easily used without a gait analysis app or tool.
>
> **NICE**: Queried how calibration is performed without use of gait analysis.
>
> **Company**: Advised that calibration of the device can be performed via clinical evaluation. There is a clinical decision tree which clinicians are trained to use to achieve calibration of Apos. 80% of the time, no changes are required after calibration. Patient feedback can inform any adjustments.

Question 4) Where is data collected on the app held, and who is able to access it?

> **Company:** Stated that the app can be set up so that it is compliant with GDPR. Currently the clinical data is collected anonymously and is stored on UK servers in an unidentifiable manner.

Question 5) Is the [redacted] App a CE marked medical device?

> **Company:** Stated that they would use a CE marked and compliant device. [redacted] are a separate company that Apos have a business arrangement with. The app is undergoing the process of getting a CE mark.
>
> **NICE**: Confirmed that the app will need a CE mark if it's being included as part of the recommendation.
>
> **EAG**: Queried if there was an expected timeline for the CE marking of the app.

Company: The timeline for this is not known in detail but the company expects it will be granted in the next few months. The company expressed that they are agnostic to the software used as the gait analysis tool. The company highlighted alternatives such as the iPhone Apple Health app. Confirmed that the economic model is based on the use of Apos with the [redacted] app but they do not feel the costs would change much if another app or software was used in its place.

NICE: Queried if the outcomes of AposHealth would be affected by the use of different methods of gait analysis.

Company: Stated that the company test the accuracy of software regularly. Emphasised that calibration is not solely dependent on the app but instead depends on the clinician's evaluation, patient history and subsequent adjustments made to the device.

NICE: Sought clarification on the CE marking class of Apos Health. The MIB and submission state Class IIA but documentation states Class I.

Company: Clarified that AposHealth is a non-invasive Class I device. Also an FDA Class I device. Stated that an administrative error led to the Class IIA description.

NICE: Confirmed that this error was replicated in the MIB and will be corrected.

EAG: requested clarification on whether AposHealth was going through UKCA process Company confirmed this was happening but no timelines available as yet.

Question 6) Can other gait analysis software/hardware be used alongside the AposHealth shoes? If yes, what are the requirements needed to be able calibrate the shoes?

NICE: Confirmed that all were satisfied that this had been covered in previous questions and from the company answers in the Table 1.

Use of the Technology (Table 1, questions 7-14)

Question 7) Could you clarify what computerised gait analysis is required during set up? Is this limited to the Apos Health [redacted] analysis using a mobile phone, or is there a requirement for a Gait lab and system? (If there is a need for a Gait lab, then does the NHS have capacity to meet this need?)

NICE: Confirmed that all were satisfied that this had been covered in previous questions and from the company answers in the Table 1. There is no absolute need for a gait lab.

Question 8) Are services expected to keep a stock of all the different sizes of shoes available?

NICE: Satisfied with company response in Table 1 but queried whether the home delivery service has extra costs associated with it.

Company: The home delivery service is not at an extra cost.

Question 9) I understand that the typical duration of treatment is one year. Is there an expectation that patients will retain the shoe at the end of that year and continue to use it? Do they normally receive follow up past this point?

NICE: Sought clarification on whether further calibration is required if the patient keeps the device after their 'course' of treatment.

Company: Stated that further calibration can be required. This is considered in the follow-up appointments built in to the pricing model.

Question 10) Are providers expected to have existing training in gait analysis at all?

NICE: Reiterated that this training is provided by the company.

Question 11) Is there an expectation around the amount of activity needed during the daily session using Apos Health device?

NICE: Stated that this has been discussed previously with the company and there is a helpful table in the scope about duration of wearing the shoes.

EAG: Sought clarification if there was any harm in wearing the shoes longer than the recommended times and where the recommendations come from.

Company: Clarified it is not dangerous; the times are specified to enable gradual adjustment of the muscles and joints to the devices.

Question 12) Is there any follow up training or assurance provided (after the initial 10 procedures) to ensure devices are being set up correctly?

NICE: Queried whether the follow-up training described by the company is free of charge.

Company: Confirmed it is free of charge.

Question 13) Although the indications exclude those people who have existing or documented history of falls or balance problems, is it possible that use of AposHealth may cause problems for people who have minor problems with balance, where this has not yet been identified?

NICE: Confirmed the company's answer provided was sufficient (see table 1).

Question 14) Is AposHealth only suitable for bilateral osteoarthritis?

Company: Reiterated that it is not only suitable for bilateral osteoarthritis; in the case of unilateral osteoarthritis, the both shoes would be worn and calibrated appropriately.

Evidence and Benefits ***(Table 1, questions 15-16)***

Question 15) How widespread is the use of AposHealth currently both within the NHS and private practice?

Question 16) Is there evidence around acceptability, compliance with daily use sessions and continued use over the one year period?

Additional comments relating to evidence: The company noted that manuscript by Green et al has been accepted for publication and is no longer AiC. EAG queried whether there was a publication date/timeline but this is not yet known. Company and EAG will follow-up on this as appropriate.

Concluding comments:

The EAG will email company if there are any further questions to be asked and clarified contacts for company related questions – company confirmed Ganit and Sachin were best to contact.

Appendix C: Questions for Clinical Experts

No.	EAG Question	Clinical Expert Response
The clinical pathway		
1	What would be considered 'treatment refractory'	
2	How long would a patient be managed non-surgically before surgical approaches are considered?	
3	The company has assumed two outpatients (one pre-surgery and one post-surgery) visits per patient having TKR. Do you agree with this? Can you provide us with any more clarification on patient care post-TKR surgery?	
The technology		
4	Is Apos Health unique in its design and/or mechanism of action?	
5	Are there any alternative devices currently being used?	
6	If so, how does their efficacy compare, and how would their use in the NHS compare to the use of AposHealth?	
Use of the technology		
7	If you have experience using AposHealth, can you describe the process of getting a patient set-up and any follow-up requirements.	
8	If using AposHealth, would gait analysis be a standard part of the assessment/validation of the device?	
9	What would you usually use in practice to measure/adjust gait? (e.g. Is it a software/app or just visual and physical examination?)	
10	Do you have experience of using Apos Health with [redacted]? How does this work?	
11	If so, do you have experience of using any other apps to measure gait, and how do they differ to [redacted]?	
12	What is compliance like amongst users of Apos Health? And how does it differ to those using standard care approaches?	
13	Are there any groups of patients you think would be unsuitable for treatment with AposHealth?	

No.	EAG Question	Clinical Expert Response
14	Other than the technology and use of the app, are there any other additional resources required when using AposHealth?	
Evidence and benefits		
15	Would users of Apos Health avoid total knee replacement altogether? Or is it more a method of delaying TKR?	
16	Are the long term outcomes (5+ years) for patients better with AposHealth, or the same as standard care?	

Appendix D: Clinical Expert Engagement Meeting Notes

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Clinical Expert Engagement Meeting
MTG570 AposHealth for osteoarthritis (OA) of the knee

This document summarises the discussions that took place at the AposHealth Expert Engagement meeting for MTG570, which took place on Tuesday 9th August 2022,13:00 to 14:30pm. A list of questions was shared with the clinical experts in advance of the meeting to allow them to prepare some responses where appropriate. Any questions which were not addressed during the course of the meeting have been noted at the end of this document and responses will be sought via e-mail.

Attendees:
NICE:

- Amy Barr
- Kimberley Carter
- Dionne Bowie
- Tara Chernick
- Helen Crosbie
- Rebecca Owens

EAG

- Susan O'Connell
- Ayesha Rahim
- Samuel Bird
- Megan Dale
- Simone Willis

Clinical Experts

- Alistair Shaw
- Adewale Adebajo
- Sue Field (Patient expert)

Welcome and introductions

NICE briefly introduced everyone on the call and outlined the format for the meeting. Discussion centred around some key topic areas including:

- The Clinical Pathway
- The technology
- Use of the technology
- Evidence and Benefits

The Clinical Pathway

- **What would be considered 'treatment refractory' in patients with knee osteoarthritis?**

One expert stated that this is difficult to define as different treatment providers will have different thresholds for what is considered refractory and there is no universal definition they are aware of. The Oxford Knee Score may be used to measure response to treatment. The same expert stated that they would define refractory as the failure of conservative management which includes all treatments prior to surgery recommended in the NICE OA management guidelines.

One expert stated that in their organisation, AposHealth sits in the pathway between conventional treatments and a referral to surgery. The criteria for being trialled on Apos in this expert's organisation is that a patient must have undergone at least one course of physiotherapy and potentially a cortisone injection or other forms of conservative management.

One expert expressed concerns that technologies such as AposHealth are not cost-saving as they are adding a new 'layer' of treatment to the existing pathway. Concerns were also expressed around the inability to predict who will and who will not respond to Apos which will have an impact on costs.

One expert agreed there is no real way to predict who will benefit the most from AposHealth.

- **How long would a patient be managed non-surgically before surgical approaches are considered?**

NICE sought clarification on how long is ideal for a patient to be managed non-surgically and what the reality of this period of management length was in practice.

One expert stated this varied geographically and was also dependent on an individual's tolerance of pain associated with the OA and their desire to avoid surgery.

The EAG added that the Royal College Guidelines (?) state 3 months of failed treatment must have elapsed before the patient is considered treatment refractory but it seems more patient-led in practice.

One expert queried what level of evidence the Royal College Guidelines were based on. The EAG did not have this information to hand.

NICE asked the patient expert to briefly describe their experience with treatment for knee OA. The patient expert stated they had bracing, physiotherapy and anti-inflammatories which settled the pain but did not eliminate it. The patient expert was offered cortisone injections. AposHealth was then offered to the patient expert after they learnt about the device from an acquaintance.

- **The company has assumed two outpatients (one pre-surgery and one post-surgery) visits per patient having TKR. Do you agree with this? Can you provide us with any more clarification on patient care post-TKR surgery?**

One expert agreed that two outpatient appointments was accurate, with one pre-surgery (a pre-op assessment) and one follow-up within 3 months. Further referrals may happen (to physiotherapy for example) but this is patient-dependant.

One expert emphasised that clarity should be sought regarding whether AposHealth is an alternative to surgery, delays surgery or makes surgery more effective.

NICE stated that the economic model does not use TKR as a comparator for AposHealth but rather an outcome. The comparator is standard care alone and the intervention is AposHealth in addition to standard care.

- **What is the current standard care pathway for knee OA?**

One expert stated that several treatments make up the standard care pathway including physiotherapy, exercise, cortisone injections, diet and weight management. The same expert stated that the earlier AposHealth is introduced, the better the outcomes could be.

The patient expert commented that AposHealth shoes are very heavy and would say that people with poor mobility would struggle to use them as it is hard-going on the muscles at the start. Good balance is also required to use the shoes.

NICE asked if there were any more queries from the EAG regarding the clinical pathway.
The EAG queried if the standard care pathway was stepped or if it is less rigid and if AposHealth is given on its own or in combination with other treatments.

One expert described the pathway as standard care first such as physiotherapy (after a GP referral), followed by referral back to the musculoskeletal service if not successful. Imaging may be performed before the next steps are discussed. AposHealth would be trialled for at least 12 months to determine if it is effective. Surgery is the last option.

The EAG sought clarification on the types of painkillers used to treat OA and whether imaging is always required prior to the use of AposHealth.

One expert stated that painkillers can include codeine, naproxen and/or paracetamol. Imaging is not always required as it can sometimes not be truly reflective of the severity of symptoms. Another expert agreed with the statement that there can be discordance between radiological presentation and the severity of symptoms experienced by the patient.

Use of the Technology

- **If you have experience using AposHealth, can you describe the process of getting a patient set-up and any follow-up requirements? If using AposHealth, would gait analysis be a standard part of the assessment/validation of the device?**

One expert stated that the set-up process would involve patient education about using the device, and a 90 minute session of setting up and calibration of the device. This is performed using an objective assessment, visual analysis and the OptoGait gait analysis system. Balance assessments may be conducted which can inform whether the patient will be suited to using Apos or not.

- **What would you usually use in practice to measure/adjust gait? (e.g. Is it a software/app or just visual and physical examination?)**

One expert stated that the OptoGait gait analysis system is used which involves a 6 metre long walkway. The same expert stated he was aware of a sensor-belt system being trialled by the AposHealth company.

NICE queried whether calibration could be done visually, without an app or software and whether this would be equivalent.

The expert stated that they could not comment on this. Technically AposHealth could be set up using visual and pain assessments, but gait analysis helps calibration and its accuracy.

The patient expert commented that they had gait analysis with OptoGait which identified a limp they were previously not aware of. The gait analysis was performed once every three months.

- **What is compliance like amongst users of AposHealth? And how does it differ to those using standard care approaches?**

One expert commented that compliance is good but there will always be a degree of non-compliance with these types of devices. There is the issue of 'over-compliance' where the user uses the device for more than the recommended time. On the whole, people are generally compliant with treatment.

One expert stated that it appeared as though compliance with AposHealth is better than in some standard care such as provision of exercise sheets.

NICE queried whether it is ever very obvious early on that a patient is not suitable for AposHealth. One expert stated that over time, identifying such patients has become easier e.g. identifying balance issues that may make AposHealth unsuitable.

- **Are there any groups of patients you think would be unsuitable for treatment with AposHealth?**

One expert stated that patients aged 82 or over may have less success with neuromuscular training. The expert also states that people with neurological conditions and people with general balance issue may also not be able to use the device.

- **Other than the technology and use of the app, are there any other additional resources required when using AposHealth?**

One expert stated that there were not any major additional resources required, other than the provision of additional exercises.

The patient expert stated that the pertupods on the shoes are changed quite frequently.

The EAG sought clarification on whether these are new pertupods or adjusted pertupods.

The patient expert confirmed they were new pertupods each time as the old ones get worn down.

The EAG queried what happens to the old pertupods.

One expert confirmed that the old pertupods are re-used if their condition is good, but they are disposed of otherwise. Around 50% are re-used and 50% are disposed of. The same expert confirmed that stock counts are done to identify if more pertupods are required (these are purchased separately).

The EAG queried whether standard physiotherapy departments in the NHS would have gait analysis facilities already or if they would need to be purchased for the use of AposHealth.

One expert stated they believe the departments would likely need to purchase the facilities/software as it is quite expensive. The use of apps is a cheaper option and is being introduced.

Evidence and Benefits

- **Would users of AposHealth avoid total knee replacement altogether? Or is it more a method of delaying TKR?**

NICE stated there is not enough long term data to answer this question.

One expert agreed and expressed that there is potential for AposHealth to result in surgery avoidance but this depends on a range of factors. Wear and tear in the joints is a natural and progressive process that AposHealth may slow down but it is a stretch to say it would eliminate the need for TKR completely.

One expert agreed and stated that the answer to this question is not known. It is highly unlikely that AposHealth will alter the physical degeneration within the knee joint but will instead result in symptom relief. This is the nature of OA in that structural degeneration is not reversible but can be managed.

NICE asked the patient expert how AposHealth had impacted on her mental health.

The patient expert stated that AposHealth has definitely helped her mental health as well as her physical health.

- **What is the impact of AposHealth on waiting lists? If a patient on a surgical waiting list was to receive AposHealth, would they be moved off the waiting list, or remain on it?**

One expert stated that guidance advised that a patient could not be on the waiting list for TKR and be receiving another active treatment such as AposHealth. However, this is not always the reality of what happens in practice (treatments do go on while patients are on the waiting list for TKR).

The EAG queried how long the waiting list for surgery is and whether AposHealth would be stopped if the patient goes onto the waiting list.

One expert stated that theoretically treatment would cease if the patient went onto the waiting list. The waiting list varies from 6 to over 12 months. Generally, patients keep their AposHealth devices whilst on the waiting list, and return them after surgery as the calibration would not be correct for the patient to use after surgery.

One expert stated that it would be surprising if patients accepted coming off the TKR waiting list in exchange for trying AposHealth.

Additional questions

A number of questions were not discussed during the meeting due to time constraints. These were circulated to the clinical experts for additional information and feedback.

- **Is AposHealth unique in its design and/or mechanism of action?**
- **Are there any alternative devices currently being used?**
- **If so, how does their efficacy compare, and how would their use in the NHS compare to the use of AposHealth?**
- **Do you have experience of using AposHealth with [redacted]? How does this work?**
- **If so, do you have experience of using any other apps to measure gait, and how do they differ to [redacted]?**
- **Are the long term outcomes (5+ years) for patients better with AposHealth, or the same as standard care?**

Appendix E: Responses from Clinical Experts not in attendance at Clinical Expert Engagement Meeting

Clinical Expert: Prof Toby Smith – Associate Professor in Physiotherapy – University of East Anglia

No.	EAG Question	Clinical Expert Response
The clinical pathway		
1.	What would be considered 'treatment refractory'	Persistent pain which cannot be managed through non-operative strategies and having an impact on disturbing activities of daily living, occupation and/or function.
2.	How long would a patient be managed non-surgically before surgical approaches are considered?	Usually, if the patient is treatment refractory, and has exhausted all non-surgical approaches, referral to a surgeon may be approximately 3 months of determining treatment refractory of non-surgical intervention…this is a shared decision with the patient but the 'discussion' could be made by this timescale.
3.	The company has assumed two outpatients (one pre-surgery and one post-surgery) visits per patient having TKR. Do you agree with this? Can you provide us with any more clarification on patient care post-TKR surgery?	Patients who are referred to primary care for surgical consideration would receive: 1. Pre-operative consultation on whether they should be considered for surgery and/or put on the surgical waiting list…then a pre-operative assessment before the operation…then the operation…and then a post-surgical follow-up appointment at 6 weeks post-TKR. Some trusts then follow their patients up at 6 months or 12 months post-TKR but this is not universal. Some patients (approximately 50%) will also receive out-patient physiotherapy (4 to 6 sessions) post-TKR admission.
The technology		
4.	Is Apos Health unique in its design and/or mechanism of action?	It is unique in its design. The principles are unique in the mechanism of action in principles although one may argue they are simply modifying the biomechanics.
5.	Are there any alternative devices currently being used?	Whilst orthotics may have a similar principles of use, they are a little difference. Accordingly I would probably argument this is unique and novel.

No.	EAG Question	Clinical Expert Response
6.	If so, how does their efficacy compare, and how would their use in the NHS compare to the use of AposHealth?	The efficacy is insufficient to state based on current evidence. I have yet to see compelling research to base the justification of use in the NHS (although I suspect that is the purpose of the assessment being undertaken here).
Use of the technology		
7.	If you have experience using AposHealth, can you describe the process of getting a patient set-up and any follow-up requirements.	I do not have experience if using AposHealth as the evidence-base (to my knowledge) is insufficient.
8.	If using AposHealth, would gait analysis be a standard part of the assessment/validation of the device?	I believe it would be and that would have a significant feasibility issue and cost implication.
9.	What would you usually use in practice to measure/adjust gait? (e.g. Is it a software/app or just visual and physical examination?)	Visual assessment i.e. no app or software but visual assessment as part of a physical examination.
10.	Do you have experience of using Apos Health with [redacted]? How does this work?	I do not have experience of using this.
11.	If so, do you have experience of using any other apps to measure gait, and how do they differ to [redacted]?	I have never used an App to measure gait.
12.	What is compliance like amongst users of Apos Health? And how does it differ to those using standard care approaches?	I do not use AposHealth and none of my colleagues do so I am unable to comment on compliance.
13.	Are there any groups of patients you think would be unsuitable for treatment with AposHealth?	Those with a falls risk. Those with marked morphological changes at their feet i.e. Rheumatoid arthritis patients. I would also be worried about people with multi-joint osteoarthritis (which is a large number of people in this population) and particularly spinal osteoarthritis where the change of biomechanics may have an implant on their other joint health. Evidence to reassure me of this would be helpful.
14.	Other than the technology and use of the app, are there any other additional resources required when using AposHealth?	I suspect there is a training requirement for those offering the technology. The requirement for space to do the assessment would also be require. Follow-up appointments to monitor and change the technology may also be required.
Evidence and benefits		

No.	EAG Question	Clinical Expert Response
15.	Would users of Apos Health avoid total knee replacement altogether? Or is it more a method of delaying TKR?	I suspect there may be a small number of patients who may avoid surgery but for the majority this would be a delay TKR or Unicompartmental Knee Replacement option.
16.	Are the long term outcomes (5+ years) for patients better with AposHealth, or the same as standard care?	I do not know of that evidence.

Clinical Expert: Ms. Robyn Hickey – First Contact Physiotherapist / Apos Certified Senior Physiotherapist – Circle Integrated Care

No.	EAG Question	Clinical Expert Response
The clinical pathway		
1.	What would be considered 'treatment refractory'	There should be significant improvement by 8 weeks, however, we usually suggest a 3 month trial prior to stopping treatment.
2.	How long would a patient be managed non-surgically before surgical approaches are considered?	3 months
3.	The company has assumed two outpatients (one pre-surgery and one post-surgery) visits per patient having TKR. Do you agree with this? Can you provide us with any more clarification on patient care post-TKR surgery?	Patient care post-TKR should include physiotherapy. Apos therapy would be an adjunct to physiotherapy to help with pain, stiffness, function and gait retraining.
The technology		
4.	Is Apos Health unique in its design and/or mechanism of action?	Yes
5.	Are there any alternative devices currently being used?	No
6.	If so, how does their efficacy compare, and how would their use in the NHS compare to the use of AposHealth?	
Use of the technology		
7.	If you have experience using AposHealth, can you describe the process of getting a patient set-up and any follow-up requirements.	In the current NHS structure at Circle Health there is a 90 minute initial appointment (Apos is custom calibrated and issued to the patient). They then have four 45 minute follow-up appointments for three years.

No.	EAG Question	Clinical Expert Response
8.	If using AposHealth, would gait analysis be a standard part of the assessment/validation of the device?	Yes
9.	What would you usually use in practice to measure/adjust gait? (e.g. Is it a software/app or just visual and physical examination?)	We use either Optogait track or an app called [redacted]. Physical adjustments are made to the Apos shoe to correct gait.
10.	Do you have experience of using Apos Health with [redacted]? How does this work?	Not yet, awaiting training. It is placed in the patient's pocked and linked to a smart phone device to measure their gait parameters.
11.	If so, do you have experience of using any other apps to measure gait, and how do they differ to [redacted]?	Optogait is a runway track on the floor that the patient walks down. It has lasers that pick up the placement of the feet to measure speed, step length and single limb stance %.
12.	What is compliance like amongst users of Apos Health? And how does it differ to those using standard care approaches?	There is an increased compliance, sometimes overcompliance to using Apos Health. As people feel better and less pain when wearing the shoes, they want to wear them all the time. We educate them to follow the treatment times so that the muscles are not overused/sore. Most people can tolerate wearing them all the time eventually which we progress to slowly to allow the body to get used to them.
13.	Are there any groups of patients you think would be unsuitable for treatment with AposHealth?	Patients who have high falls risk / poor balance, especially in addition to osteoporosis. Patients who are unable to put shoes on independently or do not have anyone to help them.
14.	Other than the technology and use of the app, are there any other additional resources required when using AposHealth?	No
Evidence and benefits		
15.	Would users of Apos Health avoid total knee replacement altogether? Or is it more a method of delaying TKR?	There is not any evidence to my knowledge of whether it is successful in avoiding or delaying the knee replacement as the results are from following patients for three years. Long term studies will be required to see the long-term benefits.
16.	Are the long term outcomes (5+ years) for patients better with AposHealth, or the same as standard care?	Unknown

Appendix F: Questions for Second Company Meeting

No.	EAG Question	Company response
1.	Please could you provide any available evidence that supports the 15% reduction in OA costs associated with use of APOS Health. Is this available in the public domain at all?	The assumption of a 15% reduction in healthcare cost utilization is based on several data sources, published and unpublished. First, an independent report by Truven Health Analytics (Supp H in the clinical submission Part 1, not published) demonstrated a significant reduction in opioids use, imaging, PT visits and OP office visits. The population comprised patients with moderate knee OA. With a more severe patient population, it is estimated that Apos will reduce other healthcare utilization (i.e., injections, braces etc) as well. Second, an internal (unpublished) member survey of a private UK insurer suggests a reduction in the utilization of health care services (Supp K in the clinical submission Part 1). For example, patients report a 72% reduction in consultant visits, 82% stopped/reduces OTC, 80% stopped/ use less prescribed medication, 78% stopped/use less NSAIDs, 86% stopped/use less injections, 83% stopped/use less Physiotherapy, 78% stopped/use less braces, 51% stopped/use less orthotics. Third, the published studies provide strong evidence of a statistical and clinically significant effect including a reduction in pain and increases in mobility and functionality, which correlates with a reduction in healthcare resource utilization. We acknowledge that Supplements H and K are unpublished and also that data from an NHS source would carry more weight. We have therefore adopted a very conservative estimate of 15%, but clearly the numbers from these datasets suggest a much larger reduction in healthcare usage.

2.	Please could you explain if there was a reason for using NHS Tariff prices rather than NHS Cost Collection values for knee replacement?	The submission document states "Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC)." On this basis, national tariff prices should surely be acceptable as a proxy for costs, and that we should in each instance choose the most relevant and robust source for cost estimation. All other things equal we would generally favour a cost, rather than a price estimate, but in these particular instances we believe that the tariff values are more appropriate as they focus discretely on the activity in question. We chose these inputs as we considered them the most robust. If reference cost values were used we would expect the savings from Apos to be higher. We chose NHS tariff prices rather than reference costs for primary knee replacement because the HRGs used for reference costs are likely to include activity other than primary knee replacement (and not all primary knee replacements may be grouped to these HRGs for costing purposes), whereas the tariff price published by the NHS is specific to primary knee replacement. The tariffs are, of course, derived from the reference cost collection. The tariff values are £6313 and £6624 in 2022-23 prices, dependent on complication and comorbidity level. The equivalent reference cost values are £6414 and £6766 in 2019-20 prices (£6951 and £7332 after inflation adjustment). As Apos averts knee replacement, the higher the cost of knee replacement, the greater the likely savings. Similarly, for rehabilitation post-discharge, the NHS tariff is specific to knee replacement, whereas the reference cost collection category is more general – rehabilitation for joint replacement - and is divided into sub-categories dependent on the level of complexity and whether the service is specialist or non-specialist. It is not possible to derive a specific knee-replacement cost estimate from published reference costs. As the tariff is the result of supplementary NHS analysis, informed by reference costs, to

No.	EAG Question	Company response
		estimate the costs associated specifically with knee replacement, we felt that it was a more robust and specific value. For outpatient attendances, again there are more discrete categories for tariffs than for reference costs. There are separate tariffs for first and follow-up attendances (£169 and £67 respectively for consultant-led single professional, Trauma and Orthopaedics Service). The equivalent reference cost value for 2019-20 was £123 per attendance (£133 after inflation adjustment). Again, we felt that the tariff values, derived from reference costs, were more specific and therefore likely to be a more robust foundation for the economic model.
3.	For Sanders did the value of 33.5% come from the graph, or another source?	Data is taken from the graph
4.	We would like to clarify the cost for additional pods that may need to be ordered at follow up appointments, and how this process works. Clinical experts advised that they may purchase these separately, but this is not included in the model.	There will be no additional costs associated with pod supply.

5.	We noted that there is additional information on rates of surgery for Knee OA. Would you please be able to provide full references for the sources listed.	We searched the document for un-cited sources and found the following: Page 54: *"Model inputs are derived from Greene et al., supplemented by additional NHS data and evidence from peer reviewed literature and expert opinion where necessary (Supp S). Overall, the model is based on hundreds of patients that were treated with AposHealth and demonstrated significant clinical improvements and very high surgery avoidance rates at two years, with preliminary data to support longer term outcomes (3.5 yrs.) to strengthen the 5-yrs assumptions"* Additional NHS data refers to sub-analysis that was done of Greene et al data set to provide additional information on: - Pre-covid surgery avoidance rates - Preliminary analysis on 3.5 years outcomes The analysis or raw data were not provided as supplements materials. Page 58: *"**Years 3-5*** *There is no published data on >3 years surgery avoidance. However, the model assumptions are based on extrapolation of the probabilities based on years 1-2. This approach is supported by unpublished long-term follow-up data for the Greene et al. cohort, which shows lower TKR probabilities beyond year 2 which are lower than those used in the model. Sensitivity analysis was performed to accommodate for the uncertainties.* *Long-term analysis of Greene's cohort data suggests a TKR rate of 6.3%, 9.9%, 6.1%, 4.5% for year 1, year 2, year 3 and year 3.5, respectively (Figure 2).* *Longer term results from this NHS setting show a reduction in TKR rates each year after year 2 (6.1 and 4.5% respectively). This is reflective of those who responded well to treatment and either self-managing or remain actively*

		attending follow-ups appointments to maintain results. *It is acknowledged that COVID-19 would have had an effect on surgery rates, but in the pre-covid cohort analysis, TKR rates were comparable up to 2 years. It is also likely that most patients that stopped treatment during the study time period (Nov 2017 – Nov 2019) and wished to access TKR surgery would have had enough time elapsed to access surgery prior to the analysis by Greene et al. (November 2021)."* This section refers to the sub-group analysis that was done on Greene et al dataset. Results are also summarised in figure 2. The data set of the sub-group analysis is internal and unpublished and was not provided in the supplementary materials. Page 60: *"The model assumes that patients cannot undergo a second TKR in the model in the first 6 months after receiving a first TKR. The 5-year probability from Sanders is therefore converted to a monthly probability over 4.5 years and this is applied in the model from month 7 after a first TKR. (It is noted that in Sanders, a large number of patients received bilateral TKR surgery (both knees at once). This was not modelled as in the UK, bilateral surgery accounts for only 1% of TKRs (National Joint Registry)."* For clarification purposes, we used the NJR 18th annual report 2021 (NJR 18th annual report) Page 65: *"…For this reason, we performed a sub-group analysis and looked at patients that were enrolled until April 2018 to allow completion of 2-yrs (free of Covid-19 effect). 86 patients were included in this analysis to present pre-covid 2-yrs surgery avoidance (9.3% in year 1 and 11.6% in year 2). This is accounted for in the sensitivity analysis"*

		As mentioned above, this is an internal, unpublished, sub-group analysis based on Greene et al. data to address any concerns regarding the impact of covid-19 on surgery rates. Page 70: *"In addition, we expect a 15% reduction in standard care costs excluding TKR (i.e. £1,286.63 for the standard care arm annually falling by 15% to £1,093.64)."* The assumption of a 15% reduction in healthcare cost utilization is based on a few data sources, published and unpublished. An independent report by Truven Health Analytics (Supp H in the clinical submission, not published). An internal (unpublished) member survey of a private UK insurer on the utilization of health care services (Supp K in the clinical submission). Peer-reviewed published studies that provide strong evidence of a statistical and clinically significant effect including a reduction in pain and increases in mobility and functionality, which correlates with a reduction in healthcare resource utilization. Page 90: "*Some uncertainty with long-term surgery avoidance (years 3-5) due to lack of published evidence. We believe, however, that the internal data on file and the preliminary results of the Greene et al., population provide support to our assumption and that most likely, the sensitivity analysis will account for this uncertainty."* Internal data on file refers to unpublished data on long-term surgery avoidance outcomes. Supp J was included in the clinical evidence submission (part 1). A summary of a 5-yrs follow-up that is an extension of the published 2-yrs outcomes of Bar-Ziv et al 2013, suggests that 15% of patients that were treated with AposHealth have had a TKR (85% surgery avoidance) compared to 45% of patients that received the standard of care (55% surgery avoidance). In additions, preliminary,

No.	EAG Question	Company response
		unpublished data from Greene et al., suggest a 21% surgery rate at 3.5 years. These were not included in the model, however they provide support to the model assumptions. As mentioned, we believe the sensitivity analysis will account for this uncertainty. We are happy to clarify additional missing references. Please advise if we have missed anything else.

Appendix G: Notes from Second Company Meeting

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Company Second Meeting
MTG570 AposHealth for osteoarthritis (OA) of the knee

This document summarises the discussions that took place at the company post clinical submission meeting for MTG570, which took place on Wednesday 31st August 2022,13:00 to 14:00pm.

Attendees:

NICE

- Amy Barr
- Kimberley Carter
- Dionne Bowie
- Lee Berry
- Chris Chesters
- Rebecca Owens

EAG (EAC)

- Susan O'Connell
- Ayesha Rahim
- Samuel Bird
- Simone Willis
- Megan Dale
- Rhys Morris

Company

- Ganit Segal
- Sachin Gohil
- Cliff Bleustein

2. Welcome and introductions

The EAC and NICE had provided the list of queries to the company and the company provided detailed responses in advance of the meeting and these are reported in Table 1. The questions provided to the company centred around some key themes including:

- Health economic model
- Evidence and Benefits

Health Economic modelling (Table 1, questions 1-5 plus additional question 6)

Question 1) Please could you provide any available evidence that supports the 15% reduction in OA costs associated with use of AposHealth. Is this available in the public domain at all?

> **NICE**: NICE checked whether the EAG needed any further information from the company regarding this query.
>
> **EAG**: The EAG were happy with the information provided

Question 2) Please could you explain if there was a reason for using NHS Tariff prices rather than NHS Cost Collection values for knee replacement?

> **NICE**: NICE checked whether the EAG needed any further information from the company regarding this query.
>
> **EAG**: The EAG were happy that the decision had been explained clearly, although the EAG normally prefer to use Reference Costs.

Question 3) For Sanders did the value of 33.5% come from the graph, or another source?

> **NICE**: NICE checked whether the EAG needed any further information from the company regarding this query.
>
> **EAG**: The EAG were happy with the information provided

Question 4) We would like to clarify the cost for additional pods that may need to be ordered at follow up appointments, and how this process works. Clinical experts advised that they may purchase these separately, but this is not included in the model.

> **NICE:** is there a limit to provision of additional supplies?
>
> **Company:** Stated that they would expect patients to go through 3 sets of pods through a lifetime, depending on clinician, but that there was no limit.
>
> **EAG:** Asked for clarification that within the NHS all items would be included in the initial cost of the shoes for the duration of treatment?
>
> **Company:** Stated that this was correct

Question 5) We noted that there is additional information on rates of surgery for knee OA. Would you please be able to provide full references for the sources listed.

EAG: Clarified that this was referring to supplement J in the submission supplementary materials.

Company: Stated that the current publication that is under review is expected to in public domain in the next couple of weeks. They will upload the Millman report to NICE, but noted that it is confidential and cannot be released externally.

Additional questions for health economics:

Question 6: Could you explain if you looked at a longer model time horizon?

Company: Explained that they had solid evidence for years 1 and 2, with less concrete evidence for subsequent years up to 5 years. They can be quite confident with 2 years, and then project to 5 year modelling. They stated that there was no data over 1 year duration for other treatments.

NICE: Explained that the committee will often ask for a longer time horizon, and we will need to consider that in the assessment report.

Additional questions for evidence base:

Question 7: For the 2 papers by Bar-Ziv, can you clarify if they contain the same patients?

Company: Yes. Originally the study was a 2 month study randomising into two groups: Apos and a sham. After 2 months it was unblinded and patients could cross over, creating a new baseline. So there is a first phase report (2010) and also a 2 year follow up (2013) that started following the cross over opportunity, with no matched control and different sample sizes.

Additional question 8-10: EAC queries about the different supplements G, H and K:

Question 8. Re. Supplement G, is this study underway/complete, is it registered anywhere?

Company: This is currently recruiting. It is not registered, but we can reach out to the researchers. Completion date is the end of this year.

Question 9. Re. Supplement H – Is this a study on Apos data, and is it published?

Company: It looks at pre and post Apos data for 12 months. It was carried out by an external company.

EAG: Is it a study that you commissioned them to do?

Company: Yes, Truven is part of IBM, they obtained data from providers and did the analysis completely independently. There are no plans to publish it, as the data is confidential.

EAG: Should it be marked as confidential in the assessment report?

Company: Reporting the change in before and after outcomes is fine, but pricing should not be reported.

EAG: if we use any of it we'll highlight and you can remove if not needed.

Question 10. Re. Supplement Supp K and NHS Audit. Can you explain a bit more about how data was collected? Are there any plans to publish?

Company: BUPA – this was a members survey. BUPA did their own survey, initiated and carried out by them, but they shared the report with us. There are no plans to publish them.
NHS audit – Based on a KPI list agreed with Apos and the CCG in question. Measuring patient satisfaction at specific points. There are no publications planned.

EAG: we are mindful of confidentiality with these unpublished supplements.

Company: results are fine, name of the payor should be confidential

Additional discussion

Company: queries about MTAC

NICE: ran through process.

NICE National Institute for Health and Care Excellence

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Pro-forma Response

External Assessment Group Report factual check

AposHealth for osteoarthritis (OA) of the knee

Please find enclosed the assessment report prepared for this assessment by the External Assessment Group (EAG).

You are asked to check the assessment report from Cedar to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by close of business, **Wednesday 28th September 2022** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAG and when appropriate, will be amended in the EAG report. This table, including EAG responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

28th September 2022

General Comments on EAG Report

AposHealth thanks the EAG for the opportunity to submit our clinical and economic evidence and their review of our innovation. We were pleased that the EAG acknowledged the following:

- Overall, the EAG believes there is potential for AposHealth to be an effective treatment in particular subgroups of knee OA patients, as patient-reported outcomes show high levels of satisfaction and significant symptom relief as a result of AposHealth intervention
- More specifically, the EAG recognises there is potential for AposHealth to be effective at delaying surgery for people who do not wish to or cannot undergo surgery when it is the recommended treatment option.
- The EAG are satisfied that there are no significant safety concerns for AposHealth
- The EAG acknowledged the positive appraisals of both clinicians and patients
- Generally, the EAG agrees that the company have made conservative assumptions throughout the economic model and accepted most of the assumptions.
- The EAG and company models both demonstrate significant cost savings at 5 years, and, although there are some differences in the models, essentially cost neutral or accretive at 10 years based on conservative assumptions.

We would like to highlight some factual errors and seek to clarify rationale from the EAG. We have used the proforma below to provide justification. The main themes of the issues raised are:

- The exclusion of the second study on surgery avoidance - Drew *et al*.
- The comparison of AposHealth to standard care - clarifications on the two studies conducted with a sham device.
- The addition of the cost of a computerised gait analysis system into the EAG economic model
- Extending the economic model out to 20-yrs - accounting for a reduction in TKR rates with ageing.
- Comparison to other biomechanical interventions - clarifications on the inherent differences between AposHealth and other biomechanical interventions.

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
Table 3 [Page 18] "Of the 17 studies included in the company submission, the EAG excluded 1 as the comparator was surgery and therefore not in scope (Drew *et al* 2022)" [Page 19] "EAG includes surgery avoidance as the primary outcome (Greene Unpublished)." [Page 47]	The study from Drew *et al*. was excluded as the EAG states that the comparator is surgery and that the study is therefore out of scope. TKR is an outcome measure in this study, not a comparator, and we consider the study relevant and within scope. Drew *et al*. provides significant additional support to the claim of surgery delay/avoidance. Drew *et al*. looked at surgery avoidance among patients who have tried and failed standard care interventions, met surgical criteria and were recommended a TKR (similar to Green *et al*., 2022). Those patients were recommended with AposHealth as a non-surgical intervention and were treated for 2 yrs. 86% of the patients avoided surgery at 2-yrs (compared to 84% in Greene *et al*.). In order to ground those results, the researchers looked at a similar group of patients (patients who have tried and failed standard care interventions, met surgical criteria and were recommended a TKR) that were not treated with AposHealth. In	Drew *et al*., abstract: "…. Our study shows how a home-based, noninvasive biomechanical intervention reduced the rate of progression to surgery for a cohort of 237 patients with knee OA deemed eligible for TKR based on pre-established clinical selection criteria. Over the 24-month study period, 204 patients (86%) avoided surgery, with only 33 patients (14%, 95% confidence interval 82%–91%) progressing to a TKR with an average length of time to TKR of 324 days (ranging from 31 to 671 days). The application of this intervention provides health plans and provider networks managing patient care under financial risk arrangements an opportunity to realise significant cost savings without compromising quality of care or clinical outcomes."	

	this group of patients, 88% proceeded with TKR in the first 2 yrs. In the economic model, we chose a conservative annual decay rate of 33% based on a UK population (instead of Drew *et al's* finding of 88% at 2-yrs) The reference to Greene *et al* being "unpublished", we would like to amend this to read "accepted for publication in the Journal of Orthopeadic Experience and innovation", as this will be available prior to publication of the final report.		

Issue 2

Description of factual inaccuracy	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
There is a lack of evidence comparing AposHealth to non-surgical standard care treatment options such as manual therapy, walking aids, and intra-articular corticosteroid injections and their respective impacts on pain and function. Additionally, there is a lack of evidence relating to the outcome of TKR surgery delay or avoidance	We propose the text is amended such that the following is acknowledged: There is evidence to support superiority of AposHealth compared to active controls (patients that follow a daily walking programme). In addition, there is evidence on the long-term clinical effect and surgery avoidance in patients with knee OA that have failed all other non-surgical interventions, were eligible for TKR and were treated with	Reichenbach et al. and Bar-Ziv *et al*. compared Apos to a sham device. Those patients allocated to a sham device arm were required to follow the same exercise program (i.e. daily walking with the device). Therefore, in practice, the control group was essentially an **active** (i.e. exercise) control group.	

and in general there is a lack of long-term follow-up data. This is a key gap in the evidence and has a particular impact on the economic assessment. [Page 8]	AposHealth. However, more evidence on TKR surgery delay or avoidance beyond 2 years is needed. This has a particular impact on the economic assessment.	Current NICE OA management guidance recommends exercise as a first-line treatment (together with weight loss, education and self-management). In addition, in Bar-Ziv *et al*, patients in both arms continued to incur other treatment modalities, i.e. reflecting standard care, albeit not reported in the manuscript. We believe that long-term evidence does exist for avoidance of TKR for AposHealth as demonstrated by Drew *et al*, Bar-Ziv *et al* and Greene *at al*. There is however a lack of data beyond 2 years for which we would urge the EAG to specify in the executive summary.	

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
Table 4, page 22 Drexler (2012)	Change to: N=654 (instead of N=250)		

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
Table 4, page 24 Elbaz (2014)	Change to: Setting: APOS Therapy Center in Singapore. (Instead of AposTherapy Center in Israel)		

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
Typographical error [Page 49]	"…determine its relative effectiveness"	"…determine is relative effectiveness"	

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
"The EAG accepts that AposHealth can be used with a variety of gait analysis tools, and is not limited to use with a particular system. However, the EAG is of the opinion that NHS providers would have to purchase additional gait analysis tools in order to use AposHealth as designed, as advised by clinical experts." [Page 52]	The EAG accepts that AposHealth can be used with a variety of gait analysis tools, and is not limited to use with a particular system. We also propose that any mention to purchasing OptoGait gait analysis is removed, as this is inaccurate.	The EAG opinion that NHS providers would need to purchase additional gait analysis tools is incorrect and unfounded. The company provides access to mobile-based gait technology at no additional cost. This gait technology has been validated with AposHealth and requires less space than other systems (for example OptoGait). As per our letter to the EAG, following our meeting on 31 August 2022, we reiterate that computerised gait analysis is not essential to be able to calibrate the Apos device and it does not feature as a pre-requisite included in our CE mark. Calibration can be completed by	

		understanding patient responses to questions on their condition, a visual gait analysis (which is taught as part of the training) and patient feedback in terms of pain and function. We would urge the EAG to remove the cost of gait analysis from the economic model and conclusions drawn thereof.	

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
Extension of time horizon to 20 years [Page 82] Application of TKR rate over an extended time period	The company acknowledge that the EAG extended the economic model out to 20 yrs. With this in mind, we believe that although a conservative approach was used in a 10-yr model, surgery rates should be amended when extending the model out to 20-yrs. The rates of TKR decrease as age increases and a 20-year model should account for that. For example, PROMs data indicate that the annual probability of TKR at age 85+ is approximately 64% lower than the probability at age 70-74.	https://digital.nhs.uk/data-and-information/publications/statistical/patient-reported-outcome-measures-proms/finalised-hip-and-knee-replacement-april-2019---march-2020	

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
Typographical error [Page 88]	Potential cost savings in the economic model are from avoiding TKR surgery	Potential cost savings in the economic model are from avoiding *TRK* surgery	

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
Typographical error [Page 88]	Currently, the case for adoption is	Currently, the case for adoption *in*	

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAG response
"The EAG believes that additional research is needed to support the adoption of AposHealth into the NHS. This is in alignment with the draft NICE guideline for the management of osteoarthritis	The EAG believes that additional research is needed to support the adoption of AposHealth into the NHS. It must be noted that the draft NICE guideline for the management of osteoarthritis (expected publication October 2022), which recommends that further	Two main considerations and clarifications should be acknowledged: 1. The NICE Guideline update was conducted before AposHealth was subject to 2	

(expected publication October 2022) which recommends that further research is needed to determine any benefit from shoes (such as AposHealth) as an intervention for knee OA. The draft guideline also states that devices such as insoles, braces, tape, splints or supports should not be routinely offered to people with osteoarthritis due to a lack of evidence behind their efficacy." [Page 89]	research is needed to determine any benefit from devices such as AposHealth as an intervention for knee OA, was written before additional evidence was published. The draft guideline states that devices such as insoles, braces, tape, splints or supports should not be routinely offered to people with osteoarthritis due to a lack of evidence behind their efficacy. AposHealth has a different mechanism of action to the devices above and therefore should not be categorised as such	new peer-reviewed long-term publications demonstrating the clinical efficacy and surgery avoidance at 2-years (Drew *et al.* 2022, Greene *et al.* 2022). Those are important when evaluating the effect of the intervention. 2. Guideline committee has mis-categorised AposHealth in the same group as insoles, splints and braces. This was also the FDA point of view when evaluating Apos as a 510(k) Medical Device. Specifically, The AposHealth was FDA cleared a 510(k) Medical Device. The predicate for the device was substantially equivalent to 21 C.F.R. 890.3475 which is the regulation for limb orthosis. The FDA created a new product code designation to represent a product that was differentiated from other limb orthosis. There is an inherent difference in the mechanism of action between Apos and other	

		biomechanical interventions (insoles, braces, tape, splints or supports etc). More specifically, the current biomechanical interventions are static devices aimed to reduce loads from the painful joint to alleviate pain. Usually, those are off-the-shelf products or a one-time set-up with no additional adjustments or follow-up. Apos is a dynamic intervention. It uses COP manipulation to shift loads from painful areas of the joint to alleviate pain. However, unlike other biomechanical devices, the unique curved pod at the bottom of the shoes creates perturbation that induces neuromuscular training. Moreover, patients receive a treatment plan that includes daily walking with the device while doing everyday activities at home or work. Patients are also advised to return to follow-up appointments for re-calibration of the device	

		based on clinical needs to optimise the therapeutic effect. Shifting forces to alleviate pain, training neuromuscular control, and daily, task-specific rehabilitation (thousands of gait repetitions) leads to new motor pattern and a carry-over effect even without the device (unlike any other biomechanical intervention).	

Issue 11

Description of factual inaccuracy	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Executive summary [Page 8] Both the company's submitted model and the EAG base case are cost saving for AposHealth at 5 years, and the company's 10-year model is also cost saving. However, the EAG base case becomes cost incurring at 10 years, and this continues when the model is extended to 20 years.	We provide two potential options for amended wording below: Option 1: Both the company's submitted model and the EAG base case are cost-saving for AposHealth at 5 years, and the company's 10-year model is also cost-saving. However, the EAG base case becomes cost-incurring at 10 years by -£46, and this continues when the model is extended to 20 years.	Generally, the EAG agrees that the company has made conservative assumptions throughout the economic model and has accepted most of the assumptions used in the company's model. With the current conservative assumptions, as acknolwdged by the EAG, the 10-yrs model is cost effective, or cost neutral in the worse case. However, with some changes to the assumptions (i.e. less	

	Option 2: "The EAG and company models have some differences, but have approximately similar findings at 5 and 10 years."	conservative) savings are substantially higher. We believe this should be highlighted in the executive summary paragraph after stating that the model in incurring at 10-yrs. (by -£46). Alternatively, we suggest replacing the sentence with a different one that the EAG wrote later in the document: "The EAG and company models have some differences, but have approximately similar findings at 5 and 10 years."	

Issue 12

Description of factual inaccuracy	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
The positioning of AposHealth in the care pathway for osteoarthritis is unclear. [Page 50]	The company suggest the following definition of eligible patients: Patients with severe knee OA who have been referred for possible TKR	Several long term studies, including current practice demonstrates clearly the pathway for AposHealth This is similar to Greene *et al* inclusion criteria: patients with knee OA deemed eligible for	

		TKR based on pre-established clinical selection criteria	