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Health Technology Assessment (HTA)

HTA Scoping Report

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Executive Summary

Osteoarthritis is a common chronic disease that causes joint stiffness and pain, most commonly in the hips, knees and hands. Chondroitin sulfate (CS) is a symptomatic slow-acting drug (SYSADOA) used to treat joint pain in osteoarthritis. Despite being used in Switzerland since the 1980s, there is ongoing debate around its clinical effectiveness. The aim of this report is to determine the feasibility of conducting a Health Technology Assessment (HTA) of CS in patients with osteoarthritis based on the clinical data identified during the scoping phase.

The objective of the HTA is to compare the safety, efficacy and effectiveness of CS to placebo, on-demand analgesics and anti-inflammatory treatments in patients with osteoarthritis of the hands, knees and hips. In addition, the cost-effectiveness and budgetary impact of CS warrants investigation. A systematic literature search was conducted in eight biomedical databases, as well as clinical trial databases and specialty websites. From 2,916 search results, 20 randomised controlled trials were suitable for inclusion. Further studies were identified as potentially relevant containing information on economic, legal, social and/or ethical aspects. No existing economic models were identified that are generalisable to the Swiss context. It is suggested that a *de novo* model be developed should a full HTA report be commissioned. The database searches identified limited data with respect to CS-related social, ethical, legal and organisational aspects.

The conclusion of the scoping report is that there is sufficient clinical data in terms of clinical effectiveness and safety for knee osteoarthritis, less so for hip and hand osteoarthritis, in patients with moderate symptomatic disease to conduct a HTA of CS. The identified data regarding economic, legal, social, ethical, legal and organisational aspects related to CS consumption was limited. In a HTA the search for more data is foreseen.

Zusammenfassung

Osteoarthrose ist eine chronische Erkrankung, die zu Gelenkversteifungen und Schmerzen vor allem in den Hüften, Knien und Händen führt. Chondroitinsulfat (CS) ist ein symptomatisch wirkendes Arzneimittel (SYSADOA), das bei der Behandlung von Gelenkschmerzen bei Osteoarthrose eingesetzt wird. Obwohl es in der Schweiz seit den 80er Jahren verwendet wird, ist die Diskussion über seine klinische Wirksamkeit anhaltend. Ziel dieses Berichts ist es, die Durchführbarkeit eines Health Technology Assessments (HTA) von CS für Patienten mit Osteoarthrose anhand der in der Scoping-Phase identifizierten Daten zu untersuchen.

Das Ziel des HTA ist die Sicherheit und Wirksamkeit von CS zu vergleichen mit jenen der Placebo, Schmerzmitteln nach Bedarf und entzündungshemmenden Medikamenten in der Behandlung von Patienten mit Hand-, Knie und Hüftosteoarthrose. Darüber hinaus werden auch die Wirtschaftlichkeit und die budgetären Auswirkungen von CS untersucht.

Eine systematische Literaturrecherche wurde in acht biomedizinischen Datenbanken sowie in den Datenbanken für klinische Versuche und auf fachspezifischen Websites durchgeführt. Von den 2,916 Suchergebnissen waren 20 randomisierte Kontrollstudien für die Auswertung geeignet. Weitere Studien wurden aufgrund wirtschaftlicher, rechtlicher, sozialer und/oder ethischer Daten als potentiell relevant bewertet. Es fanden sich keine ökonomischen Modelle, die sich verallgemeinernd auf die Situation in der Schweiz übertragen liessen. Wir schlagen deshalb vor, ein *de novo* Modell zu entwickeln, falls ein umfassender HTA-Bericht in Auftrag gegeben werden sollte. Bei der Auswertung der Datenbanken wurden begrenzt soziale, ethische, juristische und organisatorische Aspekte identifiziert.

Für Patienten mit moderaten Osteoarthrose-Beschwerden finden sich ausreichend klinische Daten in Bezug auf Knieosteoarthrose, um eine HTA-Evaluierung von CS durchzuführen; eine beschränkte Datenlage besteht für Hüft- und Handosteoarthrose. Die verfügbare Datenlage für wirtschaftliche, soziale, ethische, juristische und organisatorische Aspekte im Zusammenhang mit dem CS-Verbrauch ist begrenzt und muss in einer HTA-Bewertung erweitert werden.

Synthèse

L’arthrose est une maladie chronique qui cause une raideur des articulations, accompagnée de douleurs. Le plus souvent, elle affecte les hanches, les genoux et les mains. Le sulfate de chondroïtine (SC) est un médicament utilisé pour traiter symptomatiquement les douleurs articulaires liées à l’arthrose (anti-arthrosique symptomatique d’action lente, AASAL). Bien qu’utilisé en Suisse depuis les années 1980, le débat concernant son efficacité clinique reste d’actualité. Le but de ce rapport est de déterminer si une évaluation des technologies de santé (ETS) est faisable pour le SC prévu pour des

patients souffrant d'arthrose, et ce, en se basant sur les données identifiées durant la phase exploratoire (de *scoping)*.

L'objectif de l'ETS est de comparer, chez des patients souffrant d'arthrose des mains, des genoux et des hanches, la sécurité, l'efficacité et l'efficience du SC avec celles d'un placebo, de traitements analgésiques sur demande ainsi que d'anti-inflammatoires. À cela s'ajoute l'étude de l'économicité et l'impact budgétaire du SC.

Une recherche systématique dans la littérature a été conduite dans huit bases de données biomédicales, des bases de données d'essais cliniques et des sites internet spécialisés. Sur 2'916 résultats de recherche, 20 essais randomisés contrôlés se prêtaient à une évaluation. D'autres recherches ont été repérées comme étant potentiellement pertinentes en raison de données économiques, légales, sociales ou éthiques. Par contre, aucun des modèles économiques ne paraît transposable au contexte suisse. Aussi serait-il recommandable de développer un nouveau modèle si un rapport complet d'ETS était commandé. Les recherches dans les bases de données ont permis d'identifier un nombre limité d'aspects sociaux, éthiques, juridiques et organisationnels liés à cette thématique.

Pour les patients présentant une arthrose du genou symptomatique modérée, il existe suffisamment de données sur l'efficacité clinique et la sécurité pour réaliser une ETS du CS ; pour l'arthrose de la hanche et de la main, il en existe moins. Les bases de données disponibles sur les aspects économiques, sociaux, éthiques, juridiques et organisationels liés à la prise de CS étaient limitées et devront être étendues dans une évaluation ETS.

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Abbreviations and Acronyms

AE	Adverse Events
AUSCAN	Australia/Canadian osteoarthritis hand index subscale
CAM	Complementary and Alternative Medicines
CMA	Cost-Minimisation Analysis
CS	Chondroitin Sulfate
CUA	Cost-Utility Analysis
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Disease
EULAR	European League Against Rheumatism
EUnetHTA	European Network for Health Technology Assessment
FIHOA	Functional Index for Hand OsteoArthritis
fMRI	functional Magnetic Resonance Imaging
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire-Disability Index
HTA	Health Technology Assessment
HUI	Health Utility Index
ICER	Incremental Cost-Effectiveness Ratio
MeSH	Medical Subject Headings
NICE	National Institute for Health and Care Excellence
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug

OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology
PICO	Patients, Intervention, Comparator, Outcome
QALYs	Quality-Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
SF-12/36	Short Form-12/36
SYSADOA	SYmptomatic Slow-Acting Drugs for OsteoArthritis
VAS	Visual Analogue Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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Objective of the HTA Scoping Report

The Federal Office of Public Health (FOPH) is reviewing the public reimbursement of chondroitin sulfate for the treatment of symptomatic osteoarthritis in the hips, knees and hands. This topic was selected for a Health Technology Assessment (HTA) based on questionable clinical effectiveness of the drug compared to other available osteoarthritis treatments.

The process to evaluate health technologies involves multiple phases: 1) the pre-scoping phase, 2) the scoping phase, and 3) the HTA phase. This document represents the outcome of the scoping phase.

In the scoping phase, a health technology is examined, and a central research question is presented based on a systematic review of the literature. In addition, sub-questions are formulated, to determine the full scope of the HTA report. The target population, the appropriate comparator and the relevant health outcomes are defined.

The systematic literature search strategy directs the amount and types of studies generated during the extraction. Based on quantity and quality of the extracted evidence it is decided whether an HTA report is commissioned. An analysis of the individual study outcomes is the objective of the HTA.

1. Medical Background

Osteoarthritis is a degenerative joint disease, and a leading cause of disability in older adults worldwide. It affects joint cartilage resulting in pain, stiffness, tenderness, swelling and impaired movement. Hip, knee, and hand joints are most commonly affected.[1-3] The European League Against Rheumatism (EULAR) recommendations define knee osteoarthritis as having multifactorial aetiology.[4] The condition can be contracted via intrinsic risk factors (aging, sex, obesity, heredity & reproductive variables) and extrinsic risk factors (trauma, alignment, occupational & recreational usage). There is also a significant genetic component to the prevalence of knee osteoarthritis.

Osteoarthritis of the knee manifests in different severities or grades, and most patients progress through these grades as the disease progresses. From minor to severe osteoarthritis the severity of cartilage damage/loss, osteophyte growth, joint space narrowing, pain/inflammation increases from almost imperceptible to a near disabling. Patients in the severe group will usually be considered for surgery.[5]

The incidence and prevalence of osteoarthritis in Switzerland could not be ascertained via published literature. However, across seven other European Union member states, the self-reported prevalence of osteoarthritis in 2008-2009 varied from 1.5 per cent (males) and 4.5 per cent (females) in Romania, to 18.6 per cent (males) and 23.8 per cent (females) in Hungary.[6]

A 2010 global burden of disease study reported that, on a global scale, approximately 10 to 15 per cent of adults aged over 60 years have osteoarthritis, with the prevalence higher among women than men.[7] Hip and knee osteoarthritis was ranked as the 11th highest contributor to global disability. The global burden of disease attributable to osteoarthritis is increasing, with total disability-adjusted life-years associated with osteoarthritis rising by 35 per cent from 1990 to 2015.[7]

The primary symptoms of osteoarthritis are joint pain, stiffness and loss of function. Osteoarthritic pain can be most prevalent in the morning, following periods of physical exertion or extended standing. Pain becomes persistent at later stages of the disease, and is mostly apparent during movement and use.[8]

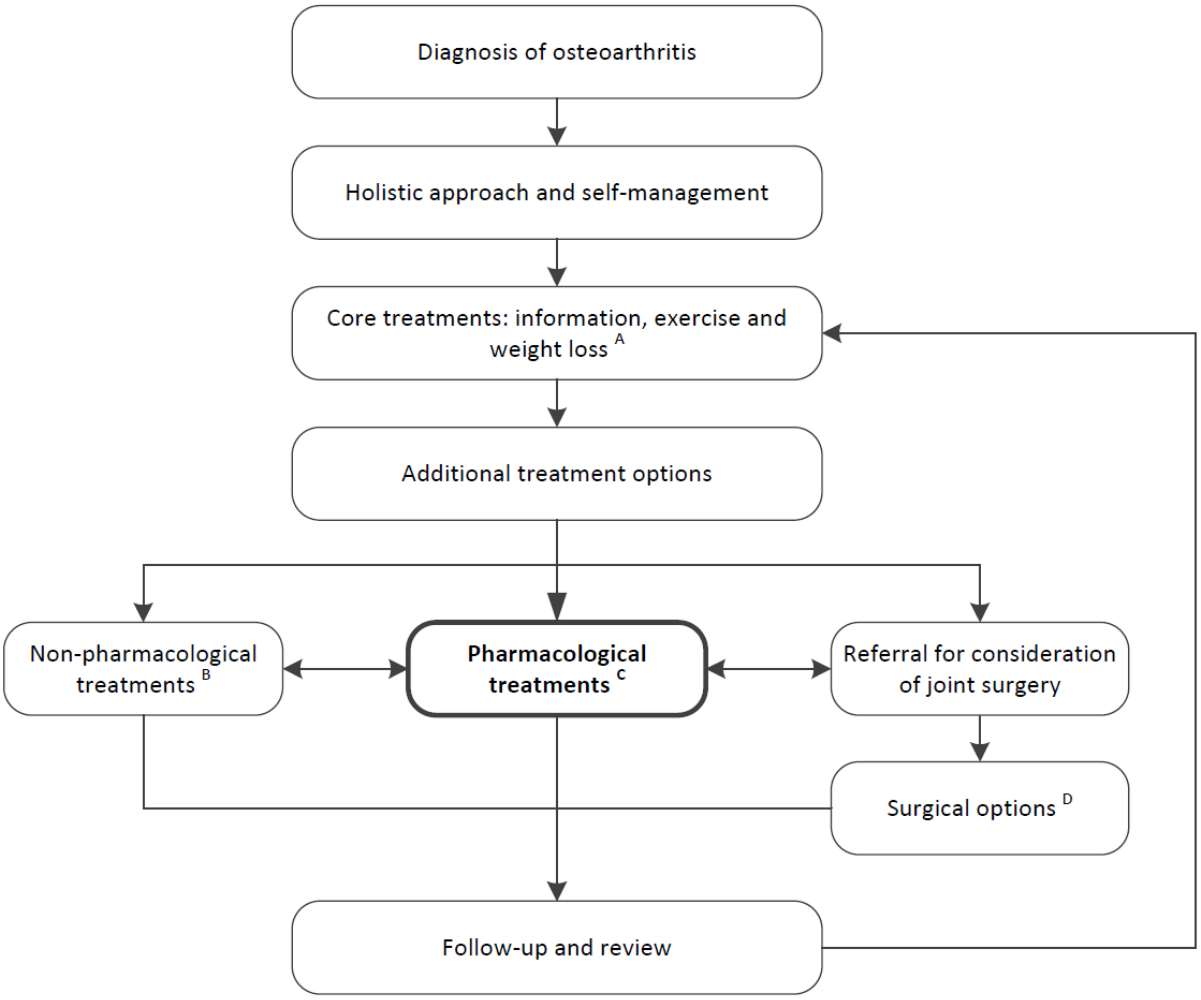
Radiologically the disease is characterised by osteophytes, subchondral sclerosis or cysts, and loss of joint spaces. Although most patients do not require radiological evidence to confirm diagnosis, assessment with computed tomography, magnetic resonance imaging and X-ray may be used to confirm differential diagnoses.[9]

In osteoarthritis synovial joint inflammation arises for several reasons, and can cause an enlargement of bone segments and the formation of osteophytes.[10] These processes result in joint pain and stiffness indicative of osteoarthritis. A number of theories surround the pathogenesis of osteoarthritis in a patient; the consensus suggests inflammatory mediators may play a pivotal role in the disease process.[11]

The disease progresses with age and is associated with multiple risk factors. Those that are modifiable, or behaviour-related, include overweight/obesity, sedentary lifestyle, and joint overload; however, these are only relevant to osteoarthritis in the hips and knees. Non-modifiable risk factors include genetic predisposition, poor bone density, inflammatory diseases, and prior injury or trauma.

There is no curative treatment for osteoarthritis. Management approaches aim to control symptoms and improve joint mobility. A summary of the recommended pathway of care for osteoarthritis from the National Institute for Health and Care Excellence (NICE) is provided in Figure 1.

Figure 1 Clinical management pathway of osteoarthritis



A Exercise and weight loss are first line treatment options for hip and knee OA; not applicable to hand OA.

B Non-pharmacological treatments include: self-management strategies (e.g. heat packs), physiotherapy (massage therapy), occupational therapy, orthotic and other devices (e.g. using a cane), psychosocial interventions, cognitive behavioural therapy, laser therapy, therapeutic ultrasound and transcutaneous electrical nerve stimulation.[9 12]

C Pharmacological treatments include: non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2 inhibitors (selective non-steroidal anti-inflammatory drugs), analgesics, corticosteroids, symptomatic slow-acting drugs for osteoarthritis such as chondroitin, topical capsaicin, and glucosamine.[12]

D Surgical options include: arthroscopy, osteotomy and arthroplasty procedures.[13]

Source: NICE pathways 2019. Available from https://pathways.nice.org.uk/pathways/osteoarthritis

Lifestyle modifications, such as weight loss and exercise, are first line treatments for osteoarthritis of the hip and knee. Depending on the disease profile and risk-factors present, second line treatments include i) pharmaceutical treatments such as symptomatic slow-acting drugs in osteoarthritis (SYSADOA), analgesics and capsaicin, and ii) non-pharmaceutical treatments such as physiotherapy or cognitive behavioural therapy. Chondroitin sulfate is a SYSADOA, which is prescribed either as a stand-alone therapy, or in combination with analgesics.

Patients who are substantially impacted by their symptoms, and those in whom pharmacological and non-pharmacological approaches are contraindicated, or after diligent attempts proven not successful, should be reasonably considered for surgical management (third line treatment).[9 13 14]

2. Technology

2.1 Technology Description

Chondroitin sulfate (CS) is a sulfated glycosaminoglycan found naturally in human cartilage and bone. As a nutritional supplement, CS is sourced from fish, bird, cow, pig, whale and shark cartilage. CS is an important structural component of cartilage, and CS supplementation is suggested to restore the extracellular matrix and to prevent further cartilage degradation.[15] Many patients use the supplement alone or in combination with glucosamine for the relief of osteoarthritic joint pain.[16] However, the relative effectiveness of CS at relieving the symptoms of osteoarthritis is subject to ongoing debate. The effects of CS, as with other SYSADOAs, require a longer administration before symptomatic relief is achieved compared to other drugs used to treat pain, such as NSAIDs; however, the effects may persist after treatment has been stopped.[32]

In Switzerland CS is available for patients with degenerative joint diseases through basic health insurance. There are two key formulations on CS available in Switzerland – Structum® and Condrosulf® – presented in Table 1. Dosage ranges from 800 to 1000mg per day, administered orally in capsule, tablet or granule form. Structum® is available in 500mg capsules which are taken twice a day, equivalent to a daily intake of 1000mg.[17] Condrosulf® is available in 400mg or 800mg formulations (tablet, capsule or granule) which are taken orally, either one or two a day, for an equivalent dose of 800mg per day.[18] Both products are manufactured in accordance with controlled and tested procedures. Dietary supplements containing CS that are available over-the-counter without a prescription vary in quality significantly.[19 20]

Table 1 Key formulations of CS available in Switzerland

Name / Registration number / manufacturer	Active ingredient / Origin of active ingredient	Composition, dosage and administration	Indications / Contraindications
Condrosulf® 42277, 48557, 51610 (Swissmedic) IBSA Institute Biochimique SA	Chondroitin sulfate Fish	Available in 400 mg and 800 mg tablets, 400 mg capsules, and 400mg granules. Dosage is 800 mg/day. Taken before a meal on an empty stomach. If there is no noticeable improvement of the symptoms within 6 months, the continuation of the therapy should be checked.	Symptomatic treatment for osteoarthritis. Hypersensitivity to the active substance or any of the excipients according to the composition.
Structum® 38477 (Swissmedic) Pierre Fabre Pharma AG	Chondroitin sulfate Bovine or avian	Available in 500mg capsules. Dosage is 1 capsule twice a day. Take the capsules whole and with a glass of water. If there is no noticeable improvement of the symptoms within 6 months, the continuation of the therapy should be checked.	Symptomatic treatment for osteoarthrosis. Known hypersensitivity to the active substance or to any of the ingredients according to the composition.

Source: Swissmedic [17] [18]

2.2 Alternative Technologies

Relevant alternative technologies to CS include on-demand analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), other anti-inflammatory treatments and no pharmaceutical treatment.

On-demand analgesics, or rescue analgesia, can be taken as needed up to a certain amount per day. For example paracetamol is a common oral analgesic of choice as it is considered safe to use up to 4g per day.[21] Analgesics are recommended as a second-line treatment for osteoarthritis, following failure of conservative management strategies. Oral analgesics are typically recommended as the first pharmaceutical therapy for osteoarthritis, due to their favourable safety profile compared to anti-inflammatory treatments.[13]

Anti-inflammatory treatments can include oral or topical corticosteroids and NSAIDs, and oral cyclo-oxygenase 2 (COS-2) inhibitors.[13] [22] Oral anti-inflammatory treatments are typically recommended following failure of other on-demand analgesics or topical NSAIDs, due to the increased risk of gastrointestinal and cardiovascular complications associated with chronic use.[13]

No pharmaceutical treatment can include self-management strategies such as heat packs and assistive devices, physiotherapy, occupational therapy, orthotic devices, therapeutic ultrasound, or transcutaneous electrical nerve stimulation.[13] Psychosocial interventions are also considered in this group.[9 12]

3. Systematic Search Strategy

3.1 Databases and Search Strategy

A systematic literature search was conducted in eight biomedical databases (PubMed, Embase, the Cochrane Library, CINAHL, York Centre for Reviews and Dissemination, CEA Registry, Econlit and Eth-med) from inception up to 28 September 2018. In addition, ongoing or unpublished clinical trials were searched from the following databases: ClinicalTrals.gov, Cochrane Central Register of Controlled Trials, EU Clinical Trials Registry, World Health Organization International Clinical Trials Registry Platform, Current Controlled Trials MetaRegister and Australian New Zealand Clinical Trials Registry. The manufacturers of Structum® and Condrosulf® were contacted to identify any published or unpublished trials missed by the search strategy.

Search terms included a combination of keywords and medical subject headings (MeSH) relating to osteoarthritis and CS. The full search strategy for each database is reported in Appendix A. No search filters were applied. All languages were screened by title and abstract; however, the selection of studies of the scoping report was limited to English language studies. Relevant studies in additional languages were identified to estimate the likelihood of language bias in the search results.

Search results were imported into Endnote X9. Study selection was conducted in duplicate by two authors. Both authors independently reviewed all records by title and abstracts, and then full-text. Differences were settled via consensus at each stage of the selection process. Studies were eligible for inclusion if they met the following inclusion criteria:

- **Patients**: Osteoarthritis of the hand, knee or hip.
- **Intervention**: Oral CS with at least the same minimum dosage as registered formulations used in Switzerland (i.e. ≥ 800mg per day).
- **Comparator**: On-demand analgesics or non-steroidal anti-inflammatory drugs, no pharmaceutical intervention, anti-inflammatory treatments, or placebo.
- **Outcomes**: Efficacy/effectiveness outcomes included pain, function, quality of life, concomitant medication use or progression to surgery. Safety outcomes included total and serious adverse events, withdrawals or discontinuations and mortality.
- **Design**: English language studies. Randomised, controlled trials with at least six months follow-up (efficacy, effectiveness, safety), non-randomised comparative trials (safety only) and single-arm studies (safety only).

Full details of the study inclusion criteria are described in Sections 5.2. to 5.5 and listed in the PICO boxes (see Section 5.6). Generic search terms for osteoarthritis were used, however the search strategy did not include specific terms for hand, finger or thumb, and may have missed studies as a result.

3.2 Other Sources

If a full HTA report is conducted, a de novo economic evaluation on the intervention is likely to be performed. The type of economic evaluations and the feasibility of performing one depends on the PICO of the HTA and clinical data availability. A classification matrix pertaining outcomes of clinical safety and effectiveness will be utilised to determine the type of economic evaluations to be conducted. Inputs for the potential economic evaluation will be identified through a range of sources, including targeted literature searches of biomedical databases, existing HTA reports, and government databases. Costs of the chondroitin products currently available in Switzerland are available from the med-drugs database (http://www.med-drugs.ch), and procedure codes and costs related to downstream treatments of osteoarthritis are available from the Swiss Tarif System TARMED. Where information cannot be identified through published sources, clinical expert advice will be sought. Key assumptions, particularly those sought from clinical advice, will be investigated through sensitivity analysis.

Patient and prescriber views are critical to the evaluation of patient and social issues related to the use of CS for osteoarthritis. Input from targeted stakeholder groups will be obtained through the FOPH's formal stakeholder engagement processes. In addition, to collect input from patients and physicians a targeted survey will be distributed among patient and physician organisations during the HTA phase.

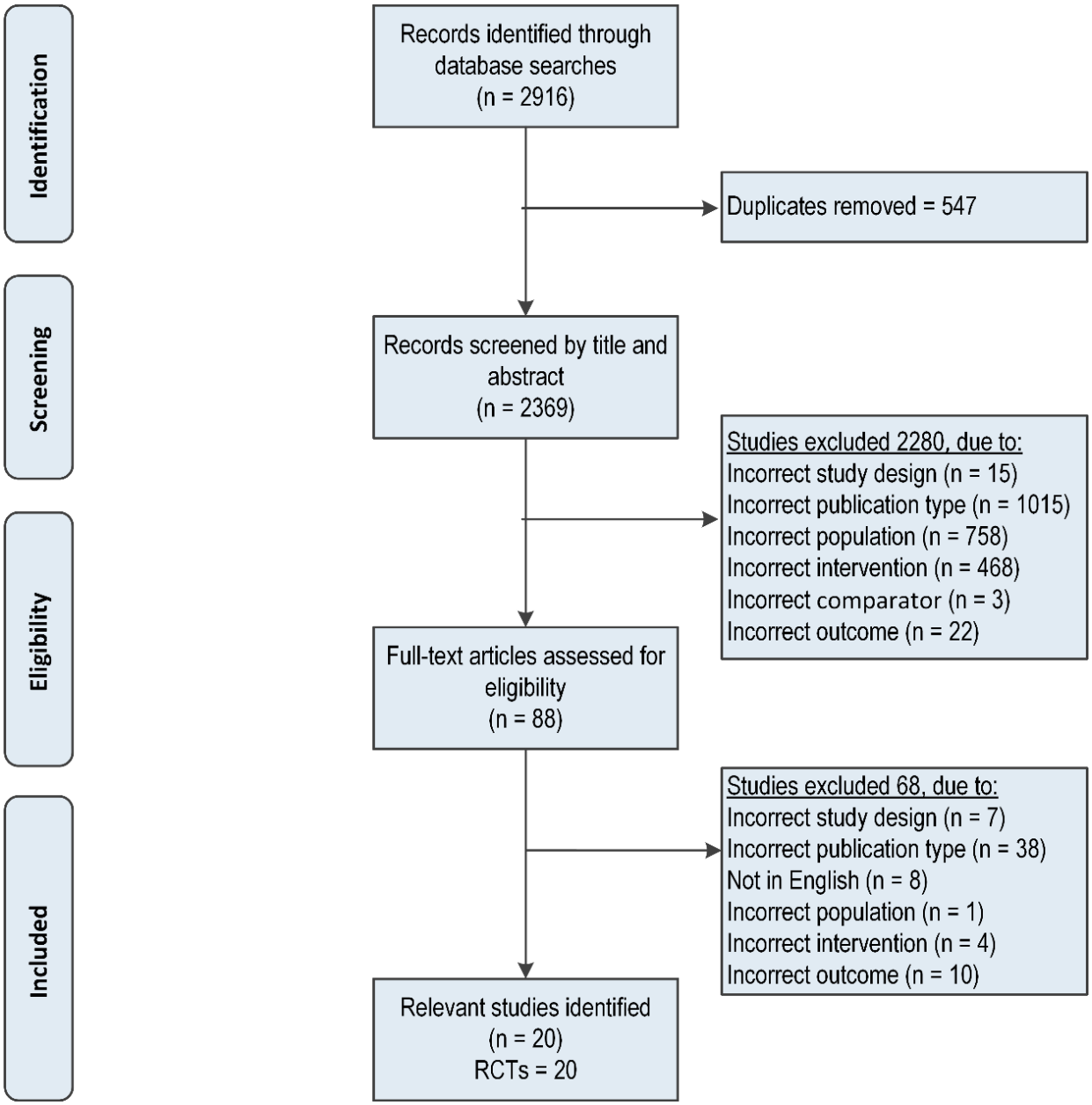
There are limited ethical or legal issues associated with CS use (see Sections 4.3.1 and 4.3.3 for more detail). Additional grey literature databases that can be searched in the full HTA are listed in Appendix A.

3.3 PRISMA Flow Diagram

The results of the systematic literature searches are presented in Figure 2. The database searches yielded a total of 2,916 results. After de-duplication, 2,369 were reviewed by title and abstract, and 88 were reviewed by full-text. In total, 20 relevant randomised controlled trials (RCTs) met the inclusion criteria for the clinical section of the scoping report.[23-42] The reasons for excluding articles reviewed by full-text are listed in Appendix C. No additional studies were identified by contacting the manufacturers of Structum® and Condrosulf®.

Non-English studies were not formally included in the scoping report but were screened by title and abstract. Of the non-English studies identified in the database searches, four RCTs [43-46] and four single-arm studies [47-50] would potentially meet the inclusion criteria for this review based on the information in the abstract.

Figure 2 PRISMA flow chart for study inclusion



In addition to the systematic searches, the following studies were identified as potentially relevant for the economic, legal, social, ethical and/or organisational data:

- **Economic**: 3 studies [51-53]
- **Legal**: 3 studies [54-56]
- **Social/patient perspectives**: 11 studies [57-67]
- **Ethical**: 5 studies [55 58 68-70]
- **Organisational**: 1 study [71]

Key themes discussed in these studies are presented in Sections 4.3 and 4.4.

4. Synthesis of Evidence Base

4.1 Evidence Base Pertaining to Efficacy, Effectiveness and Safety

In total, the searches retrieved 20 relevant studies that reported the clinical efficacy, effectiveness and safety of CS. Three studies included multiple relevant comparators (e.g. CS vs placebo vs celecoxib), and are therefore included for both efficacy (e.g. CS vs placebo) and effectiveness (e.g. CS vs celecoxib) outcomes accordingly.[25 35 37] The following studies investigating the efficacy, effectiveness and safety of CS were identified:

- **Efficacy**
  - 14 placebo-controlled RCTs [15 23-25 28-30 34-37 39-42 72]
- **Effectiveness**
  - 6 active control RCTs (6 vs NSAIDs, 1 vs paracetamol) [25 32 33 35-38]
- **Safety**
  - 10 placebo-controlled RCTs [23 28-30 35 37 39 40 42 72]
  - 4 active control RCTs (NSAIDs) [32 33 35 37]
  - 1 dosing RCT [31]
  - 1 RCT comparing CS products [26]

The characteristics of the individual included studies are summarised in Table 17 and Table 18 (Appendix B). Nineteen studies investigated the use of CS on osteoarthritis of the knees, one study investigated its use on hands, and no studies investigated hips.

Eight of the included studies were conducted totally or partly in Switzerland. The remaining studies were predominantly conducted in countries and settings that are generalisable to the Swiss context; the majority were conducted in Western European countries (n=10), while few were conducted in the USA (n=3), Canada (n=2), Japan (n=1), and Australia (n=1).

In total, the RCTs included 6,520 patients with knee osteoarthritis, and 162 patients with osteoarthritis of the hands. The included RCTs ranged in size from 46 patients to 1,583 patients (median = 146). Most studies were conducted across multiple centres (n=15). The length of follow-up ranged from 6 months (n=7), 40 weeks (n=1), 12 months (n=4), 24 months (n=6), and 48 months (n=1).

Patient indications included being diagnosed with osteoarthritis according to American College of Rheumatology (ACR) criteria, length of time pain had been experienced, Lequesne score, Kellgren & Lawrence scale, and a visual analogue scale (VAS) score for pain severity.

The chondroitin product under investigation included Condrosulf® (n=6), Structum® (n=4), Condrosan® (n=4), and non-specific chondroitin products (n=6). Some of the „non-specific“ products were sponsored

by manufacturers of other known products; however, the studies did not name the specific product under investigation.

A summary of the number of studies reporting relevant outcome measures is provided in Table 2. There is a substantial body of evidence investigating the key outcomes of pain, function, and analgesic consumption for knee osteoarthritis.

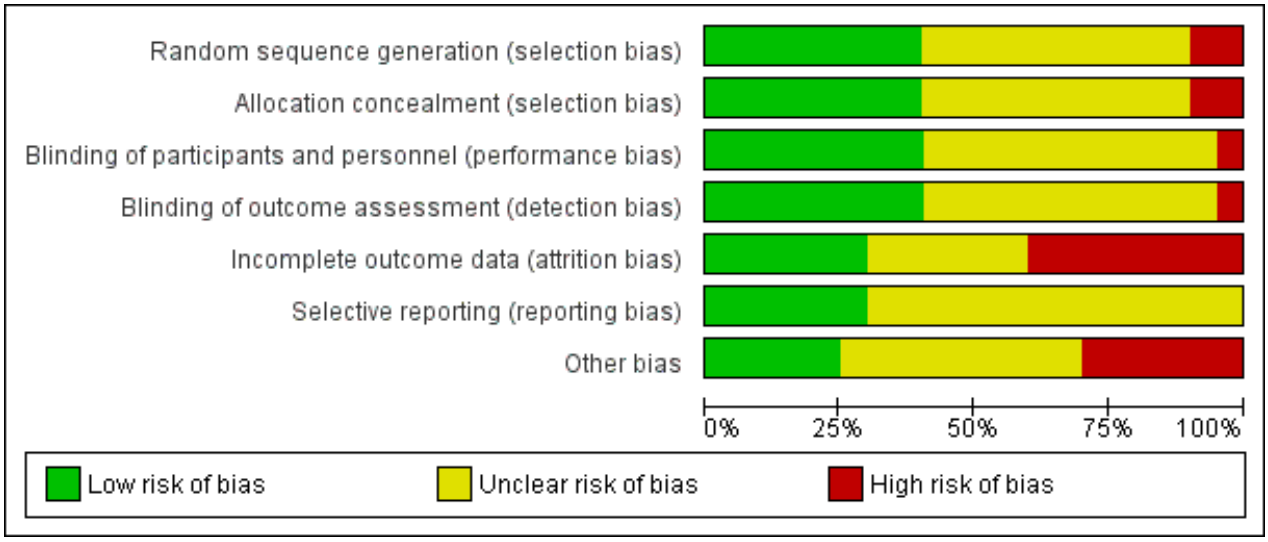
Table 2 Number of RCTs identified for the relevant outcomes, per comparison (knee)

		Comparison		
Outcome		**CS vs Placebo**	**CS vs NSAIDs**	**CS vs Paracetamol**
Pain	VAS	11	4	1
	WOMAC	6	3	0
	OMERACT/OARSI	3	2	0
Function	WOMAC	6	3	0
	Walk test	3	0	0
	VAS	2	0	0
QoL	SF-36	2	2	0
	HAQ	1	1	0
	SF-12	2	0	0
Analgesic consumption		10	4	0
Lequesne Index		6	2	1
Joint replacement		1	0	0
Safety	AE	10	4	0
	Serious AE	1	2	0
	Withdrawal due to AE	2	1	0
	Tolerability	4	0	0

Abbreviations: **AE** = adverse events, **CS** = chondroitin sulfate, **HAQ** = health assessment questionnaire, **NSAID** = non-steroidal anti-inflammatory drug, **OARSI** = Osteoarthritis Research Society International, **OMERACT** = Outcome Measures in Rheumatology, **QoL** = quality of life, **RCT** = randomised controlled trial, **SF-12/36** = Short Form-12/36, **VAS** = visual analogue scale, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index.

A summary of the overall quality of clinical evidence is provided in Figure 3. Study-specific risk of bias is reported in Figure 4 (Appendix B). The included studies were largely subject to inadequate reporting, rather than poor methodology per se. However, due to the subjective nature of the key outcomes (i.e. patient-reported pain and function), the potential for bias in the measurement of the outcome is high if blinding was not clearly established. It is suggested that blinding of patients and outcome assessors, reliable randomisation technique, allocation concealment, and the use of intention-to-treat analysis be investigated in subgroup analysis were possible. Further, over one quarter of studies had a direct conflict of interest related to the involvement of industry funding bodies in the design, conduct, analysis or reporting of the studies, while almost half had potential funding conflicts. It is suggested that the impact of financial conflicts of interest be investigated.

Figure 3 Summary of the risk of bias in the included RCTs



Ongoing or unpublished clinical trials are presented in Appendix B (Table 19), including three randomised controlled trials of CS compared with placebo in populations with osteoarthritis with follow-up more than 6 months. All of the ongoing clinical trials are well past their estimated finish date and appear to have been abandoned. As such there are no new trials on the horizon that are likely to impact the results of an HTA report.

Comparison to the 2015 Cochrane review

CS was the subject of a Cochrane review in 2015, in which searches were completed in November 2013.[16] The PICO(S) criteria in the Cochrane review differs from the current review in the following areas:

1. Population: No difference.
2. Intervention: CS combined with any other oral therapy, e.g. glucosamine plus CS, was considered in the Cochrane review.
3. Comparator: Opioids, glucosamine and other "herbal" medications were considered in the Cochrane review.
4. Outcomes: Radiographic outcomes (joint space narrowing or "other radiographic criteria"), patient and physician global assessment, and the proportion of patients that were responders were considered in the Cochrane review.
5. Study design: Follow-up of two weeks duration was considered in the Cochrane review.

The Cochrane review included 43 studies, of which twenty-six were excluded from the present review. The primary reasons were studying combined interventions (n=12) and having follow-up of less than six months (n=7). Less common reasons were having a different comparator (n=1), and a low dosage of CS (n=1), and non-English language (n=5).

Five additional studies have been published since the Cochrane review: Fransen et al. (2015),[15] Morita et al. (2018),[31] Petellier et al. (2016),[33] Reginster et al. (2017),[35] and Tio et al. (2017).[38] The additional trials investigated the safety and efficacy of CS compared to placebo,[15] NSAIDs,[33] placebo or NSAIDs,[35] and acetaminophen.[38] One additional study compared dosages of CS.[31]

4.2 Evidence Base Pertaining to Costs, Budget Impact and Cost-Effectiveness

Two articles providing an economic evaluation of CS compared to a relevant comparator were identified. Robio-Terrés et al. (2010) perform both a model-based, cost minimisation analysis and a budgetary impact analysis of CS compared to non-steroidal anti-inflammatory drugs (NSAIDs) in patients with osteoarthritis. The perspective adopted is that of the Spanish Healthcare System. Bruyère et al. (2009) carry out a basic cost-utility analysis using health-related outcome data collected during a two-year randomised control trial (RCT) of CS (800mg/day) vs. placebo for patients with osteoarthritis of the knee (the STOOP trial). The perspective adopted is not explicitly stated.

Rubio-Terrés et al. (2010)

This economic evaluation is presented alongside findings from a retrospective cohort study (VECTRA).[53] A model-based approach is taken, using a decision-tree model with a time horizon of six months. An assumption is made that the health outcomes achieved by either CS or NSAID use are identical, and a cost-minimization analysis (CMA) performed based on this assumption. Whilst the assumption is explicitly stated, a single clinical trial comparing the effectiveness of CS to diclofenac sodium is the sole basis for this assumption. This may not be enough evidence to justify a CMA approach.

Despite the stated assumption of identical efficacy, the model incorporates differing efficacy rates for each alternative. This does not seem to reflect the stated CMA approach. The intention seems to be to allow additional costs incurred by the health system in the case of inefficacy to be captured. However, if differing efficacy rates are to be considered, potential impacts on relative quality of life outcomes and/or disease progression should also be explored.

Different rates of adverse events – categorised as gastrointestinal or other – are also structured into the model. Probabilities of adverse events were obtained from the literature.

Costs associated with CS, NSAIDs, the treatment of any adverse event and additional rheumatology visits or hospitalisations are all well identified. The measurement and valuation processes lack clarity. Sources are provided for all cost valuations; however, no detail is given regarding how semi-annual costs have been estimated. Many mild/moderate gastrointestinal adverse events are listed, but only a single semi-annual cost is presented. The choice to consider only the treatment of acute urticaria in primary care in the estimation of the cost of other adverse events is not justified. Moreover, whilst data collected in the retrospective study indicated the percentage of patients taking gastroprotective agents in addition to their chosen method of treatment, it is

unclear whether a unit cost was valued for this variable, despite the percentage appearing to differ remarkably between alternative treatments modalities.

The cost due to inefficacy is equivalent to an additional physician/rheumatology visit and the subsequent use of combined CS and NSAID therapy in a percentage of cases. Expert opinion was sought to identify estimates of the percentage of patients who could switch to combined CS/NSAID therapy when monotherapy with either alternative was ineffective. Maximum and minimum estimates where included in a univariate sensitivity analysis.

Although sourced from a retrospective study which was not adequately described, the results presented do provide an indication that patients on NSAID monotherapy switch to CS monotherapy or CS and NSAID combined therapy due to the onset of adverse events or due to lack of efficacy. The authors briefly discuss other studies which have reached similar conclusions.

The budgetary impact of the use of CS as an additional treatment modality compared to NSAID treatment alone is explored. For the estimation, theoretical values of 5, 10 and 15% are used to represent percentage decreases in NSAID consumption (substitution for CS) over a 3-year period. It is unclear how these theoretical numbers have been estimated.

Bruyère et al. (2009)

This is a single study-based evaluation. The original trial was a randomised, double-blind, placebo-controlled trial with an intervention period of 24 months.[28 52] Six hundred and twenty-two participants with knee osteoarthritis received either CS (800mg) or a placebo once daily for two years. They could also take paracetamol and NSAIDs for rescue analgesia and acute pain, respectively.

Regarding the Bruyère et al. (2009) model, a lack of clarity around the objective of the economic evaluation and the failure to adopt a perspective to guide the analysis are both weaknesses.

The economic evaluation presented in this report uses Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores collected during the initial trial and maps them into utility values. This permits a cost-utility analysis to be undertaken. A previously validated formula was employed to map WOMAC scores into health utility index (HUI) utility scores. The final outcome measure of quality-adjusted life years (QALYs) gained is used in the economic evaluation.

The only cost considered on the cost side of the evaluation is the cost of CS. The authors assume that all other healthcare and non-healthcare costs were comparable between the two trial arms; however, justification for this assumption is not explicitly provided. For example, it is possible that the cost of concomitant analgesic consumption or cost to treat adverse events differs between the two trial arms. It is not clearly stated on what grounds the assumption that these costs do not differ between the alternatives is made. With regards to the cost that is included, little information is provided. The source of the daily cost of CS, detail regarding how CS

use itself is measured and how the average cost of CS used in the incremental cost-effectiveness ratio (ICER) calculations was calculated are not explicitly stated.

Limitations in the identified models

A previous HTA regarding the clinical and cost-effectiveness of glucosamine and CS supplements in patients with osteoarthritis of the knee was identified.[51] The review by Black et al. (2009) concluded that CS has no statistically significant differential effect on quality of life or disease progression compared to current care practices for the treatment and/or management of osteoarthritis of the knee.[51] They did not perform an evaluation of the cost-effectiveness or budgetary impact of CS; however, the model used to estimate the cost-effectiveness of glucosamine sulfate compared to standard care provides a relevant structure of a model if this review finds evidence that CS has a differential impact on progression to joint replacement or arthroscopy compared to relevant comparators.

Based on the studies identified above, constructing a robust and reliable economic model to evaluate the cost-effectiveness of CS may not be feasible. The quality of the two existing economic evaluations was poor. The other economic evaluation,[51] although conducted robustly, did not compare CS to its comparator due the absence of clinical superiority. The economic evaluation of CS for the current HTA, if performed, is very likely to share similar model structures and assumptions with the one on glucosamine and CS by Black et al. (2009).[51] This study reported that, when comparing glucosamine to its comparator, the quality of life changes and costs of knee arthroplasty were the two main drivers of the model; however, both of the clinical outcomes either did not demonstrate sufficient superiority, or did not have sufficient data with adequate length of follow-up to feed into an economic model. Therefore, the economic evaluation is likely to have substantial uncertainties.

Table 3 Overview of existing, relevant economic evaluations of CS

Study (author, year)	Rubio-Terrés et al. (2010)	Bruyère et al. (2009)
Country/Region	Spain	France, Belgium, Switzerland, Austria and the United States
Patient Indication	Osteoarthritis (unspecified)	Osteoarthritis of the knee
Intervention	CS	CS (800mg/day)
Comparator	NSAIDs	Placebo *Note: acetaminophen and NSAIDs taken for rescue analgesia and acute pain, respectively*
Study Design	Model-based Decision-tree	Trial-based Based on RCT (STOOP trial)
Type of Economic Evaluation	CMA (as described in article) (i.e. identical clinical efficacy of CS and NSAIDs assumed – *model structure does not seem to reflect this*)	CUA
Study Perspective	Spanish National Health System	Unclear. Cost of CS only cost considered.

Time Horizon	6-months	24-months
Sample Size	Hypothetical cohort of 10,000 for modelling	622 participants
Costs included	Direct Costs including cost of treatment, cost of treatment of Adverse Events	Cost of CS treatment only
Health-related Out-come Measure	Adverse events, especially gastro-intestinal AEs, avoided	QALYs gained WOMAC scores mapped into HUI utility scores so QALYs could be calculated.
Outcome measure for Economic Evaluation	Semi-annual cost per patient	ICER I.e. cost per QALY gained (CS vs. placebo)

Abbreviations: **CMA** = cost-minimisation analysis, **CS** = chondroitin sulfate, **CUA** = cost-utility analysis, **HUI** = Health Utility Index, **ICER** = incremental cost-effectiveness ratio, **NSAIDs** = non-steroidal anti-inflammatory drugs, **RCT** = randomised controlled trial, **QALY** = quality-adjusted life year, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index

4.3 Evidence Base Pertaining to Legal, Social and Ethical Issues

4.3.1 Legal issues

Three studies, two review articles and a case study, identified legal issues pertaining to the intervention. Key issues include: (a) challenges for physicians in the United States prescribing complementary and alternative medicines (CAM) of unknown quality, such as over the counter CS (not relevant in Switzerland), and (b) the response of industry groups to the disinvestment in another jurisdiction.

The case study described a court case where a patient organisation legally challenged the health governing body in the Netherlands for removing CS from basic health insurance. This case involved a different medical procedure — bladder instillations with CS or hyaluronic acid for patients with interstitial cystitis — where CS was removed from basic health insurance due to the paucity of scientific evidence of its effectiveness. In this case, the prosecuting party claimed that clinical expertise and patient experience should have been given more weight in the matter.[55] This case study raises the potential for backlash from industry groups if CS were to be disinvestment in Switzerland. The study is set in another European country that, like Switzerland, has a good healthcare system in place and it describes the precise situation of CS no longer being funded. This issue should be further investigated to ascertain the risk of a similar situation occurring in Switzerland.

4.3.2 Patient and social aspects

Eleven studies identified patient perspectives or social issues pertaining to the intervention.

Apart from one comparative study and two review articles, all included studies were single arm studies using survey or patient records. Authors of the studies were from the United States, Canada, Australia, India, and Korea. Key issues were patient perspectives on osteoarthritis pain treatment; predictors of use in different patient populations (age, gender etc.);[59 62 64 66 67] consequences of self-management[65] and communication with physicians about CAM use.[57 59-64 66 67]

These key issues could benefit from further investigation as patient views of treatments can provide unique insight that differs from that of clinicians, governing bodies, and social investment is important for population satisfaction.

4.3.3 Ethical issues

Five studies, a single-arm study and four review articles, identified ethical issues pertaining to the intervention. Key issues include the provision of informed consent when physicians administer CAM,[68] the sourcing of animal CS,[69] and the practice of patients delaying conventional medical treatment while attempting to treat with CAM such as CS.[58 68] Issues to do with CAM may become relevant if pharmaceutical CS is disinvested and CAM products become a substitute for some patients.

The author of one review article from the United States argued that it is unethical for medical professionals to keep supplements that are believed to be effective from patients with osteoarthritis.[70] This is an opinion that may also be held by patient/industry groups in Switzerland. In a similar vein, the court case discussed in legal issues is included here.[55] This opinion of seeming unfairness held by some groups supporting CS use should not be investigated as an ethical issue, rather as legal and social aspects issues as stated in previous sections.

4.4 Evidence Base Pertaining to Organisational Issues

No studies were identified pertaining to organisational changes that are relevant to the evaluation of CS in Switzerland.

5. Central Research Question(s)

5.1 Central Research Question(s)

The central research questions for the review are:

1. What is the effectiveness, efficacy and safety of standard CS treatment in patients with symptomatic osteoarthritis in the knees, hips or hands compared to no pharmaceutical treatment, on-demand analgesics, NSAIDs, placebo, or other anti-inflammatory treatments?
2. What are the costs, budget-impact and cost-effectiveness of treating patients with symptomatic osteoarthritis in knees, hips or hands with standard CS treatment compared to on-demand analgesics, NSAIDs, or other anti-inflammatory treatments?

The elements of the research question (i.e. the PICO criteria) are described below and summarised in Section 5.6.

5.2 Patients

The patient population is defined as patients with osteoarthritis in the hip, knee or hand (ICD-10 codes M15 – polyosteoarthritis M16 – osteoarthritis of hip, M17 – osteoarthritis of knee, M18 – osteoarthritis of carpometa-carpal joint, M19 – other and unspecified osteoarthritis).

While arthritic conditions in children exist, osteoarthritis does not occur in paediatric patients. This age group can be excluded. According to the Product Information sheets available on Swissmedic, the use and safety of Condrosulf® and Structum® in children and adolescents has not been studied.

Patients with significant physical limitation and/or non-responding to diligent pharmacotherapeutic intervention are to be considered for surgical intervention. They are excluded from the target population. Both Structum® and Condrosulf® are used to treat symptoms across these broad indications, although they should not be administered during pregnancy or breastfeeding.[17 18]

5.3 Intervention

The technology under investigation is oral CS. Two registered drugs are available in Switzerland which contain the active substance CS: Structum® and Condrosulf®. Structum® is available in 500mg capsules which are taken twice a day, equivalent to a daily intake of 1000mg.[17] Condrosulf® is available in 400mg or 800mg formulations (tablet, capsule or granule) which are taken orally, either one or two a day, for an equivalent dose of 800mg per day.[18] In addition to these specific drugs, other oral chondroitin products that deliver at least the same minimum dosage as registered formulations used in Switzerland (i.e. ≥ 800mg per day) will be included. At present, glucosamine alone or as combination formulations with CS are not approved by Swissmedic. For this reason CS-glucosamine combination products and glucosamine as concomitant treatment will not be acknowledged as relevant interventional treatments.

The symptomatic effects of Structum® and Condrosulf® are delayed, generally occurring 1 to 2 months into treatment.[17 18] In contrast, the effects of analgesics and anti-inflammatory medications are expected to act in a manner that is more immediate. Analgesics, therefore, are recommended on-demand, as concomitant treatment to CS. NSAIDs, in particular, are not recommended for chronic use, but intermittently to treat acute flares and reduce side effects of the NSAID.[14]

It is recommended that treatment with CS is discontinued if no effect is seen within 6 month.[17 18 73] However, the exact length of treatment in current practice is unclear.

5.4 Comparator

Treatment for osteoarthritis may be (a) non-pharmaceutical, (b) pharmaceutical, or (c) surgical. As CS is a pharmaceutical treatment option, the relevant comparators to CS have been identified as other pharmaceutical therapies offering symptomatic relief. Relevant pharmaceutical treatment comparators are identified as on-demand analgesics, oral or topical NSAIDS, and other anti-inflammatory treatments (i.e. corticosteroids, COX-2 inhibitors). Non-pharmaceutical interventions are expected to be offered to all osteoarthritis patients.[14] Patients who qualify for surgical intervention are excluded.

Guidelines published by the Osteoarthritis Research Society International (OARSI) for the management of hip and knee osteoarthritis state recommend paracetamol (up to 4g/day) as an effective initial oral analgesic for the treatment of mild to moderate pain.[73] However , a recent Cochrane review suggests that paracetamol provides minimal clinical benefit, that may not be clinically important.[74]

OARSI recommendations indicate that alternate treatment options may be considered in the absence of an inadequate response to paracetamol.[73] Oral NSAIDs and topical NSAIDs or capsaicin are some of the alternate pharmacological interventions discussed. Under NICE guidelines; in the event paracetamol and/or topical NSAIDs are insufficient, oral NSAIDs may be considered as an alternative treatment option.[13] Oral NSAIDs appear as a secondary option in the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Disease (ESCEO) treatment algorithm for patients whose symptoms do not respond to therapy with regular paracetamol or glucosamine sulfate and/or CS with on demand paracetamol.[14]

OARSI and ESCEO recommendations indicate the use of weak opioids should only be considered where other pharmacological agents have been ineffective or are contradicted.[22 74] Opioids are not a relevant comparator as they are a last-line pharmaceutical treatment option when other pharmaceutical therapies are ineffective, rather than an alternative for patients considering CS use.[14] Similarly, intraarticular injections are not considered to be a relevant comparator, as they are recommended for use as an adjunct to other medications, or following failure of oral NSAIDs.[14 74]

5.5 Outcomes

Oral CS is prescribed to treat symptoms associated with osteoarthritis. Considering this purpose and guided by the guideline on the clinical investigation of medicinal products in the treatment of osteoarthritis, reduction of pain in the target joint is recommended as the primary endpoint for clinical research into osteoarthritis. Patient self-assessment of pain measured using a validated tool—either measuring ‘in motion’ or ‘at rest’ separately, or a multidimensional tool with a subscale index of pain—is recommended. Physical function is also considered a critical endpoint and measurement of functional disability is recommended as an optional, co-primary endpoint.[75]

CS treatment may have structure-modifying effects;[73 76] However, biochemical markers or MRI and other imaging of bone and cartilage spacing as endpoints do not correlate with symptomatic effect experienced by patients. Further, stakeholder feedback suggests that radiographic outcomes are not commonly used in Swiss clinical practice to monitor disease progression of patients with osteoarthritis. In the context of management of symptoms, radiographic outcomes are therefore not considered clinically relevant outcomes.[75]

Efficacy/Effectiveness

Critical

Pain can be measured with the WOMAC pain subscale, VAS, OARSI-OMERACT criteria, Australia/Canadian osteoarthritis hand index (AUSCAN™) pain subscale or other validated numeric rating scales. Pain is the most clinically significant outcome; clinically relevant differences in a patient's pain have been classified as a relative reduction of 15-20% in these pain scores.[77] This is measured on a per-patient basis and presented as a mean difference across included patients. However, because pain is experienced by individuals differently, group mean change in this outcome may hold minimal relation to an important change for a single patient.[77]

Physical function can be measured with WOMAC, OARSI-OMERACT criteria, AUSCAN™ function subscale or other exercise tests. Reaching a score of 4 over two months is considered clinically relevant when using WOMAC;[78] clinically relevant outcomes for exercise tests are any noticeable increase in percentage mobility capacity—noting that most patients enter the studies with approximately 50% reduction in capacity.[40]

Quality of life (QoL) can be measured with Health Assessment Questionnaire (HAQ), SF-36, or Health Assessment Questionnaire-Disability Index (HAQ-DI). Quality of life tools directly measure clinically relevant outcomes and, as it is not known what each patient will consider important for treatment success, are perhaps more important than more objective outcome measures.[77 79]

Lequesne index is a composite measure of osteoarthritis, which summarises algofunctional parameters of pain such as the maximal walking distance, and discomfort in daily life movements. It is scored on eleven items, concerning pain and discomfort at specific times and positions, and functional abilities. Lequesne index is directly relevant to the patient's clinical experience of pain, discomfort and functional ability.[80]

Important

Concomitant analgesic or NSAID consumption, as measured as milligrams per day, or percentage/number of days analgesics are consumed compared to the days of treatment.[26 72] Reduction in analgesic consumption is expected to prevent the negative consequences of gastrointestinal side-effects or multi-organ failure.[82 83]

Progression to joint replacement or arthroscopy is an end-point of osteoarthritic treatment. Surgical approaches have inherent risks, such as surgical site infection or prosthetic joint infection, as well as the need to heal from a surgical procedure.[81]

Safety

Critical

Mortality, serious adverse events, and withdrawals or discontinuation due to adverse events are the critical safety outcomes. The importance of mortality, serious adverse events and the potential consequences of adverse events lies in the principle that patients should not be harmed in the process of treating their illness. For this reason, safety outcomes are considered critically relevant. The safety of CS is generally accepted,[16] however the comparative safety is of relevance to a disinvestment decision.

Important

The **total adverse event rate** is an important safety outcome. Total adverse events represent the overall number of events that occur in the treated population; however, total rates to not provide an indication of the clinical significance of the events. For this reason, the total event rate is an important, but not critical safety outcome.

5.6 PICO(S)-Box

The PICO criteria are separated into the three key indications for review, (1) knees, (2) hips, and (3) hands.

Table 4 PICO criteria 1: knees

P:	Patients with symptomatic osteoarthritis in the knees. *(Exclusions: paediatric indications, concomitant ligament or meniscus injury, candidates for knee arthroplasty)*
I:	Oral CS (minimum 800mg per day), initial treatment followed by maintenance treatment for 3, 6 or 12 months, with or without analgesics on demand. *(Exclusions: combination drugs – e.g. CS and glucosamine)*
C:	Placebo, on-demand analgesics (e.g. paracetamol), non-steroidal anti-inflammatory drugs (e.g. ibuprofen, celecoxib) and other anti-inflammatory treatments (e.g. corticosteroids, COX-2 inhibitors). *(Exclusions: Opioid medications, intra-articular injections)*
O:	**Efficacy/effectiveness:** • Pain (WOMAC pain subscale, NRS, VAS) • Physical function (WOMAC, exercise tests) • Lequesne index (composite measure of osteoarthritis) • Quality of life (HAQ, SF-36, HAQ-DI) • Concomitant analgesic and NSAID consumption • Progression to joint replacement or arthroscopy **Safety:** • Serious adverse events • Withdrawals or discontinuation due to adverse events • Mortality • Adverse events (total)
(S):	**Efficacy/effectiveness:** • Randomised controlled trials (with a follow-up period of at least 6-months) • In the absence of RCTs with adequate follow-up (range 6-12 months), other comparative study designs will be considered *(Exclusions: narrative reviews, letter to the editor, author response, case report)* **Safety**: • Randomised controlled trials (with a follow-up period of at least 6-months) • Prospective non-randomised controlled trials (with a follow-up period of at least 6-months) • Prospective case-series (with a follow-up period of at least 6-months) *(Exclusions: narrative reviews, letter to the editor, author response, case report)*

Abbreviations: **HAQ** = Health Assessment Questionnaire, **HAQ-DI** = Health Assessment Questionnaire Disability Index, **NRS** = Numerical rating scale, **RCT** = Randomised controlled trial, **SF-36** = Short-form 36, **VAS** = Visual analogue scale, **WOMAC** = Western Ontario & McMaster Universities Osteoarthritis Index.

Table 5 PICO criteria 2: hips

P:	Patients with symptomatic osteoarthritis in the hips. *(Exclusions: paediatric indications, concomitant ligament or meniscus injury, candidates for hip arthroplasty)*
I:	Oral CS (minimum 800mg per day), initial treatment followed by maintenance treatment for 3, 6 or 12 months, with or without analgesics on demand. *(Exclusions: combination drugs – e.g. CS and glucosamine)*
C:	Placebo, on-demand analgesics (e.g. paracetamol), non-steroidal anti-inflammatory drugs (e.g. ibuprofen, celecoxib) and other anti-inflammatory treatments (e.g. corticosteroids, COX-2 inhibitors). *(Exclusions: Opioid medications, intra-articular injections)*
O:	**Efficacy/effectiveness:** • Pain (WOMAC pain subscale, NRS, VAS) • Physical function (WOMAC, exercise tests) • Lequesne index (composite measure of osteoarthritis) • Quality of life (HAQ, SF-36, HAQ-DI) • Concomitant analgesic and NSAID consumption • Progression to joint replacement or arthroscopy **Safety:** • Serious adverse events • Withdrawals or discontinuation due to adverse events • Mortality • Adverse events (total)
(S):	**Efficacy/effectiveness:** • Randomised controlled trials (with a follow-up period of at least 6-months) • In the absence of RCTs with adequate follow-up (range 6-12 months), other comparative study designs will be considered *(Exclusions: narrative reviews, letter to the editor, author response, case report)* **Safety:** • Randomised controlled trials (with a follow-up period of at least 6-months) • Prospective non-randomised controlled trials (with a follow-up period of at least 6-months) • Prospective case-series (with a follow-up period of at least 6-months) and pharmacy/insurance databases *(Exclusions: narrative reviews, letter to the editor, author response, case report)*

Abbreviations: **HAQ** = Health Assessment Questionnaire, **HAQ-DI** = Health Assessment Questionnaire Disability Index, **NRS** = Numerical rating scale, **RCT** = Randomised controlled trial, **SF-36** = Short-form 36, **VAS** = Visual analogue scale, **WOMAC** = Western Ontario & McMaster Universities Osteoarthritis Index.

Table 6 PICO criteria 3: hands

P:	Patients with symptomatic osteoarthritis in the hands *(Exclusions: Paediatric indications)*
I:	Oral CS, initial treatment followed by maintenance treatment for 3, 6 or 12 months, with or without analgesics on demand. *(Exclusions: Combination drugs – e.g. CS and glucosamine)*
C:	• Placebo, on-demand analgesics (e.g. paracetamol), non-steroidal anti-inflammatory drugs (e.g. ibuprofen, celecoxib) and other anti-inflammatory treatments (e.g. corticosteroids, COX-2 inhibitors). *(Exclusions: Opioid medications, intra-articular injections)*
O:	**Efficacy/effectiveness:** • Pain (e.g. AUSCAN™ pain subscale, NRS, VAS) • Physical function (e.g. AUSCAN™ function subscale) • Quality of life (e.g. HAQ, HAQ-DI, SF-36) • Concomitant analgesic and NSAID consumption **Safety:** • Serious adverse events • Withdrawals or discontinuation due to adverse events • Mortality • Adverse events (total)
(S):	**Efficacy/effectiveness:** • Randomised controlled trials (with a follow-up period of at least 6-months) • In the absence of RCTs with adequate follow-up (range 6-12 months), other comparative study designs will be considered *(Exclusions: narrative reviews, letter to the editor, author response, case report)* **Safety:** • Randomised controlled trials (with a follow-up period of at least 6-months) • Prospective non-randomised controlled trials (with a follow-up period of at least 6-months) • Prospective case-series (with a follow-up period of at least 6-months) and pharmacy/insurance databases *(Exclusions: narrative reviews, letter to the editor, author response, case report)*

Abbreviations: **HAQ** = Health Assessment Questionnaire, **HAQ-DI** = Health Assessment Questionnaire Disability Index, **NRS** = Numerical rating scale, **RCT** = Randomised controlled trial, **SF-36** = Short-form 36, **VAS** = Visual analogue scale.

6. HTA Sub-Questions

Sub-questions of relevance to CS have been informed by the European Network for Health Technology Assessment (EUnetHTA) HTA Core Model® (Version 3.0).[84] All sub-questions related to the key assessment domains (i.e. efficacy, effectiveness, safety, cost-effectiveness, ethical, patient/social, legal, organisational) were considered for inclusion; however, only those deemed relevant to CS, a product supplied by community pharmacy that is used routinely in clinical practice, were included.

6.1 Sub-Questions Efficacy, Effectiveness and Safety

CS is a drug used to modify the symptoms of osteoarthritis, therefore the primary effectiveness outcomes relate to symptom control. Other outcome measures included in the PICO criteria are relevant to both efficacy and effectiveness but will be addressed by different study designs. Relevant sub-questions on safety and effectiveness from the EUnetHTA HTA Core Model® (Version 3.0) are outlined in the Table 7 and

Table 8.[84]

Table 7 Sub-questions: safety

Topic	Research Question	Element ID
Patient safety	How safe is the technology in comparison to the comparator(s)?	C0008
Patient safety	Are the harms related to dosage or frequency of applying the technology?	C0002
Patient safety	Are there susceptible patient groups that are more likely to be harmed through the use of the technology?	C0005

Table 8 Sub-questions: effectiveness

Topic	Research Question	Element ID
Mortality	Is there an expected beneficial effect of the technology on mortality?	D0001
Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	D0005
Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	D0006
Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	D0012

Topic	Research Question	Element ID
Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	D0013
Change-in management	How does the technology modify the need for hospitalisation?	D0010
Benefit-harm balance	What are the overall benefits and harms of the technology in health outcomes	D0029

6.2 Sub-Questions Costs, Budget Impact and Cost-Effectiveness

Budget impact analysis will investigate the withdrawal of an existing technology. Expected changes in the overall compulsory basic health insurance, such as resources involved in technologies needed to supplement its use will be considered, e.g. additional NSAID use and associated adverse events. Sub-questions related to costs, budget impact and cost-effectiveness that are relevant to CS are outlined in Table 9.[84] The basis of performing a model-based economic evaluations to investigate potential cost-effectiveness of CS will be determined using the matrix of health economic evaluation classification, which is provided in Table 20 in the Appendix C.

Table 9 Sub-questions: costs, budget impact and cost-effectiveness

Topic	Research Question	Element ID
Resource utilisation	What were the measured and/or estimated costs of the assessed technology and its comparator(s) (resource-use valuation)?	E0009
Resource utilisation	How does the technology modify the need for other technologies and use of resources?	D0023
Resource utilisation	What are the likely budget impacts of implementing/withdrawing the technologies being compared?	G0007
Measurement and estimation of outcomes	What is(are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s)?	E0005
Examination of costs and outcomes	What are the estimated differences in costs and outcomes between the technology and its comparator(s)?	E0006
Characterising uncertainty	What are the uncertainties surrounding the costs and economic evaluation(s) of the technology and its comparator(s)?	E0010
Characterising heterogeneity	To what extent can differences in costs, outcomes, or 'cost-effectiveness' be explained by variations between any subgroups using the technology and its comparator(s)?	E0011

Topic	Research Question	Element ID
Validity of the model(s)	What methodological assumptions were made in relation to the technology and its comparator(s)?	E0013
Validity of the model(s)	To what extent can the estimates of costs, outcomes, or economic evaluation(s) be considered as providing valid descriptions of the technology and its comparator(s)?	E0012

6.3 Sub-Questions Legal, Social and Ethical Issues

The question from the EUnetHTA Core Model related to legal aspects that is relevant to CS is outlined in Table 10.[84]

Table 10 Sub-question: legal aspects

Topic	Research Question	Element ID
Authorisation and safety	What authorisations and register listings does the technology have?	I0015

A set of ethical issues arising in the literature are likely to relate to the uncertainties around over the counter CS. This has limited consequence for the registered products available for use in Switzerland.

Potential ethical issues relate to the reaction of patient groups when this health technology is no longer accessible in their jurisdiction. Sub-questions related to ethical issues that are relevant to CS are outlined in Table 11.[84]

Table 11 Sub-questions: ethical aspects

Topic	Research Question	Element ID
Benefit-harm balance	What are the perceived benefits and harms for patients when implementing or not implementing the technology?	F0010
Autonomy	Will withdrawal of the technology affect the patient´s capability and possibility to exercise autonomy?	F0004
Respect for persons	Will withdrawal of the technology affect human dignity?	F0008
Legislation	Will withdrawal of the technology affect the realisation of basic human rights?	F0014

CS has been reimbursed in Switzerland since the 1980s, and as such there are likely to be patients that have been using it regularly for extended periods of time. Based on the reported usage rates of CS, there appears

to be a subset of the population that gain some benefit from its use (proven or otherwise). Therefore, patient and social aspects will play a role in the evaluation report. Sub-questions related to social aspects that are relevant to CS are outlined in Table 12.[84]

Table 12 Sub-questions: patient and social aspects

Topic	Research Question	Element ID
Patients' perspectives	How do patients perceive the technology under assessment?	H0006
Social group aspects	Are there groups of patients who currently don't have good access to available therapies?	H0201
Communication aspects	How are treatment choices explained to patients?	H0202

6.4 Sub-questions Organisational Issues

As CS is already reimbursed in Switzerland, there are few organisational issues involved in this application. The main issues that may arise due to the disimbursement of CS relate to the need for other technologies to supplement its use if removed, and management opportunities. The sub-question related to patient and social aspects that is relevant to CS is outlined in Table 13.[84]

Table 13 Sub-question: organisational aspects

Topic	Research Question	Element ID
Process-related costs	How does the technology modify the need for other technologies and use of resources?	D0023

7. Feasibility of HTA

Given that oral CS has been used and reimibursed for the management of osteoarthritic pain for a considerable time in the Switzerland, the review of continued support for this practice should be supported by a full assessment of the clinical evidence. This will provide the FOPH the necessary evidence to assess the effectiveness of oral CS within the current clinical management of osteoarthritsis.

This scoping review has identified a substantial body of evidence investigating the use of oral CS for the treatment of osteoarthritic pain in the knee. There is sufficient clinical data for knee osteoarthritis to conduct a full HTA with meta-analyses on the evidence for the key outcomes of VAS, WOMAC, adverse events, and

study withdrawals due to adverse events. These analyses will determine whether oral CS is efficacious, has a comparative effectiveness benefit compared to other same line interventions and is safe for the indication of knee osteoarthritis.

In contrast, evidence investigating the use of oral CS in the hips and hands is minimal. However, review of this limited evidence should be undertaken to determine whether it is sufficient to indicate qualitatively similar results to that observed for treatment of osteoarthritic pain in the knee. This will not deliver a definitive answer on CS use to manage hip or hand osteoarthritic pain, but it will provide the FOPH information on the promise and plausibility of its use for these indications. This will assist in the decision-making process to determine whether reimbursement should be continued.

The scoping searches did not identify existing economic models or budgetary impact analyses that are relevant to the Swiss context. Two published economic evaluations relevant to the current HTA were identified and reviewed; however, these evaluations have significant limitations and generalisability issues. If cost-effectiveness is evaluated in the HTA, a de novo economic model will be required; however, it is likely to contain substantial uncertainties due to the limited availability of long-term data on the relative effect of CS on joint replacement. The decision to conduct a cost-effectiveness analysis will be based on the decision matrix provided in Appendix C, following a review of the clinical safety and effectiveness of CS. A budgetary impact analysis with robust sensitivity analyses for uncertainties will be conducted to investigate financial impact of removing CS from the reimbursement list. The budget impact analysis will include the additional costs associated with adverse events caused by an increase in comparator interventions (e.g. NSAIDs).

Limited evidence was identified for organisational, legal, social and ethical issues. If reimbursement is stopped the organisational impact on the Swiss Healthcare system is likely to be minimal, given that patients will switch from using one to another drug. To acknowledge the relevance of patient and physician views within the context of a HTA disinvestment programme a targeted consultation survey will be distributed among patient and physician organisations during the HTA phase. In addition, in the full HTA the search for legal and ethical databases will be extended to collect evidence from comparable regions.

In conclusion, there is sufficient evidence to undertake a full HTA on the efficacy, effectiveness, and safety of oral CS for the management of osteoarthritis. The primary focus of the HTA should be the indication of osteoarthritic pain in the knee. A HTA should also present a profound economic analysis and review patient and physician perspectives to ensure the report is fair and also accounts for concerns of those directly involved.

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9. Appendices

9.1 Appendix A: Sources of literature (databases and websites)

Table 14 Databases searched and number of search results

Source	Location	Search results
PubMed	https://www.ncbi.nlm.nih.gov	1,097
Embase	https://www.embase.com/	889
The Cochrane Library (inc. CENTRAL)	https://www.cochranelibrary.com/	235
Cinahl	https://www.ebscohost.com/nursing/products/cinahl-databases/cinahl-complete	659
York CRD (inc HTA, NHS EED, DARE)	https://www.crd.york.ac.uk/CRDWeb/	25
CEA Registry	http://healtheconomics.tuftsmedicalcenter.org/cear4/home.aspx	1
Econlit	https://www.aeaweb.org/econlit/	7
ETHMED	http://www.ethicsweb.eu/search_ets	3
	Total	**2,916**

Table 15 Sources of literature (websites)

HTA Websites	
International	
National Information Centre of Health Services Research and Health Care Technology (NICHSR)	https://www.nlm.nih.gov/nichsr/db.html
National Library of Medicine Health Services/Technology Assessment Texts (HSTAT)	https://www.ncbi.nlm.nih.gov/books/NBK16710/
International Information Network on New and Emerging Health Technologies (EuroScan International Network)	https://www.euroscan-network.global/index.php/en/47-public-features/761-database-home
Australia	
Adelaide Health Technology Assessment	https://www.adelaide.edu.au/ahta/pubs/
Centre for Clinical Effectiveness, Monash University	http://monashhealth.org/health-professionals/cce/
Centre for Health Economics, Monash University	https://www.monash.edu/business/che
Austria	
Institute of Technology Assessment / HTA unit	https://www.oeaw.ac.at/ita/publikationen/
Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)	https://hta.lbg.ac.at/page/publikationen/en
Canada	
Institut national d'excellence en santé et en services sociaux (INESSS)	http://www.inesss.qc.ca/en/publications/publications/
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca/
Alberta Institute of Health Economics	http://www.ihe.ca/
The Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/

The Canadian Association for Health Services and Policy Research (CA-HSPR)	https://www.cahspr.ca/
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org/
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca/
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca/
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca/
Denmark	
Danish National Institute of Public Health	https://www.sdu.dk/en/sif/forskning
Finland	
Finnish National Institute for Health and Welfare	https://thl.fi/en/web/thlfi-en/publications
France	
French National Authority for Health (Haute Autorité de Santé; HAS)	https://www.hassante.fr/portail/jcms/fc_1249601/en/evaluation-recommandation
Germany	
German Institute for Medical Documentation and Information (DIMDI) / HTA	https://www.dimdi.de/dynamic/en/further-services/health-technology-assessment/
Institute for Quality and Efficiency in Health Care (IQWiG)	https://www.iqwig.de/en/projects-results/publications/iqwig-reports.1071.html
The Netherlands	
Health Council of the Netherlands (Gezondheidsraad)	https://www.gezondheidsraad.nl/
Zorginstituut Nederland	https://www.zorginstituutnederland.nl/
Norway	
Norwegian Knowledge Centre for the Health Services	https://www.fhi.no/sys/ks/
Singapore	
Agency for care effectiveness (ACE)	http://www.ace-hta.gov.sg/
Spain	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud “Carlos III”I / Health Technology Assessment Agency (AETS)	http://publicaciones.isciii.es/
Andalusian Agency for Health Technology Assessment (Spain)	http://www.aetsa.org/produccion-cientifica/
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.gencat.cat
Sweden	
Center for Medical Health Technology Assessment	http://www.cmt.liu.se/?l=en&sc=true
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
Switzerland	
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/
United Kingdom	
National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)	https://www.nihr.ac.uk/funding-and-support/funding-for-research-studies/funding-programmes/health-technology-assessment/
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
United States	

Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/research/findings/index.html
Harvard School of Public Health	http://www.hsph.harvard.edu/
Institute for Clinical and Economic Review (ICER)	http://www.icer-review.org/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Minnesota Department of Health (US)	http://www.health.state.mn.us/
Office of Health Technology Assessment Archive (US)	http://ota.fas.org/
U.S. Blue Cross / Blue Shield Association Technology Evaluation Center (Tec)	https://www.bcbs.com/the-health-of-america/topics/healthcare-technology Archived reports: https://effectivehealthcare.ahrq.gov/agency/blue-cross-and-blue-shield-association-technology-evaluation-center-tec
Veteran's Affairs Research and Development Technology Assessment Program (US)	http://www.research.va.gov/default.cfm
Clinical trial registries	
ClinicalTrials.gov	https://clinicaltrials.gov/
Cochrane Central Register of Controlled Trials	https://www.cochranelibrary.com/
EU Clinical Trials Registry	https://www.clinicaltrialsregister.eu/ctr-search/search
WHO International Clinical Trials Registry Platform (ICTRP)	http://www.who.int/ictrp/en/
Current Controlled Trials MetaRegister	http://www.isrctn.com
Australian New Zealand Clinical Trials Registry	http://www.anzctr.org.au/
Grey literature sources	
New York Academy of Medicine Grey Literature Report	http://www.greylit.org
Clinical practice guidelines	
Guidelines International Network (GIN)	https://www.g-i-n.net/library/international-guidelines-library
Association of Scientific Medical Societies (AWMF)	https://www.awmf.org/awmf-online-das-portal-der-wissenschaftlichen-medizin/awmf-aktuell.html
National Guideline Clearinghouse	https://www.ahrq.gov/gam/index.html

Search strategy, PubMed

1. Osteoarthritis[Text Word]
2. Gonarthrosis[Text Word]
3. Coxarthrosis[Text Word]
4. Arthrosis[Text Word]
5. Osteoarthrosis[Text Word]
6. Osteoarthritis[MeSH Terms]
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
8. Chondroitin[Text Word]
9. Chondroitin sulfate[Text Word]
10. Condrosulf[Text Word]
11. Structum[Text Word]
12. Chondroitin[MeSH Terms]
13. #8 OR #9 OR #10 OR ##11 OR #12
14. #7 AND #13

Search strategy, Embase

1. ‘Osteoarthritis’/exp
2. ‘Osteoarthr$’:ti,ab
3. ‘Gonarthosis’:ti,ab
4. ‘Coxarthrosis’:ti,ab
5. ‘Arthrosis’:ti,ab
6. #1 OR #2 OR #3 OR #4 OR #5
7. ‘Chondroitin sulfate’
8. ‘Chondroitin’:ti,ab
9. ‘Condrosulf’:ti,ab
10. ‘Chondrosulf’:ti,ab
11. ‘Structum’:ti,ab
12. #7 OR #8 OR #9 OR #10 OR #11
13. #6 AND #12
14. #13 AND [Embase]/lim NOT ([embsae]/lim AND [medline]/lim)

Search strategy, Econlit

1. TX chondroitin

Search Strategy, Cochrane

1. MeSH descriptor: [Chondroitin] explode all terms
2. (chondroitin);ti,ab,kw
3. #1 OR #2
4. MeSH descriptor: [Osteoarthr*] explode all trees
5. (osteoarthr*):ti,ab,kw
6. #4 OR #5
7. #3 AND #6

Search Strategy, York CRD (including DARE, NHS EED, HTA)

1. Chondroitin[Any field]
2. Osteoarthritis[Any field]
3. #1 AND #2

Search strategy, CEA Registry

1. TX Chondroitin

Search strategy, CINAHL

1. TX Osteoarthritis
2. TX Gonarthrosis
3. TX Coxarthrosis
4. TX Arthrosis
5. TX Osteoarthrosis
6. MH Osteoarthritis
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
8. TX Chondroitin
9. TX Chondroitin sulfate
10. TX Condrosulf
11. TX Structum

12. MH Chondroitin
13. #8 OR #9 OR #10 OR ##11 OR #12
14. #7 AND #13

Search strategy, Ethicsweb

1. Chondroitin

Table 16 Additional sources of literature (websites) to be searched for the full HTA report

Specialty websites	
Swiss Society of Rheumatology (SGR) (Schweizerische Gesellschaft für Rheumatologie)	https://www.rheuma-net.ch/de/
Swiss Clinical Quality Management in Rheumatic Diseases (SCQM)	https://www.scqm.ch/en/ueber-uns/
Groupe des Rhumatologues Genevois (Geneva Rheumatologists Group)	http://www.rhumage.ch/
Institute of Arthritis Research (iAR):	https://www.irr-research.org/home.html
Rheumasearch Foundation	http://www.rheumasearch.ch/
Geneva Medical Association	https://www.amge.ch/
Swiss Clinical Quality Management in Rheumatic Diseases	https://www.amge.ch/
Association Suisse des Polyarthritiques (Swiss Polyarthritis Association)	http://www.arthritis.ch/
Rheumaliga Schweiz (Swiss Association for Rheumatology Patients)	https://www.rheumaliga.ch/
Eular	https://www.eular.org/index.cfm
Rheuma-Suisse	http://www.rheuma-schweiz.ch/
Institute of Rheumatology Research (IRR)	https://www.irr-research.org/de/
Other sources	
National Institute for Heath and Care Excellence (NICE)	http://www.nice.org.uk
NHS National Institute for Health Research (NIHR), including HTA programme	http://www.nets.nihr.ac.uk/programmes/hta
EMA	http://www.ma.europa.eu/
Legal	
European Medicines Agency	https://www.ema.europa.eu/
World Medical Association	https://www.wma.net/
Ethical	
Bioethics Literature Database (BELIT)	http://www.ethicsweb.eu/search_ets
Current Contents	Access database through Ovid
Sociological Abstracts	https://www.proquest.com/products-services/socioabs-set-c.html
SIBILS	http://www.ethicsweb.eu/node/220
Bioethics Research Library Databases	https://bioethics.georgetown.edu/library-materials/bioethics-research-library-databases/
European Database on Literature of Ethics in Medicine (EUROETHICS)	http://www.ethicsweb.eu/node/238

9.2 Appendix B: Characteristics of included studies

Table 17 Characteristics of included studies for safety, efficacy and effectiveness (knee)

Author, year; country	Indication; Sample size; indication requirement	Design; Follow-up; Setting	Intervention	Relevant comparator*	Outcomes
Busci et al. 1998 Hungary	Knee n = 85 Kellgren & Lawrence scale 1-3	RCT 6 months Multi-centre trial	Chondroitin sulfate, (Condrosulf®) 800mg/day for 6 months.	Placebo Daily for 6 months	**Efficacy** • Pain (VAS) • Function (20m walk time) • Paracetamol intake • Lequesne Index **Safety** • Patient & physician judgement of global efficacy and tolerability (4-point scale)
Clegg et al. 2006 USA	Knee n = 1583 Kellgren & Lawrence grade 2-3, WOMAC pain score 125-400, knee pain >6m	RCT 24 weeks Multi-centre trial	Chondroitin sulfate (Donated by Bioiberica, S.A., Barcelona) 1200mg/day for 24 weeks.	(1) Placebo for 24 weeks (2) Celecoxib, (Celebrex, Pfizer) 200mg, once daily for 24 weeks	**Efficacy/Effectiveness** • Pain (VAS, WOMAC, OMERACT-OARSI) • Function (WOMAC, OMERACT-OARSI) • QoL (SF-36, HAQ) • Acetaminophen consumption **Safety** • Adverse events • Serious adverse events
Fardellone et al. 2013 France	Knee n = 837 OA of knee according to ACR criteria, Lequesne 7, VAS >40ml	RCT 24 weeks 126 centres in France, mostly GPs in primary care setting.	Chondroitin sulfate (Structum®) 1000mg/day for 24 weeks	Chondroitin sulfate Condrosulf® 1200mg/day for 24 weeks.	**Safety** • Adverse events • Withdrawals due to adverse events.
Fransen et al. 2015 Australia	Knee n = 605 Knee pain >6m, worst VAS >40ml	RCT 24 months Primary care setting	Chondroitin sulfate (manufactured by TSI Health Sciences Australia) 800mg/day, for 24 months.	Placebo for 24 months	**Efficacy** • Pain (10-point scale, WOMAC) • Function (WOMAC, 50-ft walk time) • QoL (SF-12) • Analgesic consumption • Radiographic joint space narrowing **Safety** • Withdrawals due to adverse events

Author, year; country	Indication; Sample size; indication requirement	Design; Follow-up; Setting	Intervention	Relevant comparator*	Outcomes
Kahan et al. 2009 France, Belgium, Switzerland, Austria, USA	Knee n = 622 Knee pain >3m, VAS >30ml	RCT 24 months Multi-centre trial	Chondroitin sulfate (manufactured by Genévrier Laboratories, Sophia Antipolis, France, and IBSA, Pambio ; Noranco, Switzerland) 800mg/day for 24 months	Placebo, once daily for 24 months	**Efficacy** • Pain (VAS, WOMAC) • Function (WOMAC) • Acetaminophen and NSAID consumption **Safety** • Adverse events • Patient assessment of tolerability (4 point ordinal scale)
Mazieres et al. 2001 France	Knee n = 132 OA of knee according to ACR criteria, Kellgren & Lawrence scale 2-3, VAS >30ml, Lequesne 4-11	RCT 6 months (3 months treatment) Rheumatology & GP clinics	Chondroitin sulfate (Structum®) 1000mg/day, for 3 months	Placebo, for 3 months	**Efficacy** • Lequesne Index • Pain (VAS) • Function (VAS) • Analgesic and NSAID (permitted) consumption **Safety** • Adverse events (spontaneously reported)
Mazieres et al. 2007 France, Switzerland	Knee n = 307 Knee pain >6m, VAS >40ml, Kellgren & Lawrence scale 2-3, Lequesne 6-12	RCT 24 weeks & a further 8 weeks follow up Rheumatologists	Chondroitin sulfate (Structum®) 1000mg/day for 24 weeks	Placebo, for 24 weeks	**Efficacy** • Pain on activity and at rest (VAS) • Lequesne Index • OMERACT-OARSI criteria responders • Analgesics and NSAID consumption • QoL (SF-12) **Safety** • Adverse events • Discontinuation of treatment due to adverse event
Michel et al. 2005 Switzerland	Knee n = 300 OA of knee according to ACR criteria, Kellgren & Lawrence scale 1-3	RCT 24 months Outpatient clinic; private rheumatology practices	Chondroitin sulfate (Condrosulf ®) 800mg/day for 24 months	Placebo, for 24 months	**Efficacy** • Pain (WOMAC) • Function (WOMAC) • Acetaminophen and NSAID consumption • Radiographic joint space narrowing **Safety** • Adverse events

Author, year; country	Indication; Sample size; indication requirement	Design; Follow-up; Setting	Intervention	Relevant comparator*	Outcomes
Morita et al. 2018 Japan	Knee n = 73 Kellgren & Lawrence scale 2-3, VAS >30ml	RCT; dose-comparison study 12 months Medical centres in Japan, hospital attended for assessments	Chondroitin sulfate, high dose (Donated by Seria Pharmaceutical Co.) 1560mg/day, for 12 months	Chondroitin sulfate, low dose (Donated by Seria Pharmaceutical Co.) 260mg/day, for 12 months	**Safety** • Adverse events
Morreale et al. 1996 Italy	Knee n = 146 Grade 1-2 OA**	RCT 6 months Two centres	Chondroitin sulfate (sponsored by IBSA, Institut Biochimique SA, Switzerland) 1200mg/day, for 3 months, followed by placebo for 3 months	Diclofenac sodium (an NSAID) 150mg/day for 1 month, followed by placebo for the 5 months.	**Effectiveness** • Lequesne Index • Spontaneous pain (VAS) • Pain on load (4 point ordinal scale) • Paracetamol consumption **Safety** • Adverse events
Pelletier et al. 2016 Canada	Knee n = 194 OA of knee according to ACR criteria, Kellgren & Lawrence scale 2-3, VAS >40ml	RCT 24 months Outpatient/private clinics, Canada	Chondroitin sulfate (Biobérica SA, Barcelona) 1200mg/day for 24 months	Celecoxib (Pfizer, Canada) 200mg/day for 24 months	**Efficacy/effectiveness** • Pain (VAS, WOMAC) • Function (WOMAC) • QoL (SF-36) • Acetaminophen consumption • Cartilage volume loss **Safety** • Withdrawal due to adverse events • Adverse events • Serious Adverse events
Railhac et al. 2012 France	Knee n = 48 OA of knee according to ACR criteria, Kellgren & Lawrence scale 2-3, VAS >30ml	RCT 48 weeks Rheumatology practice centres in France	Chondroitin sulfate (Structum®) 1000mg/day for 48 weeks	Placebo, for 48 weeks	**Efficacy/effectiveness** • Pain (VAS) • Lequesne Index • Paracetamol &/or NSAID consumption • Cartilage volume loss **Safety** • Adverse events

Author, year; country	Indication; Sample size; indication requirement	Design; Follow-up; Setting	Intervention	Relevant comparator*	Outcomes
Raynauld et al. 2013 Canada	Knee n = 57 (n=69 in original RCT) OA of knee according to ACR criteria, Kellgren & Lawrence scale 2-3, VAS >40ml	Post hoc analysis Follow-up (phone call, 4 years post study inception) (Wilde et al. 2011 report on original RCT)	Chondroitin sulfate (Condrosan®) 800mg once daily for 12 months	Placebo for 6 months, 800mg CS for following 6 months	**Effectiveness** • Progression to total knee replacement
Reginster et al. 2017 Belgium, Czech Republic, Italy, Poland, Switzerland	Knee n = 604 OA of knee according to ACR criteria, pain >3m, VAS >50ml	RCT 6 months Multi-centre	Chondroitin sulfate (Condrosulf®) 800mg/day for 6 months	(1) Placebo, for 6 months (2) Celecoxib (Celebrex, Pfizer) 200mg/day 6 months	**Efficacy/effectiveness** • Pain (VAS) • Lequesne Index • Paracetamol consumption **Safety** • Adverse events
Sawitzke et al. 2010 USA	Knee n = 622 (Ancillary to GAIT – Clegg et al. 2006; longer-term follow up here) OA of knee according to ACR criteria, Kellgren & Lawrence scale 2-3, pain >6m	RCT 24 months With participants remaining on originally assigned blinded treatment) Study centres (incl. universities and medical centres)	Chondroitin sulfate 1200mg/day	(1) Placebo for 24 weeks (2) Celecoxib, (Celebrex, Pfizer) 200mg, once daily for 24 weeks.	**Efficacy** • Pain (WOMAC, OMERACT/OARSI) • Function (WOMAC) **Safety** • Adverse events • Serious adverse events
Tio et al. 2017 Spain	Knee n = 70 OA of knee according to ACR criteria, Kellgren & Lawrence scale 2-3,	RCT 6 months Rheumatology Unit of Hospital, Spain	Chondroitin sulfate (Condrosan ®) 800mg once daily, for 6 months	Acetaminophen 3g daily for 6 months	**Effectiveness** • Pain (VAS) • Lequesne Index

Author, year; country	Indication; Sample size; indication requirement	Design; Follow-up; Setting	Intervention	Relevant comparator*	Outcomes
Uebelhart et al. 2004 Switzerland	Knee n = 120 OA of knee according to ACR criteria, Kellgren & Lawrence scale 1-3	RCT 12 months multicentre	Chondroitin sulfate (Condrosulf ®) 800mg, daily for two 3 month periods (0-3, and 6-9) over a 12-month period	Placebo	**Efficacy** • Pain (VAS) • Function (20m walk time) • Paracetamol consumption • Lequesne Index • Joint space narrowing **Safety** • Adverse events • Patient and investigator assessment of tolerability (4-point scale)
Uebelhart et al. 1998 Switzerland	Knee n = 46 NR	RCT 12 months Division of Physical Medicine Rehabilitation as in- or out-patients	Chondroitin sulfate (Condrosulf®) 800mg/day for 12 months	Placebo	**Efficacy** • Pain (VAS) • Function (VAS) • Patient and investigator judgement of tolerability using 4-point verbal score • Joint space narrowing **Safety** • Adverse events
Wildi et al. 2011 Switzerland, USA, Belgium, Italy, France,	Knee n = 69 OA of knee according to ACR criteria, Kellgren & Lawrence scale 2-3, VAS >40ml	RCT 12 months (2 phases) multicentre	(a) Double-blind phase: Chondroitin sulfate (Condrosan®) 800mg, daily for 6 months (b) Open-label phase: CS 800mg once daily for 6 months	(a) Double-blind phase: Placebo for 6 months (b) Open label phase: Open label use of CS 800mg once daily for 6 months	**Efficacy** • Pain (VAS, WOMAC) • Function (WOMAC) • QoL (SF-36) • Cartilage volume loss **Safety** • Adverse events

*Only comparators relevant to the current PICO are listed, other comparators may have been investigated. **Grading system no known.

Abbreviations: **ACR** = American College of Rheumatology, **CS** = Chondroitin Sulfate, **HAQ** = health assessment questionnaire, **NSAID** = non-steroidal anti-inflammatory drug, **OA** = osteoarthritis, **OARSI** = Osteoarthritis Research Society International, **OMERACT** = Outcome Measures in Rheumatology, **QoL** = quality of life, **RCT** = randomised controlled trial, **SF-36** = Short Form-36, **VAS** = visual analogue scale, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index

Table 18 Characteristics of included studies for safety, efficacy and effectiveness (hand)

Author, year	Indication; Sample size	Design; Follow-up; Setting	Intervention	Comparator	Outcomes
Gabay et al. 2011 Switzerland	Hand n = 162 OA of hand according to ACR criteria	RCT 6 months Rheumatology outpatient clinic, single centre	Chondroitin sulfate (Condrosulf®) 800mg/day for 6 months	Placebo, once daily for 6 months	**Efficacy** • Pain (VAS) • Function (FIHOA score, grip strength) • Acetaminophen consumption **Safety** • Adverse events • Patient assessment of tolerability (4-point ordinal scale)

Abbreviations: **ACR** = American College of Radiology, **FIHOA** = Functional Index for Hand OsteoArthritis, **OA** = osteoarthritis, **RCT** = randomised controlled trial, **VAS** = visual analogue scale.

Figure 4 Risk of bias in the included RCTs

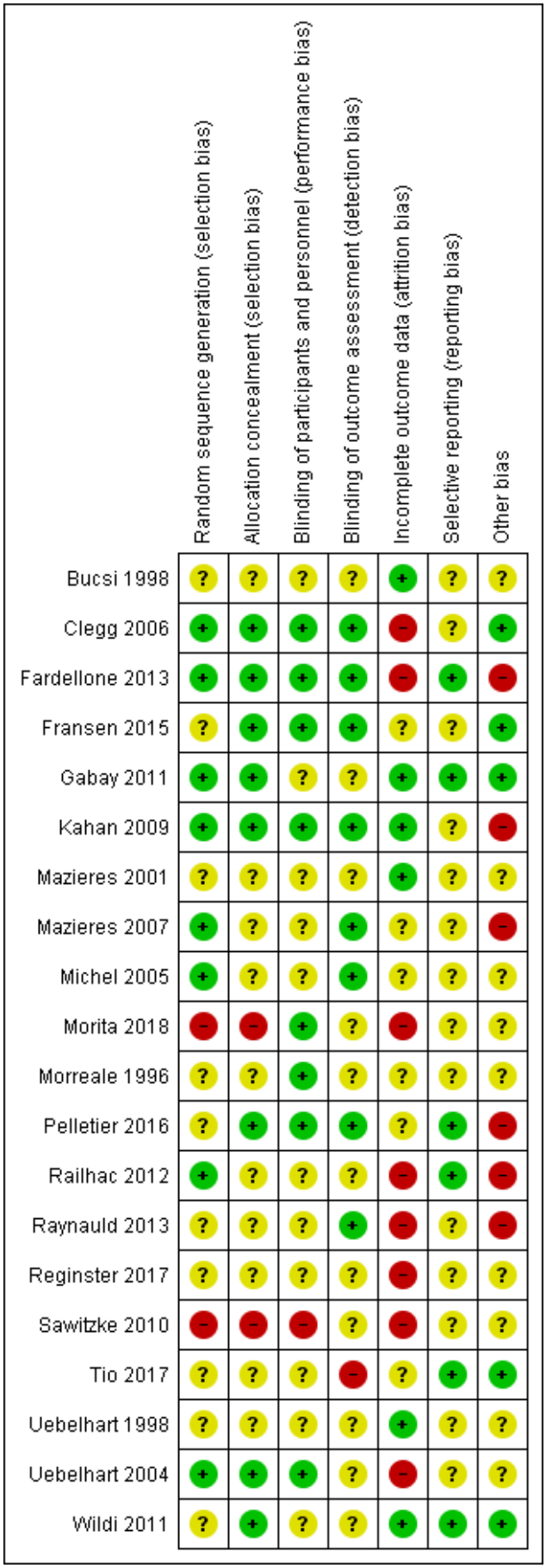

Table 19 Identified ongoing clinical trials fitting the inclusion criteria

Trial registry ID	Indication / Sample size	Intervention	Comparator	Primary outcomes	Recruitment status / Expected completion date
NCT01233739	Rhizarthrosis n=108	Chondroitin sulfate	Placebo	VAS pain score	Unknown April 2013
NCT00838487	Knee osteoarthritis n=240	Chondroitin sulfate	Placebo + exercise	Improvement in pain	Unknown March 2010
EUCTR2009-014516-35-FR	Symptomatic knee osteoarthritis n=460	Chondroitin sulfate	Placebo	Pain and function with WOMAC	Completed: 3 locations Ongoing: 1 location July 2011

Abbreviations: **fMRI** = functional magnetic resonance imaging, **NR** = not reported, **VAS** = visual analogue scale, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index.

9.3 Appendix C: Matrix of classification for economic evaluation

Table 20 Classification of economic evaluation types

		Comparative effectiveness			
Comparative safety		**Inferior**	**Uncertain[a]**	**Non-inferior[b]**	**Superior**
	Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
	Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
	Non-inferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
	Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

Abbreviations: **CEA**=cost-effectiveness analysis; **CMA**=cost-minimisation analysis; **CUA**=cost-utility analysis

Notes: **?** = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis; **a** Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations; **b** An adequate assessment of 'non-inferiority' is the preferred basis for demonstrating equivalence

9.4 Appendix D: Studies excluded at full-text review

Wrong Study Design

1. Barnhill JG, Fye CL, Williams DW, et al. Chondroitin product selection for the glucosamine/chondroitin arthritis intervention trial. J Am Pharm Assoc (2003) 2006;46(1):14-24.
2. Bourgeois P, Chales G, Dehais J, et al. Efficacy and tolerability of chondroitin sulfate 1200 mg/day vs chondroitin sulfate 3 x 400 mg/day vs placebo. Osteoarthritis Cartilage 1998;6 Suppl A:25-30.
3. Mazieres B, Loyau G, Menkes CJ, et al. [Chondroitin sulfate in the treatment of gonarthrosis and coxarthrosis. 5-months result of a multicenter double-blind controlled prospective study using placebo]. Rev Rhum Mal Osteoartic 1992;59(7-8):466-72.
4. Mazieres B, Loyau G, Menkes CJ, et al. Chondroitin sulfate for the treatment of coxarthrosis and gonarthrosis. A prospective, multicenter, placebo-controlled, double-blind trial with five months follow-up. Revue du rhumatisme et des maladies osteo-articulaires 1992;59(7):466-72.
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6. Zegels B, Crozes P, Uebelhart D, et al. Equivalence of a single dose (1200 mg) compared to a three-time a day dose (400 mg) of chondroitin 4&6 sulfate in patients with knee osteoarthritis. Results of a randomized double blind placebo controlled study. Osteoarthritis Cartilage 2013;21(1):22-7.
7. Zotkin EG, Kharitonova TV, Shkireeva S. [Clinical use of chondroitin sulfate in patients with osteoarthritis in geriatric practice]. Adv Gerontol 2014;27(2):366-75.

Wrong Intervention

8. Alekseeva LI, Benevolenskaia LI, Nasonov EL, et al. [Structum (chondroitin sulfate)--a new agent for the treatment of osteoarthrosis]. Ter Arkh 1999;71(5):51-3.
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11. Yang S, Dube CE, Eaton CB, et al. Longitudinal use of complementary and alternative medicine among older adults with radiographic knee osteoarthritis. Clin Ther 2013;35(11):1690-702.

Wrong Outcomes

12. Alekseeva LI, Mednikov BL, Piiavskii SA, et al. [Pharmacoeconomic aspects of use of structum in osteoarthrosis]. Ter Arkh 2001;73(11):90-2.
13. Conrozier T. [Chondroitin sulfates (CS 4&6): practical applications and economic impact]. Presse Med 1998;27(36):1866-8.
14. Mathieu P. Radiological progression of internal femorotibial osteoarthritis in gonarthrosis: effect of chondroitin sulfates ACS4-ACS6 as a structure modifying drug in knee OA (SMOAD). Presse medicale 2002;31(29):1386-90.
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Wrong Population

22. Brasky TM, Lampe JW, Slatore CG, et al. Long-term use of glucosamine and chondroitin and lung cancer risk in the vitamins and lifestyle (VITAL) cohort. Cancer Research 2011;71(8)

Wrong Publication Type

23. Demehri S, Hafezi Nejad N, Roemer F, et al. Chondroitin sulfate and glucosamine supplementation is associated with higher incidence of radiographic knee osteoarthritis and subsequent knee replacement: Nine years of follow-up data from the osteoarthritis initiative. Osteoarthritis and Cartilage 2016;24:S307.
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33. Möller I. Effcacy of chondroitin sulfate on synovitis in patients with knee osteoarthritis: An ultrasound study. Cartilage 2010;1(2):138S-39S.
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