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HTA Report

Title	Chondroitin Sulfate in Osteoarthritis
Author/Affiliation	JonHenry Jacobsen, Royal Australasian College of Surgeons Ross McLeod, eSYS Development Pty Limited Anje Scarfe, Royal Australasian College of Surgeons Thomas Vreugdenburg, Royal Australasian College of Surgeons David Tivey, Royal Australasian College of Surgeons

Bundesamt für Gesundheit
Sektion Health Technology Assessment
Schwarzenburgstrasse 157
CH-3003 Bern
Schweiz
Tel.: +41 58 462 92 30
E-mail: hta@bag.admin.ch

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Conflicts of Interest

The authors have no financial, academic, personal or any other conflicts of interest to declare in relation to this project.

Executive Summary

Chondroitin sulfate (CS) is available in Switzerland through mandatory health insurance for patients diagnosed with symptomatic osteoarthritis. The clinical effectiveness of CS, and consequently its reimbursement status, are being reviewed considering recently published evidence. To inform the coverage policy decision, this health technology assessment (HTA) report investigates the efficacy, effectiveness, safety, costs and cost-utility of CS used to treat osteoarthritis in the knees, hips and hands. Legal, social, ethical and organisational issues are also explored.

Clinical Evaluation

Safety, effectiveness and efficacy were assessed from 26 randomised controlled trials (RCTs). The included studies are of low to moderate quality. Most reported limitation was under-reporting of study methods. Knee is the most commonly studied indication (k = 23), followed by hand (k = 2) and hip (k = 1).

Knee Osteoarthritis

At six months, CS shows statistically significant differences to placebo in terms of pain (standardised mean difference [SMD], -0.28, 95% CI, -0.47, -0.09, p = 0.004), Lequesne index (mean difference [MD], -1.02, 95% CI, -1.73, -0.31, p = 0.005) and OMERACT-OARSI responder rate (risk ratio [RR], 1.18, 95% CI, 1.08, 1.29, p = 0.0001). The differences did not persist at later time points. The clinical relevance of these results is unclear, owing to small effect sizes and the absence of a clearly defined minimum clinically important difference for the Lequesne index. There is moderate heterogeneity between studies.

Subgroup and sensitivity analyses show that studies using (i) the lowest CS dose per day (800mg), (ii) IBSA CS, or (iii) studies with unclear randomisation report higher effect sizes for pain and Lequesne index than the overall meta-analysis results.

There is no difference in minimum joint space width between CS and placebo at 24 months. Other outcomes such as quality of life, function and progression to joint replacement were infrequently reported.

In terms of effectiveness, CS patients experience a slightly lower loss of medial cartilage volume at 24 months compared to patients on non-selective non-steroidal anti-inflammatory drugs (NSAID) (6.6% ± 3.3 vs 8.4% ± 4.2, P = 0.02), but there is no difference in lateral cartilage volume; the relevance of this finding is limited by the small number of participants and a lack of defined important

differences. No other significant differences between CS, NSAIDs or paracetamol are reported for any other effectiveness outcome at any time point.

Minor gastrointestinal-related adverse events are the most frequently reported safety concern. However, the relative safety of CS compared to placebo, paracetamol and NSAIDs is uncertain due to the low number of reported events in the included RCTs. Known side effects of comparator interventions (e.g. gastrointestinal events related to NSAID use) were not captured in the included RCTs and are therefore not reflected in this report. Safety data for CS is only available from the identified RCTs, so an expanded analysis of safety for the comparator interventions beyond RCT evidence was not conducted.

Hand Osteoarthritis

In only one study, pain, function and duration of morning stiffness were evaluated. Compared to placebo the outcomes improved, but the effect sizes were small and it was unclear whether these translate to clinically important differences. Paracetamol intake, grip strength, anatomical lesion progression scores and withdrawal rates did not differ statistically between the two groups. Comparative safety could not be determined due to the low number of adverse events in the study.

Hip Osteoarthritis

The only study to evaluate hip osteoarthritis found a statistically significant difference between CS and placebo with respect to pain and Lequesne index. The size and clinical importance of this difference is unknown due to unclear reporting of statistical methods in the study. Comparative safety could not be determined due to the low number of adverse events.

Ongoing Clinical Trials

No ongoing clinical trials were identified. Therefore, the results of the meta-analyses are unlikely to be affected by new information in the near future.

Costs and Cost-Effectiveness

A cost-utility analysis compares CS to placebo and cyclooxygenase-2 (COX-2) inhibitors in patients with knee osteoarthritis. Other indications (hips and hands) are not modelled due to the absence of available clinical data.

The incremental cost-effectiveness ratio (ICER) comparing CS to placebo is estimated to be CHF 30,451 per quality-adjusted life year (QALY) gained. Probabilistic sensitivity analysis using a hypothetical willingness-to-pay threshold of CHF 100,000 per QALY gained is associated with a 60% probability of CS being cost effective compared to placebo. CS is also compared to COX-2 selective NSAIDs in a trial-based economic analysis. Probabilistic sensitivity analysis indicates that

CS has a 34% probability of being superior (incremental cost <0, incremental effectiveness >0) to COX-2 selective NSAIDs. The uncertainty in the results of both economic analyses reflects the non-significant differences between treatments in longer-term health outcomes.

A budget impact analysis presents three scenarios of medicine substitution if CS were to be delisted:

1. The first scenario assumes 25% of current CS patients will substitute to other health insurance provider-supported medicines for osteoarthritis (i.e. paracetamol, non-selective NSAIDs plus proton pump inhibitors [PPIs] or COX-2 selective NSAIDs plus PPIs) in the event of CS being delisted. This results in an initial health insurance provider saving of CHF 18.2 million per year.
2. The second scenario assumes 50% of current CS patients will substitute to other health insurance provider-supported medicines for osteoarthritis, resulting in a saving of CHF 2.4 million per year.
3. In the third scenario, if 75% of current users substituted to other medicines, a net cost of CHF 13.3 million per year is estimated to be incurred. This net cost is a result of the higher cost of non-selective NSAIDs, PPIs and COX-2 selective NSAIDs compared to CS.

These scenarios were investigated due to a lack of public data relating to price and volume relationships between CS and other osteoarthritis medicines.

Social, Legal, Ethical, Organisational Issues

No major social, legal, ethical or organisational issues relating to CS were identified. Feedback from Swiss patient organisations estimated that approximately 50% of those patients currently prescribed CS may be unable or unwilling to pay out of pocket for the medication if it were to be delisted. It would still be available to patients wishing to pay (estimated annual out-of-pocket costs range from CHF 322 to CHF 381). Patients unable or unwilling to pay for CS will retain access to alternative medications reimbursed through mandatory health insurance (e.g. paracetamol, ibuprofen, COX-2).

Conclusion

The clinical findings of this report are extracted from a substantial body of evidence of low to moderate quality. Patients treated with CS report slightly greater reductions in osteoarthritic pain up to 6 months compared to placebo, but no difference compared to NSAIDs. The relative benefits are not demonstrated beyond 6 months. The rate of serious adverse events related to CS use is low, noting that this estimate is based on evidence with limited sample sizes and 12 months of follow-up.

Results of the economic and budget impact analyses should be interpreted with caution given the limitations in the evidence base and uncertainty in the findings. CS is associated with a 60%

probability of being cost-effective compared to placebo, and a 34% probability of being superior to COX-2 selective NSAIDs. The impact that delisting CS will have on the overall healthcare budget depends on the number of patients that change to alternative medications reimbursed through the mandatory health insurance.

Synthèse

En Suisse, le sulfate de chondroïtine (SC) est pris en charge par l'assurance-maladie obligatoire pour les patients chez lesquels une arthrose symptomatique est diagnostiquée. Son efficacité clinique et, partant, son remboursement font l'objet d'une réévaluation à l'aune de résultats de recherche récemment publiés. Afin d'éclairer la décision quant à la prise en charge, le présent rapport d'ETS (évaluation des technologies de la santé ou *health technology assessment*) étudie l'efficacité (en conditions idéales et réelles), l'innocuité, les coûts et le rapport coût-utilité du SC lorsqu'il est utilisé pour traiter l'arthrose du genou, de la hanche et de la main. Il explore également les questions juridiques, sociales, éthiques et organisationnelles.

Évaluation clinique

L'innocuité et l'efficacité (en conditions idéales et réelles) ont été évaluées à partir de 26 essais contrôlés randomisés (ECR). Les études incluses sont de qualité faible ou moyenne. La limitation la plus souvent constatée est une description insuffisante des méthodes employées. L'indication la plus étudiée est l'arthrose du genou (k = 23), suivie par l'arthrose de la main (k = 2) et celle de la hanche (k = 1).

Arthrose du genou

À six mois, le SC affiche des différences statistiquement significatives par rapport au placebo concernant la douleur (différence moyenne standardisée [DMS], -0,28, intervalle de confiance [IC] de 95 %, -0,47, -0,09, p = 0,004), l'indice de Lequesne (différence moyenne [DM], -1,02, IC de 95 %, -1,73, -0,31, p = 0,005) et la proportion de patients répondeurs selon les critères OMERACT-OARSI (ratio de risques [RR], 1,18, IC de 95 %, 1,08, 1,29, p = 0.0001) Par la suite, les différences ne persistent pas. La pertinence clinique de ces résultats est incertaine, étant donné les faibles tailles d'effet et l'absence de définition claire de la différence minimale cliniquement importante pour l'indice de Lequesne. L'hétérogénéité entre les études est moyenne.

Les analyses par sous-groupes et les analyses de sensibilité montrent que les études utilisant (i) la plus faible dose quotidienne de SC (800 mg) ou (ii) du SC d'IBSA et (iii) celles dont la randomisation est incertaine font état de tailles d'effet plus élevées concernant la douleur et l'indice de Lequesne que celles observées dans les résultats globaux de la méta-analyse.

S'agissant de la largeur minimale de l'interligne articulaire, on ne constate aucune différence entre le SC et le placebo à 24 mois. Les autres aspects, tels que la qualité de vie, le niveau de

fonctionnement du patient et la progression jusqu'au remplacement de l'articulation ont rarement été décrits.

En termes d'efficacité dans des conditions réelles, la perte de volume du cartilage médian est légèrement plus faible à 24 mois chez les patients traités au SC que chez ceux prenant des AINS (6,6 % ± 3,3 contre 8,4 % ± 4,2, P = 0,02), mais il n'y pas de différence dans le volume du cartilage latéral. La pertinence de ce résultat est toutefois limitée par le petit nombre de participants et un manque de définition des différences importantes. Pour tous les autres aspects relatifs à l'efficacité en conditions réelles, aucune différence significative entre le SC, les AINS et le paracétamol n'est rapportée, quel que soit le moment considéré.

S'agissant des problèmes d'innocuité, les sources mentionnent principalement des effets indésirables mineurs sur l'appareil gastro-intestinal. Cependant, l'innocuité relative du SC par rapport au placebo, au paracétamol et aux AINS est incertaine, en raison du faible nombre d'effets indésirables rapportés dans les ECR inclus. Les effets secondaires connus des interventions avec lesquelles le SC était comparé (p. ex. les effets gastro-intestinaux des AINS) n'ont pas été relevés au cours des ECR inclus et ne sont donc pas reflétés dans le présent rapport. Comme seuls les ECR identifiés fournissent des données sur l'innocuité du SC, il n'a pas été procédé à une analyse d'innocuité élargie au-delà des preuves fournies par les ECR pour les comparateurs.

Arthrose de la main

Une seule étude a évalué la douleur, le niveau de fonctionnement du patient et la durée de la raideur matinale. Les résultats sont meilleurs qu'avec le placebo, mais les tailles d'effet sont faibles, et il n'est pas certain qu'elles se traduisent par des différences cliniquement importantes. La consommation de paracétamol, la force de préhension, les scores de progression des lésions anatomiques et les taux de retrait des participants ne diffèrent pas statistiquement entre les deux groupes. L'innocuité comparée n'a pas pu être déterminée, en raison du faible nombre d'effets indésirables survenus pendant l'étude.

Arthrose de la hanche

La seule étude à évaluer l'arthrose de la hanche relève une différence statistiquement significative entre le SC et le placebo en ce qui concerne la douleur et l'indice de Lequesne. L'ampleur et l'importance clinique de cette différence sont inconnues, car les méthodes statistiques ne sont pas décrites suffisamment clairement dans l'étude. L'innocuité comparée n'a pas pu être déterminée, en raison du faible nombre d'effets indésirables survenus.

Essais cliniques en cours

Aucun essai clinique en cours n'a été identifié. Par conséquent, il est peu probable que les résultats des méta-analyses soient affectés par de nouvelles informations dans un avenir proche.

Coûts et rapport coût-efficacité

Une analyse coût-utilité compare le SC au placebo et aux inhibiteurs de la cyclooxygénase-2 (COX-2) chez les patients souffrant d'une arthrose du genou. Les autres indications (hanche et main) ne sont pas modélisées faute de données cliniques disponibles.

Le rapport coût-efficacité différentiel comparant le SC au placebo est estimé à 30 451 francs par année de vie pondérée par la qualité (QALY) gagnée. Selon une analyse de sensibilité probabiliste utilisant un seuil hypothétique de consentement à payer de 100 000 francs par QALY gagnée, la probabilité que le SC ait un bon rapport coût-efficacité par rapport au placebo est de 60 %. Le SC est également comparé aux AINS sélectifs de la COX-2 au moyen d'une analyse économique fondée sur les essais cliniques. L'analyse de sensibilité probabiliste indique que le SC a une probabilité de 34 % d'être meilleur (coût incrémental < 0, efficacité différentielle > 0) que les AINS sélectifs de la COX-2. Le caractère incertain des résultats des deux analyses économiques reflète l'absence de différence significative entre les traitements s'agissant des bénéfices à long terme pour la santé des patients.

Une analyse d'impact budgétaire présente trois scénarios partant de l'hypothèse que le SC serait retiré de la liste des médicaments remboursables et remplacé par d'autres traitements :

1. Le premier scénario postule que 25 % des patients prenant actuellement du SC le remplaceront par d'autres médicaments pris en charge par leur assurance-maladie pour le traitement de l'arthrose (p. ex. le paracétamol, les AINS non sélectifs combinés aux inhibiteurs de la pompe à protons [IPP], les AINS sélectifs de la COX-2 combinés aux IPP). Il en résulterait une économie initiale de 18,2 millions de francs par an pour les assureurs-maladie.
2. Le second scénario suppose que 50 % des patients concernés remplaceront le SC par d'autres médicaments pris en charge par leur assurance-maladie, générant une économie de 2,4 millions de francs par an.
3. Dans le troisième scénario, 75 % des utilisateurs du SC se tournent vers d'autres médicaments, entraînant un coût net estimé à 13,3 millions de francs par an. En effet, les AINS non sélectifs, les IPP et les AINS sélectifs de la COX-2 coûtent plus cher que le SC.

Ces scénarios ont été étudiés en raison d'un manque de données publiques concernant les relations en termes de prix et de volume entre le SC et les autres médicaments contre l'arthrose.

Questions sociales, juridiques, éthiques et organisationnelles

Aucun problème majeur d'ordre social, juridique, éthique ou organisationnel n'a été identifié en ce qui concerne le SC. Selon les indications des organisations de patients suisses, on peut estimer qu'environ 50 % des patients à qui le SC est actuellement prescrit seraient susceptibles de ne pas pouvoir ou de ne pas vouloir payer ce médicament de leur poche s'il cessait d'être remboursé. Les personnes disposées à payer pourraient toujours se le procurer (ce qui représenteraient pour elles un coût annuel estimé entre 322 et 381 francs par an). Les patients ne souhaitant pas ou ne pouvant pas payer le SC auraient toujours accès à des médicaments alternatifs remboursés par l'assurance-maladie obligatoire (p. ex. le paracétamol, l'ibuprofène et la COX-2).

Conclusions

Les résultats cliniques présentés dans ce rapport sont extraits d'une quantité substantielle de sources, dont la qualité est moyenne ou faible. Jusqu'à six mois, la réduction de la douleur liée à l'arthrose, telle que rapportée par les patients, est légèrement plus importante avec le SC qu'avec le placebo. On ne constate cependant aucune différence par rapport aux AINS. Au-delà de six mois, les bénéfices relatifs ne sont pas démontrés. Le taux d'effets indésirables liés à l'utilisation du SC est faible, mais il faut garder à l'esprit que cette estimation repose sur des études utilisant des échantillons de taille limitée et suivis pendant seulement 12 mois.

Les résultats des analyses économiques et d'impact budgétaire doivent être interprétés avec prudence étant donné les limitations des données sur lesquelles elles reposent et l'incertitude quant aux résultats La probabilité que le SC ait un bon rapport coût-efficacité par rapport au placebo est de 60 %, celle qu'il surpasse les AINS sélectifs du COX-2 s'élève à 34 %. L'impact du déremboursement du SC sur les coûts globaux de la santé dépendra du nombre de patients qui se tourneront vers des médicaments alternatifs remboursés par l'assurance-maladie obligatoire.

Zusammenfassung

Chondroitinsulfat (CS) wird in der Schweiz bei Patientinnen und Patienten, bei denen eine symptomatische Arthrose diagnostiziert wurde, von der obligatorischen Krankenversicherung übernommen. Die klinische Wirksamkeit von CS und demzufolge der Vergütung des Präparats sind unter Berücksichtigung kürzlich veröffentlichter evidenzbasierter Erkenntnisse überprüft worden. Um Informationen für die Entscheidung über die Vergütungsregelung bereitzustellen, wurden in diesem Bericht zur Bewertung von Gesundheitstechnologien (HTA) die Wirksamkeit unter idealen Bedingungen und unter Alltagsbedingungen, die Sicherheit sowie die Kosten und das Kosten-Nutzwert-Verhältnis von CS bei der Behandlung von Knie-, Hüft- und Handarthrose untersucht. Zudem wurde auf rechtliche, soziale, ethische und organisatorische Probleme eingegangen.

Klinische Beurteilung

Die Sicherheit sowie die Wirksamkeit unter Alltagsbedingungen und unter idealen Bedingungen wurden anhand von 26 randomisierten kontrollierten Studien (RKS) beurteilt. Die berücksichtigten Studien sind von geringer bis mittlerer Qualität. Die am häufigsten genannte Einschränkung in den Studien war die unzureichende Darlegung der Studienmethoden. Das Knie war die am häufigsten untersuchte Indikation (k = 23), gefolgt von der Hand (k = 2) und der Hüfte (k = 1).

Kniearthrose

Nach sechs Monaten zeigten sich unter CS statistisch signifikante Unterschiede zu Placebo hinsichtlich der Schmerzen (standardisierte mittlere Differenz [SMD] -0,28, 95% VI, -0,47, -0,09, p = 0,004), des Lequesne-Index (mittlere Differenz [MD] -1,02, 95% VI, -1,73, -0,31, p = 0,005) und der OMERACT-OARSI-Ansprechrate (relatives Risiko [RR] 1,18, 95% VI, 1,08, 1,29, p = 0,0001). Zu späteren Zeitpunkten bestanden keine Unterschiede mehr. Die klinische Relevanz dieser Ergebnisse ist nicht klar, da die Effektstärken klein sind und ein klar definierter klinisch bedeutsamer Mindestunterschied für den Lequesne-Index fehlt. Zwischen den Studien besteht eine mässige Heterogenität.

Untergruppen- und Sensitivitätsanalysen zeigten, dass in Studien, in denen (i) die tiefste Tagesdosis CS (800 mg) oder (ii) IBSA CS angewandt wurde, oder in (iii) Studien mit unklarer Randomisierung höhere Effektstärken hinsichtlich der Schmerzen und des Lequesne-Index angegeben wurden als in den Resultaten der Metaanalyse insgesamt.

Nach 24 Monaten war in Bezug auf die minimale Gelenkspaltbreite kein Unterschied zwischen CS und Placebo festzustellen. Weitere Behandlungsergebnisse wie Lebensqualität, Funktion der Gelenke und das Fortschreiten der Krankheit bis zum Gelenkersatz, wurden selten berichtet.

Was die Wirksamkeit unter Alltagsbedingungen anbelangt, ist bei CS-Patienten im Vergleich zu Patienten unter nichtsteroidalen Antirheumatika (NSAR) nach 24 Monaten eine etwas geringere Abnahme des medialen Knorpelvolumens festgestellt worden (6,6% ± 3,3 gegenüber 8,4% ± 4,2, P = 0,02). Beim lateralen Knorpelvolumen liess sich jedoch kein Unterschied beobachten. Aufgrund der geringen Teilnehmerzahl und des Fehlens von einem klar definierten klinisch bedeutsamen Mindestunterschied ist dieses Resultat nur von beschränkter Relevanz. In Bezug auf andere Behandlungsergebnisse, welche die Wirksamkeit unter Alltagsbedingungen betreffen, wurde zu keinem Zeitpunkt über weitere signifikante Unterschiede zwischen CS, NSAR oder Paracetamol berichtet.

Hinsichtlich der Sicherheit wurden am häufigsten leichte unerwünschte Ereignisse genannt, die den Magen-Darm-Trakt betrafen. Aufgrund der geringen Zahl von gemeldeten Ereignissen in den berücksichtigten RKS ist die relative Sicherheit von CS im Vergleich zu Placebo, Paracetamol und NSAR jedoch nicht klar. Bekannte Nebenwirkungen von Vergleichsinterventionen (z. B. gastrointestinale Ereignisse im Zusammenhang mit der Einnahme von NSAR) wurden in den berücksichtigten RKS nicht erfasst und kommen somit in diesem Bericht nicht zum Ausdruck. Die Sicherheitsdaten für CS sind nur aus den herangezogenen RKS verfügbar. Somit wurde keine erweiterte Sicherheitsanalyse für die Vergleichsinterventionen durchgeführt, die über die RKS-Evidenz hinausgeht.

Handarthrose

Nur in einer Studie wurden Schmerzen, Gelenksfunktion und Dauer der Morgensteifigkeit untersucht. Im Vergleich zu Placebo wurden bessere Behandlungsergebnisse erzielt, doch die Effektstärken waren gering und es war unklar, ob diese zu klinisch bedeutsamen Unterschieden führen. In Bezug auf die Paracetamol-Einnahme, die Greifkraft, die Werte hinsichtlich des Fortschreitens der anatomischen Läsion und die Ausstiegsraten waren keine statistischen Unterschiede zwischen den beiden Gruppen festzustellen. Aufgrund der geringen Zahl von unerwünschten Ereignissen in der Studie war kein Sicherheitsvergleich möglich.

Hüftarthrose

In der einzigen Studie zu Hüftarthrose wurde in Bezug auf Schmerzen und den Lequesne-Index ein statistisch signifikanter Unterschied zwischen CS und Placebo festgestellt. Das Ausmass und die klinische Bedeutung dieses Unterschieds sind nicht bekannt, da in der Studie keine klaren Angaben

zu den statistischen Methoden gemacht werden. Aufgrund der geringen Zahl von unerwünschten Ereignissen war kein Sicherheitsvergleich möglich.

Laufende klinische Studien

Es wurden keine laufenden klinischen Studien identifiziert. Somit ist es unwahrscheinlich, dass die Ergebnisse der Metaanalysen in naher Zukunft durch neue Informationen beeinflusst werden.

Kosten und Kosteneffektivität

In einer Kosten-Nutzwert-Analyse wurde CS mit Placebo und Cyclooxygenase-2-Hemmern (COX-2-Hemmer) bei Patienten mit Kniearthrose verglichen. Andere Indikationen (Hüfte und Hand) wurden nicht modelliert, da keine klinischen Daten verfügbar sind.

Das inkrementelle Kosten-Effektivitäts-Verhältnis (ICER) für den Vergleich zwischen CS und Placebo wurde auf CHF 30’451 pro gewonnenes qualitätsbereinigtes Lebensjahr (QALY) geschätzt. Die probabilistische Sensitivitätsanalyse, für die eine hypothetische Zahlungsbereitschaftsschwelle von CHF 100’000 pro gewonnenes QALY herangezogen wurde, ergab eine Wahrscheinlichkeit von 60%, dass CS im Vergleich zu Placebo kosteneffektiv ist. In einer studienbasierten Wirtschaftlichkeitsanalyse wurde CS auch mit COX-2-selektiven NSAR verglichen. Die probabilistische Sensitivitätsanalyse wies darauf hin, dass CS COX-2-selektiven NSAR mit einer Wahrscheinlichkeit von 34% überlegen ist (inkrementelle Kosten <0, inkrementelle Effektivität >0). Die Unsicherheit der Resultate der beiden Wirtschaftlichkeitsanalysen widerspiegelt die nicht signifikanten Unterschiede zwischen den Behandlungen bei den längerfristigen Behandlungsergebnissen.

In einer Budget-Impact Analyse werden drei Szenarien für den Ersatz des Medikaments präsentiert, falls CS aus der Liste gestrichen werden sollte:

1. Beim ersten Szenario wird davon ausgegangen, dass 25% der derzeitigen CS-Patienten auf andere von der Krankenversicherung übernommene Arthrosemedikamente umsteigen werden (d. h. Paracetamol, nichtselektive NSAR in Kombination mit Protonenpumpenhemmern [PPI] oder COX-2-selektive NSAR in Kombination mit PPI), falls CS aus der Liste gestrichen wird. Dies führt zu anfänglichen Einsparungen für die Krankenversicherer in Höhe von CHF 18,2 Millionen pro Jahr.
2. Beim zweiten Szenario wird angenommen, dass 50% der derzeitigen CS-Patienten auf andere von der Krankenversicherung übernommene Arthrosemedikamente umsteigen werden, was Einsparungen im Umfang von CHF 2,4 Millionen pro Jahr zur Folge haben wird.

3. Falls wie im dritten Szenario 75% der derzeitigen Anwender auf andere Medikamente umsteigen, werden gemäss den Schätzungen Nettokosten von CHF 13,3 Millionen pro Jahr anfallen. Diese Nettokosten sind darauf zurückzuführen, dass nichtselektive NSAR, PPI und COX-2 selektive NSAR höhere Kosten verursachen als CS.

Diese Szenarien wurden geprüft, weil keine öffentlichen Daten zu den Preis- und Volumenverhältnissen zwischen CS und anderen Arthrosemedikamenten verfügbar sind.

Soziale, rechtliche, ethische und organisatorische Probleme

Es wurden keine bedeutenden sozialen, rechtlichen, ethischen oder organisatorischen Probleme im Zusammenhang mit CS festgestellt. Gemäss Schätzungen in Rückmeldungen von Schweizer Patientenorganisationen sind möglicherweise etwa 50% der Patienten, denen zurzeit CS verschrieben wird, nicht in der Lage oder bereit, das Medikament selbst zu bezahlen, falls es aus der Liste gestrichen werden sollte. Für Patienten, die das Medikament selbst bezahlen möchten, wäre es weiterhin erhältlich (geschätzte selbst aufzubringende Kosten pro Jahr: CHF 322 bis 381). Patienten, die CS nicht selbst bezahlen können oder möchten, werden weiterhin Zugang zu anderen Medikamenten haben, die von der obligatorischen Krankenversicherung übernommen werden (z. B. Paracetamol, Ibuprofen, COX-2-Hemmer).

Fazit

Die klinischen Erkenntnisse in diesem Bericht stammen aus umfangreichen evidenzbasierten Daten von mittlerer bis geringer Qualität. Mit CS behandelte Patienten gaben im Vergleich zu Placebo während bis zu sechs Monaten eine leicht stärkere Linderung der Arthroseschmerzen, aber keinen Unterschied zu NSAR an. Über sechs Monate hinaus wurde kein relativer Nutzen aufgezeigt. Die Rate der schweren unerwünschten Ereignisse im Zusammenhang mit CS war niedrig. Allerdings ist zu beachten, dass diese Schätzung auf evidenzbasierten Daten mit beschränkten Stichprobengrössen und einer 12-monatigen Nachkontrolle beruht.

Angesichts der eingeschränkten Evidenzbasis und der unsicheren Erkenntnisse ist bei der Interpretation der Ergebnisse der Wirtschaftlichkeits- und Budget-Impact Analysen Zurückhaltung angebracht. Im Vergleich zu Placebo ist CS mit einer Wahrscheinlichkeit von 60% kosteneffektiv. Zudem ist das Präparat COX-2-selektiven NSAR mit einer Wahrscheinlichkeit von 34% überlegen. Die Wirkung, welche die Streichung von CS aus der Liste auf die gesamten Gesundheitsausgaben haben wird, hängt davon ab, wie viele Patienten auf andere Medikamente umsteigen werden, die von der obligatorischen Krankenversicherung übernommen werden.

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Abbreviations and Acronyms

AAOS	American Academy of Orthopaedic Surgeons
ACR	American College of Rheumatology
AQol	Australian Assessment of Quality of life
CAM	Complementary and Alternative Medicines
CHF	Swiss Franc
CI	Confidence Interval
COX-2	Cyclooxygenase-2
CS	Chondroitin Sulfate
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Disease
EQ-5D	EuroQol 5 Dimensions
EULAR	European League Against Rheumatism
EUnetHTA	European Network for Health Technology Assessment
FIHOA	Functional Index for Hand OsteoArthritis
FOPH	Federal Office of Public Health
GP	General Practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire-Disability Index
HTA	Health Technology Assessment
HUI	Health Utility Index
ICER	Incremental Cost-Effectiveness Ratio
MD	Mean Difference
MeSH	Medical Subject Headings
NCC-CC	National Collaborating Centre for Chronic Conditions
NICE	National Institute for Health and Care Excellence
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug

ns-NSAID	non-selective Non-Steroidal Anti-Inflammatory Drug
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology
OR	Odds Ratio
PANLAR	Panamerican League of Associations for Rheumatology
PICO	Patients, Intervention, Comparator, Outcome
PPI	Proton Pump Inhibitor
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
RACGP	The Royal Australian College of General Practitioners
RR	Risk Ratio
SD	Standard Deviation
SF-12/36	Short Form-12/36
SMD	Standardised Mean Difference
SYSADOA	SYmptomatic Slow-Acting Drugs for OsteoArthritis
VAS	Visual Analogue Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Objective of the HTA Report

The Federal Office of Public Health (FOPH) is reviewing the public reimbursement of chondroitin sulfate (CS) for the treatment of symptomatic osteoarthritis in the hips, knees and hands.

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

The objective of an HTA report is to generate a focused assessment on various aspects of a health technology. HTA reports address well-defined research questions (established in the scoping phase), search bibliographic databases or generate data directly, select appropriate studies, apply analytical methodology, and synthesise and qualify the available evidence. In addition to the clinical evidence, the HTA report presents an economic and financial analysis and investigates the social, ethical, legal and organisational issues of removing the technology from the reimbursement list.

1. Policy Question and Context

CS is currently available in Switzerland through mandatory health insurance for patients diagnosed with symptomatic osteoarthritis. The two primary formulations of CS available in Switzerland, Structum® and Condrosulf®, were added to the drug list for reimbursement in the 1980s. For both formulations, it is advised that if patients experience no improvement in joint pain within six months, continuation of therapy should be re-assessed.

Contemporary clinical practice guidelines from North America, Australia and Europe do not agree on whether CS is effective at treating osteoarthritis. Several published guidelines recommend against the intervention, including the American Academy of Orthopaedic Surgeons (AAOS)[1], American College of Rheumatology (ACR)[2], the National Collaborating Centre for Chronic Conditions (NCC-CC)[3], the National Institute for Health and Care Excellence (NICE)[4] and The Royal Australian College of General Practitioners (RACGP)[5]. In contrast, the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Disease (ESCEO), European League Against Rheumatism (EULAR) and the Panamerican league of Associations for Rheumatology recommend CS use for patients with osteoarthritis (see ***Table 68, Section 14***). In Switzerland, much debate exists around the clinical effectiveness of CS, and consequently its reimbursement status.

When CS was first reimbursed in the 1980s, clinical effectiveness was only investigated up to three months. Only in recent years has evidence become available on the safety and effectiveness of CS from studies following patients for longer periods. This HTA report was commissioned to evaluate evidence with mid-term (6 months) and long-term (12 and 24 months) follow-up data. This report also includes the first cost-utility and budget-impact analysis conducted in the Swiss context.

The evaluation of the safety, efficacy, effectiveness, and economic impact of CS in patients with osteoarthritis, as well as an analysis of social, legal, ethical and organisational issues related to CS consumption, will inform the coverage policy decision. The focus of this report is on osteoarthritis in the hips, knees and hands as these indications have the most available evidence.

2. Research Question(s)

1. What is the efficacy, effectiveness and safety of CS treatment in patients with symptomatic osteoarthritis in the knees, hips or hands compared to no pharmaceutical treatment, on-demand analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), placebo, or other anti-inflammatory treatments?
2. What are the costs, cost-effectiveness and impact of treating patients with symptomatic osteoarthritis in knees, hips or hands with CS compared to on-demand analgesics, NSAIDs, or other anti-inflammatory therapies?
3. What are the social, ethical, legal and organisational issues of treating patients with symptomatic osteoarthritis in knees, hips or hands budget with CS compared to on-demand analgesics, NSAIDs, or other anti-inflammatory therapies?

3. Medical Background

3.1 Disease Description

Osteoarthritis is a common degenerative joint condition and a leading cause of disability among the elderly worldwide. Initially thought to arise from general "wear and tear" of joints,[6] osteoarthritis is now considered an inflammatory disease influenced by intrinsic risk factors (aging, gender, obesity, heredity and reproductive variables), extrinsic risk factors (trauma, alignment, occupational and recreational usage) and genetics.[7 8] These factors culminate to induce pathological changes across the entire joint including alterations to the bone, cartilage, ligaments and muscles,[7 8] which manifests radiographically as osteophytes (bone spurs), subchondral sclerosis or cysts (thickening of the bone in joints), and narrowing of joint spaces.[5] However, it is worth noting that radiography is not required to diagnose osteoarthritis, and it often does not correlate with symptom severity.[9] Diagnosis is commonly based on physical examination and the patient's description of symptoms. Radiography and blood tests may be used to rule out other forms of arthritis.

Osteoarthritis can affect any joint, with the knees, hips and hands most commonly affected.[10-12] The natural course of osteoarthritis of the knee advances through grades of severity, ranging from minor to severe, where the severity of cartilage damage/loss, osteophyte growth, joint space narrowing, and pain/inflammation increases from almost imperceptible to near-disabling.[13] Clinically significant symptoms of osteoarthritis include joint pain, stiffness and loss of function. In later stages of the disease, osteoarthritic pain becomes persistent, and it is most apparent during movement of the affected joints.[14]

Individuals with osteoarthritis are more likely to have comorbidities compared to the general population.[15] Specifically, individuals with osteoarthritis are more likely to report concurrent chronic diseases such as hypertension, dyslipidaemia, back pain and thyroid disorders. These comorbidities increase the complexity of treating patients with osteoarthritis, as patients are more likely to be taking multiple medications.[15]

Osteoarthritis of the hand, hip and knee differ in their presentation and prevalence. In the United States and United Kingdom, knee and hand are the most frequently affected locations followed by the hip.[16 17] The incidence is influenced by gender and BMI with different rates among men, women and obese individuals.[18] Furthermore, hand osteoarthritis differs from the knee and hip with respect to inflammatory signs, acute symptom onset, structural progression and degree of disability. Hand osteoarthritis also has several disease phenotypes (e.g. erosive and non-erosive) that may reflect different pathological mechanisms.[19] Due to the functional and pathological differences between the joints, the European Medicines Agency (EMA) notes the efficacy of drugs for knee and hip osteoarthritis may not extrapolate to the hand.[20]

3.2 Incidence and Prevalence of Osteoarthritis

The proportion of elderly adults in Switzerland has increased substantially due to longer life expectancy at birth and declining mortality after age 80.[21 22] This means the country has a high burden of age-related diseases, and as the population continues to age, the burden is likely to increase.[23]

A 2010 global burden of disease study published in the British Medical Journal in 2014 reported approximately 10 to 15% of adults aged over 60 years have osteoarthritis, with a higher prevalence among women than men.[24] Hip and knee osteoarthritis was ranked as the 11th highest contributor to global disability. The report noted that the worldwide burden of disease attributable to osteoarthritis is increasing, with the total disability-adjusted life-years associated with osteoarthritis rising by 35% between 1990 and 2015.[24]

The Institute for Health Metrics and Evaluation estimates that the prevalence and incidence of osteoarthritis in Switzerland was 570,984.45 (lower limit: 509,986.57; upper: 642,110.60) and 25,785.22 (lower limit: 22,829.29; upper: 29,053.76) respectively, in 2017. The prevalence and incidence were higher among females than males at all ages. Further, the prevalence was greatest in individuals above 70, followed by 50–69-year olds and 15–49-year olds.[25]

3.3 Management

Two treatment management guidelines for knee (ESCEO)[26] and hand (EULAR) osteoarthritis[27] are presented below. It is unclear which treatment pathway is followed by Swiss Clinicians. The pathways reflect a stepwise approach to treating osteoarthritis based on systematic literature searches and the consensus of ESCEO and EULAR working group members. The treatment recommendations are not intended to be prescriptive; rather, treatment should reflect individual need considering patient age, presence of comorbidities and inflammation. These guidelines were selected because they represent the latest guidelines from European organisations. It is worth noting that multiple management guidelines exist, and they differ in their recommendations, specifically with respect to CS (***Table 68***).

Knee Osteoarthritis

First-line treatments recommended by ESCEO include physical therapy, education, weight loss and exercise. Patients should be referred to a physical therapist to determine whether physical treatments should be initiated and if they require correction for varus/valgus malalignment. Physical therapists should be engaged throughout the entire disease management process as they can provide other physical treatments that may provide symptom relief in parallel to pharmacological treatments. Additionally, patients should receive disease management education focusing on the promotion and implementation of lifestyle changes and the development of coping strategies. Exercise can include aerobic, resistance-training and/or strengthening exercises focusing on joint mobility.[26]

If patients remain symptomatic, pharmaceutical grade glucosamine and/or CS are recommended as a possible long-term therapy. Paracetamol is recommended as a rescue analgesic, owing to uncertain efficacy and safety. The guidelines recommend topical NSAIDs be considered in patients who remain symptomatic after utilising glucosamine or CS.[26]

NSAIDs are recommended for patients who failed previous treatments or have moderate-severe pain. Oral NSAIDs should be used intermittently or in short cycles owing to the gastrointestinal (GI) and cardiovascular risks associated with NSAIDs. The dose and duration of NSAIDs should be determined in accordance with the patient's risk profile. If patients are contraindicated for NSAIDs or remain symptomatic despite their use, ESCEO recommends intra-articular injections of hyaluronic acid and corticosteroids. Duloxetine and weak opioids are considered the last pharmacological treatment option for patients with osteoarthritis.[26]

Surgery is generally considered the last treatment option for patients with severe osteoarthritis. Surgical treatments include osteotomy or total or uni-compartmental knee replacement. Patients contraindicated for or unwilling to undergo surgery, may use opioids.[26] For further information refer to ***Figure 1***.

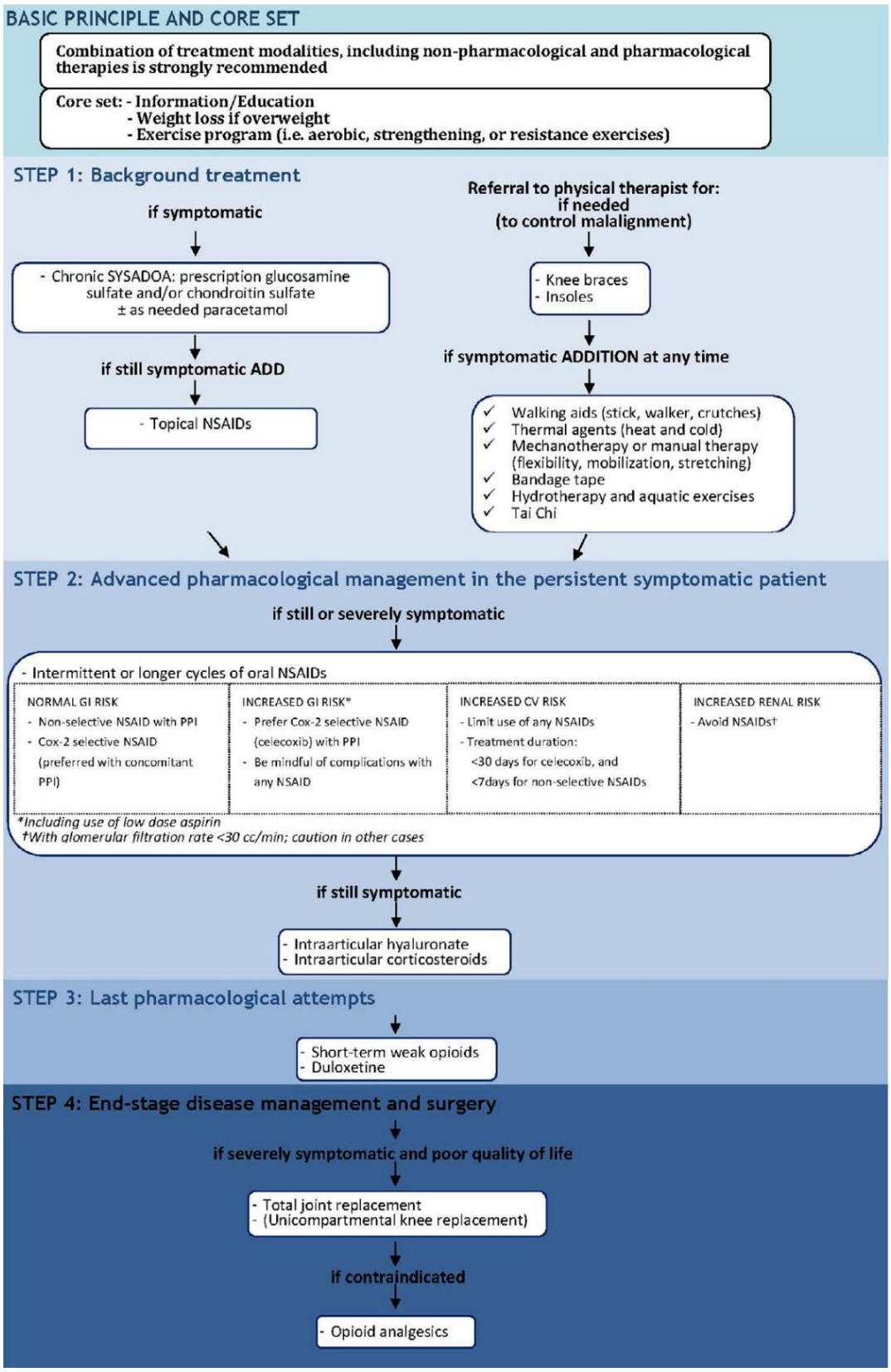


Figure 1 Clinical management pathway of osteoarthritis

Abbreviations
NSAIDs = non-steroidal anti-inflammatory drugs, **PPI** = proton pump inhibitor.
Source
Bruyere[26]

Hip Osteoarthritis

There were no recent European treatment management guidelines for hip osteoarthritis. The European Medicines Agency (EMA) suggests that extrapolating the findings of interventions targeting knee osteoarthritis to hip osteoarthritis is appropriate.[20] Thus, ESCEO recommendations for knee osteoarthritis could extend to the hip, noting that the last treatment option would be hip, rather than knee, replacement.

Hand Osteoarthritis

Treatment management guidelines for hand osteoarthritis are similar to those for the knee. Education, hand-specific exercises and orthoses comprise first-line treatment options for hand osteoarthritis as recommended by EULAR.[27] If pain persists, local treatments such as topical NSAIDs are recommended over systemic therapies if pain is moderate and only a few joints are affected. Paracetamol is the preferred long-term analgesic if well tolerated. For patients who do not respond to paracetamol, oral NSAIDs are recommended. EULAR suggests NSAIDs should be used at their lowest effective dose for the shortest duration. Individuals at risk of gastrointestinal side effects should consume a gastroprotective agent concomitantly. Symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) such as CS may provide pain relief and improve function. Intra-articular injections of corticosteroid are recommended for painful flares in individuals who do not respond to NSAIDs. For individuals with osteoarthritis of the thumb base unresponsive to conservative treatments, EULAR recommends surgery (e.g. arthroplasty or trapeziectomy. No management diagram was provided in EULAR.[27]

4. Technology

4.1 Technology Description

CS is a sulfated glycosaminoglycan found naturally in human bone and cartilage. It is a nutritional supplement that can be sourced from fish, bird, cow, pig, whale and shark cartilage. As an important structural component of cartilage, supplementation with CS is thought to restore the extracellular matrix, to prevent further cartilage degradation and to assist cartilage regeneration.[5,28] Specifically, CS is thought to reduce chondrocyte cell death (the primary cells involved in the synthesis of extracellular matrix and regulation of cartilage metabolism); increase the synthesis of proteoglycans and other components of the extracellular matrix; reduce the effects of proteinases involved in remodelling of the extracellular matrix; and reduce inflammatory mediators and free radicals.[29] These provide plausible mechanisms for the action of CS in osteoarthritis, although the mechanism of action of CS has primarily been tested in preclinical studies that may not be generalisable to human extremities. Therefore, clinical trials are required to confirm these observations.

The effects of CS, as with other SYSADOAs require extended administration before symptomatic relief is achieved. Many people use the supplement alone or in combination with glucosamine for the relief of osteoarthritic joint pain.[30]

Structum® and Condrosulf® are the two primary formulations of CS available in Switzerland. Structum® is bovine or avian derived (manufactured by Pierre Fabre, Switzerland), available in 500mg capsules taken orally twice a day (***Table 1***).[31 32] Condrosulf® is fish-derived (manufactured by IBSA, Switzerland), available in 400mg or 800mg doses (tablet, capsule or granule) taken orally, either one or two a day. Both products are manufactured in accordance with controlled and tested procedures. The recommended therapeutic dose of CS is 800–1200mg per day.[29]

CS is available through mandatory health insurance in Switzerland for patients with degenerative joint diseases. It can be prescribed by General Practitioners (GP) and Rheumatologists.[33] For both formulations, if there is no noticeable improvement of symptoms within six months, continuation of therapy should be re-assessed.[31 32] Dietary supplements containing CS are also available over the counter without a prescription; these products vary significantly in dose and quality and are not being considered in this assessment.[34 35]

Table 1 Key formulations of chondroitin sulfate 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 400mg and 800mg tablets, 400mg capsules, and 400mg granules. Dosage is 800mg/day. Taken before meals on an empty stomach. If no noticeable improvement of symptoms within 6 months, continuation of therapy should be checked.	Symptomatic treatment for osteoarthritis. Hypersensitivity to active substance or any 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/day. Taken with a glass of water. If no noticeable improvement of symptoms within 6 months, continuation of therapy should be checked.	Symptomatic treatment for osteoarthrosis. Known hypersensitivity to active substance or any ingredients according to the composition.

Abbreviations
mg = milligrams.
Source
Swissmedic.[31] [32]

4.2 Contraindications

There are few contraindications for CS. Product information documents from IBSA (Condrosulf®)[31] [36] and Pierre Fabre (Structum®)[32] indicate the product should not be taken by individuals allergic to the active ingredient, or those pregnant or breastfeeding.

Contemporary clinical practice guidelines (AAOS[1], ACR[2], NICE[4], ESCEO[26], EULAR[27] [37]European League against Rheumatism (EULAR)[27] [37], Osteoarthritis Research Society International (OARSI)[38] and Panamerican League of Associations for Rheumatology (PANLAR)[39]) do not report contraindications relating to CS. Swissmedic reports known hypersensitivity to Condrosulf® and Structum® as the only contraindication.[31] [32]

The French Agency for Food, Environmental and Occupational Health and Safety reported additional contraindications including diabetes, pre-diabetes, asthma or individuals receiving vitamin K antagonists (VKA sodium, potassium or calcium-restricted diets).[40] As Condrosulf® is derived from fish,[31] it is recommended that individuals with allergies to fish avoid consuming the product.[28]

4.3 Alternative Technologies

CS is usually prescribed either as a stand-alone therapy or in combination with glucosamine or analgesics. Relevant alternative technologies for osteoarthritis patients include on-demand analgesics and NSAIDs, other anti-inflammatory treatments, other pharmaceutical treatments, and non-pharmaceutical treatments.

On-demand analgesic use, or rescue analgesia, is recommended as a second-line treatment for osteoarthritis following the failure of conservative management. Oral analgesics are typically recommended as the first pharmaceutical therapy for osteoarthritis, due to their favourable safety profile compared to NSAIDs.[4] For example, paracetamol is the oral analgesic of choice as it is safe to use up to 4g per day.[37]

Anti-inflammatory treatments can include oral or topical corticosteroids and non-selective NSAIDs (ns-NSAIDs), and oral cyclooxygenase-2 (COX-2) selective inhibitors.[4 41] Due to the increased risk of gastrointestinal and cardiovascular complications associated with chronic use, oral anti-inflammatory treatments are typically recommended following failure of other on-demand analgesics or topical NSAIDs.[4]

Other pharmaceutical treatments could be topical creams with capsaicin,[42] or other SYSADOAs such as glucosamine.[33]

Non-pharmaceutical treatments can include self-management strategies such as heat packs and assistive devices (cane or walking frame), physiotherapy, massage therapy, occupational therapy, therapeutic ultrasound, laser therapy, or transcutaneous electrical nerve stimulation.[4] These are the approaches taken when no pharmaceutical treatment is prescribed. Psychosocial interventions and cognitive behavioural therapy are also considered non-pharmaceutical treatments.[2 5]

4.4 Regulatory Status / Provider

In Switzerland two CS preparations, Condrosulf® and Structum®, are listed on the “Spezialitätenliste” (***Table 1***) and both are currently reimbursed through mandatory health insurance. Physicians can prescribe either drug without additional training or further credentials.

Information was sought on reimbursement practices in other European countries. A search of the Danish Medicines Agency,[43] Norwegian Medicines Agency,[44] the Swedish Dental and Pharmaceutical Benefits Agency[45] for Structum®, Condrosulf®, or Chondroitin(e) did not produce any results.

CS is not listed on the Deutsche Institut fur Medizinische fixed medicines list,[46] National Health Service (NHS) medicine list[47] or by European Medicine Agency (Medicine or Herbal Medicine list).[48] Therefore,

CS is unlikely to be reimbursed by the respective government agencies. It is not recommended for prescription by the NHS.[49]

Condrosulf® but not Structum® is listed on the Italian Medicines Agency of authorised drugs, but it is unclear whether the drug is reimbursed.[50]

In France, the National Solidarity considers Structum®[51] and Condrosulf®[51] to have insufficient benefit and they are not reimbursed by health insurers for osteoarthritis of the hip or knee.[52] No pending decisions were found. CS is available in most countries as an over-the-counter dietary supplement.

5. Patients, Intervention, Comparator, Outcome (PICO)

5.1 Patients

The eligible 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 carpometacarpal joint, M19 – other and unspecified osteoarthritis).

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. While arthritic conditions in children exist, osteoarthritis does not occur in paediatric patients. Therefore, this age group is excluded from the current evaluation.

Patients with significant physical limitation and/or those non-responding to diligent pharmacotherapeutic intervention are 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.[31 32]

5.2 Intervention

The technology under investigation is oral pharmaceutical-grade CS. Two registered drugs are available in Switzerland that contain the active substance CS: Structum® and Condrosulf®. Structum® is available in 500mg capsules that are taken twice a day, equivalent to a daily intake of 1000mg.[32] Condrosulf® is available in 400mg or 800mg doses (tablet, capsule or granule) that are taken orally, either one or two a day, for an equivalent maximum dose of 800mg per day.[31] Other pharmaceutical-grade CS products that deliver at least the same minimum dosage as Structum® and Condrosulf® will also be included.

Drugs used in combination with CS, including glucosamine, is not relevant to the present investigation as they are not reimbursed or commonly used in Switzerland. No combination products are available on the Swissmedic database.

The symptomatic effects of Structum® and Condrosulf® are delayed, generally occurring one to two months into treatment.[31 32] In contrast, the effects of analgesics and anti-inflammatory medications are expected to act in a more immediate manner. Analgesics are recommended on-demand. NSAIDs, in particular, are not recommended for chronic use, but intermittently to treat acute flares and reduce side effects of the NSAID.[26]

It is recommended that treatment with CS is discontinued if no effect is seen within six months.[31 32 38] The exact length of treatment in current practice is unclear.

5.3 Comparator

Treatment for osteoarthritis may be non-pharmaceutical, pharmaceutical or surgical. As CS is a pharmaceutical treatment option, the relevant comparators to CS are other pharmaceutical therapies offering symptomatic relief, including on-demand analgesics, oral or topical NSAIDs, and other anti-inflammatory treatments (i.e. corticosteroids, COX-2). Opioids are excluded as they are last-line pharmaceutical treatments due to their addictive properties and long-term side effects. Non-pharmaceutical interventions are expected to be offered to all osteoarthritis patients.[26] Surgery is not included as a relevant comparator, as it is used as a last-line treatment in patients with severe osteoarthritis.

Recommendations published by OARSI for the management of hip and knee osteoarthritis state that paracetamol (up to 4g/day) can be an effective initial oral analgesic for the treatment of mild to moderate pain.[38]

OARSI recommendations state that alternative treatment options may be considered in patients that have an inadequate response to paracetamol.[38] Oral NSAIDs and topical NSAIDs or capsaicin are some of the alternative pharmacological interventions discussed. Under NICE guidelines, in the event that paracetamol and/or topical NSAIDs are insufficient, oral NSAIDs may be considered as an alternative treatment option.[4] Oral NSAIDs appear as a secondary option in the 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.[26] However, paracetamol and other analgesics are symptom-modifying drugs and do not affect the underlying pathology.[53]

OARSI and ESCEO recommendations state that the use of weak opioids should only be considered where other pharmacological agents have been ineffective or are contraindicated.[41 54] 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.[26] Similarly, intra-articular 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.[26 54]

5.4 Outcomes

Pharmaceutical-grade CS is prescribed to treat symptoms associated with osteoarthritis, with reduction of pain in the target joint 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.[9] Lastly, CS treatment may have structure-modifying effects and is considered an important endpoint[38] noting however, biochemical markers and imaging of bone and cartilage spacing do not correlate with symptoms experienced by patients.[9]

Minimally clinical important differences (MCIDs) for many of the outcomes can be found in ***18.1 Appendix D***.

Efficacy/Effectiveness

Critical

Pain can be measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale, Visual Analogue Scale (VAS) and Osteoarthritis Research Society International Outcome Measures in Rheumatology (OARSI-OMERACT) criteria. The pain domain of WOMAC is a five-item questionnaire measured using a four-point Likert scale or continuous scale (0 - 10).[55] Pain by VAS utilises a 10cm or 100mm scale with 0 reflecting no pain and 10 or 100 reflecting pain as bad it as it could be.[56]

Pain is the most clinically significant outcome. Clinically relevant differences in a patient's pain have been classified as a relative reduction of 15% to 20% in pain scores.[57] This is measured on a per-patient basis and presented as a mean difference (MD) 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.[57] For additional pain-scale-specific MCIDs refer to ***Table 84.***

Physical function can be measured with WOMAC, OARSI-OMERACT criteria, or other exercise tests (walk tests). The function domain of WOMAC consists of a 17-item questionnaire measured using a four-point Likert scale or continuous scale (0—10).[55] Reaching a score of four over two months is

considered clinically relevant when using WOMAC.[58] 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.[59] For further MCIDs refer to ***Table 84.***

Quality of Life (QoL) can be measured with Health Assessment Questionnaire (HAQ), Short form-36 questionnaire (SF-36), or Health Assessment Questionnaire-Disability Index (HAQ-DI). Quality of life tools directly measure clinically relevant outcomes.[57 60] For HAQ and SF-36 MCIDs refer to ***Table 84.***

The **Lequesne index** is a composite measure of osteoarthritis, which summarises algofunctional parameters of pain such as maximal walking distance and discomfort in daily life movements. It is scored on 11 items concerning pain and discomfort at specific times and positions, and functional abilities. The Lequesne index is directly relevant to a patient's clinical experience of pain, discomfort and functional ability.[61] No MCID for Lequesne index was identified.

Important

The important efficacy/effectiveness outcomes are concomitant analgesic consumption, progression to joint replacement or arthroscopy and radiographic evidence of disease progression.

Progression to joint replacement or arthroscopy is the endpoint of osteoarthritic treatment. Surgical approaches have inherent risks such as surgical site infection or prosthetic joint infection, and the need to heal from a surgical procedure.[62] Joint replacement is one of the last treatment options for patients with osteoarthritis so patients requiring joint replacement are indicative of disease progression and potentially treatment failure.

Concomitant analgesic or NSAID consumption is measured as mg per day, or percentage/number of days analgesics are consumed compared to the days of treatment.[63 64] Reduction in analgesic consumption is expected to prevent the negative consequences of gastrointestinal side effects or multi-organ failure.[65 66] Concomitant analgesics included paracetamol (acetaminophen), however, the type of NSAID was generally not specified. Consumption of analgesics and NSAIDs is reflective of pain experienced by the individual.

Radiographic evidence of disease progression of osteoarthritis is inferred by a reduction in cartilage volume or synovial membrane thickness.[67] Cartilage volume and synovial membrane thickness are measured directly via magnetic resonance imaging or ultrasound. However, cartilage volume is most frequently measured using joint space width on x-rays. In the context of knee osteoarthritis, joint space width is the distance from the tibial plateau to the femoral condyle (femorotibial compartment).[67] The distance between the two joints indirectly reflects the volume of cartilage. The minimum space between the two joints is the most frequently reported outcome, however, mean space (across the entire joint) is

often reported. For radiographic outcomes, only studies reporting at least 24-months follow-up are considered.[20] For MCIDs refer to ***Table 84***.

Safety

Critical

Mortality, serious adverse events, treatment-related serious adverse events, and withdrawals or discontinuation due to adverse events are 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,[30] however the comparative safety is of relevance to a disinvestment decision.

Important

Total, treatment- and gastrointestinal-related adverse events are important safety outcomes. Total adverse events represent the overall number of events that occur in the treated population, however, total rates do not provide an indication of the clinical significance of the events. For this reason, total, treatment- and gastrointestinal-related adverse events are important, but not critical safety outcomes.

5.5 Deviations from the Scoping Report

Deviations from the PICO criteria defined in the scoping report are as follows:

- For safety outcomes, the length of follow-up was changed from a minimum of six months to no minimum duration. This decision was made to allow all treatment-related adverse events to be identified in the analysis.
- Serious adverse events and adverse events were further refined into total, treatment-related and gastrointestinal-related events.
- For safety and efficacy outcomes, French, German and Spanish language articles were included.

Radiographic evidence of disease progression as inferred by joint space width, cartilage volume and synovial membrane thickness were considered for inclusion in the assessment of efficacy because they present the next-best available evidence for the effect of CS on disease progression following progression to joint replacement. Following EMA guidance, only outcomes with a minimum of 24 months follow-up were considered eligible for inclusion.[20]

5.6 PICO-Boxes

Table 2 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	Pharmaceutical grade CS (minimum 800mg per day) initial treatment followed by maintenance treatment for 3, 6, 12 or 24 months with or without analgesics on demand. *(Exclusions: combination drugs e.g. CS and glucosamine)*
C	Placebo, on-demand analgesics (e.g. paracetamol), NSAIDs (e.g. ibuprofen, COX-2) and other anti-inflammatory treatments (e.g. corticosteroids). *(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 • Radiographic evidence of disease progression (joint space width, cartilage volume, synovial membrane thickness) **Safety:** • Serious adverse events (total and treatment-related) • Withdrawals or discontinuation due to adverse events • Mortality Adverse events (total, treatment- and gastrointestinal-related)
S	**Efficacy/effectiveness:** • RCTs (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 review, letter to the editor, author response, case report)* **Safety:** • RCTs (with no minimum follow-up) • Prospective non-RCTs (with no minimum follow-up) • Prospective case series (with no minimum follow-up) and pharmacy/insurance databases *(Exclusions: narrative review, letter to the editor, author response, case report)*

Abbreviations

CS = chondroitin sulfate, **COX-2** = cyclooxygenase-2 inhibitor, **HAQ** = Health Assessment Questionnaire, **HAQ-DI** = Health Assessment Questionnaire Disability Index, **NRS** = numerical rating scale, **NSAIDs** = non-steroidal anti-inflammatory drugs, **PICO** = patients, intervention, comparator, outcomes, **RCT** = randomised controlled trial, **SF-36** = Short Form 36, **VAS** = visual analogue scale, **WOMAC** = Western Ontario & McMaster Universities Osteoarthritis Index.

Table 3 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	Pharmaceutical grade CS (minimum 800mg per day) initial treatment followed by maintenance treatment for 3, 6, 12 or 24 months with or without analgesics on demand. *(Exclusions: combination drugs e.g. CS and glucosamine)*
C	Placebo, on-demand analgesics (e.g. paracetamol), NSAIDs (e.g. ibuprofen, COX-2) and other anti-inflammatory treatments (e.g. corticosteroids). *(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 • Radiographic evidence of disease progression (joint space width, cartilage volume, synovial membrane thickness) **Safety:** • Serious adverse events (total and treatment-related) • Withdrawals or discontinuation due to adverse events • Mortality • Adverse events (total, treatment- and gastrointestinal-related)
S	**Efficacy/effectiveness:** • RCTs (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 review, letter to the editor, author response, case report)* **Safety:** • RCTs (with no minimum follow-up) • Prospective non-RCTs (with no minimum follow-up) • Prospective case-series (with no minimum follow-up) and pharmacy/insurance databases *(Exclusions: narrative review, letter to the editor, author response, case report)*

Abbreviations

CS = chondroitin sulfate, **COX-2** = cyclooxygenase-2 inhibitor, **HAQ** = Health Assessment Questionnaire, **HAQ-DI** = Health Assessment Questionnaire Disability Index, **NRS** = numerical rating scale, **NSAIDs** = non-steroidal anti-inflammatory drugs, **PICO** = patients, intervention, comparator**, RCT** = randomised controlled trial, **SF-36** = Short Form 36, **VAS** = visual analogue scale, **WOMAC** = Western Ontario & McMaster Universities Osteoarthritis Index.

Table 4 PICO criteria 3: Hands

P	Patients with symptomatic osteoarthritis in the hands *(Exclusions: Paediatric indications)*
I	Pharmaceutical grade CS (minimum 800mg per day) initial treatment followed by maintenance treatment for 3, 6, 12 or 24 months, with or without analgesics on demand. *(Exclusions: Combination drugs e.g. CS and glucosamine)*
C	Placebo, on-demand analgesics (e.g. paracetamol), NSAIDs (e.g. ibuprofen, COX-2) and other anti-inflammatory treatments (e.g. corticosteroids). *(Exclusions: Opioid medications, intra-articular injections)*
O	**Efficacy/effectiveness:** • Pain (e.g. NRS, VAS) • Physical function • Quality of life (e.g. HAQ, HAQ-DI, SF-36) • Concomitant analgesic and NSAID consumption • Radiographic evidence of disease progression (anatomical lesion progression score) **Safety:** • Serious adverse events (total and treatment-related) • Withdrawals or discontinuation due to adverse events • Mortality • Adverse events (total, treatment- and gastrointestinal-related)
S	**Efficacy/effectiveness:** • RCTs (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 review, letter to the editor, author response, case report)* **Safety:** • RCTs (with no minimum follow-up) • Prospective non-RCTs (with no minimum follow-up) • Prospective case-series (with no minimum follow-up) and pharmacy/insurance databases *(Exclusions: narrative review, letter to the editor, author response, case report)*

Abbreviations

CS = chondroitin sulfate, **COX-2** = cyclooxygenase-2 inhibitor, **HAQ** = Health Assessment Questionnaire, **HAQ-DI** = Health Assessment Questionnaire Disability Index, **NRS** = numerical rating scale, **NSAIDs** = non-steroidal anti-inflammatory drugs, **PICO** = patients, intervention, comparator, **RCT** = randomised controlled trial, **SF-36** = Short Form 36, **VAS** = visual analogue scale, **WOMAC** = Western Ontario & McMaster Universities Osteoarthritis Index.

6. HTA Key Questions

For the evaluation of the technology the following key questions covering central HTA domains, as designated by the European Network for Health Technology Assessment (EUnetHTA) Core Model (clinical effectiveness, safety, costs, cost-effectiveness, budget impact, legal, social, ethical and organisational aspects), are addressed:

1. Is CS efficacious/effective compared to placebo, NSAIDs and paracetamol?
2. Is CS safe compared to placebo, NSAIDs and paracetamol?
3. What are the costs of CS?
4. What is the budget impact of CS?
5. Is CS cost-effective compared to placebo, NSAIDs, and paracetamol?
6. Are there legal, social or ethical issues related to CS?
7. Are there organisational issues related to CS?

6.1 Additional Questions

Additional sub-questions relating to clinical, cost, legal, social, ethical and organisational aspects were derived from the EUnetHTA core model and are outlined below.

Table 5 Sub-questions: efficacy

Topic	Research Question	Element ID
Mortality	What is the 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
Function	What is the effect of the technology on patient body function?	D0011
Function	What is the effect of the technology on work ability?	D0014
Function	How does the use of technology affect activities of daily living?	D0016
Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	D0012
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

Table 6 Sub-questions: effectiveness

Topic	Research Question	Element ID
Mortality	What is the 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
Function	What is the effect of the technology on patient body function?	D0011
Function	What is the effect of the technology on work ability?	D0014
Function	How does the use of technology affect activities of daily living?	D0016
Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	D0012
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

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	How does the frequency or severity of harms change over time or in different settings?	C0004
Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	C0005

Table 8 Sub-questions: costs

Topic	Research Question	Element ID
Resource utilisation	What types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?	E0001
Resource utilisation	What amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?	E0002
Resource utilisation	What were the measured and/or estimated costs of the assessed technology and its comparator(s) (resource-use valuation)?	E0009

Table 9 Sub-questions: cost-effectiveness

Topic	Research Question	Element ID
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) (outcome identification, measurement and valuation)?	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 sub-groups using the technology and its comparator(s)?	E0011
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

Table 10 Sub-questions: budget impact

Topic	Research Question	Element ID
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

Table 11 Sub-questions: legal aspects

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

Table 12 Sub-questions: patient and social aspects

Topic	Research Question	Element ID
Patient 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

Table 13 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

Table 14 Sub-questions: 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. Methodology Literature Search

7.1 Databases and Search Strategy

A systematic literature search was conducted on eight biomedical databases (PubMed, Embase, the Cochrane Library, CINAHL, York Centre for Reviews and Dissemination, CEA Registry, Econlit and Ethmed) from inception up to 28 September 2018. An updated search was performed to identify additional studies published between the completion of the scoping report and commencement of the HTA report. The search was run from 28 September 2018 to 23 April 2019. 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 and 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. Selection of studies was limited to English, French, German and Spanish 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 who independently reviewed all records by title and abstract, 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**: Pharmaceutical-grade CS.
- **Comparator**: On-demand analgesics or NSAIDs, no pharmaceutical intervention, anti-inflammatory treatments, or placebo.
- **Outcomes**: Efficacy/effectiveness outcomes included pain, function, QoL, concomitant medication use or progression to surgery. Safety outcomes included total and serious adverse events, withdrawals or discontinuations and mortality.
- **Design**: English, French, German and Spanish language studies. randomised controlled trials (RCTs) with at least six months follow-up were included or efficacy and effectiveness outcomes. RCTs, non-randomised comparative and single-arm studies with no minimum follow-up were included for safety-related outcomes.

Full details of the study inclusion criteria are described in ***Sections 5.1—5.4***. and listed in the PICO boxes (see ***Section 5.6***). Generic search terms for osteoarthritis were used. The search strategy did not include specific terms for hand, finger or thumb, and may have missed studies as a result.

Additional grey literature databases that were searched for the full HTA are listed in ***Appendix A***.

7.2 Patient and Physician Input

Targeted physician and patient input was sought for specific research questions where no evidence was identified in the published or grey literature. This process is atypical for HTA reports. A brief list of questions was sent to 28 organisations representing patients with osteoarthritis, and physicians treating osteoarthritis. Questions were based around the specific EUnetHTA Core Model questions related to social, ethical and organisational aspects. The questions sent to organisations are presented in ***Appendix G.***

7.3 Assessment of Quality of Evidence

The risk of bias of included trials was assessed using the Cochrane risk of bias tool for randomised trials 2.0. In addition, the overall strength of evidence for each key outcome measure was evaluated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. For GRADE summary tables refer to ***Section 8.1***, ***Table 47 — Table 51***. For study specific risk of bias refer to ***Section 8.4.***

8. Efficacy, Effectiveness and Safety

8.1 Summary Statement Efficacy, Effectiveness and Safety

A moderate number of trials formed the evidence base for CS (k = 26). When the trials were meta-analysed, there was a statistically significant effect of CS on pain, Lequesne index and OMERAC-OARSI responder rate at six months. The effects were subject to moderate levels of heterogeneity; did not persist to later time points (12 and 24 months); and it was unclear if they translated into clinically important differences. There was generally no effect of CS on other critical and important outcomes including function, radiographic evidence of disease progression and quality of life. The comparative safety of CS relative to NSAIDs, paracetamol and placebo is unclear owing to the lack of power in the analyses. Further, most studies evaluated CS in the context of knee osteoarthritis. As such, the effects of CS on the hand and hip is uncertain. There are few ongoing clinical trials, so it is unlikely that uncertainties within the current evidence base will be addressed in the near future. For the summary of findings tables refer to ***Table 47, Table 48, Table 49, Table 50*** and ***Table 51***.

8.2 Methods

Appraisal

Two independent researchers conducted the quality appraisal, including risk of bias assessment with differences settled via consensus. Studies were appraised for risk of bias using the Cochrane risk-of-bias tool for randomised trials version 2.0. The overall quality of the evidence per outcome was assessed using GRADE.

Meta-Analysis

Safety, efficacy and effectiveness outcomes containing at least two RCTs were meta-analysed using Review Manager Version 5.3 (The Cochrane Collaboration, 2014). Dichotomous outcomes were analysed using the Mantel-Haenszel statistical method with random effects models. The results of the analyses were reported as risk ratio (RR) with 95% confidence interval (95% CI). Continuous outcomes were analysed using the inverse variance method with random effects meta-analysis. Continuous outcomes were reported as MD or standardised mean difference (SMD) with 95% CI, reflecting the heterogeneity of the scales and measures used to assess the outcome. Random-effects models were used to account for variation in disease severity (or other population-based factors), CS manufacturer

and/or dosage across the included studies. The results from the meta-analyses were considered statistically significant if the confidence intervals around point estimates did not cross the null.

For pain outcomes, studies reporting VAS and WOMAC were pooled. If a study reported both measures, the most frequently reported measure (out of all included studies) was included in the meta-analysis. For a list of studies reporting both measures and the effect the measure had on the meta-analysis, refer to ***Table 71***.

For outcomes with less than two trials, or where it was inappropriate to pool trials, the results were described narratively.

A SMD of 0.2, 0.5 and 0.8 represent small, moderate and large effect sizes as suggested by the Cochrane Handbook (v5.1.0).[68]

Sub-Group Analysis

Sub-group analyses included the dose of CS, use of minimum pain score, pain assessment instrument and manufacturer of CS. The manufacturer sub-group replaced the species sub-group as few studies reported the origin of CS. For pain and function outcomes, baseline pain scores (< 40 and > 40mm or per cent of total score) and assessment instruments (VAS and WOMAC) constituted additional sub-groups. Further, treatment duration (short-term [< 6 months] compared to long-term [> 6 months]) was an additional sub-group consideration for the safety-related outcomes.

Sensitivity Analysis

Sensitivity analysis was performed to evaluate the effect of study-level characteristics, specifically risk of bias, on the outcomes of the outcomes of the meta-analyses. The sensitivity analysis utilised the same meta-analysis methodology as mentioned above. However, the studies are stratified into groups based on funding, randomisation, allocation, blinding of participants, and outcomes and intention-to-treat analysis domains.

Heterogeneity

The results of the meta-analysis were presented using forest plots that presented a visual representation of variability in the reported effect sizes across studies. Heterogeneity and inconsistency were assessed statistically using the Chi^2 test (whereby $P < 0.10$ represents significant heterogeneity) and the I^2 statistic. The thresholds for low, moderate, substantial and considerable heterogeneity followed those proposed in the Cochrane handbook (0—40% might not be important; 30—60 moderate; 50—90 substantial; and 75—100 considerable heterogeneity). It is worth noting that the importance of the I^2

result was dependent on the size and direction of the measured effect, and the strength of evidence for heterogeneity (i.e. Chi^2 result).

Assessment of Publication Bias

The risk of publication bias was assessed for analyses including at least 10 studies by visual inspection of the funnel plot.[71] In addition, clinical trial registries (e.g. clinicaltrials.gov) were searched to identify unpublished studies as a means of narratively describing the risk of publication bias.

Missing Values

Missing standard deviations (SDs) were obtained from available standard errors using the following formula:

$$SD = SE \times \sqrt{N}$$

To meta-analyse paracetamol utilisation, the results were standardised to the number of tablets per day. This was achieved by dividing the number of tablets per month, or total cumulative dose, by 30 or the number of days during follow-up, respectively.

Studies reporting VAS in centimetres were converted to scores in millimetres.

To meta-analyse the VAS mobility scores, the values were reversed to generate a consistent effect direction and measurement. For example, the scores for CS and placebo at 12 months were 86.0 and 68.0 (out of 100), respectively.[59] Therefore, to use these results in the meta-analysis, the final value was subtracted from 100 (14.0 and 32.0, respectively).

For studies which only reported the outcomes graphically, Webplot digitizer was used to generate numerical values.

Efficacy and Effectiveness

The **efficacy** of CS is informed by trials with a placebo comparator arm. There are, however, no real-world trials evaluating CS. Consequently, the relative **effectiveness** of CS is informed by trials comparing the drug to an active comparator. In this instance, NSAIDs and paracetamol were selected as the appropriate comparators as these drugs reflect real-world practice. It is important to note, the statistical interpretation of studies using an active comparator differs from that of placebo trials. A lack of statistically significant difference between treatment groups could indicate that the two drugs are equally effective, ineffective or unable to tell the difference between the two groups.

Safety

For safety-related outcomes, the number of patients experiencing an event was reported unless otherwise stated.

The ICH guidelines note that severe and serious events are not synonymous.[72] Rather, "severe" describes the intensity of the event, noting the event may not necessarily be of medical significance. "Serious" events are those that pose a threat to the life or function of a patient. A serious adverse event is a reaction that results in death or is life-threatening (an event resulting in hospitalisation or incapacitation or disablement of an individual).[72] The included studies did not specify whether they defined adverse events based on these criteria. It is therefore inappropriate to retrospectively apply the guidelines to the current studies, given the general under-reporting of adverse events, which often lack detail. Rather, the study's definition of severe and serious will be used. The lack of standardisation of adverse events may over- or under-estimate the true effect, thereby limiting the conclusions of the safety sections.

Individual populations indicated for CS treatments have been analysed separately, in order to determine whether population differences led to differences in adverse event rates. It is acknowledged that the results could have been combined across the three indications, noting that this does not change the overall outcome of the safety analysis.

8.3 PRISMA Flow Diagram

The results of the systematic literature searches are presented in ***Figure 2***. The database searches yielded a total of 3,182 results. The results from each database are listed in ***Appendix A***. After de-duplication, 2,638 were reviewed by title and abstract, and 105 were reviewed by full-text. In total, 26 relevant RCTs met the inclusion criteria for the clinical section of the scoping report.[28 59 64 69 73-94] The reasons for excluding articles reviewed by full text are listed in ***Appendix B***. No additional studies were identified by the manufacturers of Structum® and Condrosulf®.

English, French, German and Spanish articles were included in the HTA report. Russian studies were not included in the scoping report but were screened by title and abstract. Of the Russian studies identified in the database searches, two RCTs[95 96] and four single-arm studies[97-100] potentially met the inclusion criteria for this review based on the information in the abstract. Two French articles were unable to be sourced and covered studies shorter than six months and were thus excluded from the report.[101 102]

No PRISMA diagrams are provided for ethical, legal, social and organisational issues as the searches were conducted in both a systematic and non-systematic (targeted) manner.

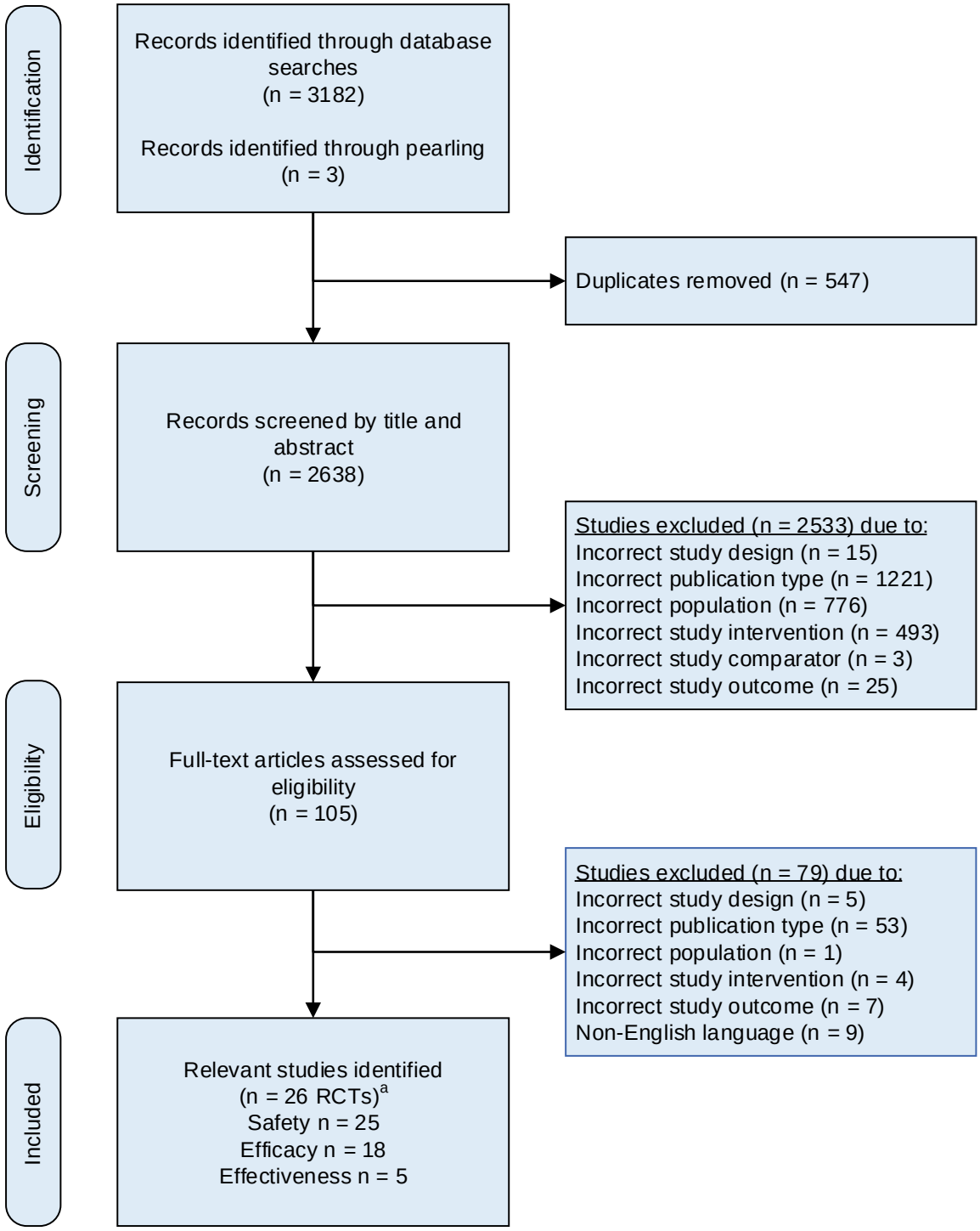


Figure 2 PRISMA flow chart for study inclusion

Notes
a = studies may report safety, efficacy and/or effectiveness data.

8.4 Evidence Tables: Study Characteristics and Risk of Bias

Twenty-six studies were included in the assessment of safety (k = 25),[28 59 64 73-75 77-86 88-94] efficacy (k = 18)[28 59 64 69 74 75 78 80 82 86-88 90 92 94 103] and effectiveness (k = 5)[75 85 88 89 94] of CS (***Table 15***—***Table 17***). Raynauld[87] utilised the data from Wildi[92], similarly, the cohort assessed in Sawitzke 2008[103] is likely captured in Sawitzke 2010[88]. Therefore, to prevent double counting, only the study characteristics from Wildi[92] and Sawitzke 2010[88] will be discussed. It is worth noting, the studies did not significantly differ in risk of bias scores. The trials were conducted in Europe (k = 20) or North America (k = 4), with France and Switzerland reporting the greatest number of studies (k = 8 and 9, respectively). The majority of studies were reported in English with two trials translated from French [78 79] and one trial[76] from German. Most trials evaluated CS in the context of knee osteoarthritis (k = 21)[28 59 64 69 73-75 78-81 83 85 86 88-90 92-94] followed by hand (k = 2)[77 91] and hip (k = 1).[76] The number of patients assessed from each trial ranged from 43[86] to 953[75] (median n = 131) with the length of follow-up ranging from 3 to 24 months for safety, and 6 to 24 months for efficacy studies.[75 88]

Inclusion criteria were similar across all knee studies and generally encompassed patients who were at least 40 years of age and had symptomatic osteoarthritis as inferred by the ARC criteria for osteoarthritis, Kellgren & Lawrence scale (two to three) and VAS scores (> 40mm). The symptoms of osteoarthritis had to be present for at least one to six months prior to entry to the study. Patients were excluded if they had severe osteoarthritis, knee lesions or deformities or previous joint surgery or intraarticular injections within the past six months. To be eligible for hand osteoarthritis studies, patients were required to have symptomatic (> 12 months) osteoarthritis affecting two joints as inferred by the ARC criteria and/or radiographic evidence. The inclusion criteria for hip osteoarthritis was not reported.

CS was administered daily in 400, 500 or 800mg tablets or sachets; 400mg tablets were taken twice or three times per day to achieve total doses of 800mg (k = 12)[28 59 69 74 77 82 83 89 90 92 94] and 1,200mg, respectively (k = 8)[73 75 76 78 85 88 91 93]; 500mg tablets were taken twice a day to achieve a total dose of 1,000mg (k = 3).[64 80 86] One trial did not report the dose used.[81] IBSA (k = 13)[59 69 73 74 76-79 82Reginster, 2017 #15 90 91 93] was the most frequently reported manufacturer of CS followed by Bioiberica (k = 6)[75 83 85 88 89 92], Pierre Fabre (k = 4)[64 80 81 86 93] and TSI Health (k = 1).[28] The placebo treatments were poorly reported. However, when mentioned, they were indistinguishable from the active treatment in terms of appearance and taste. Active comparators included paracetamol[89] and COX-2 selective NSAIDs: Celecoxib (Pfizer)[75 85 88 94]. Celecoxib was dosed at 200mg/day. Paracetamol (manufacturer NR) was dosed at 3g/day for six months. In addition, most studies included paracetamol as a rescue analgesic.

Of the patients enrolled, most were in their late 50s or early 60s, female (55—70%), overweight (BMI ≈ 30kg/m^2) and had Kellgren & Lawrence and ACR function scores of two and VAS scores of 50—70mm,

suggesting moderate painful osteoarthritis. Patients reported experiencing osteoarthritis symptoms for approximately five to ten years before participating in the study. One study included patients with concomitant knee osteoarthritis and psoriasis.[83] Generally, there was no difference in baseline demographics between patients receiving CS, placebo, NSAIDs or paracetamol.

The most commonly reported outcome for safety-related studies was withdrawal due to adverse events (k = 23) and gastrointestinal events (k = 12). The most frequently reported outcome for efficacy and effectiveness was pain at six months as measured by WOMAC, VAS or a 10-point scale (k = 9 and 5 respectively). Few studies evaluated the long-term effects of CS (≥ 12 months), the comparative effectiveness (k = 4 for celecoxib and k = 1 for paracetamol), and the critical and important outcomes of 'quality of life' and 'progression to joint replacement or arthroscopy'.

The study-specific risk of bias for efficacy-, effectiveness-, and safety-related outcomes are reported in ***Figure 3***, and the summaries of risk of bias are presented in ***Figure 4*** and ***Figure 5***. Overall, the included studies were largely subject to inadequate reporting, rather than poor methodology per se. Most studies had unclear randomisation procedures, allocation concealment and blinding procedures. This was most evident in older, foreign language articles. Further, 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. Intention-to-treat was the predominate method of data analysis with few studies utilising per-protocol analyses. Several studies had incomplete or selectively reported data as baseline but not follow-up measurements were presented. No reason was provided over the omission of these measurements. Over one quarter of the 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 15 of the 25 studies had declared funding conflicts. The overall level of bias was similar across studies included for the analysis of safety, effectiveness and efficacy of CS and between studies evaluating the knee, hip or hand.

Sawitzke[88 103] studied a subset of patients who were enrolled in the GAIT trial.[75] Patients received their respective treatments (placebo, glucosamine, CS, glucosamine plus CS, or celecoxib) for an additional 18 months (total of 24 months). Given the overlap of participants, the 12- and 24-month data from Sawitzke[88 103] have been used in the efficacy and effectiveness sections. The six-month results from the GAIT trial were informed by Clegg.[75] However, both trials will be included in the assessment of safety as the safety outcomes were reported as of the last follow-up.

Table 15 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*	Relevant outcomes
Bourgeois 1998[73] France	Knee n = 127 ACR stages I to III	RCT 3 months Single centre trial	Chondroitin sulfate (Condrosulf®) 1,200mg/day	Placebo	***Safety*** Adverse events Gastrointestinal adverse events Withdrawals due to adverse events
Bucsi 1998[74] Hungary	Knee n = 85 Kellgren & Lawrence scale 1-3	RCT 6 months Multi-centre trial	Chondroitin sulfate (Condrosulf®) 800mg/day	Placebo	***Efficacy*** Pain (VAS) Function (20m walk time) Paracetamol intake Lequesne index ***Safety*** Patient & physician judgement of global efficacy and tolerability (4-point scale)
Clegg 2006[75] USA	Knee n = 1583 Kellgren & Lawrence scale 2-3, WOMAC pain score 125-400, knee pain >6m	RCT 24 weeks Multi-centre trial	Chondroitin sulfate (Donated by Bioiberica, S.A., Barcelona) 1,200mg/day	Placebo Celecoxib, (Celebrex, Pfizer) 200mg/day	***Efficacy/Effectiveness*** Pain (VAS, WOMAC, OMERACT-OARSI) Function (WOMAC, OMERACT-OARSI) QoL (SF-36, HAQ) Acetaminophen consumption ***Safety*** Adverse events Serious adverse events
Fransen 2015[28] 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	Placebo	***Efficacy*** Pain (10-point scale, WOMAC) Function (WOMAC, 50-ft walk time) QoL (SF-12) Analgesic consumption Joint space width ***Safety*** Withdrawals due to adverse events

Author, year; country	Indication; Sample size; indication requirement	Design; Follow-up; Setting	Intervention	Relevant comparator*	Relevant outcomes
Kahan 2009[69] France, Belgium, Switzerland, Austria, USA	Knee n = 622 Knee pain >3m, VAS >30mm	RCT 24 months Multi-centre trial	Chondroitin sulfate (manufactured by Genevrier Laboratories, France, and IBSA, Switzerland) 800mg/day	Placebo	**Efficacy** Pain (VAS, WOMAC) Function (WOMAC) Acetaminophen and NSAID consumption Joint space width ***Safety*** Adverse events Patient assessment of tolerability (4-point ordinal scale)
L'Hirondel 1992[78] Germany	Knee n = 125 Knee pain	RCT 6 months Single centre trial	Chondroitin sulfate (Condrosulf®) 1,200mg/day	Placebo	***Efficacy*** Lequesne index Pain (VAS) Acetaminophen and NSAID consumption ***Safety*** Adverse events
Mathieu 2002[79] Switzerland	Knee n = 300 Osteoarthritis of the knee according to the ACR criteria	RCT 24 months Single centre Rheumatology clinic	Chondroitin sulfate 800mg/day	Placebo	***Safety*** Withdrawal due to adverse events
Mazieres 1992[81] France	Knee n = 114 Osteoarthritis of knee according to ACR criteria, Kellgren & Lawrence scale 1-3, VAS >40mm, Lequesne ≥4	RCT 5 months (3 months treatment) Single centre trial	Chondroitin sulfate (Structum®)	Placebo for 3 months	***Efficacy*** Lequesne index Pain (VAS) Analgesic and NSAID (permitted) consumption ***Safety*** Adverse events Discontinuation of treatment due to adverse event

Author, year; country	Indication; Sample size; indication requirement	Design; Follow-up; Setting	Intervention	Relevant comparator*	Relevant outcomes
Mazieres 2001[64] France	Knee n = 132 Osteoarthritis of knee according to ACR criteria, Kellgren & Lawrence scale 2-3, VAS >30mm, Lequesne 4-11	RCT 6 months (3 months treatment) Rheumatology & GP clinics	Chondroitin sulfate (Structum®) 1,000mg/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) Discontinuation of treatment due to adverse event
Mazieres 2007[80] France, Switzerland	Knee n = 307 Knee pain >6m, VAS >40mm, Kellgren & Lawrence scale 2-3, Lequesne 6-12	RCT 24 weeks plus further 8 weeks follow-up Rheumatology clinics	Chondroitin sulfate (Structum®) 1,000mg/day	Placebo	***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 2005[82] Switzerland	Knee n = 300 Osteoarthritis of knee according to ACR criteria, Kellgren & Lawrence scale 1-3	RCT 24 months Outpatient clinic; private rheumatology practices	Chondroitin sulfate (Condrosulf®) 800mg/day	Placebo	***Efficacy*** Pain (WOMAC) Function (WOMAC) Acetaminophen and NSAID consumption Joint space width ***Safety*** Adverse events

Author, year; country	Indication; Sample size; indication requirement	Design; Follow-up; Setting	Intervention	Relevant comparator*	Relevant outcomes
Möller 2010[83] Spain	Knee n = 129 Osteoarthritis of knee according to ACR criteria, Psoriasis	RCT 3 months Multi-centre trial	Chondroitin sulfate (supported by Bioiberica) 800mg/day	Placebo	***Efficacy*** [a] Pain (VAS) Lequesne index Acetaminophen consumption Assessment of efficacy (patient and investigator) QoL (SF-36, DLQL) ***Safety*** Adverse events Tolerability
Pelletier 2016[85] Canada	Knee n = 194 Osteoarthritis of knee according to ACR criteria, Kellgren & Lawrence scale 2-3, VAS >40mm	RCT 24 months Outpatient and private clinics, Canada	Chondroitin sulfate (Bioiberica SA, Barcelona) 1,200mg/day	Celecoxib (Pfizer, Canada) 200mg/day	***Efficacy/effectiveness*** Pain (VAS, WOMAC) Function (WOMAC) QoL (SF-36) Acetaminophen consumption Cartilage volume Synovial membrane thickness ***Safety*** Withdrawal due to adverse events Adverse events Serious adverse events
Railhac 2012[86] France	Knee n = 48 Osteoarthritis of knee according to ACR criteria, Kellgren & Lawrence scale 2-3, VAS >30mm	RCT 48 weeks Rheumatology clinics	Chondroitin sulfate (Structum®) 1,000mg/day	Placebo	***Efficacy/effectiveness*** Pain (VAS) Lequesne index Paracetamol &/or NSAID consumption ***Safety*** Adverse events

Author, year; country	Indication; Sample size; indication requirement	Design; Follow-up; Setting	Intervention	Relevant comparator*	Relevant outcomes
Raynauld 2013[87] Canada	Knee n = 57 (n=69 in original RCT) Osteoarthritis of knee according to ACR criteria, Kellgren & Lawrence scale 2-3, VAS >40mm	Post-hoc analysis Follow-up (phone call, 4 years post study inception) (Wilde 2011 report on original RCT)	Chondroitin sulfate (Condrosan®) 800mg/day	Placebo for 6 months, 800mg CS for following 6 months	***Effectiveness*** Progression to total knee replacement
Reginster 2017[94] Belgium, Czech Republic, Italy, Poland, Switzerland	Knee n = 604 Osteoarthritis of knee according to ACR criteria, pain >3m, VAS >50mm	RCT 6 months Multi-centre trial	Chondroitin sulfate (Condrosulf®) 800mg/day	Placebo Celecoxib (Celebrex, Pfizer) 200mg/day	***Efficacy/effectiveness*** Pain (VAS) Lequesne index Paracetamol consumption ***Safety*** Adverse events
Sawitzke 2010[88] USA	Knee n = 662 (Ancillary to GAIT – Clegg 2006; longer-term follow-up data) Osteoarthritis of knee according to ACR criteria, Kellgren & Lawrence scale 2-3, pain >6m	RCT 24 months (participants remaining on originally assigned blinded treatment) Multi-centre trail	Chondroitin sulfate 1,200mg/day	Placebo Celecoxib, (Celebrex, Pfizer) 200mg/day	***Efficacy*** Pain (WOMAC, OMERACT/OARSI) Function (WOMAC) ***Safety*** Adverse events Serious adverse events

Author, year; country	Indication; Sample size; indication requirement	Design; Follow-up; Setting	Intervention	Relevant comparator*	Relevant outcomes
Sawitzke 2008[103] USA	Knee n = 357 (Ancillary to GAIT – Clegg 2006; longer-term follow-up data) Osteoarthritis of knee according to ACR criteria, Kellgren & Lawrence scale 2-3, pain >6m	RCT 24 months (participants remaining on originally assigned blinded treatment) Multi-centre trial	Chondroitin sulfate 1,200mg/day	Placebo Celecoxib, (Celebrex, Pfizer) 200mg/day	***Efficacy*** Joint space width
Tio 2017[89] Spain	Knee n = 70 Osteoarthritis of knee according to ACR criteria, Kellgren & Lawrence scale 2-3,	RCT 6 months Rheumatology unit of hospital, Spain	Chondroitin sulfate (Condrosan®) 800mg/day	Paracetamol 3g/day	***Effectiveness*** Pain (VAS) Lequesne index
Uebelhart 2004[90] Switzerland	Knee n = 120 Osteoarthritis of knee according to ACR criteria, Kellgren & Lawrence scale 1-3	RCT 12 months Multi-centre trial	Chondroitin sulfate (Condrosulf®) 800mg/day 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 ***Safety*** Adverse events
Uebelhart 1998[59] Switzerland	Knee n = 46 NR	RCT 12 months Division of physical medicine rehabilitation as in- or out-patients	Chondroitin sulfate (Condrosulf®) 800mg/day	Placebo	***Efficacy*** Pain (VAS) Function (VAS) ***Safety*** Adverse events

Author, year; country	Indication; Sample size; indication requirement	Design; Follow-up; Setting	Intervention	Relevant comparator*	Relevant outcomes
Wildi 2011[104] Switzerland, USA, Belgium, Italy, France	Knee n = 69 Osteoarthritis of knee according to ACR criteria, Kellgren & Lawrence scale 2-3, VAS >40mm	RCT 12 months (2 phases) Multi-centre trial	Double-blind phase: Chondroitin sulfate (Condrosan®) 800mg/day for 6 months Open-label phase: CS 800mg/day for 6 months	Double-blind phase: Placebo for 6 months Open label phase: Open label use of chondroitin sulfate 800mg/day for 6 months	***Efficacy*** Pain (VAS, WOMAC) Function (WOMAC) QoL (SF-36) ***Safety*** Adverse events
Zegels 2013[93] Belgium, France, Switzerland	Knee Osteoarthritis of knee according to ACR, VAS >40mm, Lequesne index ≥ 7	RCT 3 months Multi-centre trial	Chondroitin sulfate (Condrosulf®) 1,200mg/day	Chondroitin sulfate gel (Condrosulf®) 1,200mg/day Placebo	***Efficacy*** Function (Algo-functional LI) Pain (VAS) Consumption of paracetamol ***Safety*** Adverse events

Abbreviations

ACR = American College of Rheumatology, **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-36** = Short Form-36, **VAS** = visual analogue scale, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index.

Notes

* = Only comparators relevant to the current PICO are listed, other comparators may have been investigated**, ****** = grading system no known, a = study only used in safety analysis.

Table 16 Characteristics of included studies for safety, efficacy and effectiveness (hand)

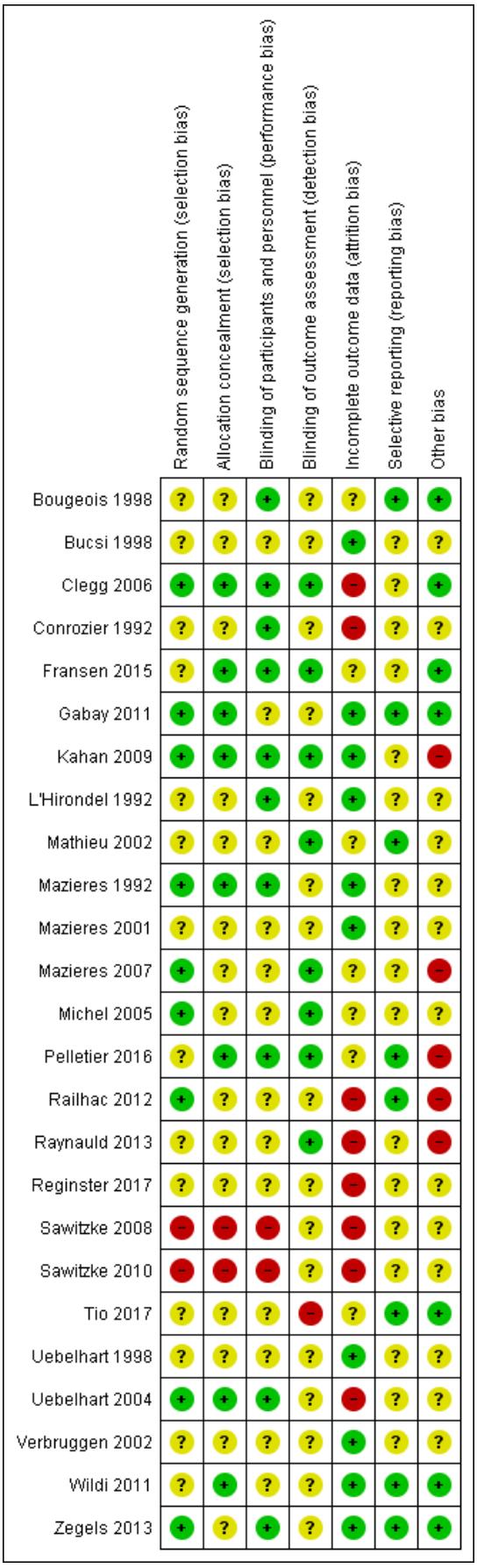
Author, year	Indication; Sample size	Design; Follow-up; Setting	Intervention	Comparator	Outcomes
Gabay 2011[77] Switzerland	Osteoarthritis of hand according to ACR criteria n = 162	RCT 6 months Rheumatology outpatient clinic, single centre	Chondroitin sulfate (Condrosulf®) 800mg/day	Placebo	***Efficacy*** Pain (VAS) Function (FIHOA score, grip strength) Acetaminophen consumption ***Safety*** Adverse events Patient assessment of tolerability (4-point ordinal scale)
Verbruggen 2002[91] Belgium	Hand Osteoarthritis of hand according to radiological evidence n = 165	RCT 36 months Rheumatology clinic	Chondroitin sulfate (Condrosulf®) 1,200mg/day	Placebo (lactose-monohydrate) 1,500mg/day	***Efficacy*** Progression of osteoarthritis Developing, worsening of erosive osteoarthritis ***Safety*** Withdrawal due to adverse events

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

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

Author, year	Indication; Sample size	Design; Follow-up; Setting	Intervention	Comparator	Outcomes
Conrozier & Vignon 1992[76] Germany	Osteoarthritis of the hip n = 56	RCT 6 months Single centre	Chondroitin sulfate (Condrosulf®) 1,200mg/day for 6 months	Placebo, once daily for six months	***Efficacy*** Pain (VAS) Lequesne index Function (Maximum walking distance, morning stiffness) Frequency of waking each night Acetaminophen consumption ***Safety*** Adverse events

Abbreviations
NR = not reported, **RCT** = randomised controlled trial, **VAS** = visual analogue scale.



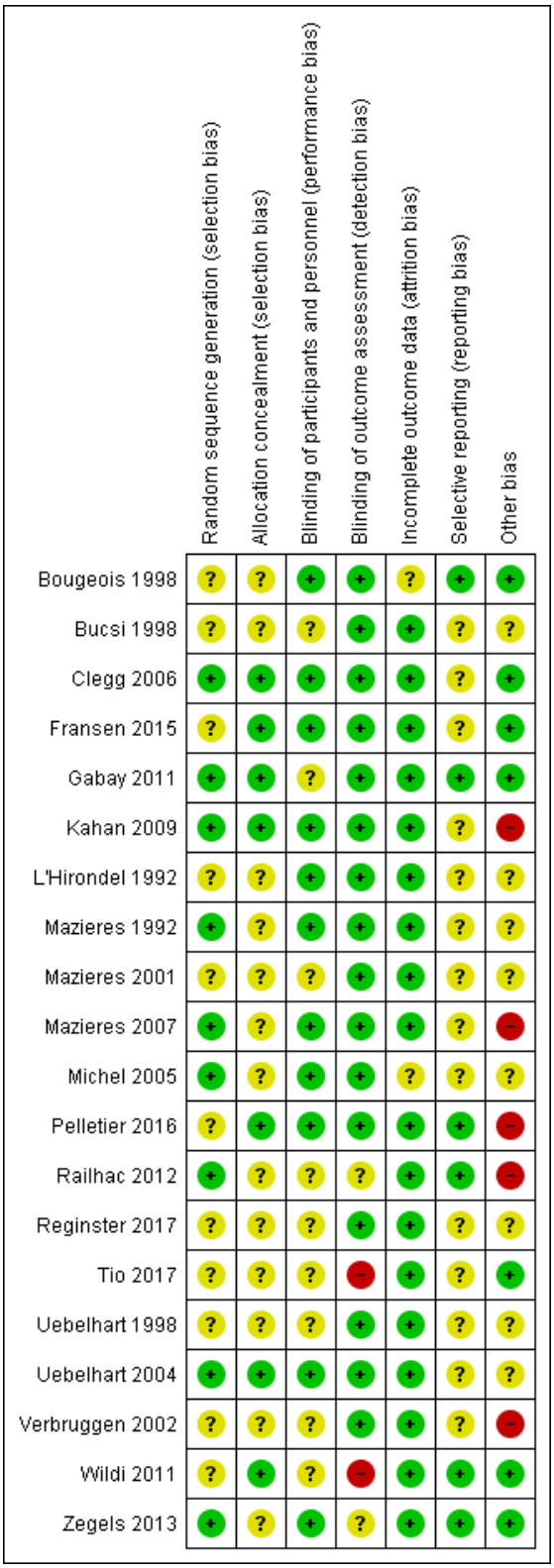


Figure 3 Study-specific risk of bias for efficacy/effectiveness (left) and safety (right) outcomes

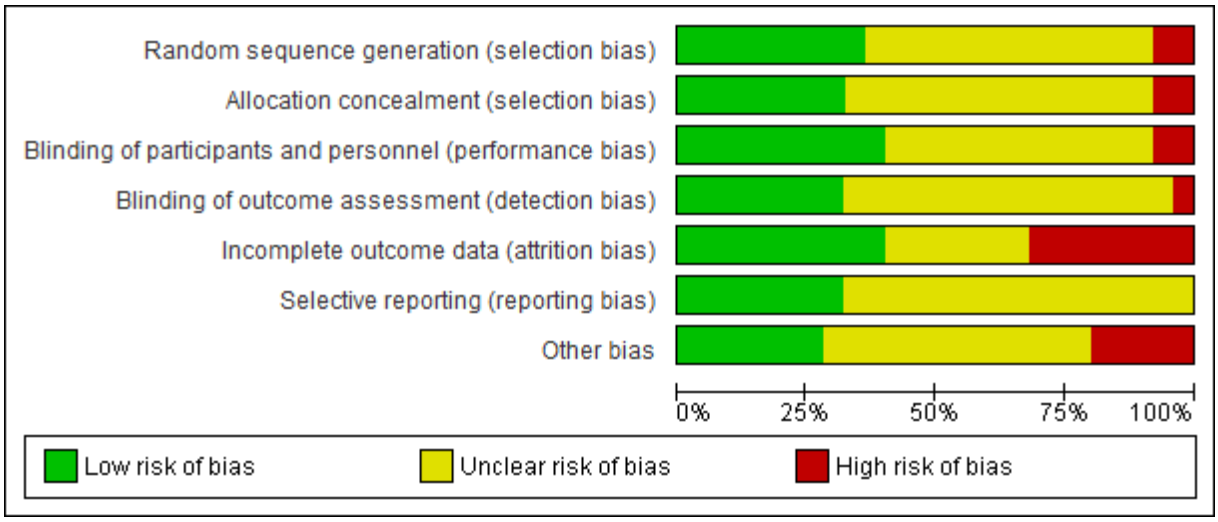


Figure 4 Summary of the risk of bias in the included RCTs assessing efficacy and effectiveness

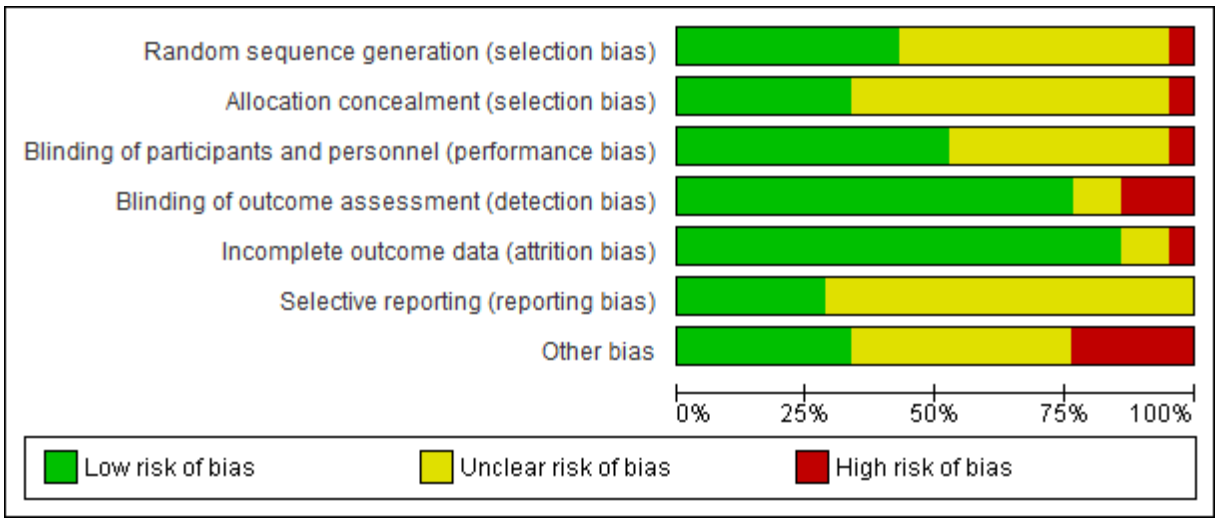


Figure 5 Summary of the risk of bias in the included RCTs assessing safety

8.5 Results: Efficacy

D001 What is the expected beneficial effect of the technology on mortality?

Osteoarthritis is not life-threatening, and CS is not expected to improve survival or life expectancy. Therefore, this question is not considered relevant to the current HTA.

D005 How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?

The critical outcome—pain—and the important outcomes—analgesic and NSAID use—were considered when answering this research question.

Knee Osteoarthritis: CS vs Placebo

Knee osteoarthritis: CS vs Placebo, Pain at six months

Nine studies provide evidence on pain as measured by VAS and WOMAC at six months.[59 69 74 75 80 86 90 92 94] All nine studies are included in the meta-analysis. Overall, there are statistically significant differences between the CS and placebo groups (SMD -0.28, 95% CI -0.47, -0.09, p = 0.004). The Chi^2 test and I^2 statistic indicate considerable levels of heterogeneity and inconsistency ($p < 0.0001$ and $I^2 = 75\%$). For further information regarding pain at six months and the corresponding forest plot refer to ***Figure 6.***

Much of the heterogeneity relates to the effect sizes observed in Bucsi[74] and Uebelhart.[59] These studies were at high and low risk of bias, respectively, and are among the oldest studies evaluating the effects of CS. Given Uebelhart[59] was at low risk of bias it suggests that the results are unlikely to stem from poor methodology or reporting of outcomes.

Sub-group analyses determined there are significant differences between CS and placebo groups in studies that: use VAS to measure pain (p = 0.0009); IBSA CS (p = 0.0001); 800mg/day of CS (p = 0.02); have a baseline pain ≤ 40mm or 40% of total score (p = 0.001) and did not specify or had a broad inclusion criteria with respect to pain (p = 0.05). There are no further sub-group differences when factoring manufacturer, dose or baseline pain. Sensitivity analyses determined, studies that have unclear randomisation (p = 0.02), allocation (p = 0.0008), blinding of participants (p = 0.0008) and outcomes (p = 0.0004) report statistical differences between the treatment groups. Lastly, studies that blinded appropriately (p = 0.02), use intention-to-treat analysis (p = 0.003) and declare funding from

sponsors (p = 0.004) also report differences between treatment groups. There are no further sensitivity differences when considering intention-to-treat analysis, funding source and risk of bias parameters (randomisation, allocation and blinding of participant) (***Table 73***).

The measures of WOMAC and VAS differ between the included studies. For example, studies utilise scales between 0 – 500[75] for WOMAC or note VAS reflected spontaneous pain[59 90], pain during activity[80 86] or do not report the context in which pain was felt.[69 92] Further, studies report final scores[59 74 75 80 86 90 94] or change from baseline.[92]

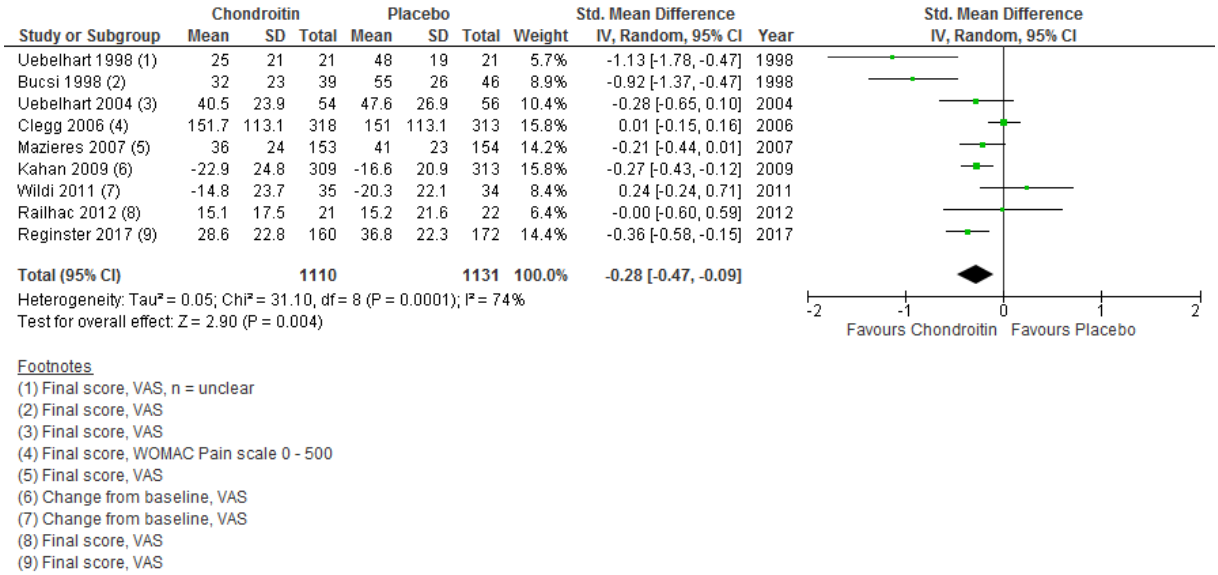


Figure 6 Forest plot indicating the standardised mean difference in pain for chondroitin sulfate compared to placebo at six months (knee)

Knee osteoarthritis: CS vs Placebo, Pain at 12 months

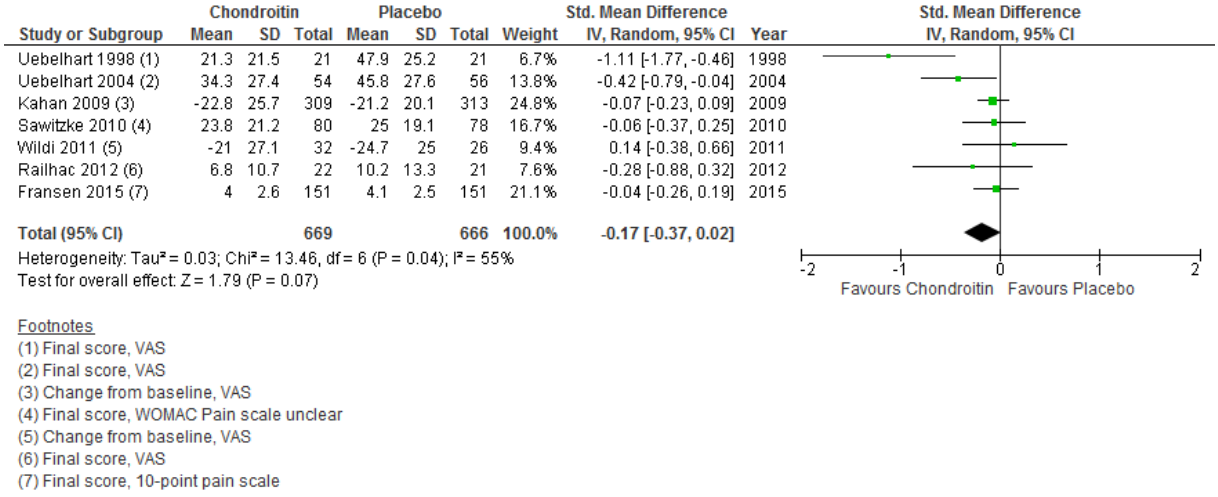
Seven studies provide evidence on pain as measured by VAS, WOMAC and a 10-point scale at 12 months.[28 59 69 86 88 90 92] All seven studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and placebo groups (SMD -0.17, 95% CI -0.37, 0.02, p = 0.07). The Chi^2 test and I^2 statistic indicate moderate levels of heterogeneity and inconsistency (p = 0.04 and I^2 = 55%). For further information regarding pain at 12 months and the corresponding forest plot refer to ***Figure 7***.

There are no significant sub-group differences between CS and placebo groups when factoring manufacturer, dose or baseline pain. Sensitivity analyses determined there are significant differences between CS and placebo groups in studies that had unclear allocation (p = 0.01). There are no further

sensitivity differences in intention-to-treat analysis, funding source and risk of bias parameters (randomisation, allocation and blinding of participant) (***Table 74***).

Much of the heterogeneity relates to the effect size reported in Uebelhart[59], this study was at 'low' risk of bias suggesting the results are unlikely to stem from poor methodology or reporting of outcomes.

The measures of pain differ between the included studies. For example, studies using scales between 0—10[28], are unclear in their reporting of WOMAC scales[88] or use VAS.[59 69 90 92] VAS measures assess spontaneous pain[59 90], pain during activity[86] or do not report the context in which pain was felt.[92] Further, studies report final scores[59 86 88 90] or change from baseline.[69 92] If the WOMAC scores are used instead of VAS scores from Fransen[28], the p-value for the 12-month pain analysis changes from 0.07 to 0.05 indicating a statistically significant difference between the two groups.



Footnotes
(1) Final score, VAS
(2) Final score, VAS
(3) Change from baseline, VAS
(4) Final score, WOMAC Pain scale unclear
(5) Change from baseline, VAS
(6) Final score, VAS
(7) Final score, 10-point pain scale

Figure 7 Forest plot indicating the standardised mean difference in pain for chondroitin sulfate compared to placebo at 12 months (knee)

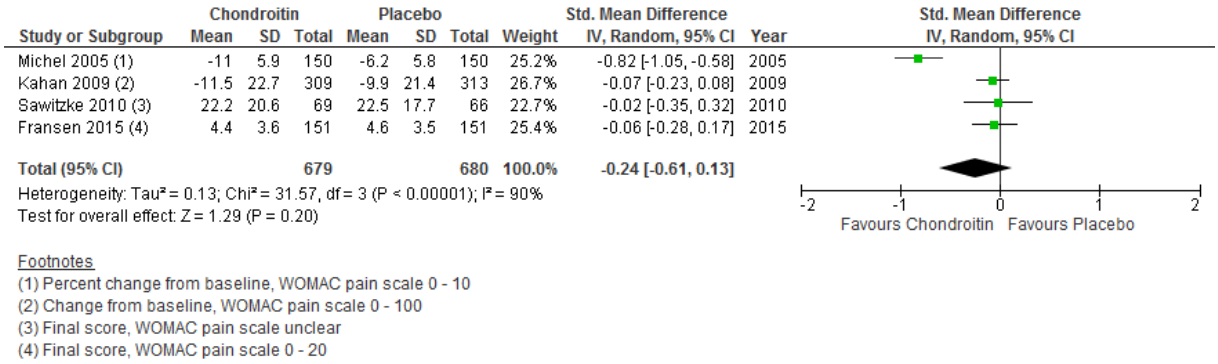
Knee osteoarthritis: CS vs Placebo, Pain at 24 months

Four studies provide evidence on pain as measured by WOMAC and a 10-point scale at 24 months.[28 69 82 88] All studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and placebo groups (SMD -0.24, 95% CI -0.61, 0.13, p = 0.20). The Chi^2 test and I^2 statistic indicate considerable levels of heterogeneity and inconsistency ($p < 0.0001$ and $I^2 = 90\%$). For further information regarding pain at 24 months and the corresponding forest plot refer to ***Figure 8.***

There are no significant sub-group differences when factoring manufacturer, dose or baseline pain. Sensitivity analyses determined there are significant differences between CS and placebo groups in

studies that have unclear allocation, blinding of participants and funding ($p < 0.00001$ for all groupings). There are no further differences when factoring intention-to-treat analysis, funding source or risk of bias parameters (randomisation, allocation and blinding of participants). The sensitivity differences occur when Michel[82] is the only included study in the analysis. This study has 'some' risk of bias owing to unclear allocation, blinding of participants, incomplete data and selective reporting (***Table 75***).

The measurements of WOMAC differ between the included studies. For example, studies utilise scales between 0—10[82], 0—20[28] or 0—100[69] or are unclear regarding the scale used.[88] Further, studies report final scores[28 88], change from baseline[69] or per cent change from baseline.[82] No VAS scores are included in the meta-analysis.



Footnotes
(1) Percent change from baseline, WOMAC pain scale 0 - 10
(2) Change from baseline, WOMAC pain scale 0 - 100
(3) Final score, WOMAC pain scale unclear
(4) Final score, WOMAC pain scale 0 - 20

Figure 8 Forest plot indicating the standardised mean difference in pain for chondroitin sulfate compared to placebo at 24 months (knee)

Knee Osteoarthritis: CS vs Placebo, OMERACT-OARSI at 6 months

Four studies provide evidence on the OMERACT-OARSI responder rate.[75 80 88 94] Three studies are included in the meta-analysis[75 80 94] and one is narratively described.[88]

Overall, there are statistically significant differences between the CS and placebo groups (RR, 1.18, 95% CI 1.08, 1.29, $p = 0.0001$). The Chi^2 test and I^2 statistic indicate low levels of heterogeneity and inconsistency ($p = 0.85$ and $I^2 = 0\%$). Sub-group and sensitivity analyses are not performed owing to the number of studies in the meta-analysis. For further information regarding OMERACT-OARSI responder rate at six months and the corresponding forest plot refer to ***Figure 9***.

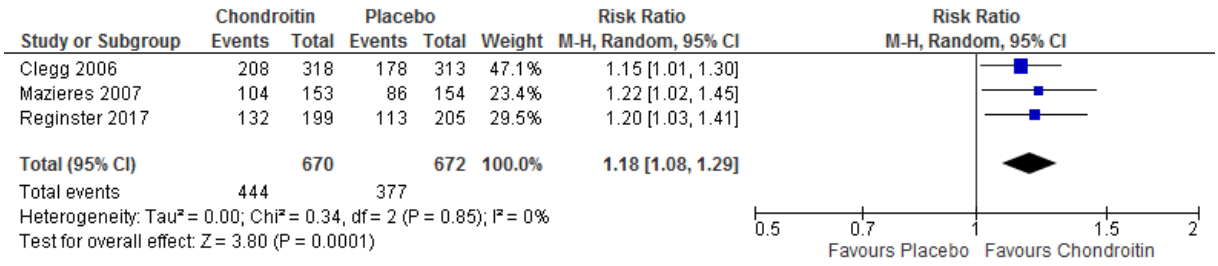


Figure 9 Forest plot indicating the risk ratio in the OMERACT-OARSI responder rate at 6 months (knee)

One study was not included in the meta-analysis as it reported the adjusted odds ratio (OR) rather than absolute values.[88] The analysis controlled for age, gender, body mass index class, pain, Kellgren & Lawrence grade and time. The authors concluded that there was no statistically significant difference between the treatment groups regarding OMERACT-OARSI responder rate (OR 0.89, 95% CI 0.53, 1.50, p = NR).

Knee Osteoarthritis: CS vs Placebo, OMERACT-OARSI at 12 and 24 months

No study reported OMERACT-OARSI responder rate at 12 or 24 months.

Knee Osteoarthritis: CS vs Placebo, Paracetamol Intake at six months

Five studies provide evidence on the use of paracetamol at six months.[69 74 75 78] Four are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and placebo groups (MD -0.01, 95% CI -0.07, 0.04, p = 0.62). The Chi^2 test and the I^2 statistic indicate low levels of heterogeneity and inconsistency (p = 0.49 and I^2 = 0%). For further information regarding paracetamol use at six months and the corresponding forest plot refer to ***Figure 10***.

Sub-group and sensitivity analyses determined there are no significant differences when factoring intention-to-treat analysis, manufacturer, dose, funding source and risk of bias parameters (randomisation, allocation and blinding of participants and outcomes) (***Table 76***).

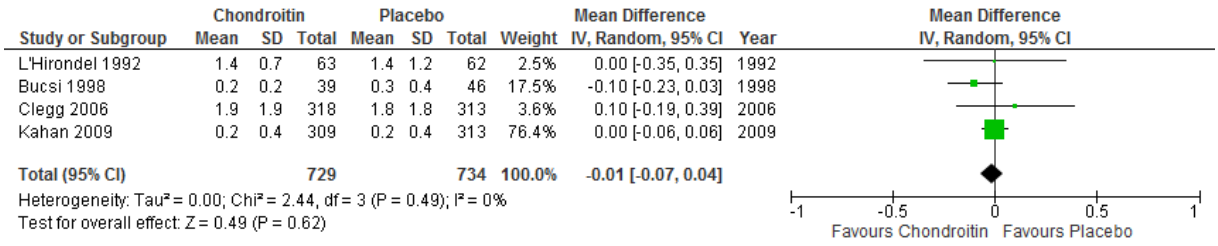


Figure 10 Forest plot indicating the mean difference in daily paracetamol intake for chondroitin sulfate compared to placebo at six months (knee)

One study reports the number of patients who consumed paracetamol over the study period and was consequently not included in the meta-analysis. Overall, the study concluded there was no statistically significant difference between the number of patients utilising paracetamol at six months (p = 0.76). For further information refer to ***Table 18.***

Table 18 Chondroitin sulfate compared to placebo: Paracetamol intake at six months (knee)

Author year	Outcome reported	Chondroitin sulfate Mean ± SD n/N (%)	Placebo Mean ± SD n/N (%)	p-value
Wildi 2011[92]	Number of patients using paracetamol	25/32 (78.1%)	19/26 (73.1%)	0.76

Abbreviations
n = number of patients, **N** = total number of patients, **SD** = standard deviation.

Knee Osteoarthritis: CS vs Placebo, Paracetamol Intake at 12 months

One study provides evidence on the use of paracetamol at 12 months.[90 92] The study concluded there was a statistically significant difference between CS and placebo groups (p < 0.05). For further information refer to ***Table 19***.

Table 19 Chondroitin sulfate compared to placebo: Paracetamol intake at 12 months (knee)

Author year	Outcome reported	Chondroitin sulfate Mean ± SD n/N (%)	Placebo Mean ± SD n/N (%)	p-value
Uebelhart 2004[90]	Number of tablets/days	0.3 ± 0.4	0.6 ± 0.8	< 0.05

Abbreviations
n = number of patients, **N** = total number of patients, **SD** = standard deviation.

Knee Osteoarthritis: CS vs Placebo, Paracetamol Intake at 24 months

One study provides evidence on the use of paracetamol at 24 months.[88] Overall, the mean number of tablets per day was similar between the two groups. However, given that statistical significance was not reported, it is unclear whether the two groups differed. For further information refer to ***Table 20***.

Table 20 Chondroitin sulfate compared to placebo: Paracetamol intake at 24 months (knee)

Author year	Chondroitin sulfate Mean ± SD	Placebo Mean ± SD	p-value
Sawitzke 2010[88]	1.3 ± 1.6	1.3 ± 1.8	NR

Abbreviations
SD = standard deviation

Knee Osteoarthritis: CS vs Placebo, NSAID Intake at six months

Three studies provide evidence on the use of rescue NSAIDs.[78 80 92] A meta-analysis was not performed owing to the different measures of NSAID use (number of patients[92], units per month[78], and number of days used[80]), therefore, the results are described narratively.

Two studies concluded there was no statistically significant difference between CS and placebo groups.[80 92] One study noted a statistically significant difference between the treatment groups when the number of units per month was considered.[78] However, the variance and the statistical test underlying this result were not reported. For further information refer to ***Table 21***.

Table 21 Chondroitin sulfate compared to placebo: NSAID intake at six months (knee)

Author year	Outcome reported		Chondroitin sulfate n/N (%) or mean ± SD	Placebo n/N (%) or mean ± SD	p-value
L'Hirondel 1992[78]	NSAID units per month		3 ± NR	8 ± NR	< 0.01
Mazieres 2007[80]	Number of days used		6.9 ± 20.2	9.2 ± 24.6	0.38
Wildi 2011[92]	Number of patients, %		25/32 (78.1%)	19/26 (73.1%)	0.76

Abbreviations
g = grams, **mg** = milligrams, **n** = number of patients, **N** = total number of patients, **NR** = not reported, **NSAIDs** = non-steroidal anti-inflammatory drugs, **SD** = standard deviation.

Knee Osteoarthritis: CS vs Placebo, NSAID Intake at 12 months

No study reported NSAID utilisation at 12 months.

Knee Osteoarthritis: CS vs Placebo, NSAID Intake at 24 months

Two studies provide evidence on the use of rescue NSAIDs at 24 months.[28 69] A meta-analysis was not performed owing to the different measurements of NSAID use (number of patients[28] and cumulative dose[69]). Therefore, the results are described narratively. Both studies concluded there was no statistically significant difference between CS and placebo groups. For further information refer to ***Table 22***.

The studies did not report which NSAID was used throughout the follow-up period and one study included simple opioids and NSAIDs in their measure.[28]

Table 22 Chondroitin sulfate compared to placebo: NSAID intake at 24 months (knee)

Author year	Outcome reported	Chondroitin sulfate n/N (%) or mean ± SD	Placebo n/N (%) or mean ± SD	p-value
Fransen 2015[28]	Number of patients, %	17/151 (11.3%)	28/151 (18.5%)	0.20
Kahan 2009[69]	Cumulative ibuprofen equivalent (g)	189 ± 22	226 ± 24	0.30

Abbreviations
g = grams, **mg** = milligrams, **n** = number of patients, **N** = total number of patients, **NR** = not reported, **NSAIDs** = non-steroidal anti-inflammatory drugs, **SD** = standard deviation.

Hip Osteoarthritis: CS vs Placebo

Hip Osteoarthritis: CS vs Placebo, Pain at 6 months

One study provides evidence on pain as measured by VAS at six months.[76] There was a statistically significant difference between the CS and placebo groups with respect to VAS scores at the end of the study. For further information refer to ***Table 23***.

Table 23 Chondroitin sulfate compared to placebo: Pain at six months (hip)

Author year	Outcome	Chondroitin sulfate Mean ± SD	Placebo Mean ± SD	p-value
Conrozier & Vignon 1992[76]	Pain VAS 0—100mm (change from baseline %)	-42.6 ± NR	-2 ± NR	< 0.001

Abbreviations
mm = millimetres, **NR** = not reported, **SD** = standard deviation, **VAS** = visual analogue scale.

Hip Osteoarthritis: CS vs Placebo, Pain at 12 or 24 months

No study reported pain at 12 or 24 months.

Hand Osteoarthritis: CS vs Placebo

Hand Osteoarthritis: CS vs Placebo, Pain and Paracetamol Intake at six months

One study provides evidence on pain as measured by VAS and paracetamol use at six months.[77] The study reported statistically significant differences between the CS and placebo groups with respect to hand pain (p = 0.016). However, the intake of paracetamol did not differ between the two groups (p = NR). For further information refer to ***Table 24***.

Table 24 Chondroitin sulfate compared to placebo: Pain and paracetamol intake at six months (hand)

Author year	Outcome	Time point	Chondroitin sulfate Mean ± SD	Placebo Mean ± SD	p-value
Gabay 2011[77]	Global assessment of hand pain (VAS 0—100mm)	Baseline 6 months	54.9 ± 14.2 34.9 ± 25.3	53.6 ± 14.2 42.3 ± 24.9	NR 0.016
	Paracetamol consumption (tablets/week)	6 months	1.9 ± 2.8	2.0 ± 4.2	NS

Abbreviations
mm = millimetres, **NR** = not reported, **NS** = not significant, **SD** = standard deviation, **VAS** = visual analogue scale for pain.

Hand Osteoarthritis: CS vs Placebo, Pain or Paracetamol Intake at 12 and 24 months

No study reported pain or paracetamol use at 12 or 24 months.

D006 How does the technology affect progression (or recurrence) of the disease or health condition?

The important outcomes of progression to joint replacement or arthroscopy and radiographic evidence of disease progression were considered when answering this research question.

Knee Osteoarthritis: CS vs Placebo

Knee osteoarthritis: CS vs Placebo, Progression to knee replacement at 48 months

One study provides evidence on the incidence of total knee replacement following CS.[87] The authors contacted 57 participants from Wildi[92] four years after completing the study to determine how many had undergone a total knee replacement (TKR). Of the original cohort, 13 underwent TKR, however, there was no statistically significant difference between patients who received CS (n = 4/30) and placebo (n = 9/27) (p = 0.094). A multivariate regression determined that significant predictors of knee replacement included baseline pain (WOMAC) (HR 1.1, 95% CI 1.0, 1.2, p = 0.001), bone marrow lesions in the medial compartment (HR 2.1, 95% CI 1.4, 3.3, p = 0.001), and C-reactive protein levels (HR 1.2, 95% CI 1.0, 1.5, p = 0.024). It is worth noting, this study is likely underpowered to detect differences between the CS and placebo groups.

Knee Osteoarthritis: CS vs Placebo, Minimum Joint Space Width at 24 months

Four studies provide evidence on minimum joint space width at 24 months.[28 69 82 103 105] Three studies are included in the meta-analysis[28 69 82] and one is described narratively.[103] Overall, there is no statistically significant difference between the CS and placebo groups (SMD 0.19, 95% CI -0.06, 0.45, p = 0.14). The Chi^2 test and I^2 statistic indicate considerable level of heterogeneity and inconsistency (p = 0.01 and I^2 = 77%). For further information regarding joint space width at 12 months and corresponding forest plot refer to ***Figure 11***.

If the change in joint space width scores are used instead of final scores from Fransen[28], the p-value for the 24-month analysis remains unchanged (p = 0.07). The final scores were presented because the number of patients reporting this outcome was higher.

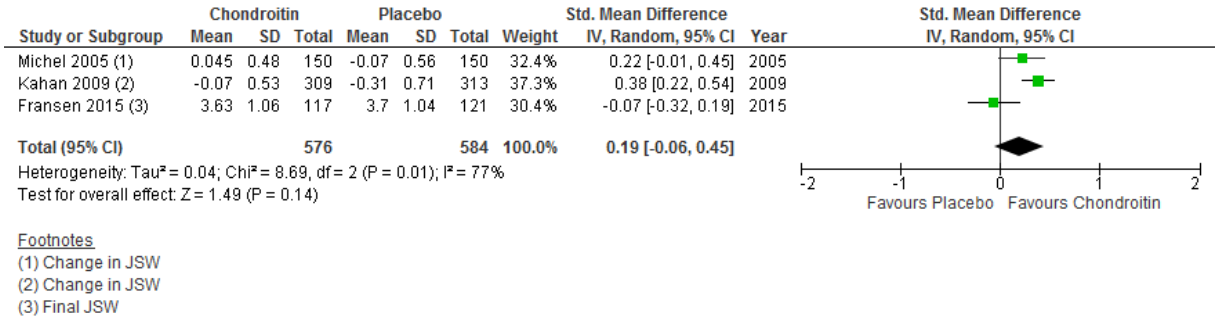


Figure 11 Forest plot indicating the standardised mean difference in minimum joint space width for chondroitin sulfate compared to placebo at 24 months (knee)

One study utilised mixed-effects regression to evaluate mean joint space width after adjusting for baseline joint space width, pain score, disease duration, weight status, Kellgren/Lawrence grade and weeks of treatment, gender, and recruitment site.[103] Given the unadjusted values were not reported the study was excluded from the meta-analysis. It is worth noting, if the results are included, the results from the meta-analysis remain unchanged (SMD 0.18, -0.01, 0.37, p = 0.07). For further information refer to ***Table 25***.

Table 25 Chondroitin sulfate compared to placebo: minimum joint space width at 24 months (knee)

Author year	Chondroitin sulfate Mean ± SD	Placebo Mean ± SD	Difference from placebo (95% CI)
Sawitzke 2008	0.107 ± NR	0.166 ± NR	-0.059 (-0.287, 0.169)

Abbreviations
CI = confidence interval, **NR** = not reported, **SD** = standard deviation.

Knee Osteoarthritis: CS vs Placebo, Cartilage Volume at 24 months

No study reported cartilage volume at 24 months.

Hip Osteoarthritis: CS vs Placebo

Joint space width, cartilage volume or synovial membrane thickness was not assessed in any study evaluating hip osteoarthritis.

Hand Osteoarthritis: CS vs Placebo

Hand Osteoarthritis: CS vs Placebo, Anatomical Lesion Progression Scores at 36 months

One study reports a cumulative measure of joint space width, changes to osteophytes and subchondral cysts.[91] The study concluded there were no statistically significant differences between CS and placebo with respect to distal, proximal and metacarpophalangeal joint lesion progression scores. The standard deviation was not reported for any variable. For further information refer to ***Table 26***.

Table 26 Chondroitin sulfate compared to placebo: Anatomical lesion progression score at 36 months (hand)

Author year	Joint	Chondroitin sulfate mean ± SD	Placebo mean ± SD	p-value
Verbruggen 2002	Distal interphalangeal joint	2.6 ± NR	3.5 ± NR	0.16
	Proximal interphalangeal joint	2.3 ± NR	2.8 ± NR	0.37
	Metacarpophalangeal joint	0.4 ± NR	0.5 ± NR	0.70

Abbreviations
NR = not reported, **SD** = standard deviation.

D0011 What is the effect of the technology on patient body function?

The critical outcome function and the Lequesne index were considered when addressing this question.

Knee Osteoarthritis: CS vs Placebo

Knee Osteoarthritis: CS vs Placebo, Function at six months

Three studies provide evidence on function as measured by VAS and WOMAC at six months.[28 59 88] Overall, there are no statistically significant differences between the CS and placebo groups (SMD -0.02, 95% CI -0.24, 0.21, p = 0.88). The Chi^2 test and I^2 statistic indicate moderate levels of heterogeneity and inconsistency (p = 0.15 and I^2 = 46%). Sub-group and sensitivity analyses are not performed owing to the number of studies in the meta-analysis. For further information regarding function at 12 months and the corresponding forest plot refer to ***Figure 13***.

The measurements of WOMAC differ between the included studies. For example, studies use scales between 0—68[28] or are unclear in their reporting of scales.[88] One study reports VAS mobility as a measure of function.[59] All studies report final scores.[28 59 88]

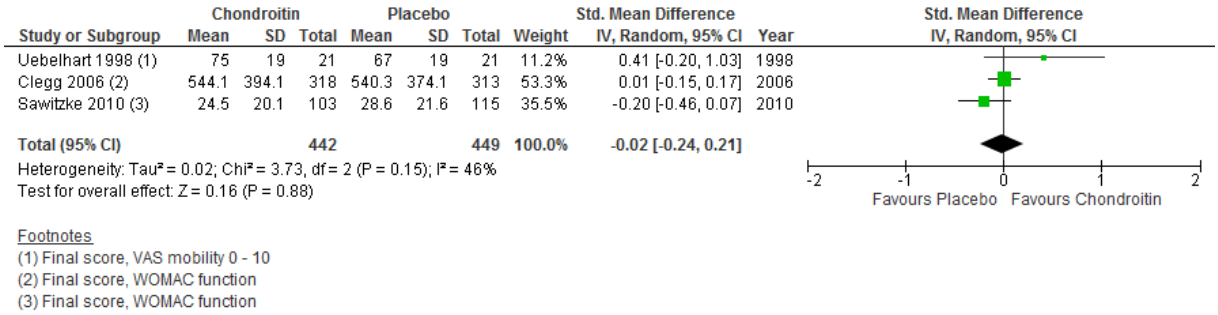


Figure 12 Forest plot indicating the standardised mean difference in function for chondroitin sulfate compared to placebo at six months (knee)

Knee Osteoarthritis: CS vs Placebo, Function at 12 months

Three studies provide evidence on function as measured by VAS and WOMAC at 12 months.[28 59 88] All three studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and placebo groups (SMD 0.17, 95% CI -0.25, 0.58, p = 0.43). The Chi^2 test and I^2 statistic indicate considerable levels of heterogeneity and inconsistency (p = 0.02 and I^2 = 76%). Sub-group and sensitivity analyses are not performed owing to the number of studies in the meta-analysis. For further information regarding function at 12 months and the corresponding forest plot refer to ***Figure 13.***

The measurements of WOMAC differ between the included studies. For example, studies utilise scales between 0—68[28] or are unclear in their reporting of scales.[88] One study reports VAS mobility as a measure of function.[59] All studies report final scores.[28 59 88]

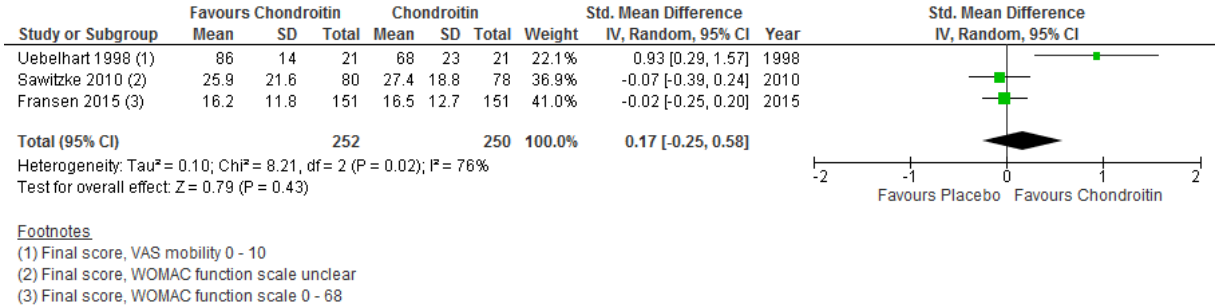


Figure 13 Forest plot indicating the standardised mean difference in function for chondroitin sulfate compared to placebo at 12 months (knee)

Knee Osteoarthritis: CS vs Placebo, Function at 24 months

Two studies provide evidence on function as measured by WOMAC at 24 months.[28 59 88 88] Both studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and placebo groups (SMD -0.04, 95% CI -0.23, 0.14, p = 0.65). The Chi^2 test and I^2 statistic indicate low levels of heterogeneity and inconsistency (p = 0.85 and I^2 = 0%). Sub-group and sensitivity analyses are not performed owing to the number of studies in the meta-analysis. For further information regarding function at 24 months and the corresponding forest plot refer to ***Figure 14***.

The measurements of WOMAC differ between the included studies. For example, studies utilise scales between 0—68[28] or are unclear in their reporting of scales.[88] All studies reported final scores.[28 59 88 88]

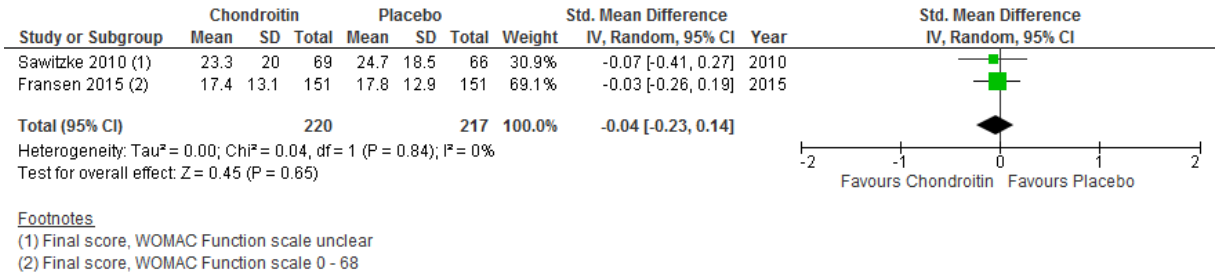


Figure 14 Forest plot indicating the standardised mean difference in function for chondroitin sulfate compared to placebo at 24 months (knee)

Knee Osteoarthritis: CS vs Placebo, Walk Test at six months

Two studies provide evidence on knee function as inferred by a 20m walk test at six months.[74 90] All studies are included in the meta-analysis. Overall, there are no statistically significant differences

between the CS and placebo groups (MD -2.08, 95% CI -4.37, 0.20, p = 0.07). The Chi^2 test and I^2 statistic indicate low levels of heterogeneity and inconsistency (p = 0.70 and I^2 = 0%). Sub-group analyses were not performed owing to the number of studies in the meta-analysis. For further information regarding the 20m walk test at six months and the corresponding forest plot refer to ***Figure 15***.

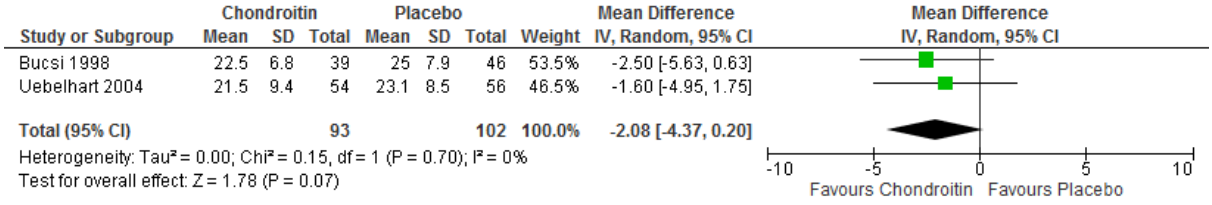


Figure 15 Forest plot indicating the mean difference in 20m walk time for chondroitin sulfate compared to placebo at six months (knee)

Knee Osteoarthritis: CS vs Placebo, Walk Test at 12 months

Two studies provide evidence on knee function as inferred by a walk test at 12 months.[28 90] All studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and placebo groups (SMD -0.17, 95% CI -0.45, 0.12, p = 0.26). The Chi^2 test and I^2 statistic indicate moderate levels of heterogeneity and inconsistency (p = 0.18 and I^2 = 45%). Sub-group and sensitivity analyses are not performed owing to the number of studies in the meta-analysis. For further information regarding the walk test at 12 months and the corresponding forest plot refer to ***Figure 16***.

The studies utilise different distances to assess knee function (15[28] and 20m[90] respectively). This may underscore the moderate levels of heterogeneity observed in the analysis.

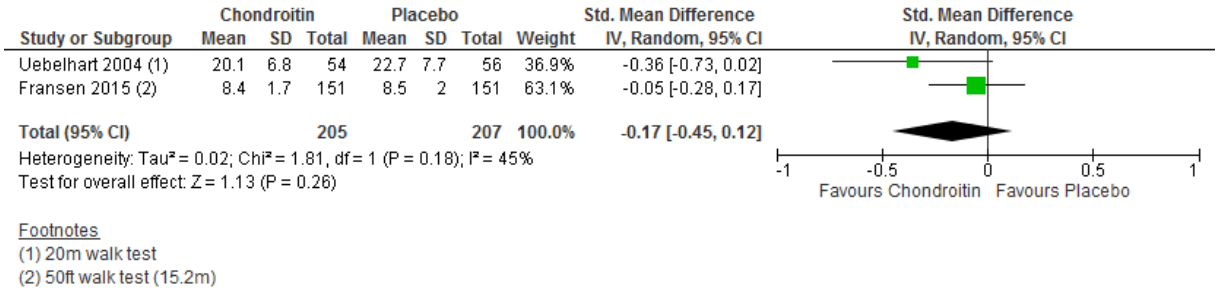


Figure 16 Forest plot indicating the standardised mean difference in 20m walk time for chondroitin sulfate compared to placebo at 12 months (knee)

Knee Osteoarthritis: CS vs Placebo, Walk Test at 24 months

One study provides evidence on knee function as inferred by a walk test at 24 months.[28] The study concluded there was no statistically significant difference between the two treatment groups with respect to walk time at 24 months (p = 0.61). For further information refer to ***Table 27***.

Table 27 Chondroitin sulfate compared to placebo: 20m walk time at 24 months (knee)

Author year	Chondroitin sulfate Walk time (s) mean ± SD	Placebo Walk time (s) mean ± SD	p-value
Fransen 2015[28]	8.4 ± 1.7	8.4 ± 1.9	0.61

Abbreviations
CI = confidence interval, **m** = metres, **s** = seconds, **SD** = standard deviation.

Knee Osteoarthritis: CS vs Placebo, Lequesne Index at six months

Seven studies provide evidence on Lequesne index at six months.[64 74 78 80 86 90 94] Six studies are included in the meta-analysis[64 74 80 86 90 94] and one study is described narratively.[78]

Overall, there are statistically significant differences between CS and placebo groups (MD -1.02, 95% CI -1.73, -0.31, p = 0.005). The Chi^2 test and the I^2 statistic indicate moderate levels of heterogeneity and inconsistencies between the studies (p = 0.09 and I^2 = 47%). For further information regarding the Lequesne index score at six months and the corresponding forest plot refer to ***Figure 17.***

Sub-group analyses determined there are significant differences between CS and placebo groups in studies that use IBSA CS (p = 0.03) and 800mg/day of CS (p = 0.03). There are no further differences when factoring manufacturer or dose. Sensitivity analyses identified statistically significant differences between CS and placebo groups in studies which: declare funding from the manufacturer (p = 0.005) or have unclear randomisation (p = 0.03), allocation (p = 0.005) and blinding of participants (p = 0.005). Further, studies that do not adequately blind outcomes (p = 0.05) and perform an intention-to-treat analysis (p = 0.005) also report statistically significant differences between the groups. There are no further differences considering intention-to-treat analysis, funding source and risk of bias parameters (randomisation, allocation and blinding of participant) (***Table 77***).

Busci[74] reports the Lequesne index for both left and right knees. The left knee data is presented, although the overall conclusions of the meta-analysis do not change depending if the right knee is used in the analysis (MD, -0.81, 95% CI -1.28, -0.34, p = 0.0008).

Much of the heterogeneity relates to the effect size reported in Bucsi.[74] This study is at a high risk of bias.

No MCIDs for Lequesne index were identified. However, a MD of 1.02 (95% CI -1.73, -0.31]) corresponds to a 4.3% (95% CI 1.3, 7.2%) change in the Lequesne index. It is unclear whether this per cent change translates to a clinically meaningful difference.

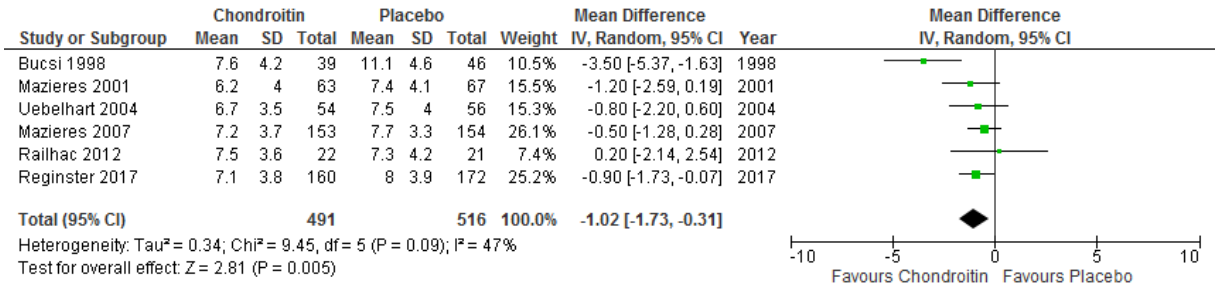


Figure 17 Forest plot indicating the mean difference in Lequesne index score for chondroitin sulfate compared to placebo at six months (knee)

One study was not included in the meta-analysis as the measure of variance (SD) was not reported. The study did note a statistically significant difference between the two treatment groups at six months (p = 0.01). For further information, refer to ***Table 28***.

Table 28 Chondroitin sulfate compared to placebo: Lequesne index at six months (knee)

Author year	Chondroitin Lequesne index mean ± SD	Placebo Lequesne index mean ± SD	p-value
L'Hirondel 1992[78]	4.6 ± NR	8.8 ± NR	0.01

Abbreviations
NR = not reported, **SD** = standard deviation.

Knee Osteoarthritis: CS vs Placebo, Lequesne Index at 12 months

Two studies provide evidence on the Lequesne index at 12 months. Both studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and placebo groups (MD -0.89, 95% CI -2.11, 0.34, p = 0.16). The Chi^2 test and I^2 statistic indicate low levels of heterogeneity and inconsistency (p = 0.37 and I^2 = 0%). Sub-group and sensitivity analyses are not performed owing to the number of studies in the meta-analysis. For further information regarding the Lequesne index score at 12 months and the corresponding forest plot refer to ***Figure 18***.

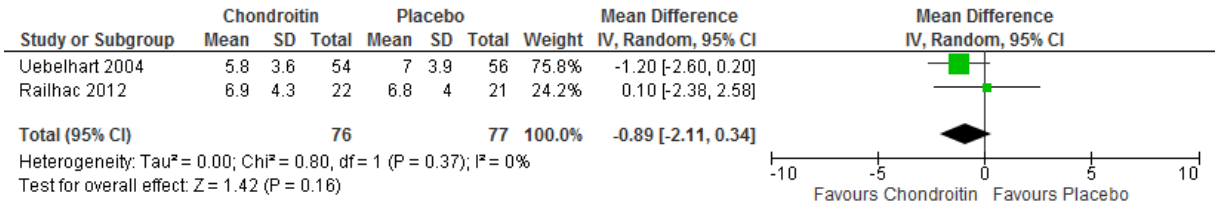


Figure 18 Forest plot indicating the standardised mean difference in Lequesne index for chondroitin sulfate compared to placebo at 12 months (knee)

Knee Osteoarthritis: CS vs Placebo, Lequesne Index at 24 months

No study reported Lequesne index score at 24 months.

Hip Osteoarthritis: CS vs Placebo

Hip Osteoarthritis: CS vs Placebo, Walk test and Lequesne Index at six months

One study provides evidence on walk test and the Lequesne index at six months.[76] The study reported a statistically significant difference between the CS and placebo groups with respect to the Lequesne index score ($p < 0.001$). However, the maximum walking distance did not differ between the two. For further information refer to ***Table 29***.

Table 29 Chondroitin sulfate compared to placebo: Lequesne index and walking distance at six months (hip)

Author year	Outcome	Chondroitin sulfate Mean ± SD	Placebo Mean ± SD	p-value
Conrozier & Vignon 1992[76]	Lequesne index (change from baseline %)	-36 ± NR	-6 ± NR	< 0.001
	Maximum walking distance (m)	1,727.3 ± 848.5	1,015.2 ± 454.5	NS

Abbreviations
m = metres, **NR** = not reported, **NS** = not significant, **SD** = standard deviation.

Hand Osteoarthritis: CS vs Placebo

Hand Osteoarthritis: CS vs Placebo, Morning Stiffness, Functional Index for Hand Osteoarthritis and Grip Strength at six months

One study provides evidence on functional measures of hand osteoarthritis including morning stiffness, functional index for hand osteoarthritis (FIHOA) and grip strength at six months.[77] Overall, there were statistically significant differences between the CS and placebo groups with respect to functional index hand osteoarthritis and duration of morning stiffness. Grip strength did not differ between the two groups (p = 0.13). For further information refer to ***Table 30***.

Table 30 Chondroitin sulfate compared to placebo: Morning stiffness, functional index and grip strength at six months (hand)

Author year	Outcome	Chondroitin sulfate Mean ± SD	Placebo Mean ± SD	p-value
Gabay 2011[77]	Duration of morning stiffness (minutes)	11.4 ±16.6	12.0 ± 12.7	0.031
	FIHOA	8.2 ± 5.9	9.6 ± 5.6	0.008
	Grip strength (kg/cm^2)	26.5 ± 10.8	25.6 ± 9.9	0.13

Abbreviations
FIHOA = functional index for hand osteoarthritis, **kg/cm^2** = kilogram per centimetre^2, **SD** = standard deviation.

Hand Osteoarthritis: CS vs Placebo, Morning Stiffness, Functional Index for Hand Osteoarthritis and Grip Strength at 12 and 24 months

No study reported functional outcomes at 12 or 24 months.

D0014 What is the effect of the technology on work ability?

This question could not be addressed with the current evidence base.

D0016 How does the use of technology affect activities of daily living?

This question could not be addressed with the current evidence base.

D0012 What is the effect of the technology on generic health-related quality of life?

The critical outcome 'quality of life' was considered when addressing this question.

Knee Osteoarthritis: CS vs Placebo

Knee Osteoarthritis: CS vs Placebo, SF-12 and Health Assessment Questionnaire at six months

Two studies provide evidence on quality of life using the SF-12 and HAQ at six months.[75 80] Owing to the different domains measured in the SF-12 and HAQ a meta-analysis was not performed. Rather, the results are described narratively.

There was a statistically significant difference between the CS and placebo groups with respect to the physical domain in the SF-12 questionnaire (p = 0.021).[80] However, there was no difference between the groups with respect to the mental health domain for SF-12 (p = 0.72)[80] and for the pain and disability domains in HAQ (p = 0.60 and p = 0.93, respectively).[75] For further information refer to ***Table 31***.

It is unclear whether the change in SF-12 scores resulted in clinically meaningful differences. MCIDs for SF-12 range from 1.7 to 5.0 across published studies. However, intervention and population differences potentially limit the applicability of the results (for further information refer to ***Table 84***).

Table 31 Chondroitin sulfate compared to placebo: SF-12 and HAQ scores at six months (knee)

Study	Outcome	Measure	Chondroitin sulfate mean ± SD	Placebo mean ± SD	p-value
Mazieres 2007[80]	SF-12 physical domain	Change from baseline	5.8 ± 9.0	3.8 ± 10.2	0.021
	SF-12 mental health domain		1.2 ± 10.4	0.3 ± 11.3	0.72
Clegg 2006[75]	HAQ Pain	Change from baseline	-15.4 ± 25.5	-16.6 ± 28.0	0.60
	HAQ Disability		-0.17 ± 0.34	-0.16 ± 0.36	0.93

Abbreviations
HAQ = health assessment questionnaire, **SD** = standard deviation, **SF-12** = short form-12 health survey.

Knee Osteoarthritis: CS vs Placebo, SF-12 and Health Assessment Questionnaire at 12 and 24 months

One study provides evidence on quality of life using the SF-12 survey at 12 and 24 months.[28] The study reported a statistically significant difference between the CS and placebo groups in the mental health domain at 24 months (p = 0.05). There were no further statistical differences between the two treatment groups for the mental health or physical domain at any time point. For further information refer to ***Table 32***.

It is unclear whether the statistically significant difference observed for the mental health component translates to an important clinical difference. MCIDs for the SF-12 mental health component range from 1.8 to 5.4. However, intervention and population differences potentially limit the applicability of the results (for further information refer to ***Table 84***).

Table 32 Chondroitin sulfate compared to placebo: SF-12 at 12 and 24 months (knee)

Author year	SF-12 domain	Follow-up duration	Chondroitin sulfate mean ± SD	Placebo mean ± SD	p-value
Fransen 2015[28]	Physical	Baseline	41.0 ± 8.9	42.1 ± 9.6	0.72
		12m	44.7 ± 8.9	44.0 ± 9.5	0.51
		24m	44.1 ± 9.4	44.2 ± 9.7	0.47
	Mental health	Baseline	52.7 ± 10.3	51.6 ± 10.7	0.21
		12m	52.4 ± 9.2	51.3 ± 10.6	0.53
		24m	53.6 ± 9.8	51.6 ± 10.0	0.05

Abbreviations
m = months, **SD** = standard deviation, **SF-12** = short form-12 health survey.

Hip Osteoarthritis: CS vs Placebo

Hip Osteoarthritis: Chondroitin Sulfate Compared to Placebo

No study reported quality of life measures for hip osteoarthritis.

Hand Osteoarthritis: CS vs Placebo

Hand Osteoarthritis: Chondroitin Sulfate Compared to Placebo

No study reported quality of life measures for hand osteoarthritis.

D0013 What is the effect of the technology on disease-specific quality of life?

This question could not be addressed with the current evidence base.

D0010 How does the technology modify the need for hospitalisation?

This question could not be addressed with the current evidence base.

D0029 What are the overall benefits and harms of the technology in health outcomes?

Twenty studies were included to evaluate the safety of CS compared to placebo for knee osteoarthritis and 15 included studies evaluated the efficacy. Overall, there was a statistically significant difference between CS and placebo for pain, Lequesne index and OMERACT-OARSI responder rate at six months. However, the outcomes reported moderate levels of heterogeneity and the clinical relevance was unclear owing to small effect sizes and lack of MCID guidelines for the Lequesne index. The effects did not persist at later time points (12 and 24 months). Generally, there were no statistical differences between the two groups with respect to function, quality of life and paracetamol intake or any safety-related outcomes.

Two studies evaluated the efficacy of CS for hand and hip osteoarthritis. Overall, there was a significant difference between CS and placebo for hand- and hip-related pain and some functional indices. The two treatment groups demonstrated comparable safety profiles, however, adverse events were poorly reported in trials evaluating hip osteoarthritis.

8.6 Results: Effectiveness

D001 What is the expected beneficial effect of the technology on mortality?

This question could not be addressed with the current evidence base.

D005 How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?

The critical outcome pain and the important outcome analgesic use were considered when answering this research question.

Knee Osteoarthritis: CS vs NSAIDs

Knee Osteoarthritis: CS vs NSAIDs, Pain at six months

Three studies provide evidence on pain as measured by VAS and WOMAC at six months.[75 85 94] All three studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and NSAIDs group (SMD -0.25, 95% CI -0.13, 0.64, p = 0.20). The Chi^2 test and I^2 statistic indicate considerable levels of heterogeneity and inconsistency (p < 0.00001 and I^2 = 89%). Sub-group and sensitivity analyses are not performed owing to the number of studies in the meta-analysis. For further information regarding pain at six months and the corresponding forest plot refer to ***Figure 19***.

The measures of WOMAC and VAS differ between the included studies. For example, studies utilised WOMAC scales between 0—500[75] or VAS,[85 94] assessed pain on walking,[85] or did not report the context in which pain was felt. [75 94] Further, studies reported final scores[75 94] or change from baseline.[85]

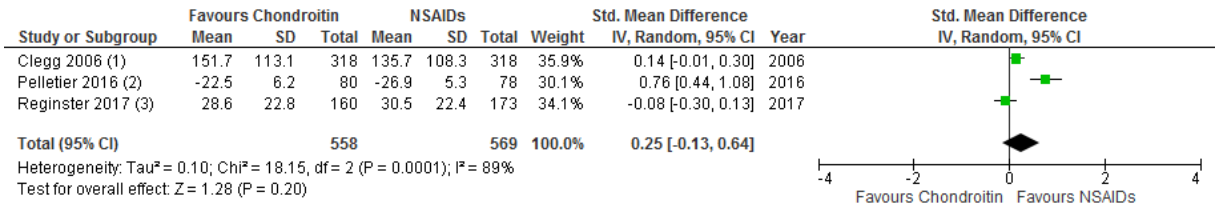


Figure 19 Forest plot indicating the standardised mean difference in pain for chondroitin sulfate compared to NSAIDs at six months (knee)

Knee Osteoarthritis: CS vs NSAIDs, Pain at 12 months

Two studies provide evidence on pain as measured by WOMAC at 12 months.[85 88] Both studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and NSAID groups (SMD 0.19, 95% CI -0.03, 0.42, p = 0.09). The Chi^2 test and I^2 statistic indicate low levels of heterogeneity and inconsistency (p = 0.74 and I^2 = 0%). Sub-group and sensitivity analyses are not performed owing to the number of studies in the meta-analysis. For further information regarding pain at 12 months and the corresponding forest plot refer to ***Figure 20***.

The measures of WOMAC differ between the included studies. For example, studies utilise scales between 0—50[85] or are unclear in their reporting of scales.[88] Further, studies report final scores[88] or change from baseline.[85]

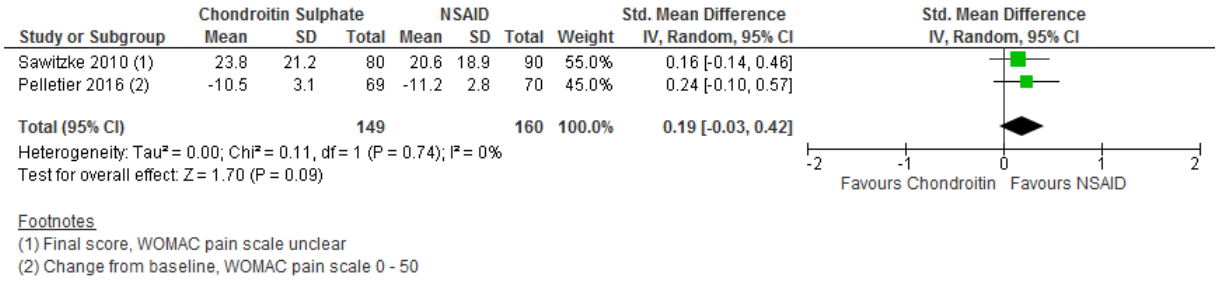


Figure 20 Forest plot indicating the standardised mean in pain for chondroitin sulfate compared to NSAIDs at 12 months (knee)

Knee Osteoarthritis: CS vs NSAIDs, Pain at 24 months

Two studies provide evidence on pain as measured by WOMAC at 24 months.[85 88] Both studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and NSAID groups (SMD 0.52, 95% CI -0.11, 1.14, p = 0.10). The Chi^2 test and I^2 statistic indicate considerable levels of heterogeneity and inconsistency (p = 0.005 and I^2 = 87%). Sub-group and sensitivity analyses are not performed owing to the number of studies in the meta-analysis. For further information regarding pain at 24 months and the corresponding forest plot refer to ***Figure 21***.

The measures of WOMAC differ between the included studies. For example, studies utilise scales between 0—50[85] or are unclear in their reporting of scales.[88] Further, studies report final scores[88] or change from baseline.[85]

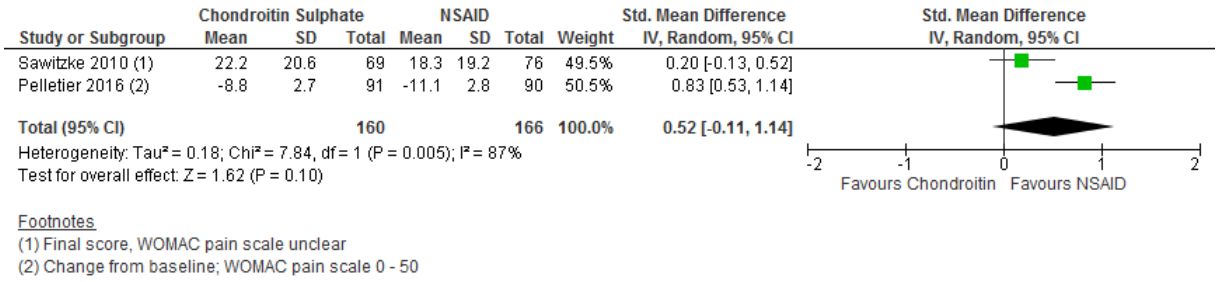


Figure 21 Forest plot indicating the standardised mean difference in pain for chondroitin sulfate compared to NSAIDs at 24 months (knee)

Knee Osteoarthritis: CS vs NSAIDs, OMERACT-OARSI at six months

Two studies provide evidence on the OMERACT-OARSI responder rate at six months. Both are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and NSAID group (RR 0.98, 95% CI 0.90, 1.07, p = 0.65). The Chi^2 test and the I^2 statistic indicate low levels of heterogeneity and inconsistency (p = 0.82 and I^2 = 0%). Sub-group and sensitivity analyses are not performed owing to the number of studies in the meta-analysis. For further information regarding OMERACT-OARSI responder rate at six months and the corresponding forest plot refer to ***Figure 22***.

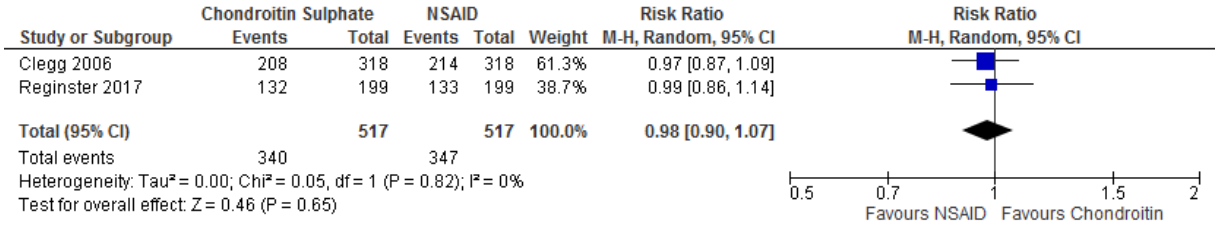


Figure 22 Forest plot indicating the risk ratio in the OMERACT-OARSI responder rate at six months (knee)

Knee Osteoarthritis: CS vs NSAIDs, OMERACT-OARSI at 12 and 24 months

No study reported OMERACT-OARSI responder rate at 12 or 24 months.

Knee Osteoarthritis: CS vs NSAIDs, Paracetamol use at six months

One study provides evidence on the use of paracetamol at six months.[75] Overall, the mean number of tablets per day was similar between the two groups. However, given that the statistical significance was

not reported in either study, it is unclear whether the two groups differed. For further information refer to ***Table 33***.

Table 33 Chondroitin sulfate compared to NSAIDs: Paracetamol intake at six months (knee)

Author year	Outcome reported	Chondroitin sulfate Mean ± SD	NSAIDs Mean ± SD	p-value
Clegg 2006[75]	Number of tablets/days	1.9 ± 1.9	1.6 ± 1.7	NR

Abbreviations
SD = standard deviation.

Knee Osteoarthritis: CS vs NSAIDs, Paracetamol use at 12 months

No study reported paracetamol utilisation at 12 months.

Knee Osteoarthritis: CS vs NSAIDs, Paracetamol use at 24 months

Two studies provide evidence on the use of paracetamol (tablets/day) at 24 months.[85 88] A meta-analysis was not performed as the measure of variance was not reported in one study.[85] As such, the results are described narratively. Overall, the mean number of tablets per day was similar between the two groups in both studies. However, given that the statistical significance was not reported in either study, it is unclear whether the two groups differed. For further information refer to ***Table 34***.

Table 34 Chondroitin sulfate compared to NSAIDs: Paracetamol intake at 24 months (knee)

Author year	Chondroitin sulfate mg/day mean ± SD	NSAIDs mg/day mean ± SD	p-value
Sawitzke 2010[a]	0.9 ± 1.2	1.3 ± 1.7	NR
Pelletier 2016	1.2 ± NR	0.9 ± NR	NR

Abbreviations
mg = milligrams, **NR** = not reported, **NSAID** = non-steroidal anti-inflammatory drug, **SD** = standard deviation.
Notes
a = unclear how many patients in each arm.

Knee Osteoarthritis: CS vs Paracetamol

Knee Osteoarthritis: CS vs Paracetamol, Pain at six months

One study provides evidence on pain as measured by VAS (0—100mm).[89] The study concluded there were no statistically significant differences between CS and paracetamol with respect to VAS score at six months (p = 0.92). For further information refer to ***Table 35***.

Table 35 Chondroitin sulfate compared to paracetamol: Pain at six months (knee)

Author year	Chondroitin sulfate mean ± SD	Paracetamol mean ± SD	p-value
Tio 2017[89]	40.8 ± 22.0	38.9 ± 27.7	0.92

Abbreviations
SD = standard deviation, **VAS** = visual analogue scale.

Knee Osteoarthritis: CS vs Paracetamol, Pain at 12 and 24 months

No study reported pain at 12 or 24 months.

D006 How does the technology affect progression (or recurrence) of the disease or health condition?

The important outcome of radiographic evidence of disease progression was considered when answering this research question.

Knee Osteoarthritis: CS vs NSAIDs

Knee Osteoarthritis: CS vs NSAIDs, Cartilage Volume and Synovial Membrane Thickness at 24 months

One study provides evidence on cartilage volume and synovial membrane thickness at 24 months.[85] The study concludes there is no statistically significant difference in the lateral cartilage volume and synovial membrane thickness between CS and NSAIDs at the end of the study (p = 0.75 and 0.73, respectively). However, there are significant differences in medial cartilage volume at 24 months (p = 0.02). For further information refer to ***Table 36***.

Table 36 Chondroitin sulfate compared to NSAIDs: Cartilage volume and synovial membrane thickness at 24 months (knee)

Author year	Outcome	Chondroitin sulfate mean ± SD	NSAIDs mean ± SD	p-value
Pelletier 2016[85]	Cartilage volume (%) Lateral compartment	-4.6 ± 3.0	-4.4 ± 2.8	0.75
	Cartilage volume (%) Medial compartment	-6.6 ± 3.3	-8.4 ± 4.2	0.02
	Synovial membrane thickness, mm	0.15 ± 0.26	0.15 ± 0.24	0.73

Abbreviations

m = months, **mm** = millimetres, **NSAIDs** = non-steroidal anti-inflammatory drugs, **SD** = standard deviation.

Knee Osteoarthritis: CS vs Paracetamol

Knee Osteoarthritis: CS vs Paracetamol, Joint Space Width, Cartilage Volume, Synovial Membrane Thickness at 24 months

No study reported joint space width, cartilage volume or synovial membrane thickness at 24 months.

D0011 What is the effect of the technology on patient body function?

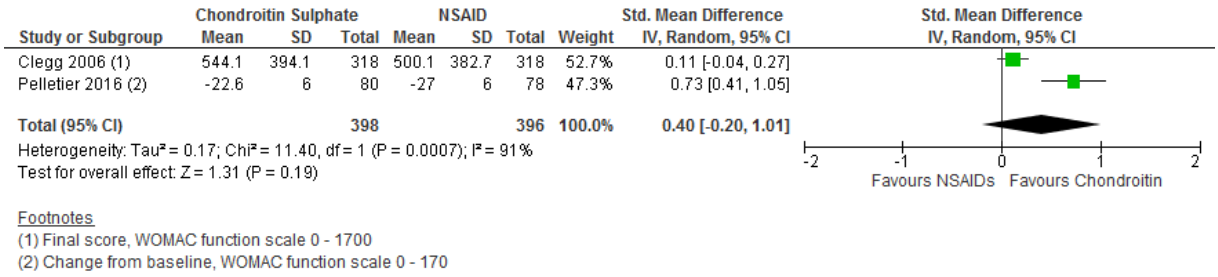
The critical outcome function and the Lequesne index were considered when addressing this question.

Knee Osteoarthritis: CS vs NSAIDs

Knee Osteoarthritis: CS vs NSAIDs, Function at six months

Two studies provide evidence on knee function as measured by WOMAC at six months.[75 85] Both studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and NSAID groups (SMD 0.40, 95% CI -0.20, 1.01, p = 0.19). The Chi^2 test and I^2 statistic indicate considerable levels of heterogeneity and inconsistency (p = 0.0007 and I^2 = 91%). Sub-group and sensitivity analyses are not performed owing to the number of studies included in the meta-analysis. For further information regarding function at six months and the corresponding forest plot refer to ***Figure 23***.

The measures of WOMAC differ between the included studies. For example, studies utilise scales between 0—170[85] or 0—1700.[75] Further, studies report final scores[75] or change from baseline.[85] This may add to the heterogeneity and differing effect sizes.



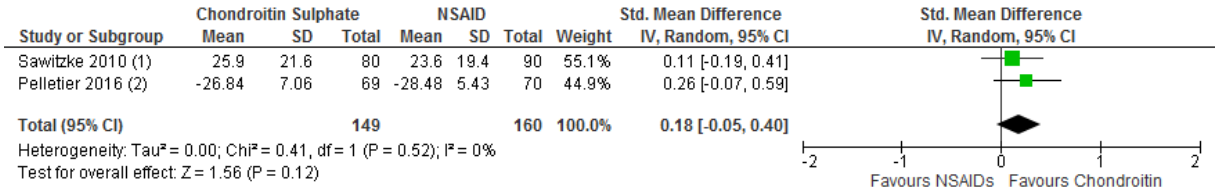
Footnotes
(1) Final score, WOMAC function scale 0 - 1700
(2) Change from baseline, WOMAC function scale 0 - 170

Figure 23 Forest plot indicating the standardised mean difference in function for chondroitin sulfate compared to NSAIDs at six months (knee)

Knee Osteoarthritis: CS vs NSAIDs, Function at 12 months

Two studies provide evidence on function as measured by WOMAC at 12 months.[85 88] All studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and NSAIDs groups (SMD 0.18, 95% CI -0.05, 0.40, p = 0.12). The Chi^2 test and I^2 statistic indicate low levels of heterogeneity and inconsistency (p = 0.52 and I^2 = 0%). Sub-group and sensitivity analyses are not performed owing to the number of studies included in the meta-analysis. For further information regarding function at 12 months and the corresponding forest plot refer to ***Figure 24***.

The measures of WOMAC differ between the included studies. For example, studies utilise scales between 0—170[85] or are unclear in their reporting of scales.[88] Further, studies report final scores[88] or change from baseline.[85]



Footnotes
(1) Final score, WOMAC function scale unclear
(2) Change from baseline, WOMAC function scale 0 - 170

Figure 24 Forest plot indicating the standardised mean difference in function for chondroitin sulfate compared to NSAIDs at 12 months (knee)

Knee Osteoarthritis: CS vs NSAIDs, Function at 24 months

Two studies provide evidence on function as measured by WOMAC at 24 months.[85 88] Both studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and NSAIDs groups (SMD 0.18, 95% CI -0.04, 0.40, p = 0.10). The Chi^2 test and I^2 statistic indicate low levels of heterogeneity and inconsistency (p = 0.43 and I^2 = 0%). Sub-group and sensitivity analyses are not performed owing to the number of studies in the meta-analysis. For further information regarding function at 12 months and the corresponding forest plot refer to ***Figure 25.***

The measures of WOMAC differ between the included studies. For example, studies utilise scales between 0—170[85] or are unclear in their reporting of scales.[88] Further, studies report final scores[88] or change from baseline.[85]

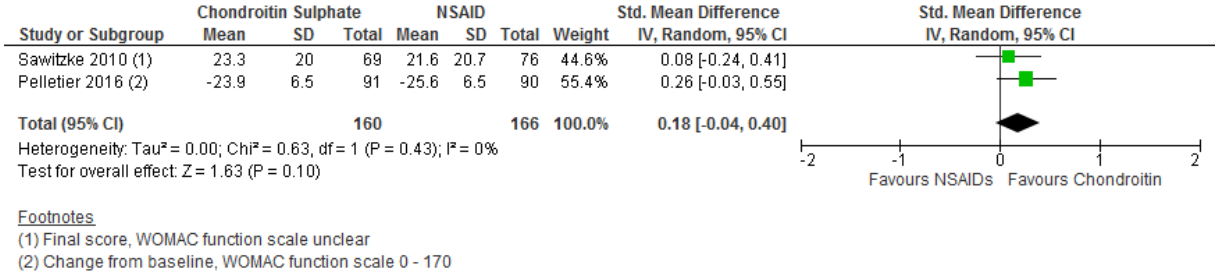


Figure 25 Forest plot indicating the standardised mean difference in function for chondroitin sulfate compared to NSAIDs at 24 months (knee)

Knee Osteoarthritis: CS vs NSAIDs, Lequesne Index at six months

One study provides evidence on Lequesne index at six months.[75 94] Overall, mean Lequesne index was similar between the two groups. However, given that the statistical significance was not reported in either study, it is unclear whether the two groups differed. For further information refer to ***Table 37***.

Table 37 Chondroitin sulfate compared to NSAIDs: Lequesne index 6 months (knee)

Author year	Chondroitin sulfate Mean ± SD	NSAIDs Mean ± SD	p-value
Reginster 2017[94]	7.1 ± 3.8	7.0 ± 3.9	NR

Abbreviations
SD = standard deviation.

Knee Osteoarthritis: CS vs NSAIDs, Lequesne Index at 12 and 24 months

No study reported Lequesne index at 12 or 24 months.

Knee Osteoarthritis: CS vs Paracetamol

Knee Osteoarthritis: CS vs Paracetamol, Lequesne Index at six months

One study provides evidence on the Lequesne index score at six months.[89] The study concluded there were no statistically significant differences between CS and paracetamol groups with respect to Lequesne index scores (p = 0.22). For further information refer to ***Table 38***.

Table 38 Chondroitin sulfate compared to paracetamol: Lequesne index scores at six months (knee)

Author year	Chondroitin sulfate mean ± SD	Paracetamol mean ± SD	p-value
Tio 2017[89]	7.7 ± 3.3	8.5 ±4.6	0.22

Abbreviations
SD = standard deviation.

Knee Osteoarthritis: CS vs Paracetamol, Lequesne Index at 12 and 24 months

No study reported Lequesne index scores at 12 or 24 months.

D0014 What is the effect of the technology on work ability?

This question could not be addressed with the current evidence base.

D0016 How does the use of the technology affect activities of daily living?

This question could not be addressed with the current evidence base.

D0012 What is the effect of the technology on generic health-related quality of life?

The critical outcome ‘quality of life’ was considered when addressing this question.

Knee Osteoarthritis: CS vs NSAIDs

Knee Osteoarthritis: CS vs NSAIDs, Health Assessment Questionnaire at six months

One study provides evidence on the HAQ at six months. There was no statistically significant difference between the CS and NSAIDs groups in either the pain or disability domains (p = NR). For further information, refer to ***Table 39.***

MCIDs for the HAQ disability domain ranged from 0.36 to 0.58. Given the CS and NSAIDs groups are lower than the reported MCIDs, it is unlikely the differences observed for the disability domain translate to an important clinical difference. However, intervention and population differences potentially limit the applicability of the results (for further information refer to ***Table 84***). No MCIDs were identified for the pain domain.

Table 39 Chondroitin sulfate compared to NSAIDs: HAQ scores at six months (knee)

Author year	HAQ Domain	Measure	Chondroitin sulfate mean ± SD	NSAIDs mean ± SD	p-value
Clegg 2006[75]	Pain	Change from baseline	-15.4 ± 25.5	-20.2 ± 27.4	NR
	Disability		-0.17 ± 0.34	-0.20 ± 0.35	NR

Abbreviations
HAQ = health assessment questionnaire, **NR** = not reported, **NSAIDs** = non-steroidal anti-inflammatory drugs, **SD** = standard deviation.

Knee Osteoarthritis: CS vs NSAIDs, Health Assessment Questionnaire at 12 and 24 months

No study reported HAQ scores at 12 or 24 months.

Knee Osteoarthritis: CS vs Paracetamol, Quality of Life at six, 12 and 24 months

No study reported any quality of life measures at six, 12 or 24 months.

D0013 What is the effect of the technology on disease-specific quality of life?

This question could not be addressed with the current evidence base.

D0010 How does the technology modify the need for hospitalisation?

This question could not be addressed with the current evidence base.

D0029 What are the overall benefits and harms of the technology in health outcomes?

Five studies were included to evaluate the comparative safety and effectiveness of CS to NSAIDs and paracetamol. Overall, there were no statistically significant differences between CS and NSAIDs with respect to measures of pain, function, Lequesne index and quality of life outcomes at 6, 12 or 24 months. Furthermore, there was no difference between the two treatment groups for any safety-related outcomes. Similarly, there was no difference between CS and paracetamol for pain or function outcomes at six months. There were higher adverse event rates in the paracetamol group however, the statistical significance was not reported (36.4% versus 2.9%, respectively).

8.7 Results: Safety

C0008 How safe is the technology in comparison to the comparator(s)?

The critical outcomes of mortality, severe adverse events, treatment-related severe adverse events and withdrawal due to adverse event, in addition to the important outcomes of any-, treatment- and gastrointestinal-related adverse events were considered when answering this question.

Knee Osteoarthritis: CS vs Placebo

Knee Osteoarthritis: CS vs Placebo, Mortality

Three studies provide evidence on mortality.[59 75 88] However, owing to the rarity of the event and number of studies reporting the outcome, a meta-analysis was not performed. The incidence of mortality is described narratively.

Two deaths were reported across three studies (n = 939). One death was reported in each treatment arm.[59 88] The death in the placebo arm was deemed unrelated to the intervention (completed suicide).[88] By contrast, the cause of death and the relatedness to the intervention in the CS arm was not reported.[59] However, owing to the composition and nature of CS, it is unlikely related to the intervention. For further details on the incidence of mortality see ***Table 40***.

Table 40 Chondroitin sulfate compared to placebo: Mortality (knee)

Author year	Follow-up	Chondroitin sulfate n/N (%)	Placebo n/N (%)
Uebelhart 1998[a 59]	12 months	1/23 (4.3%)	0/23 (0.0%)
Clegg 2006[75]	6 months	0/318 (0.0%)	0/318 (0.0%)
Sawitzke 2010[b 88]	24 months	0/126 (0.0%)	1/131 (0.8%)

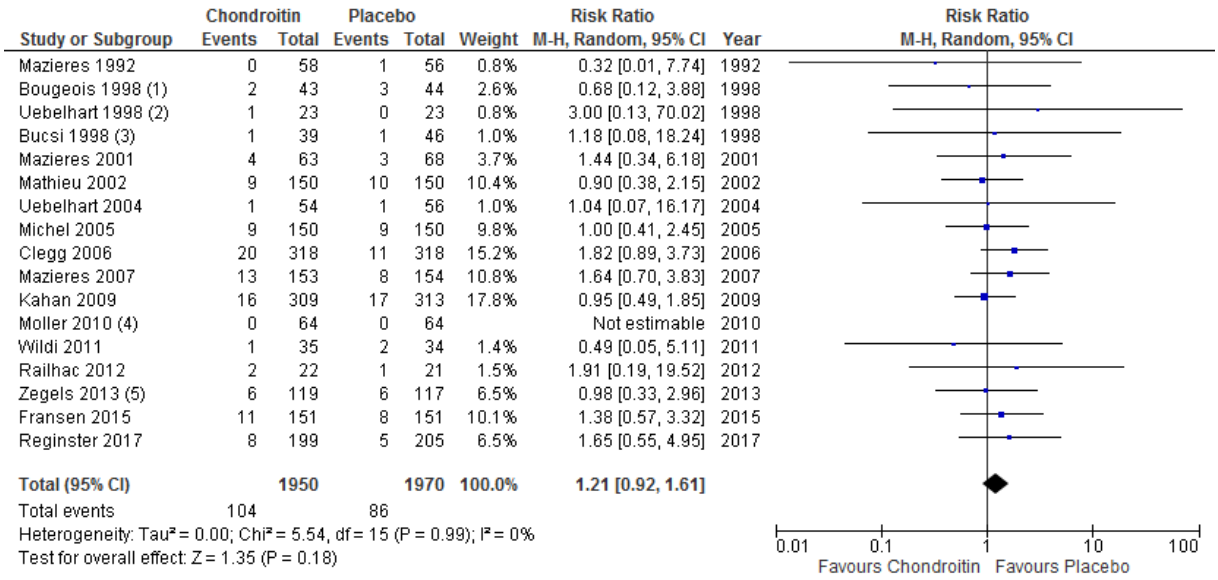
Abbreviations
n = number of patients, **N** = total number of patients.
Notes
a = unclear whether patient death was attributable to the intervention, **b** = patient death was not attributable to the intervention.

Knee Osteoarthritis: CS vs Placebo, Withdrawal Due to Adverse Events

Seventeen studies provide evidence on withdrawal due to adverse events.[28 59 64 69 73-75 80-83 86 90 92-94] All studies are included in the meta-analysis. Overall, there are no statistically significant differences

between the CS and placebo groups (RR 1.21, 95% CI 0.92, 1.61, p = 0.18). The absolute risk for CS and placebo groups are 5.3% and 4.4%, respectively. The Chi^2 test and I^2 statistic indicate low levels of heterogeneity and inconsistency (p = 0.99 and I^2 = 0%). For further information regarding withdrawal due to adverse events and the corresponding forest plot refer to ***Figure 26.***

There are no significant sub-group differences between CS and placebo groups when factoring manufacturer, dose or duration of follow-up. Sensitivity analyses determined there are significant differences in studies that did not adequately blind the outcome (p = 0.05). There are no further sensitivity differences when factoring intention-to-treat analysis, funding source and risk of bias parameters (randomisation, allocation and blinding of participant) (***Table 78***).



Footnotes
(1) Represents the minimum number of patients who withdrew
(2) Withdrawal due to death, unclear whether it was related to treatment
(3) Withdrawal due to adverse event but thought unrelated to treatment
(4) No withdrawal was attributed to adverse event
(5) 1200mg/day tablet data reported, data from the 1200mg gel group was omitted from the analysis

Figure 26 Forest plot indicating the risk ratio of withdrawals due to adverse events for chondroitin sulfate compared to placebo (knee)

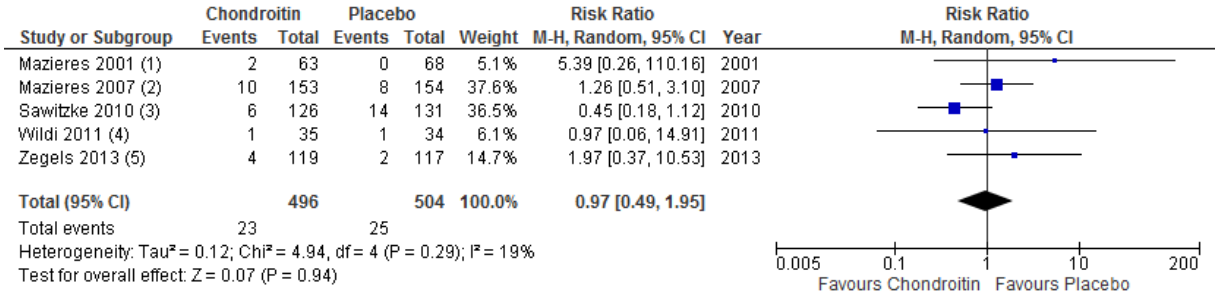
Knee Osteoarthritis: CS vs Placebo, Severe Adverse Events

Five studies provide evidence on severe adverse events.[64 80 88 92 93] All five studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and placebo groups (RR 0.97, 95% CI 0.49, 1.95, p = 0.94). The absolute risk for CS and placebo groups are 4.6 and 5.0%, respectively. The Chi^2 test and I^2 statistic indicate low levels of heterogeneity and

inconsistency (p = 0.29 and I^2 = 19%) For further information regarding severe adverse events and the corresponding forest plot refer to ***Figure 27***.

There are no significant sub-group or sensitivity analyses differences when factoring manufacturer, dose and duration of follow-up or intention-to-treat analysis, funding source and several risk of bias parameters (randomisation, allocation, blinding of participant and blinding of outcomes), respectively (***Table 79***).

Only two studies provide definitions of adverse events (ICH guidelines)[88 93] and they use different measures of reporting severe adverse events. For example, studies report the number of patients with at least one severe adverse event[64 80] or are unclear regarding the number of severe adverse events per patient.[88 92 93] For the latter group, as the incidence of severe adverse events is less than the total number of patients, it is likely that patients experience a maximum of one or two events per study. Given the limitations of the evidence base, the findings from the meta-analysis should be interpreted with caution.



Footnotes
(1) Number of patients with at least one severe adverse event
(2) Number of patients with at least one severe adverse event
(3) Patients likely had one to two severe adverse events
(4) Patients likely had one to two severe adverse events; first six months of treatment reported
(5) Patients likely had one to two severe adverse events; 1200mg/day tablet data reported, data from the 1200mg gel group was omitted

Notes

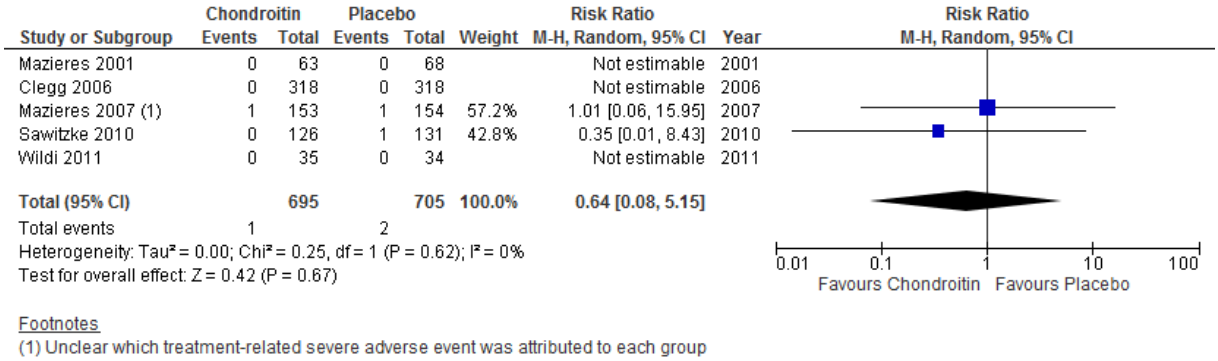
Events represent the number of patients experiencing an adverse event.

Figure 27 Forest plot indicating the risk ratio of severe adverse events for chondroitin sulfate compared to placebo (knee)

Knee Osteoarthritis: CS vs Placebo, Treatment-Related Severe Adverse Events

Five studies provide evidence on treatment-related severe adverse events [64 75 80 88 92] and all are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and placebo groups (RR 0.64, 95% CI 0.08, 5.15, p = 0.67). The absolute risk for CS and placebo groups is 0.1% and 0.3%, respectively. The Chi^2 test and I^2 statistic indicate low levels of heterogeneity and inconsistency (p = 0.62 and I^2 = 0%). For further information regarding treatment-related severe adverse events and the corresponding forest plot refer to ***Figure 28***. The treatment-related severe adverse events included a coronary angioplasty (placebo)[88], and eczema and urticaria (unclear which treatment group, however, the authors note only one treatment-related severe adverse event per group).[80] The studies did not report whether the treatment-related serve adverse events resolved.

There are no significant differences in sub-group or sensitivity analyses when considering manufacturer, dose, duration of follow-up, intention-to-treat analysis, funding source or several risk of bias parameters (randomisation, allocation, blinding of participant and blinding of outcomes) (***Table 80***).



Notes

Events represent the number of patients experiencing an adverse event.

Figure 28 Forest plot indicating the risk ratio of treatment-related severe adverse events for chondroitin sulfate compared to placebo (knee)

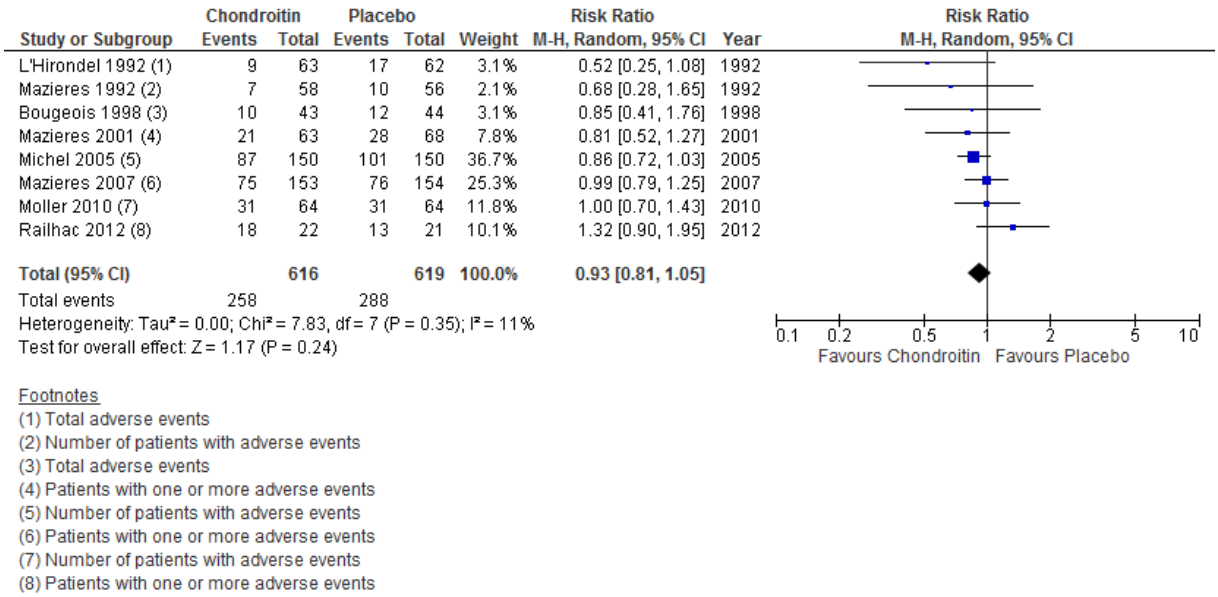
Knee Osteoarthritis: CS vs Placebo, Any Adverse Events

Ten studies provide evidence on any adverse event.[64 73 78 80-83 86 92 93] Eight are included in the meta-analysis and two are described narratively. Overall, there are no statistically significant differences between the CS and placebo groups (RR 0.93, 95% CI 0.81, 1.05, p = 0.24). The absolute risk for CS and placebo groups is 41.9% and 46.5%, respectively. The Chi^2 test and I^2 statistic indicate low levels of heterogeneity and inconsistency (p = 0.35 and I^2 = 11%). For further information regarding any adverse events and the corresponding forest plot refer to ***Figure 29***.

Sub-group analyses determined there are significant differences between CS and placebo groups in studies that use IBSA CS (p = 0.05). There are no further differences when factoring manufacturer, dose or duration of follow-up. Sensitivity analyses determined studies that have unclear blinded outcomes report statistical differences between CS and placebo groups (p = 0.04). There are no further differences when factoring intention-to-treat analysis, funding source and several risk of bias parameters (randomisation, allocation and blinding of participant) (***Table 81***).

The included studies use different measures of reporting adverse events. For example, studies report the number of patients with adverse events[83 86], the number of patients with at least one adverse event[64 80 82], or the total number of adverse events.[73 78] The latter category was included in the meta-analysis if the number of patients was notably less than the number of adverse events suggesting approximately one adverse event per person.

Two studies report the incidence of adverse events;[92 93] however, they are omitted from the meta-analysis as the number of patients experiencing adverse events could not be accurately determined. Wildi[92] reported 55 and 38 adverse events in the CS (n = 35) and the placebo (n = 35) groups within the first six months of treatment respectively. Zegels[93] reported there was no difference between individuals receiving CS 1,200mg once per day, 400mg/three times per day and placebo in terms of the mean number of adverse events or the number of patients with at least one adverse event. Two studies note the adverse events were typically mild to moderate in severity.[83 86]



Footnotes
(1) Total adverse events
(2) Number of patients with adverse events
(3) Total adverse events
(4) Patients with one or more adverse events
(5) Number of patients with adverse events
(6) Patients with one or more adverse events
(7) Number of patients with adverse events
(8) Patients with one or more adverse events

Notes

Events represent the number of patients experiencing an adverse event.

Figure 29 Forest plot indicating the risk ratio of any adverse events for chondroitin sulfate compared to placebo (knee)

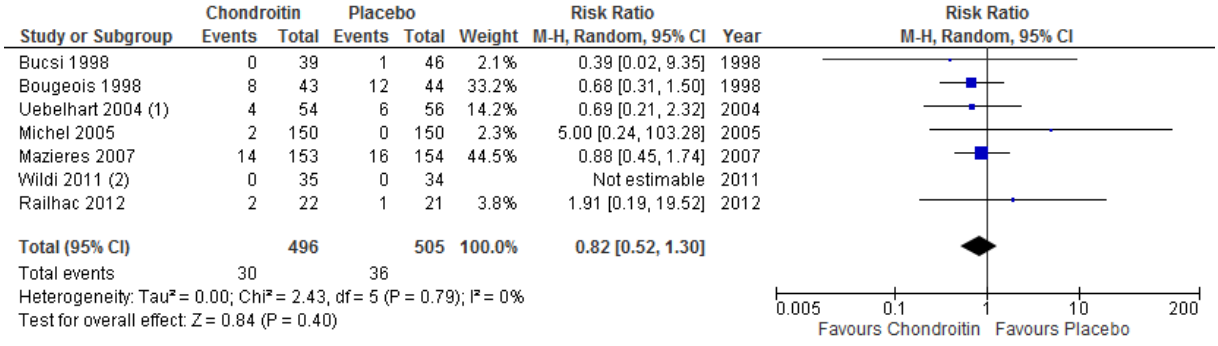
Knee Osteoarthritis: CS vs Placebo, Treatment-Related Adverse Event

Eight studies provide evidence on any treatment-related adverse events. Seven studies are included in the meta-analysis and one study is described narratively.[73 74 80 82 90 92 93] Overall, there are no statistically significant differences between the CS and placebo groups (RR 0.82, 95% CI 0.52, 1.30, p = 0.40). The absolute risk for CS and placebo groups is 6.0% and 7.1%, respectively. The Chi^2 test and I^2 statistic indicate low levels of heterogeneity and inconsistency (p = 0.79 and I^2 = 0%). For further information regarding treatment-related adverse events and the corresponding forest plot refer to ***Figure 30***.

There are no significant sub-group or sensitivity analyses differences when factoring manufacturer, dose and duration of follow-up or intention-to-treat analysis, funding source and several risk of bias parameters (randomisation, allocation, blinding of participant and blinding of outcomes), respectively (***Table 82***).

One study[93] reports the incidence of treatment-related adverse events, however, this was omitted from the meta-analysis as the number of patients experiencing adverse events could not be accurately determined. Zegels[93] reported 26.4%, 26.0% and 41.7% of treatment-emergent adverse events were experienced by individuals in the CS 1,200mg/once per day, 400mg/three times per day and placebo groups, respectively. Given the number of adverse events (n = 260) was greater than the number of patients (N = 161), it is unclear how many patients per treatment group had an adverse event.

Four studies report that most of the treatment-related adverse event were gastrointestinal in nature.[74 80 82 90]



Footnotes
(1) Patients may have experienced more than one adverse event
(2) Patients may have experienced more than one adverse event

Notes

Events represent the number of patients experiencing an adverse event.

Figure 30 Forest plot indicating the risk ratio of treatment-related adverse events for chondroitin sulfate compared to placebo (knee)

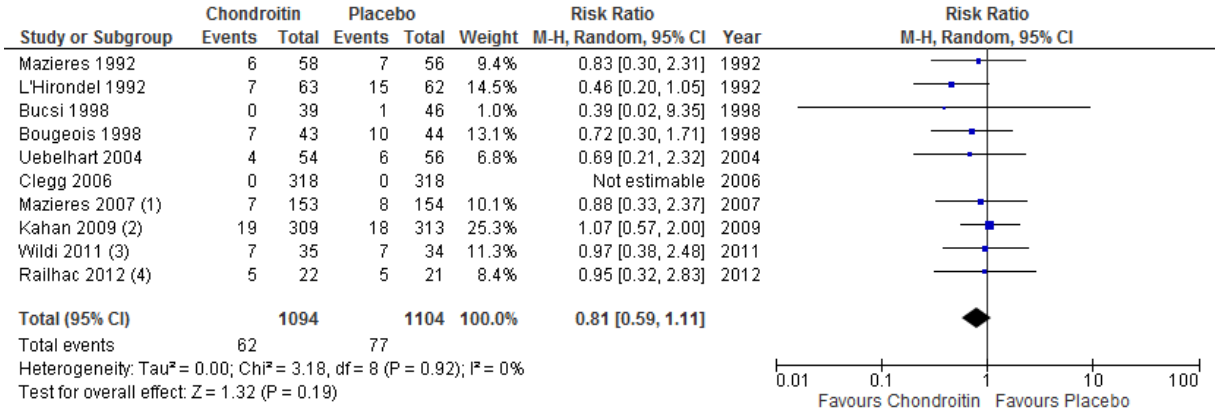
Knee Osteoarthritis: CS vs Placebo, Gastrointestinal-Related Adverse Event

Ten studies provide evidence on gastrointestinal-related adverse events. All ten studies are included in the meta-analysis.[69 73-75 78 80 81 86 90 92] Overall, there are no statistically significant differences between the CS and placebo groups (RR 0.81, 95% CI 0.59, 1.11, p = 0.19). The absolute risk for CS and placebo groups is 5.7% and 7.0%, respectively. The Chi^2 test and I^2 statistic indicate low levels of heterogeneity and inconsistency (p = 0.92 and I^2 = 0% respectively). For further information regarding gastrointestinal-related adverse events and the corresponding forest plot refer to ***Figure 31.***

There are no significant sub-group or sensitivity analyses differences when factoring manufacturer, dose and duration of follow-up or intention-to-treat analysis, funding source and several risk of bias parameters (randomisation, allocation, blinding of participant and blinding of outcomes), respectively (***Table 83***).

Specific gastrointestinal adverse events are reported in five studies.[73 78 80 81 90] Gastralgia, dyspepsia, nausea, vomiting, diarrhoea and abdominal pain are the most commonly reported adverse events relating to the gastrointestinal system.

One study reports that symptoms were self-limiting or resolved by symptomatic treatment.[73]



Footnotes
(1) Majority (50%) of adverse event were related to gastrointestinal system
(2) Number approximated based on the values provided in the manuscript (6 and 5.9% for chondroitin and placebo respectively)
(3) Adverse events reported in the first six months
(4) Number approximated based on the values provided in the manuscript (20 and 22% for chondroitin and placebo respectively)

Notes

Events represent the number of adverse events.

Figure 31 Forest plot indicating the risk ratio of gastrointestinal-related adverse events for chondroitin sulfate compared to placebo (knee)

Hip Osteoarthritis: CS vs Placebo

Hip Osteoarthritis: CS vs Placebo, Withdrawal Due to Adverse Events and Adverse Events

One study provides evidence comparing CS to placebo for hip osteoarthritis (***Table 41***).[76] As such, the outcomes were described narratively. Overall, the number of individuals who withdrew due to adverse events was zero in the CS group and three in the placebo group. The statistical significance was not reported in the study.

There were no adverse events in patients receiving CS. The study did not report whether patients in the placebo group experienced adverse events, therefore it is unclear whether the two groups differed statistically.

Table 41 Chondroitin sulfate compared to placebo: Withdrawals due to, and any adverse event (hip)

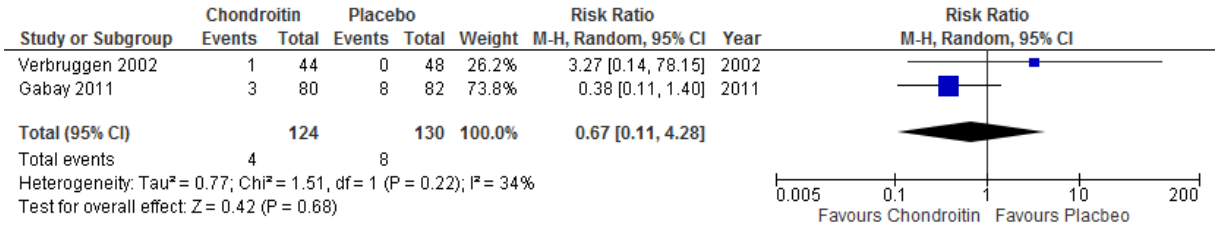
Author year	Outcome	Chondroitin sulfate n/N (%)	Placebo n/N (%)	p-value
Conrozier & Vignon 1992[76]	Withdrawal due to adverse event	0/29 (0.0%)	3/27 (11.1%)	NR
	Any adverse event	0/29 (0.0%)	NR	NR

Abbreviations
n = number of patients, **N** = total number of patients, **NR** = not reported.

Hand Osteoarthritis: CS vs Placebo

Hand Osteoarthritis: CS vs Placebo, Withdrawal Due to Adverse Events

Two studies provide evidence comparing CS to placebo for hand osteoarthritis.[77 91] Both studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and placebo groups regarding withdrawal due to adverse events (RR 0.67, 95% CI 0.11, 4.28, p = 0.68). The absolute risk for CS and placebo groups is 3.2% and 6.2%, respectively. The Chi^2 test and I^2 statistic indicate low levels of heterogeneity and inconsistency (p = 0.22, I^2 = 34%). Sub-group and sensitivity analyses are not performed owing to the number of studies in the meta-analysis. For further information regarding withdrawals due to adverse events and the corresponding forest plot refer to ***Figure 32***.



Notes

Events represent the number of patients withdrawing.

Figure 32 Forest plot indicating the risk ratio of withdrawals due to adverse events for chondroitin sulfate compared to placebo (hand)

Hand Osteoarthritis: CS vs Placebo, Adverse Events

One study provides evidence on any adverse events including those that were treatment-related and gastrointestinal-related.[77] As such, this outcome is described narratively. The study reported similar rates of adverse events in patients receiving CS and placebo, however, it is unclear whether the two groups differed statistically. The treatment-related severe adverse event included one case of abdominal pain in the placebo group. For further information regarding safety outcomes refer to ***Table 42***.

Table 42 Chondroitin sulfate compared to placebo: Severe, treatment-related and gastrointestinal adverse events (hand)

Author year	Outcome	Chondroitin sulfate n/N (%)	Placebo n/N (%)	p-value
Gabay 2011[77]	Severe adverse event	2/80 (2.5%)	2/82 (2.4%)	NR
	Treatment-related severe adverse event	0/80 (0.0%)	1/82 (1.2%)	NR
	Any adverse event	34/80 (42.5%)	34/82 (41.5%)	NR
	Treatment-related adverse event	13/80 (16.3%)	19/82 (23.2%)	NR
	Gastrointestinal adverse event	12/80 (15.0%)	14/82 (17.1%)	NR

Abbreviations

n = number of patients, **N** = total number of patients.

Knee Osteoarthritis: CS vs NSAIDs

Knee Osteoarthritis: CS vs NSAIDs, Mortality

Three studies provide evidence on mortality,[75 85 88] however, owing to the rarity of the event and number of studies reporting the outcome, a meta-analysis was not performed. The incidence of mortality was described narratively.

There were no deaths across the three studies (n = 1,098). For further details on the incidence of mortality see ***Table 43***.

Table 43 Chondroitin sulfate compared to NSAIDs: Mortality (knee)

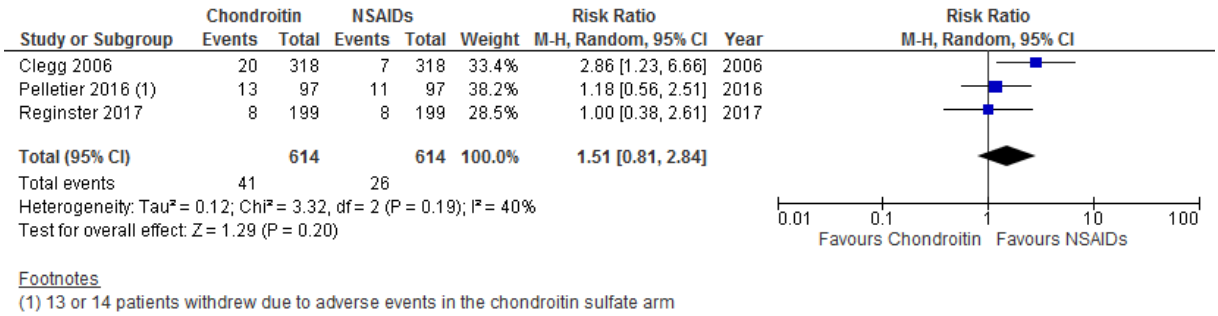
Author year	Follow-up	Chondroitin sulfate n/N (%)	NSAIDs n/N (%)
Clegg 2006[75]	6 months	0/318 (0.0%)	0/318 (0.0%)
Sawitzke 2010[88]	24 months	0/126 (0.0%)	0/142 (0.0%)
Pelletier 2016[85]	24 months	0/97 (0.0%)	0/97 (0.0%)

Abbreviations
n = number of patients, **N** = total number of patients, **NSAIDs** = non-steroidal anti-inflammatory drugs.

Knee Osteoarthritis: CS vs NSAIDs, Withdrawal Due to Adverse Events

Three studies provide evidence on withdrawals due to adverse events.[75 85 94] All three are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and NSAIDs groups (RR 1.51, 95% CI 0.81, 2.84, p = 0.20). The absolute risk for CS and placebo groups is 6.7% and 4.2%, respectively. The Chi^2 test and I^2 statistic indicate low levels of heterogeneity and inconsistency (p = 0.19, I^2 = 40%). Sub-group and sensitivity analyses were not performed owing to the number of studies in the meta-analysis. For further information regarding withdrawals due to adverse events and the corresponding forest plot refer to ***Figure 33***.

The number of patients who withdrew due to adverse events was inconsistently reported in Pelletier[85] (13 or 14 patients in the CS group purportedly withdrew due to adverse events). However, the discrepancy did not affect the overall result of the meta-analysis.



Footnotes
(1) 13 or 14 patients withdrew due to adverse events in the chondroitin sulfate arm

Notes

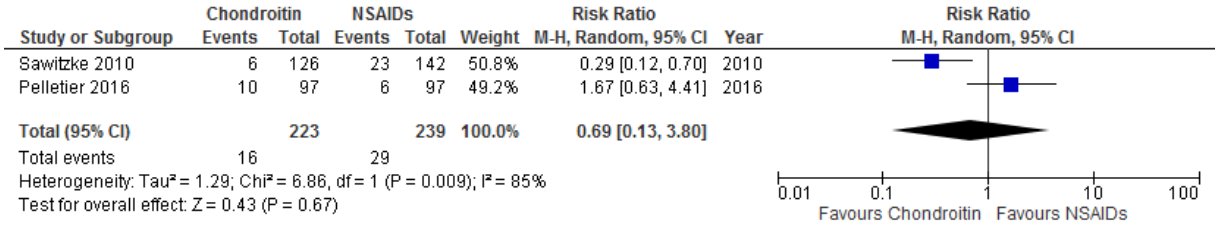
Events represent the number of patients withdrawing.

Figure 33 Forest plot indicating the risk ratio of withdrawals due to adverse events for chondroitin sulfate compared to NSAIDs (knee)

Knee Osteoarthritis: CS vs NSAIDs, Severe Adverse Events

Two studies provide evidence on severe adverse events.[85 88] Both studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and NSAIDs groups (RR 0.69, 95% CI 0.13, 3.80, p = 0.67). The absolute risk for CS and placebo groups is 7.2% and 12.1%, respectively. The Chi^2 test and I^2 statistic indicate high levels of heterogeneity and inconsistency (p = 0.009, I^2 = 89%). Sub-group and sensitivity analyses were not performed owing to the number of studies in the meta-analysis. For further information regarding severe adverse events and the corresponding forest plot refer to ***Figure 34.***

Both studies report the number of people with severe adverse events,[85 88] although only one study defines severe adverse events (ICH guidelines).[88]



Notes

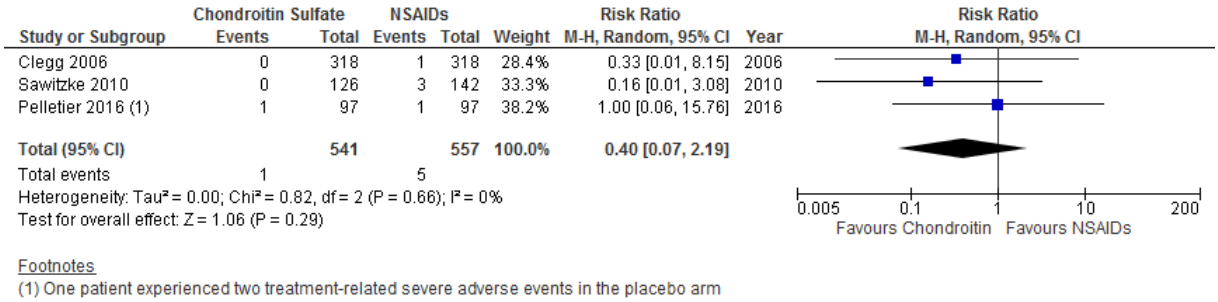
Events represent the number of patients experiencing an adverse event.

Figure 34 Forest plot indicating the risk ratio of severe adverse events for chondroitin sulfate compared to NSAIDs (knee)

Knee Osteoarthritis: CS vs NSAIDs, Treatment-Related Severe Adverse Event

Three studies provide evidence on treatment-related severe adverse events.[75 85 88] All studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and NSAIDs groups (RR 0.40, 95% CI 0.07, 2.19, p = 0.29). The absolute risk for CS and placebo groups is 0.2% and 0.9%, respectively. The Chi^2 test and I^2 statistic indicate high levels of heterogeneity and inconsistency (p = 0.66, I^2 = 0%). Sub-group and sensitivity analyses were not performed owing to the number of studies included in the meta-analysis. For further information regarding treatment-related severe adverse events and the corresponding forest plot refer to ***Figure 35.***

Treatment-related severe adverse events include iron-deficiency anaemia (CS)[85], pulmonary embolism[85], pneumonia[85], stroke[75], hip arthroplasty[88], cerebrovascular accident[88] and abdominal wall abscess[88] (NSAIDs). The studies did not report whether the treatment-related serve adverse events resolved.



Notes

Events represent the number of patients experiencing an adverse event.

Figure 35 Forest plot indicating the risk ratio of treatment-related severe adverse events for chondroitin sulfate compared to NSAIDs (knee)

Knee Osteoarthritis: CS vs NSAIDs, Any Adverse Event

One study provides evidence on any adverse event,[85] so the occurrence is described narratively. Overall, there was no statistically significant difference between patients receiving CS and celecoxib (p > 0.99).[85] Musculoskeletal, infection and gastrointestinal-related events were the most common adverse events reported in the study. The adverse events were generally mild, with approximately 95 adverse events in the CS group and 100 adverse events in the NSAIDs group ongoing at the end of the study.

For further details on the incidence of mortality see ***Table 44***.

Table 44 Chondroitin sulfate compared to NSAIDs: Any adverse events (knee)

Author year	Chondroitin sulfate n/N (%)	NSAIDs n/N (%)	p-value
Pelletier 2016[85]	78/97 (80.4%)	77/97 (79.4%)	> 0.99

Abbreviations
n = number of patients, **N** = total number of patients, **NSAIDs** = non-steroidal anti-inflammatory drugs.

Knee Osteoarthritis: CS vs NSAIDs, Treatment-Related Adverse Event

One study provides evidence on any treatment-related adverse event,[85] so the occurrence is described narratively. Overall, there was no statistically significant difference between patients receiving CS and celecoxib (p = 0.75).[85] The type of treatment-related adverse events was not reported. For further details on the incidence of mortality see ***Table 44***.

Table 45 Chondroitin sulfate compared to NSAIDs: Treatment-related adverse events (knee)

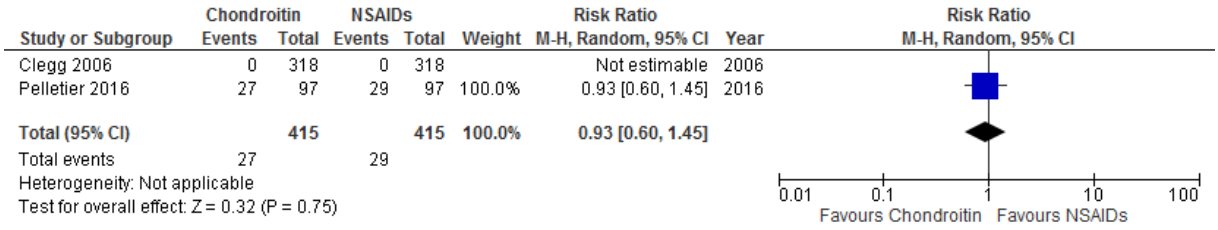
Author year	Chondroitin sulfate n/N (%)	NSAIDs n/N (%)	p-value
Pelletier 2016[85]	27/97 (27.8%)	24/97 (24.7%)	0.75

Abbreviations
n = number of patients, **N** = total number of patients, **NSAIDs** = non-steroidal anti-inflammatory drugs.

Knee Osteoarthritis: CS vs NSAIDs, Gastrointestinal Adverse Event

Two studies provide evidence on gastrointestinal-related severe adverse events.[75 85] Both studies are included in the meta-analysis. Overall, there are no statistically significant differences between the CS and NSAIDs groups (RR 0.93, 95% CI 0.60, 1.45, p = 0.75). The absolute risk for CS and placebo groups is 6.5% and 7.0%, respectively. The Chi^2 test and I^2 statistic could not be calculated owing to the lack of events in the Clegg study. Sub-group and sensitivity analyses were not performed owing to the number of studies in the meta-analysis. For further information regarding gastrointestinal-related adverse events and the corresponding forest plot refer to ***Figure 36***.

One study reported specific gastrointestinal adverse events.[85] Gastroesophageal reflux disease and dyspepsia are the most commonly reported adverse events. Further, proton pump inhibitors (PPIs) were concomitantly used by 32% (n = 31/97) and 30% (n = 29/97) of patients in the CS and NSAID groups, respectively (p = 0.88). This may influence the occurrence of gastrointestinal-related adverse events.



Notes

Events represent the number of patients experiencing an adverse event.

Figure 36 Forest plot between the risk ratio of gastrointestinal-related adverse events for chondroitin sulfate compared to NSAIDs (knee)

Knee Osteoarthritis: CS vs Paracetamol

Knee Osteoarthritis: CS vs Paracetamol, Withdrawal Due to Adverse Events, Any Adverse Events and Treatment-Related Adverse Events

One study provides evidence comparing CS to paracetamol for knee osteoarthritis,[89] so the outcomes are described narratively. There were no withdrawals or any treatment-related adverse events. The paracetamol group reported more adverse events, however, it was not reported whether this finding was statistically significant. For further information regarding safety outcomes refer to ***Table 46***.

Table 46 Chondroitin compared to paracetamol: Withdrawl due to, any and treatment-related adverse events (knee)

Author year	Outcome	Chondroitin sulfate n/N (%)	Paracetamol n/N (%)	p-value
Tio 2017[89]	Withdrawal due to adverse events	0/35 (0.0%)	0/33 (0.0%)	NR
	Any adverse events	1/35 (2.9%)	12/33 (36.4%) [a]	NR
	Treatment-related adverse events	0/35 (0.0%)	0/33 (0.0%)	NR

Abbreviations

n = number of patients, **N** = total number of patients, **NR** = not reported.

Notes

a = two patients experienced more than one adverse event.

C0002 Are the harms related to dosage or frequency of applying the technology?

This question was addressed in the preceding section (C0008 How safe is the technology in comparison to the comparator(s)?). Sub-group analysis determined there was no difference between the treatment groups with respect to dose of CS or duration of follow-up.

C0004 How does the frequency or severity of harms change over time or in different settings?

This question was addressed in the preceding section (C0008 How safe is the technology in comparison to the comparator(s)?). Sub-group analysis determined there was no difference between the treatment groups with respect to dose of CS or duration of follow-up.

C0005 What are the susceptible patient groups that are more likely to be harmed through the use of the technology?

This question could not be addressed with the current evidence base.

8.8 Risk of Bias in Included Studies

See ***Section 8.4*** for description of risk of bias.

8.9 GRADE Summary of Findings Tables

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Table 47 GRADE summary of findings table: chondroitin sulfate compared to placebo for knee osteoarthritis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Chondroitin sulfate				
Pain Assessed with WOMAC and VAS (0–100mm) Follow-up: 6 months	-	SMD 0.28 lower (0.47 lower to 0.09 lower)	-	2,245 (9 RCTs)	⊕⊕◯◯ LOW [a,b,c,d]	Chondroitin sulfate statistically differed from placebo at 6 months. The effect size is small** and unlikely to translate to a clinically important difference.
Pain Assessed with WOMAC and VAS (0–100mm) Follow-up: 12 months	-	SMD 0.17 lower (0.37 lower to 0.02 higher)	-	1,335 (7 RCTs)	⊕⊕◯◯ LOW [a,b,d,e]	Chondroitin sulfate did not statistically differ from placebo at 12 months (no effect).***
Function Assessed with WOMAC Follow-up: 6 months	-	SMD 0.02 lower (0.24 lower to 0.21 higher)	-	849 (2 RCTs)	⊕⊕◯◯ LOW [a,b]	Chondroitin sulfate did not statistically differ from placebo at 6 months (no effect).
Function Assessed with WOMAC Follow-up: 12 months	-	SMD 0.17 lower (0.25 lower to 0.58 higher)	-	506 (3 RCTs)	⊕⊕◯◯ LOW [a,b]	Chondroitin sulfate did not statistically differ from placebo at 12 months (no effect).
Lequesne index (lower score represents a better clinical outcome) Follow-up: 6 months	Baseline mean score ranged from 6.2 to 7.6 units	MD 1.02 units lower (1.73 lower to 0.31 lower)	-	1,007 (6 RCTs)	⊕◯◯◯ VERY LOW [a,b,d,e]	Chondroitin sulfate statistically differed from placebo at 6 months. The effect size is small and unlikely to translate to a clinically important difference (4.1% change).

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Chondroitin sulfate				
Withdrawal due to adverse events Assessed with total number of patients Follow-up: 3—24 months	44 per 1,000	53 per 1,000 (40—70)	RR 1.21 (0.92—1.61)	3,492 (15 RCTs)	⨁⨁⨁◯ MODERATE [a]	Chondroitin sulfate did not statistically differ from placebo (no effect).
Severe adverse events Assessed with total number of patients Follow-up: 3—24 months	50 per 1,000	48 per 1,000 (24—97)	RR 0.97 (0.49—1.95)	743 (4 RCTs)	⨁⨁⨁◯ MODERATE [a]	Chondroitin sulfate did not statistically differ from placebo (no effect).

Abbreviations

CI = confidence interval, **GRADE** = Grading of Recommendations, Assessment, Development and Evaluations**, SMD** = standardised mean difference, **RCT** = randomised controlled trial, **RR** = risk ratio, **MD** = mean difference, **mm** = millimetre, **VAS** = visual analogue scale, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index.

Notes

***** = risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

****** = SMD of 0.2, 0.5 and 0.8 represent small, moderate and large effect sizes as suggested by the Cochrane Handbook (v5.1.0).[68]

******* = if the WOMAC score from Kahan[69] is used instead of VAS, the statistical significance changes from p = 0.07 to p = 0.05.

a = variance (95% CI) is moderate/large.

b = measures of heterogeneity are moderate/large.

c = effect explained by manufacturer sub-group.

d = confidence intervals do not overlap in one or more studies.

e = heterogeneity is not adequately explained by sub-group analysis.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Table 48 GRADE summary of findings table: chondroitin sulfate compared to placebo for hand osteoarthritis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Chondroitin sulfate				
Pain Assessed with: VAS (0—100mm, lower represents less pain) Follow-up: 6 months	Chondroitin sulfate vs placebo 34.9 ± 25.3 vs 42.3 ± 24.9 p = 0.016			162 (1 RCT)	⊕⊕⊕◯ MODERATE [a,b]	Chondroitin sulfate differed statistically from placebo. The effect size is small (MD -7.4mm) and does not reach minimal clinically important differences.** This evidence is uncertain (k = 1)
Withdrawal due to adverse events Assessed with total number of patients Follow-up: 6—36 months	62 per 1,000	41 per 1,000 (7—263)	RR 0.67 (0.11—4.28)	254 (2 RCTs)	⊕⊕◯◯ LOW [a,b]	Chondroitin sulfate did not differ statistically from placebo (no effect).
Severe adverse events Assessed with total number of patients Follow-up: 6 months	24 per 1,000	0 per 1,000 (0—0)	not estimable	162 (1 RCT)	⊕⊕⊕◯ MODERATE [b]	Chondroitin sulfate did not differ statistically from placebo (no effect).

Abbreviations

CI = confidence interval, **GRADE** = Grading of Recommendations, Assessment, Development and Evaluations**, k** = number of studies, **mm** = millimetre, **MD** = mean difference, **RCT** = randomised controlled trial, **RR** = risk ratio, **VAS** = visual analogue scale, **vs** = versus.

Notes

***** = the risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

****** = MCID for hand pain as specified by Tubach[70] was 16mm (95% CI 13, 19) and 23mm (95% CI 20, 26) for absolute and relative measures respectively.

a = variance (95% CI) is moderate/large.

b = small number of studies, participants or events.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

*Low certa*inty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Table 49 GRADE summary of findings table: chondroitin sulfate compared to placebo for hip osteoarthritis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Chondroitin sulfate				
Pain Assessed with VAS (0—100mm) Follow-up: 6 months	Chondroitin sulfate vs placebo -42.6% ± NR versus -2% ± NR p < 0.0001		not estimable	56 (1 RCT)	⊕⊕◯◯ LOW [a,b,c]	Chondroitin sulfate statistically differed from placebo. The effect size is uncertain as baseline scores were not reported. This evidence is very uncertain (k = 1)
Lequesne index score (lower score represents better clinical outcome) Follow-up: 6 months	Chondroitin sulfate vs placebo -36% ± NR versus -6% ± NR p < 0.0001		not estimable	56 (1 RCT)	⊕⊕◯◯ LOW [a,b,c]	Chondroitin sulfate statistically differed from placebo. The effect size is uncertain as baseline scores were not reported. This evidence is very uncertain (k = 1)
Withdrawal due to adverse event Assessed with total number of patients Follow-up: 6 months	111 per 1,000	0 per 1,000 (0—0)	not estimable	56 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	Chondroitin sulfate did not statistically differ from placebo (no effect).

Abbreviations

CI = confidence interval, **GRADE** = Grading of Recommendations, Assessment, Development and Evaluations**, mm** = millimetre, **RCT** = randomised controlled trial, **RR** = risk ratio, **VAS** = visual analogue scale, **VS** = versus.

Notes

* = the risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a = notable drop-outs; unclear whether intention-to-treat analysis was performed; randomisation methods not reported.

b = measure of variance not reported.

c = small number of studies, participants or events.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

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Table 50 GRADE summary of findings table: chondroitin sulfate compared to NSAIDs for knee osteoarthritis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with NSAIDs	Risk with Chondroitin sulfate				
Pain Assessed with VAS (0—100mm) and WOMAC Follow-up: 6 months	-	SMD 0.25 lower (0.13 lower to 0.64 higher)	-	1,127 (3 RCTs)	⊕⊕◯◯ LOW [a,b,c]	Chondroitin sulfate did not statistically differ from NSAIDs at 6 months (no effect).
Pain Assessed with WOMAC Follow-up: 12 months	-	SMD 0.19 higher (0.03 lower to 0.42 higher)	-	309 (2 RCTs)	⊕⊕⊕◯ MODERATE [a,d,e]	Chondroitin sulfate did not statistically differ from NSAIDs at 12 months (no effect).
Function Assessed with WOMAC Follow-up: 6 months	-	SMD 0.40 higher (0.20 lower to 1.01 higher)	-	794 (2 RCTs)	⊕⊕◯◯ LOW [a,b,c]	Chondroitin sulfate did not statistically differ from NSAIDs at 6 months (no effect).
Function Assessed with WOMAC Follow-up: 12 months	-	SMD 0.18 higher (0.05 lower to 0.40 higher)	-	309 (2 RCTs)	⊕⊕⊕◯ MODERATE [c,f]	Chondroitin sulfate did not statistically differ from NSAIDs at 12 months (no effect).
Lequesne index (lower score represents better clinical outcome) Follow-up: 6 months	Chondroitin sulfate vs NSAIDs 7.1 ± 3.8 vs 7.10± 3.9 p = NR		-	333 (1 RCTs)	⊕⊕◯◯ LOW [c,f]	Chondroitin sulfate did not statistically differ from NSAIDs at 6 months (no effect).
Withdrawal due to adverse events Assessed with total number of patients Follow-up: 6—24 months	42 per 1,000	22 per 1,000 (8— 78)	RR 1.51 (0.81—2.84)	1,228 (3 RCTs)	⊕⊕⊕◯ MODERATE [c]	Chondroitin sulfate did not statistically differ from NSAIDs (no effect).

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with NSAIDs	Risk with Chondroitin sulfate				
Severe adverse events Assessed with total number of patients Follow-up: 24 months	121 per 1,000	84 per 1,000 (16—461)	RR 0.69 (0.13—3.80)	462 (2 RCTs)	⨁⨁◯◯ LOW [b,c]	Chondroitin sulfate did not statistically differ from NSAIDs (no effect).

Abbreviations

CI = confidence interval, **GRADE** = Grading of Recommendations, Assessment, Development and Evaluations**, SMD** = standardised mean difference, **RCT** = randomised controlled trial, **RR** = risk ratio, **MD** = mean difference, **mm** = millimetre, **VAS** = visual analogue scale, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index.

Notes

***** = the risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a = confidence intervals do not overlap in one or more studies

b = measures of heterogeneity are moderate/large.

c = variance (95% CI) is moderate/large.

d = measures of heterogeneity are low.

e = small number of studies/participants.

f = notable drop-outs; performed per-protocol analysis and provided limited information regarding the randomisation process and blinding of treatments.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Table 51 GRADE summary of findings table: chondroitin sulfate compared to paracetamol for knee osteoarthritis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Paracetamol	Risk with Chondroitin sulfate				
Pain Assessed with VAS (0—100mm, lower scores represent less pain) Follow-up: 6 months	Chondroitin sulfate vs paracetamol 40.8 ± 22.0 vs 38.9 ± 27.7 p = 0.92		not estimable	48 (1 RCT)	⊕⊕◯◯ LOW [a,b,c]	Chondroitin sulfate did not statistically differ from paracetamol (no effect).
Lequesne index (lower scores represent better outcomes) Follow-up: 6 months	Chondroitin sulfate vs paracetamol 7.7 ± 3.3 versus 8.5 ± 4.6 p = 0.22		not estimable	48 (1 RCT)	⊕⊕◯◯ LOW [a,b,c]	Chondroitin sulfate did not statistically differ from paracetamol (no effect).
Withdrawal due to adverse events Assessed with total number of patients Follow-up: 6 months	0 per 1,000	0 per 1,000 (0—0)	not estimable	68 (1 RCT)	⊕⊕⊕◯ MODERATE [c]	Chondroitin sulfate did not statistically differ from paracetamol (no effect).

Abbreviations

CI = confidence interval, **mm** = millimetre, **RCT** = randomised controlled trial, **VAS** = visual analogue scale, **VS** = versus.

Notes

***** = the risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a = single-blinded; per protocol analysis.

b = measure of variance moderate/large.

c = small number of studies, participants or events.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

9. Costs, Budget Impact and Cost-Effectiveness

9.1 Summary Statement Costs, Budget Impact and Cost-Effectiveness

The clinical evaluation found CS to have significant improvements in pain compared to placebo in the short-term; however, there is uncertainty whether it provides a benefit after six months. A model-based economic analysis was conducted, with an incremental cost-effectiveness ratio (ICER) estimated to be CHF 30,451 per quality-adjusted life year (QALY). A hypothetical willingness-to-pay threshold of CHF 100,000/QALY is associated with a 60% probability of CS being cost-effective compared to placebo. CS was also compared to COX-2 in a trial-based economic analysis. Probabilistic sensitivity analysis indicates CS has a 34% probability of being superior (incremental cost < 0, incremental effectiveness > 0) to COX-2. The uncertain results of both economic analyses reflect the non-significant differences between treatments for longer-term health outcomes.

A budget impact analysis was undertaken. Three scenarios were included to gauge financial impacts of 25%, 50% and 75% of current CS patients substituting to other health insurance provider-supported osteoarthritis medicines if CS was delisted. The first scenario assumes 25% of current CS patients would substitute to paracetamol, ns-NSAIDs plus proton pump inhibitors (PPIs) or COX-2 selective NSAIDs plus PPIs in the event of CS being delisted. This results in an initial health insurance provider saving of CHF 18.2 million per year. If 50% of current CS patients substituted to other health insurance provider-supported medicines for osteoarthritis, a saving of CHF 2.4 million per year would be realised. If 75% of current users substituted to these medicines a net *cost* of CHF 13.3 million per year is estimated to be incurred. The net cost is a result of the higher cost of ns-NSAIDs plus PPIs, and COX-2 selective NSAIDs plus PPIs, compared to CS.

9.2 Methods

The cost-effectiveness section addresses questions associated with measuring health-related outcomes of the assessed technology and its comparators, differences in costs and outcomes between the technology and its comparators, and identifying the uncertainties surrounding the costs and economic evaluation of the technology. Specific sub-questions addressed in the cost-effectiveness section are outlined in ***Table 9*** while the budget impact analysis is provided at the end of the section.

Economic analysis is undertaken using data from the 24-month RCT by Pelletier[85] that compared CS with COX-2 over two years, and the RCT by Kahan[69] for the comparison versus placebo. These trials were selected from the clinical evidence as they provide longer term follow-up (> one year) and report health utility or total WOMAC scores that can be translated into health utility.

In the case of Kahan[69], 622 patients were enrolled in the study (200 patients in France, 193 in Belgium, 129 in Switzerland, 65 in the US, and 35 in Austria) and randomised to CS (309 patients) or placebo (313 patients) over a period from February 2000 to July 2002. Patients were randomly assigned to receive either an 800-mg sachet daily of CS (Genevrier Laboratories, France, and IBSA, Switzerland) or an identical sachet of placebo. In the study by Pelletier[85], 194 patients enrolled between 21 June 2011 and 10 September 2014 were administered pharmaceutical-grade CS (Bioiberica S.A., Spain) 1,200 mg (three 400 mg capsules in the morning) or celecoxib (Pfizer Canada, Saint-Laurent, QC, Canada) 200 mg (one 200 mg capsule plus two placebo capsules in the morning) for 24 months.

Annual costs for CS and COX-2 medicines were derived from public prices in the Swiss Spezialitätenliste (accessed 17 July 2019) combined with recommended CS and COX-2 dosing from Swiss Medic. TARMED was used to derive general doctor costs for the annual prescription of medicines, in consultation with the FOPH. Adverse event rates were not found to differ between treatments among the trials reviewed as part of the clinical effectiveness analysis. They are not included in the economic model.

The reporting of WOMAC total and sub-scores by month of follow-up in the key trials included in the clinical effectiveness review is summarised in ***Table 56*** for CS versus placebo and ***Table 59*** for CS versus COX-2. The studies by Pelletier[85] and Bruyere[106] were identified as providing the most consistent reporting of utility or total WOMAC. Health utility from the Kahan[69] trial comparing CS with placebo was provided in the analysis by Bruyere.[106] Pelletier[85] reports a CS versus COX-2 comparison. Translation of total WOMAC to utility is undertaken in this section based on the approach outlined by Barton.[107] Incremental gains in utility are taken from these studies and included in the base case economic model calculations.

Incremental cost-effectiveness ratios (ICER) for CS versus placebo and COX-2 are calculated using base case unit costs. Probabilistic sensitivity analysis is performed to account for uncertainty in the input parameters. (See evidence table, ***Table 54***, for assumptions). The analysis involves 10,000 iterations which were used to calculate a 95% CI. The probability of the ICER being cost effective is based on a hypothetical willingness-to-pay threshold of CHF 100,000. Analyses are performed using TreeAge Pro (TreeAge Software, Inc, One Bank Street Williamstown, MA, 01267 USA).

9.2.1 Economic Modelling Background

Review of Economic Literature

The scoping report included a systematic review that covered published economic studies on CS. Two published economic evaluations relevant to the current HTA were identified (Robio-Terrés[108] and Bruyere[106]). An HTA for glucosamine undertaken by Black[109] and a study by NCC-CC[3] were also included. They are summarised in ***Table 52***.

Table 52 Overview of existing, relevant economic evaluations of chondroitin sulfate

Study	Method	Relevance
Rubio-Terrés 2010[108]	A model-based approach was taken, using a decision-tree model with a time horizon of six months and results of a retrospective cohort study (VECTRA).[108] Different rates of adverse events—categorised as gastrointestinal or other—were also included in the model. Probabilities of adverse events were obtained from the literature. The budgetary impact of the use of CS as an additional treatment modality compared to NSAID treatment alone was explored. For the estimation, theoretical values of 5, 10 and 15% were used to represent percentage decreases in NSAID consumption (substitution CS) over a 3-year period.	The scoping report noted that data sources were provided for all cost valuations, however, no detail was given regarding how semi-annual costs have been estimated. Many mild/moderate gastrointestinal adverse events were listed, but only a single semi-annual cost presented.
Black 2009[109]	The authors provided a cost-effectiveness analysis of glucosamine and CS supplements in patients with osteoarthritis of the knee.[109] 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. CS had a differential impact on progression to joint replacement or arthroscopy compared to relevant comparators.	The study (Table 19) concluded that CS had no evidence of impact on knee arthroplasty, and pain/function outcomes reflected a heterogeneity of results.[109] They did not perform an evaluation of the cost effectiveness or budgetary impact of CS.

Study	Method	Relevance
Bruyere 2009[106]	This was a single study-based evaluation. The original trial was a randomised, double-blind, placebo-controlled trial with an intervention period of 24 months.[69 106] The only cost considered on the cost side of the evaluation was the cost of CS. The authors assumed that all other healthcare and non-healthcare costs were comparable between the two trial arms, however, justification for this assumption was not explicitly provided.	The economic evaluation presented in this report used WOMAC scores collected during the initial trial and mapped them to utility values. The source of the daily cost of CS was not provided.
NCC-CC 2008[3]	The study was undertaken to support the development of the NICE clinical guidelines for osteoarthritis. Economic studies were reviewed for ns-NSAID/COX-2 selective NSAID and other treatments – which included: hyalgan, artz, durolane, glucosamine, CS, and acupuncture. The authors noted it was not possible to build economic models for all these interventions due to time and data limitations. They presented a cost-consequence analysis, which included the direct United Kingdom costs of the intervention alongside the efficacy of the intervention as found in the clinical evidence review. The study includes CS evidence from Michel[82] and Clegg,[75] which was included in the clinical effectiveness section of this report.	The authors concluded: "ICERs should be treated with care as they are often based on fairly scarce clinical evidence which has been transformed into a QALY score using the transfer-to-utility technique" (p. 330). "No adverse events were included [and] the effectiveness measure is compared with placebo rather than no treatment, as often studies do not include a 'no treatment' or 'usual care' arm" (p. 330)

Abbreviations
COX-2 = cyclooxygenase-2 inhibitor, **CS** = chondroitin sulfate, **ICER** = incremental cost-effectiveness ratio, **NICE** = National Institute for Health and Care Excellence, **NSAIDs** = non-steroidal anti-inflammatory drugs, ns-NSAIDs = non-selective non-steroidal anti-inflammatory drugs, **QALY** = quality-adjusted life year, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index.

Rubio-Terrés[108] performed both a model-based cost minimisation analysis and a budgetary impact analysis of CS compared to NSAIDs in patients with osteoarthritis. The study used data from the VECTRA study, but no estimate of improvement in quality of life was included. The previous CS economic study by Bruyere[106] converted WOMAC scores reported in the Kahan[69] trial comparing CS - with placebo using the validated formula of Grootendorst.[110]

When the NCC-CC[3] reviewed the osteoarthritis treatment economic literature, they concluded: *"the vast majority of osteoarthritis intervention literature does not present utility scores which are ideal for use in economic analyses. However, a significant number of studies do present WOMAC scores"* (NCC-CC, p. 330).[3]

Correspondingly, NCC-CC[3] included studies that reported total WOMAC scores that had a sample size greater than 90; for treatments such as hyalgan, artz, durolane, glucosamine, CS and acupuncture. They included the two-year study by Michel,[82] which examined CS versus placebo in 300 patients with osteoarthritis of the knee (Kellgren & Lawrence grade 1—3). A mean cost (assuming one GP

consultation per year and two tablets per day) of GBP 272.14 and 0.0074 additional QALYs compared with placebo were combined to generate an ICER of GBP 42,255. This ranged from GBP -13,667 to 75,723. For the average ICER to be under GBP 20,000, a QALY gain of 0.014 was estimated to be needed.

The NCC-CC review[3] also included the 24-week trial of Clegg,[75] which included 631 patients with knee osteoarthritis (Kellgren & Lawrence grade 2-3). A mean cost (assuming one GP consultation and three tablets per day) of GBP 101.32 for CS, was combined with –0.0014 additional QALYs compared with placebo to generate a negative ICER. The QALY gain would need to be 0.0051 for the ICER to be less than 20,000 GBP per additional QALY. The authors concluded that glucosamine alone, any type of CS, or a combination of glucosamine and CS are not likely to be cost-effective. The UK studies appear to use a threshold of GBP 20,000 or CHF 23,900 (based on GBP:CHF rate of 1.197, 25 August 2019), which is lower than the hypothetical willingness-to-pay of CHF 100,000 employed in Swiss health economic studies.[111] It is noted that willingness-to-pay thresholds cannot be transferred from one country to another by simply applying currency exchange rates. Differences in income and prices between countries need to be considered.

The NCC-CC review[3] included economic studies with outdated CS medicine costs; the Clegg[75] study is short in duration; and no CS versus COX-2 comparison economic study has been conducted. Correspondingly, an updated CS versus placebo economic analysis is presented using current CS prices in Switzerland, and a COX-2 comparison is undertaken.

Overview of economic model

The scoping report noted that there is sufficient clinical data for knee osteoarthritis, but less so for hip and hand osteoarthritis to conduct a HTA evaluation of CS in patients with moderate symptomatic disease. Correspondingly, economic analyses of trials that compare CS use for knee osteoarthritis against COX-2 and placebo was conducted. These comparators were selected largely due to the availability of health outcome data (total WOMAC scores, or health utility) for COX-2 and placebo, that could be translated in quality-adjusted life years for cost-utility analyses.

A simple economic decision model is used to generate results for a representative patient (summarised in ***Table 53***). Patient characteristics are defined according to the baseline clinical characteristics reported within trials reporting WOMAC scores and health utility. Health utility indices are taken from the Bruyere[106] study for the CS versus placebo comparison, and total WOMAC scores from Pelletier[85] for CS compared to COX-2. Total WOMAC scores are converted to utility based on the regression of Barton.[107] The evaluation then compares the costs and clinical outcomes (QALYs) between the treatment options.

Table 53 Summary of the economic evaluation

Perspective	This economic evaluation takes a health insurance provider perspective
Patient population	Osteoarthritis of the knee
Intervention	Chondroitin sulfate
Comparator	COX-2, placebo
Type of economic evaluation	Cost-utility analysis
Sources of evidence	Medicines costs from the Spezialitätenliste, total WOMAC scores from Pelletier 2016[85] for chondroitin sulfate versus COX-2 converted using the formula of Barton 2008[A,107] and health utility gains from Bruyere 2009[106] for chondroitin sulfate versus placebo.
Time horizon	Two years
Outcomes	Quality-adjusted life years/ total WOMAC
Methods used to generate results	Decision model
Software packages used	TreeAge Pro

Abbreviations
COX-2 = cyclooxygenase-2 inhibitor, **FOPH** = Federal Office of Public Health, **WOMAC** = Western Ontario and McMaster Osteoarthritis.
Notes
Barton[107] compared their preferred model with the Grootendorst model used in Bryuere[106]. The preferred model had the lowest mean absolute error (MAE) in predicting EQ-5D. The MAE of the preferred model was 0.129 compared to 0.142 for Grootendorst. Correspondingly, the Barton[107] preferred model is used for translation of total WOMAC outcomes for CS and COX-2 from the Pelletier[85] study.

9.3 Evidence Table

Model assumptions are derived for patient characteristics, costs and health outcomes (summarised in ***Table 54*** along with sources). The derivation of each assumption is described in the text that follows.

Table 54 Summary of evidence for the economic evaluation

Assumption	Value	Source of Evidence and Comments
Patient		
Age	60	Average age in Kahan 2009[69] was 62—63 years, and in Pelletier 2016[85] 61 years old.
Gender	Female	In Kahan 2009[69] 66%—70% of participants were women, while 55%—63% were women in Pelletier 2016[85].
Cost		

Assumption	Value	Source of Evidence and Comments
CS	CHF 281 per year is included in the base case. A range of costs for CS input are included in a univariate sensitivity analysis with Condrosulf® 800 as an upper value, and 2 years of Structum® 500 as a lower value.	The base case includes CS (Condrosulf® 800). The annual cost assumes 800mg per day, at a pack cost of CHF 69.20 for a 90-tablet pack and 800mg tablet. Prices are taken from the Swiss Spezialitätenliste (accessed 17 July 2019). This cost is included as a point estimate in the probabilistic sensitivity analyses given that more than 85% of CS sales in 2018 were associated with this product. A univariate sensitivity analysis includes CS (Structum® 500) at 1,000mg per day, CHF 73.05 per pack, 500mg per tablet, and a pack size of 240. This results in an annual value of CHF 222, which is included as a lower value.
COX-2	CHF 468 per year is included for the base case. This cost is included as a uniform distribution in the probabilistic sensitivity analysis. A higher annual cost of COX-2 of CHF 711 per year is used, which includes Omeprazole. The lower and an upper bound are included as 2-year costs.	The base case includes COX-2 (Celebrex, 200mg). The annual cost assumes 200mg per day, at pack cost of CHF 128.25 for 100-tablet pack and 200mg tablet. Prices are taken from the Swiss Spezialitätenliste (accessed 17/7/2019). An upper cost is included in a probabilistic sensitivity analysis. It assumes the addition of Omeprazole at 20mg per day. A pack is estimated to cost CHF 66.65 and include 100 tables of 20mg.
No treatment	0	The placebo, or no treatment, assumes zero resources are attributed to osteoarthritis management.
Total WOMAC Outcome		
Chondroitin sulfate compared to COX-2: Pelletier 2016[85]		
Change in total WOMAC from baseline for CS (0—240 scale)	6m -39.34 12m -51.38 24m -38.88	Pelletier 2016[85] reported differences in total WOMAC scores from baseline for COX-2 and CS. They are included at 6, 12 and 24 months as per the clinical effectiveness section of this report. Upper and lower values are also included by assuming they are equivalent to 3 SDs from the mean value. Using this approach, the total WOMAC for CS at 24 months has lower and upper values of 45.8 and 126.2, and an expected value of 86.0. These values are used to generate a triangular distribution for probabilistic sensitivity analysis.
Change in total WOMAC from baselines for COX-2 (0—240 scale)	6m -52.13 12m -51.80 24m -49.31	Changes in total WOMAC scores are included in the economic analysis using base results from Pelletier 2016[85]. They are included at 6, 12 and 24 months as per the clinical effectiveness section of this report. Upper and lower values are also estimated by assuming they are equivalent to 3 SDs from the mean value. Using this approach, the total WOMAC score for COX-2 at 24 months has lower and upper values of 41.4 and 113.4, and an expected value of 77.4. These values are used to generate a triangular distribution for probabilistic sensitivity analysis.
Utility Outcome		
Chondroitin sulfate compared to COX-2: Pelletier 2016[85]		

Assumption	Value	Source of Evidence and Comments
Cumulative QALYs gained by month of follow-up for CS	6m 0.038 12m 0.124 24m 0.293	This difference at 6, 12 and 24 months is included in the mapping Barton 2008[107] algorithm, assuming an age of 60 years and a female patient. The formula is: (-0.3474012785 + (-0.0005977709*(WOMAC) + (-0.000108156*(WOMAC)^2)) + (0.0326027536*Age) + (-0.0002352456*Age^2) + (0.0475889687*Gender)). After 24 months the difference between CS and COX-2 QALYs gained is -0.041. The change is also included in a probabilistic sensitivity analysis, using high and low QALY gain estimates. Using this approach, high cumulative QALY gains at 24 months are 0.454 and 0.472 for CS and COX-2, and lower 0.040 and 0.123 for CS and COX-2.
Cumulative QALYs gained by month of follow-up for COX-2	6m 0.049 12m 0.145 24m 0.335	
Chondroitin sulfate compared to placebo: Kahan 2009[69] reported in Bruyere 2009[106]		
Cumulative QALYs gained by month of follow-up	CS 6m 0.018 12m 0.044 24m 0.097 Placebo 6m 0.007 12m 0.026 24m 0.072	Bruyere 2009[106] provided the health utility index gains for WOMAC scores reported in the Kahan 2009[69] study. The health utility index at 6 months was 0.03 higher for CS over placebo but decreases to 0.01 at 24 months. The improvement at 6 months is significant (p = 0.03), but not at 24 months (p = 0.37). After 24 months the difference between utility gained for CS of 0.10 and placebo of 0.07 is 0.025. These values are included in the two-year economic model as the most likely CS versus placebo estimate. Upper and lower values are included in a triangular distribution for a probabilistic sensitivity analysis. These values were estimated using Figure 1, p.358 using WebPlotDigitizer. The analysis assumes upper and lower values correspond with 3 standard deviations from average values. Using this approach, higher QALY gains at 24 months are 0.212 for CS and 0.201 for placebo, and lower QALY gains are -0.001 for CS and -0.044 for placebo.

Abbreviations
CHF = Swiss Francs, **COX-2** = cyclooxygenase-2 inhibitor, **CS** = chondroitin sulfate, **m** = months, **mg** = milligrams, **NSAIDs** = non-steroidal anti-inflammatory drugs, **PSA** = probability sensitivity analysis, **QALY** = quality-adjusted life year, **SD** = standard deviation, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index.

Applicability of Trial Evidence

E0012 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)?

Applicability describes the way the participants and circumstances of use in key trials and studies differ from the Swiss population indicated for treatment. This section addresses how the characteristics of patients in the clinical evidence compare with the Swiss Medic description of circumstances of use. Patient characteristics are reviewed and compared with the current criteria for CS use in Switzerland (see ***Table 55***).

Table 55 Features of chondroitin sulfate patient populations assumed in model

Parameter	Value	Sources/Comments
Demographics	55—65 years More women	The base analysis of the economic model includes an age of 60 years. Average age in Kahan 2009[69] was 62 and 63 years for CS and placebo groups, respectively, and average age in Pelletier 2016[85] was 61 years old. Trial participants age at baseline varies from 55 years in Morreale[84] to 67 years in Mazieres 2001[64]. Participants in Kahan 2009[69] were 66%—70% women, compared to 55%—63% in Pelletier 2016.[85]
Clinical characteristics	Scores of Kellgren & Lawrence scale 1—3 were included	Swiss Medic indicates CS is indicated for the treatment of osteoarthritis. A Kellgren & Lawrence scale score of 1—3 is not required prior to use, which was often an inclusion criterion for trials. Patients with less severe osteoarthritis may therefore be using CS.
Setting	Outpatient for GP and some adverse event procedures	Osteoarthritis patients using CS and comparator medicines are assumed to present once per year in general practice. Pelletier 2016[85] recruited patients from four private clinics and one outpatient clinic in Canada. Kahan 2009[69] recruited patients from more than 20 health facilities in France, Belgium, Switzerland, Austria and the United States. Other studies also include outpatient and rheumatology practices.
CS usage	800mg/day is included for base analysis	Trials include CS use at 800mg and 1,200mg per day. The key CS medicines available in Switzerland are recommended at these doses. The most widely used product is Condrosulf® 800 (tablet 800mg), which has dosage instructions for use of 1x800 or 2x400mg sachets or tablets per day. A higher dosage of 1,000mg/day is included as a sensitivity analysis.
Comparator	COX-2 (Celebrex)	200mg/day
	Placebo	No treatment.

Abbreviations
COX-2 = cyclooxygenase-2 inhibitor, **CS** = chondroitin sulfate, **GP** = general practitioner, **mg** = milligrams, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index.

Demographics (Age and Gender)

An average age of 60 years and female gender were included for utility calculation using the Barton[107] utility mapping equation in the economic model. The average age in Kahan[69] was 62 years for placebo and 63 years for CS groups. The average age in Pelletier[85] was 61 years. Age varies across included clinical evidence studies in the effectiveness review, however most trials include participants from 55 to 65 years of age. For example, in Bucsi[74], trial participants had average ages of 60.6 and 59.4 years old on each arm and gender ratios of 17/22 and 17/29 male/female. The average age of patients in the Clegg[75] trial was 59 years, with 64% women; most patients were women (68%) in Fardellone[63] and aged 65 years. Fransen[28] participants had a baseline average age of 60 years; around half were female. Mazieres[64] reported the average ages of 66.9 and 67.3 years of age, with 78% and 71% being female in the placebo and CS groups, respectively. Michel[82] had an average age of 63 years, whereas

Morreale[84] average ages were 55 and 56 on each arm. In Railhac[86] the average age was 65 years at baseline, with 65% being women.

Clinical Characteristics

Many trials included participants with specified degrees of osteoarthritis, most often using the Kellgren & Lawrence radiographic system. Kahan[69] included those with primary knee osteoarthritis of the medial tibiofemoral compartment diagnosed according to the clinical and radiographic criteria of the ACR, but excluded patients with grade four radiographic osteoarthritis according to the Kellgren & Lawrence grading system. Pelletier[85] included patients with disease severity grade of two to three based on Kellgren–Lawrence scoring.

Trials such as Bucsi[74] included patients with Kellgren & Lawrence scale scores of one to three. Clegg[75] included patients with Kellgren & Lawrence grade two or three, WOMAC pain score 125—400, and knee pain > 6 months. Excluded patients were those: *"with concurrent medical or arthritic conditions that could confound index joint, predominant patellofemoral disease, trauma or surgery or coexisting disease"* (ibid p. 796)[75]. Fardellone[63] excluded those with secondary knee osteoarthritis, hip osteoarthritis, predominant patella-femoral disease, planned surgery, treatment with systemic steroids, SYSADOA, bisphosphonates, strontium ranelate, or hyaluronic acid injections, and NSAIDs during the two days prior to inclusion or paracetamol in the 12 hours prior to inclusion.

Swiss Medic indicates CS is indicated for the treatment of osteoarthritis. A Kellgren & Lawrence scale score of one to three is not required prior to use, thus patients with less severe osteoarthritis may be using CS. The direction of this bias is not clear, however, total WOMAC improvements appear to be less in patients with mild osteoarthritis. This issue is discussed by Bruyere.[106]

Setting

Pelletier[85] recruited patients from four private clinics and one outpatient clinic in Canada. Kahan[69] recruited patients in France, Belgium, Switzerland, Austria and the US. Other studies also included outpatient and rheumatology practices. Bucsi[74] conducted a multi-centre trial, with hospitalised or out-patients with idiopathic or secondary clinically symptomatic knee osteoarthritis for more than six months. Mazieres[80] used rheumatologists trained for clinical trials. Michel[82] included patients at the Outpatient Clinic of Rheumatology of the University Hospital Zurich, and from rheumatology practices in the Zurich area. Fransen[28] recruited patients in primary care settings.

CS Usage and Comparator

Pelletier[85] administered pharmaceutical-grade CS (Bioiberica S.A., Spain) at 1,200 mg per day (three 400 mg capsules in the morning). Kahan[69] administered daily 800mg sachets of CS (Genevrier Laboratories, France and IBSA, Switzerland).

Clegg[75] administered CS at 1,200mg/day. In Michel[82], 800mg tablets of CS-4 and -6 sulfate (Condrosulf®; IBSA, Switzerland) were administered for two years. In Fransen[28], two CS capsules containing 400 mg of bovine-derived, low molecular weight CS were administered (manufactured by TSI Health Sciences, Australia). Sawitzke[88] administered sodium CS at 400mg three times daily. The key CS medicines available in Switzerland are recommended at these doses. The most widely used product is Condrosulf® 800 (tablet 800mg), which has dosage instructions for use of one 800mg sachet or tablet once per day or one 400mg sachet or tablet twice a day.

In many studies the comparator is placebo, with limited description provided about the nature of the intervention. Clegg[75] provided no details about the placebo, Fransen[28] indicated the placebo involved a placebo capsule once per day, whereas Kahan[69] noted an identical sachet of placebo was provided daily to participants. The authors note that CS and placebo were packed in anonymous sachets of identical appearance, containing oral gel with the same aspect, odour and flavour. Both CS and placebo sachets contained sodium benzoate and potassium sorbate. Michel[82] also provided an identical tablet of placebo daily for two years. Both the active agent and placebo pills contained magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

COX-2 is generally provided at 200mg per day. Clegg[75] included Celebrex at 200mg per day. Pelletier[85] used celecoxib (Pfizer Canada) at 200mg per day (one 200 mg capsule plus two placebo capsules in the morning) for 24 months, and Sawitzke[88] used celecoxib 200mg once daily. Rescue medicines, such as acetaminophen were allowed in some studies. For example, in Pelletier[85], patients were not permitted to take other NSAIDs during the study (or during the week before randomisation) but could take acetaminophen (paracetamol) (up to 3g/day) 48 hours before evaluations. PPIs were concomitantly used by 30% of the individuals taking NSAIDs in the Pelletier study.[85]

Patient Summary

The estimates of inputs and outcomes in the key clinical trials largely provide valid descriptions of the technology and its comparator. The key issues are that many of the trials used Kellgren & Lawrence radiographic systems for patients to be included, which differs from clinical practice in Switzerland. Many patients are prescribed CS and its comparators without radiographic grading of osteoarthritis severity. The dosing in key trials appears similar to Swiss practice.

Treatment Effects

Literature searches outlined in the clinical evidence section retrieved 26 relevant RCTs reporting clinical efficacy, effectiveness and safety of CS. Considerable evidence was found in relation to pain, function, and analgesic consumption for knee osteoarthritis, which is outlined in the clinical evaluation section of the report.

Cost-utility analysis involves an estimation of quality of life change between the intervention and comparators. Economic evaluations of osteoarthritis treatments have been undertaken where WOMAC scores are converted into health utility index (HUI) utility scores. The model developed as part of the evaluation estimates cost per QALY as an ICER. The economic model compares CS with COX-2 and placebo. Prior to outlining the studies for the clinical effectiveness review where WOMAC scores were sourced, an overview of methodological assumptions underpinning translation is provided.

E0013 What methodological assumptions were made in relation to the technology and its comparator(s)?

Several studies presented in the clinical evidence reported WOMAC scores. This measure is specific to osteoarthritis and needs to be translated to a utility scale using the transfer-to-utility technique for cost-utility analysis. Three studies were identified that developed this approach for osteoarthritis. They include Segal,[112] Barton[107] and Grootendorst.[110]

Segal[112] collected QoL responses from osteoarthritis patients, along with SF-36, VAS for pain, and the WOMAC pain scale. Measures of QoL were regressed against WOMAC outcomes. Viney[113] expressed concern about the approach as it does not appropriately account for preference. Additionally, changes in utility scores are solely due to changes in the WOMAC and the regression does not consider confounders such as patient age. These problems were overcome by Barton[107], where regressions allowing the estimation of EuroQol 5 Dimensions (EQ-5D) using WOMAC scores along with other factors such as age and sex are considered.

Segal[112]

The authors undertook an Australian Assessment of Quality of Life (AQoL) survey in parallel with SF-36, a VAS for pain, and the Western Ontario and McMaster Arthritis Index in 303 people with osteoarthritis. Participants were recruited from rheumatology clinics, orthopaedic waiting lists and the Arthritis Foundation of Victoria. The AQoL scores were regressed on SF-36 subscale scores and NC-CC[3] noted QALYs were generated using the formula EQ-5D = 0.7100 – 0.00097 W100 – 0.000073 (W100)[A].

Grootendorst[110]

Grootendorst[110] developed a prediction model using linear regression[1] to map the WOMAC along with basic demographic and osteoarthritis disease-severity data into utility scores. Data from a previously

[A] Predicted HUI utility score = 0.5274776 + 0.0079767 × Pain +.0065111 × Stiffness -0.0059571 × Function + 0.0019928 × Pain × Stiffness + 0.0010734 × Pain × Function + 0.0001018 × Stiffness × Function – 0.0030813 × Pain² – 0.0016583 × Stiffness² – 0.000243 × Function² + 0.0113565 × Age in years – 0.0000961 × Age in years² –

published open-label RCT of appropriate care with hylan G-F 20 in 255 outpatients with knee osteoarthritis were used for the analysis. The formula included WOMAC pain, stiffness, function subscales and demographic variables. This formula is used by Bruyere[106] to translate total WOMAC scores in Kahan[69] into a health utility index.

Barton[107]

The authors surveyed 389 individuals taking part in the UK Lifestyle Interventions for Knee Pain (LIKP) study using the EQ-5D and the WOMAC at baseline, six, 12, and 24 months post-intervention. Recruitment into the LIKP study began in May 2003 and ended in March 2005, and involved patients in Nottingham general practices. Several mapping models were developed, where WOMAC scores were used to predict the EQ-5D scores. The performance of these models was tested by predicting the EQ-5D post-intervention scores. The model with the lowest mean absolute error was identified. Unlike Segal[112], this model includes gender and age. This model is applied to transform total WOMAC in the Pelletier[85] COX-2 versus CS comparison. It is preferred over the model developed by Grootendorst[110] and used in Bruyere[106] to translate total WOMAC scores in Kahan[69] due to the better fit of the Barton[107]-preferred model.

E0005 What are the measured and/or estimated health-related outcomes of the assessed technology and its comparator(s) (outcome identification, measurement and valuation)?

The derivation of utility requires total WOMAC scores being reported in trials. These outcomes were available for CS versus placebo and COX-2 selective NSAIDs, but not for other ns-NSAIDs or paracetamol. In the case of ns-NSAIDs, Morreale[84] reported a randomised, multicentre, double blind, double dummy study that included 146 patients with knee osteoarthritis. The NSAIDs group was treated with DS (diclofenac sodium). Clinical efficacy was evaluated with the Lequesne index, spontaneous pain (VAS), pain on load (using a 4-point ordinal scale), and paracetamol consumption. Both treatments caused decreases in scores, although more in DS compared with CS after the first month ($p < 0.01$). After this period the Lequesne index scores were similar. The study was undertaken over 180 days but did not report WOMAC scores.

0.0172294 × Female – 0.0057865 × Years since onset of osteoarthritis in the study knee + 0.0001609 × Years since onset of osteoarthritis in the study knee

CS versus placebo

Health utility, total WOMAC and WOMAC sub-scores (pain, stiffness and function) were not consistently reported across studies identified in the clinical effectiveness review (***Table 56***). Bruyere[106] is the only study to report health utility at six, 12 and 24 months using the data from Kahan.[69]

Table 56 WOMAC scores reported for key chondroitin sulfate versus placebo studies

	Months of follow-up				
Study	**6**	**12**	**18**	**24**	**Comments**
Health utility					
Bruyere 2009[106]	X	X		X	Uses total WOMAC scores from Kahan 2009[69], with WOMAC transformed using the formula in Grootendorst 2007[110]. Utility gains were reported in the paper at 6, 12 and 24 months.
Total WOMAC					
Michel 2006[82]				X	WOMAC scores were only reported at 24 months.
Clegg 2006[75]	X				Change in WOMAC from baseline was reported at 6 months only.
Pain WOMAC					
Fransen 2015[28]		X		X	Only WOMAC sub-scores were reported. This included WOMAC pain (0—20) at 12 and 24 months.
Clegg 2006[75]	X				Total at baseline, value at end of follow-up and change from baseline were reported. Follow-up limited to 6 months.
Sawitzke 2010[88]	X	X	X	X	The authors report at baseline and change from baseline.
Michel 2005[82]				X	WOMAC score, range 0—10, only reported at 24 months.
Kahan 2009[69]	X	X	X	X	WOMAC score, normalised 0—100, reported on chart up to 24 months.
Function WOMAC					
Fransen 2015[28]		X		X	WOMAC physical function (0—68) reported at 12 and 24 months.
Clegg 2006[75]	X				Total at baseline, value at end of follow-up and change from baseline reported at 6 months.
Sawitzke 2010[88]	X	X	X	X	Reported at baseline and from chart over 24 months of follow-up
Michel 2005[82]				X	WOMAC score reported at 24 months.
Stiffness WOMAC					
Clegg 2006[75]	X				Total at baseline, value at end of follow-up and change from baseline reported at 6 months.
Michel 2005[82]				X	WOMAC score reported at 24 months.

Abbreviations
WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Total WOMAC is reported by Clegg[75] and Michel[82] (***Table 57***), however, scores are only presented at six months for Clegg[75] and 24 months for Michel[82]. Both of these studies were included in the NCC-CC[3] review and results were provided in an earlier part of this report. The p-values for Michel[82] were not explicitly stated although the authors indicated: *"over the two-year study period, the total WOMAC score did not show a significant improvement, either for study completers analysis or for the intent-to-treat analysis. The intent-to-treat analysis yielded improvement for the CS group on all WOMAC subscales, including pain, stiffness, and function, while the placebo group showed less improvement on the pain and stiffness subscales and some worsening on the function subscale on average. However, there were no statistically significant differences between the two groups"* (p. 783).

Clegg[75] assigned 1,583 patients with symptomatic knee osteoarthritis to receive 1,500mg of glucosamine daily, 1,200mg of CS daily, both glucosamine and CS, 200mg of celecoxib daily, or placebo for 24 weeks. Overall, glucosamine and CS were not significantly better than placebo in reducing knee pain by 20%. Compared to placebo, CS was 5.3 percentage points higher (p = 0.17), and celecoxib 10.0 percentage points higher (p = 0.008). Adverse events were mild, infrequent and evenly distributed among the groups. They also found non-significant differences between arms with a greater decrease in total WOMAC in placebo of -48.9 compared to CS of -46.0 (p = 0.61) after six months.

Table 57 Total WOMAC scores reported in key studies comparing chondroitin sulfate to placebo

Study; Intervention	Participants (n)			Mean Total WOMAC		
	0 months	6 months	24 months	0 months	6 months	24 months
Michel 2005[82]						
CS	150	NR	150	2.3	NR	-0.09
Placebo	150	NR	150	2.6	NR	-0.05
p-value	NR	NR	NR	NR	NR	NR
Clegg 2006[75]						
CS	318	318	NA	146	-46.2	NA
Placebo	313	313	NA	146	-48.6	NA
p-value	NR	NR	NR	NR	0.61	NR

Abbreviations
CS =chondroitin sulfate, **n** = number of participants, **NA** = not applicable, **NR** = not reported, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index.

Singh[30] found a MD of -10.14 units (95% CI, -14.58, -5.71) between CS and placebo arms on a 0—100 pain scale in eight short-term studies and -9.00 (95% CI -17.7, -0.34) on a 0—100 scale in six long-term

studies in a Cochrane review. Meta-analysis was confounded, as pain, stiffness and function WOMAC sub-scores were not consistently reported. For example, Sawitzke[88] reported a 24-month, double-blind, placebo-controlled study conducted at nine sites in the US. The authors evaluated the efficacy and safety of glucosamine and CS alone or in combination, as well as celecoxib and placebo. The primary outcome measure was the number of patients who reached a 20% reduction in WOMAC pain over 24 months. Pain and function scores were not accompanied by total WOMAC scores. Similarly, sub-scores for Fransen[28] were not accompanied with total WOMAC scores.

Correspondingly, only studies reporting total WOMAC that have been transformed to health utilities are summarised in this report for CS versus placebo (see ***Table 58***). A difference of 0.007 for CS versus placebo is estimated at 24 months follow-up by Michel,[82] and -0.001 by Clegg[75] after six months. Bruyere[106] provided the QALY gains for WOMAC scores reported in the Kahan[69] study. The QALY index at six months was 0.03 higher for CS over placebo but decreased to 0.01 at 24 months. The improvement at six months is significant (p = 0.03), but not at 24 months (p = 0.37). The authors indicated that: "*The main explanation, as acknowledged [Kahan[69]], for these variations are that since a significant proportion of patients had no or mild symptoms at one year (because of the treatment or the placebo effects), a further symptomatic effect of CS was unlikely to be observed*" (ibid, p. 358). Over 24 months CS gained 0.097 QALYs, while placebo was only 0.072. This resulted in a difference of 0.025 QALYs. This difference is included in the base economic model for the CS versus placebo comparison, as Clegg[75] only has short follow-up and Michel[69] reports for one period of follow-up. The differences in QALYs gained at 24 months are similar (Michel[82] and Bruyere[106]) ranging from 0.01 to 0.025 QALYs.

Table 58 Reported QALYs gained in key studies comparing chondroitin sulfate to placebo

Study; Outcome	QALYs Gained		
	6 months	12 months	24 months
Michel 2005[82]			
Difference (reported in NCC-CC 2008[3])	NA	NA	0.007
Clegg 2006[75]			
Difference (reported in NCC-CC 2008)[3]	-0.0014	NA	NA
Kahan 2009[69] (reported in Bruyere 2009[106])			
CS	0.018	0.044	0.097
Placebo	0.007	0.026	0.072
Difference	0.011	0.018	0.025

Abbreviations
CS = chondroitin sulfate, **NCC-CC** = National Collaborating Centre for Chronic Conditions, **NA** = not applicable, **QALY** = quality-adjusted life years.

The clinical effectiveness evaluation noted that ten studies provided evidence on any adverse event.[64 73 78 80-83 86 92 93] Eight were included in the meta-analysis and two were described narratively. Overall, there was no statistically significant difference between the CS and placebo groups (RR 0.93, 95% CI 0.81, 1.05, p = 0.24). Ten studies provided evidence on gastrointestinal-related adverse events, and all ten were included in the meta-analysis.[69 73-75 78 80 81 86 90 92] Overall, there was no statistically significant difference between the CS and placebo groups (RR 0.81, 95% CI 0.59, 1.11, p = 0.19). Correspondingly, no costs are included for adverse events.

CS versus COX-2

Two studies that included total WOMAC measurements for CS versus COX-2 comparisons were identified in the clinical effectiveness review. The reporting of total WOMAC by month of follow-up is summarised in ***Table 59***. The Pelletier[85] study measured this outcome over 24 months, whereas Clegg[75] was limited to six months of follow-up.

Table 59 Change in WOMAC scores reported in key studies comparing chondroitin sulfate to COX-2 inhibitor

	Mean Total WOMAC (0—240 or 0—300)				Mean Total WOMAC (Rescale 0—96)			
	Month of follow-up				Month of follow-up			
	0	6	12	24	0	6	12	24
Pelletier et al. 2016[85]								
CS	124.90	-39.34	-51.38	-38.88	49.96	-15.74	-20.55	-15.55
COX-2	126.70	-52.13	-51.80	-49.31	50.68	-20.85	-20.72	-19.72
p-value	NR	0.109	0.96	0.227	NR	NR	NR	NR
Clegg et al. 2006[75]								
CS	146.00	-46.00	NA	NA	46.72	-14.72	NA	NA
COX-2	147.00	-57.10	NA	NA	47	-18.27	NA	NA
p-value	NR	0.08	NA	NA	NR	NR	NA	NA

Abbreviations
COX-2 = cyclooxygenase-2 inhibitor, **CS** = chondroitin sulfate, **NA** = not applicable, **NR** = not reported, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index.

Pelletier[85] found differences in total WOMAC scores between COX-2 and CS on a 0—240 scale. The change from baseline was only significant at three months (not presented in clinical effectiveness review). At six, 12 and 24 months the WOMAC reduction was 12.8 (p = 0.109), 0.4 (p = 0.96) and 10.4 (p = 0.227) more for COX-2 compared with CS. The difference in the total WOMAC at 24 months between CS and COX-2 on a 0—96 scale is around 3.5 units. This difference at six, 12 and 24 months is included in the mapping algorithm[107] assuming an age of 60 years and a female patient. The utility gain for CS is -0.04 compared to COX-2 at 24 months using the Barton[107] model. A difference in utility gains of -0.01 for CS versus COX-2 is estimated at six months using results of the Clegg [75] and Pelletier[85] studies.

Table 60 Reported QALYs gained in key studies comparing chondroitin sulfate to COX-2 inhibitor

Total WOMAC	QALY				QALYs Gained		
	Month of follow-up				Month of follow-up		
	0	6	12	24	6	12	24
Pelletier et al 2016[85]							
CS	0.510	0.662	0.698	0.661	0.038	0.124	0.293
COX-2	0.501	0.695	0.694	0.687	0.049	0.145	0.335
Difference					-0.010	-0.022	-0.041
Clegg et al 2006[75]							
CS	0.550	0.684	NA	NA	0.034	NA	NA
COX-2	0.550	0.709	NA	NA	0.040	NA	NA
Difference					-0.006	NA	NA

Abbreviations
COX-2 = cyclooxygenase-2 inhibitor, **CS** = chondroitin sulfate, **NA** = not applicable, **QALY** = quality-adjusted life years, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index.

Pelletier[85] was a key study identified in the clinical evaluation to provide evidence on any adverse event. There was no statistically significant difference between patients receiving CS and celecoxib (p > 0.99).[85] Musculoskeletal, infection and gastrointestinal-related events were the most common adverse events reported in the study. The adverse events were generally mild, with approximately 95 and 100 adverse events in the CS and NSAIDs groups ongoing at the end of the study, respectively. Three studies were identified that provided evidence on gastrointestinal-related severe adverse events[75 84 85], and all three were included in the meta-analysis. Overall, there was no statistically significant difference between the CS and NSAIDs groups (RR 0.93, 95% CI 0.61, 1.43, p = 0.75). Correspondingly, no costs are included for adverse events.

9.4 Results: Costs

The costs section addresses questions about what types and amounts of resources are used when delivering the assessed technology and its comparators (resource-use identification) (see ***Table 8***

). CS is available for patients with degenerative joint diseases through mandatory health insurance. There are two key CS formulations available in Switzerland—Structum® and Condrosulf®. Structum® is available in 500mg capsules that are taken twice a day, equivalent to a daily intake of 1,000mg. Condrosulf® is available in 400mg or 800mg doses (tablet, capsule or granule) that are taken orally at a dose of 800mg per day. Alternative treatments for CS include COX-2 selective NSAIDs, ns-NSAIDs or placebo (no treatment). A doctor's appointment is required each year for prescribing the medicines.

Annual costs of CS use and comparator medicines are outlined in ***Table 61***. The table includes Spezialitätenliste public prices and dosing. Annual costs for included CS products vary from CHF 222—281 per year. Costs are included in ***Table 61*** using the Spezialitätenliste public price for COX-2, paracetamol, a PPI and ns-NSAID. Paracetamol costs and ns-NSAID costs are used in the budget impact analysis, which follows the economic model results.

Medicine costs are highest for COX-2 at CHF 468 per year (assuming COX-2 at 200mg per day) and least for ns-NSAIDs at CHF 214 per year. The addition of a PPI medication increases annual medicines costs to CHF 457 and CHF 711, for COX-2 and ns-NSAIDs, respectively.

Table 61 Annual costs for osteoarthritis medicines (CHF)

Medicine	Dose (mg) per day	Cost per pack (CHF)	mg/tablet	Tablets per pack	Medicine cost per year (CHF)	Source	Doctor visit for prescription (CHF)	Total per year (CHF)
CS (Condrosulf® 800)	800	69.20	800	90	281	Spezialitätenliste (accessed 17 July 2019)	100	381
CS (Structum® 500)	1,000	73.05	500	240	222	Spezialitätenliste (accessed 17 July 2019)	100	322
COX-2 (Celebrex, 200mg)	200	128.25	200	100	468	Spezialitätenliste (accessed 17 July 2019)	100	568
ns-NSAIDs (Diclofenac)	150	19.50	50	100	214	Spezialitätenliste (accessed 17 July 2019)	100	314
Paracetamol	3,000	15.50	500	100	339	Spezialitätenliste (accessed 17 July 2019)	100	439

Medicine	Dose (mg) per day	Cost per pack (CHF)	mg/tablet	Tablets per pack	Medicine cost per year (CHF)	Source	Doctor visit for prescription (CHF)	Total per year (CHF)
Omeprazole	20	66.65	20	100	243	Spezialitätenliste (accessed 17 July 2019)	100	343
Celecoxib + Omeprazole					711	Calculated	100	811
Diclofenac + Omeprazole					457	Calculated	100	557

Abbreviations
CHF = Swiss Francs, **COX-2** = cyclooxygenase-2 inhibitor, **CS** = chondroitin sulfate, **mg** = milligrams, ns-**NSAIDs** = non-selective non-steroidal anti-inflammatory drugs.

E0009 What were the measured and/or estimated costs of the assessed technology and its comparator(s) (resource-use valuation)?

Medicines and medical service costs are combined in ***Table 61*** for each treatment. The addition of a doctor's visit each year for prescriptions increases these costs by a further CHF 100. This cost is derived from TARMED. No adverse event costs for CS, NSAIDs and COX-2 regimens are included, as rates were found to be non-significantly different in trials (24 months maximum follow-up).

The clinical evidence for joint replacement is limited. Raynaud[87] included 57 patients with four-year follow-up and directly measured joint replacement. There was no statistically significant difference in the short-term surgery rate between CS and comparator arms. Fransen[28] included 302 patients with two-year follow-up. The authors measured joint space narrowing as a surrogate outcome for joint replacement and referenced a study that conducted regression analysis on patients that did or didn't have replacement at their clinic to determine how predictive joint space narrowing is on future replacement. Given the limited clinical evidence on joint replacement, this cost impact is not included in budget impact estimates.

9.5 Results: Cost-Effectiveness

E0006 What are the estimated differences in costs and outcomes between the technology and its comparator(s)?

Base results are presented as a cost-effectiveness ratio, or ICER. The ICER captures the incremental cost and QALYs for CS compared to COX-2 and placebo. ***Table 62*** outlines the results for the two-year model period.

Table 62 Incremental cost-effectiveness ratios at two years

	Cost (CHF)	Incremental cost (CHF)	Effectiveness (QALYs gained)	Incremental effectiveness	ICER (CHF per QALY)
CS versus COX-2 (Pelletier 2016[85])					
CS	761		0.293		
COX-2	1,136	-375	0.335	-0.041	9,065
CS versus placebo (Bruyère 2009[106])					
CS	761		0.097		
Placebo	0	761	0.072	0.025	30,451

Abbreviations
COX-2 = cyclooxygenase-2 inhibitor, **CS** = chondroitin sulfate, **ICER** = incremental cost-effectiveness ratio, **QALYs** = quality-adjusted life years.

The base case ICER for CS versus placebo is estimated to be CHF 30,451 per QALY. The cost of CS is CHF 761 (there is no cost for placebo), along with CS QALYs being 0.097 and 0.072 for placebo. CS has higher cost than placebo, but is more effective, i.e. 0.025 incremental QALYs. Bruyere[106] estimated an ICER of EUR 12,985—20,866, or CHF 14,153—22,743 at 24 months (EUR 1.00 : CHF 1.09, 25 August 2019). NCC-CC[3] included the two-year study by Michel[82] with a cost of GBP 272.14 (assuming one GP consultation/year and two tablets/day) and 0.0074 additional QALYs compared with placebo. The reported ICER was GBP 42,255 (range GBP -13,667—75,723), which is similar to the ICER in the present evaluation, in that it is less than the hypothetical willingness-to-pay threshold of CHF 100,000 per QALY.

The estimated base case two-year ICER for CS versus COX-2 is CHF 9,065 per QALY. The cost of CS is CHF 761 and of COX-2 CHF 1,136, along with QALYs being 0.293 for CS and 0.335 for COX-2. CS is less costly but has less QALYs when compared to COX-2 over two years. The ratio cannot be directly compared with that for CS versus placebo, as it reflects the lower cost of CS and -0.041 less QALYS gained, as opposed to higher cost and increased effectiveness of CS in the placebo comparison. Additionally, health outcome differences are non-significant at some points of follow-up in each of the

trials. For example Bruyere[106], who compared CS with placebo, found differences in the health utility index to be significant at six months, but not at 12 and 24 months. Correspondingly, a probabilistic sensitivity analysis is undertaken where utility differences are specified as likely, maximum and minimum values.

E0010 What are the uncertainties surrounding the costs and economic evaluation(s) of the technology and its comparator(s)?

Univariate Sensitivity Analysis

The sensitivity of the results to different model assumptions is explored in univariate sensitivity analysis. CS costs are varied to include Structum® 500 at 1,000mg per day to Condrosulf® 800 at 800mg per day. Prices are taken from the Swiss Spezialitätenliste (accessed 17 July 2019). This results in a lower annual value of CHF 222, or an annual cost of CHF 641 per year. Utility estimates are also varied by ±10%. Results are presented in ***Figure 37***. ICER estimates are most affected by changes in the utility gains and the cost of COX-2 and CS products, but results remain within the hypothetical willingness-to-pay threshold of CHF 100,000/QALY.

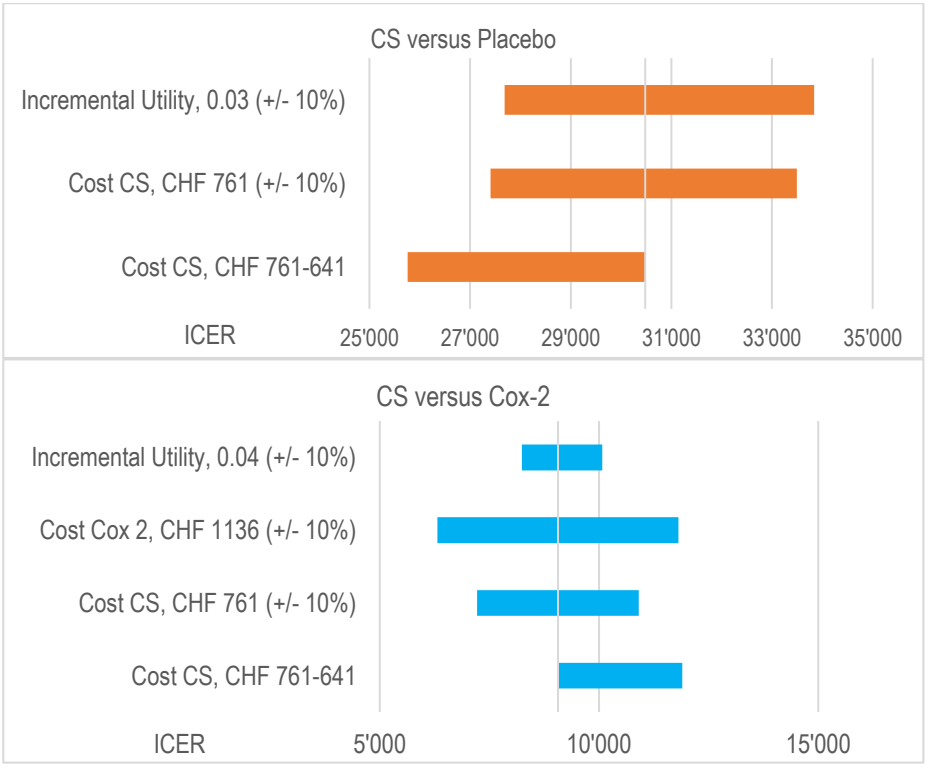

Figure 37 Incremental cost-effectiveness tornado graphs

Abbreviations
CHF = Swiss Francs, **COX-2** = cyclooxygenase-2 inhibitor, **CS** = chondroitin sulfate, **ICER** = incremental cost-effectiveness ratio.

Probabilistic Sensitivity Analysis (PSA)

Inputs are specified as distributions (described in ***Table 54***) for a CS versus placebo PSA, resulting in a mean expected ICER of CHF 28,616/QALY (95% CI, from PSA CHF -150,527—162,591, ***Figure 38***). It is evident in the scatter plot that CS is more expensive than placebo and marginally more effective. When results of the Kahan trial were transformed to utilities by Bruyere, the analysis indicated small but statistically non-significant (except at 6 months) utility benefits for the CS arm. The results of this PSA reflect the uncertainty about clinical benefits exceeding costs.

Using a hypothetical willingness-to-pay threshold of CHF100,000/QALY, there is a 60% probability that CS is cost effective when compared with placebo. When compared to other European willingness-to-pay thresholds of CHF 30,000 for the UK and CHF 180,000 for Sweden there are 50% and 63% probabilities, respectively, that CS is cost effective when compared with placebo.[114]

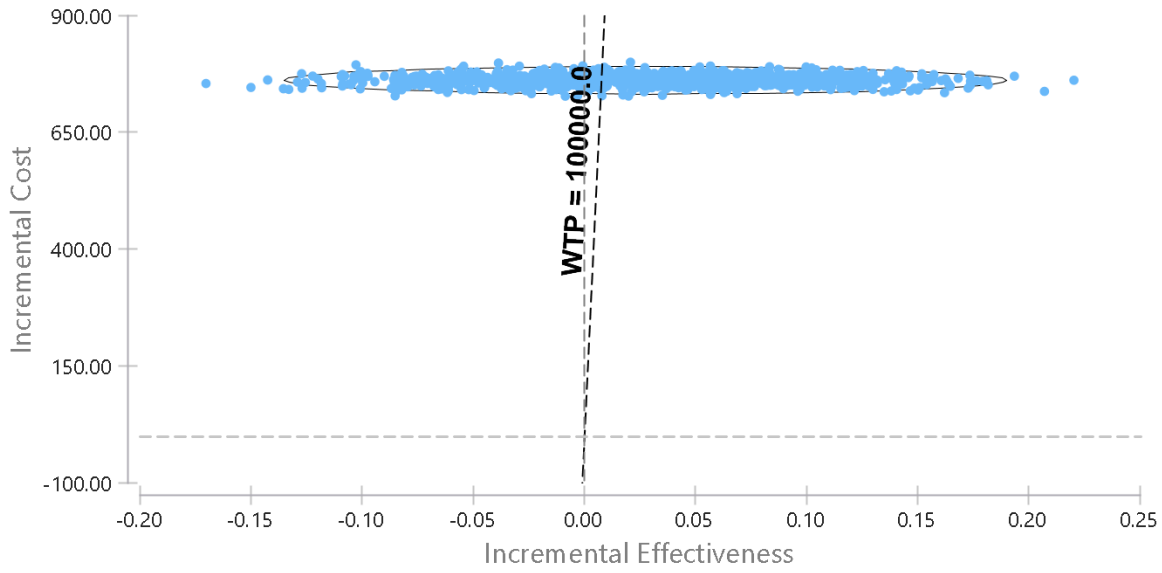

Figure 38 Incremental cost-effectiveness scatterplot (CS versus placebo)

Inputs are specified as distributions (described in ***Table 54***) for a CS versus COX-2 PSA, resulting in a mean expected ICER of CHF 3,770/QALY (95% CI, CHF -91,467, 99,120 from PSA; ***Figure 39***). The mean ICER is a result of negative cost difference (CS less expensive than COX-2) and negative QALY difference (CS less effective than COX-2). There is a 34% probability that CS is superior (incremental cost < 0, incremental effectiveness > 0) to COX-2. Like the CS versus placebo analysis, results of the CS versus COX-2 PSA reflect the small short-term difference in clinical outcomes for these treatments. COX-2 costs (with and without PPIs) are included as a uniform distribution, which results in the rectangular shape of the scatterplot.

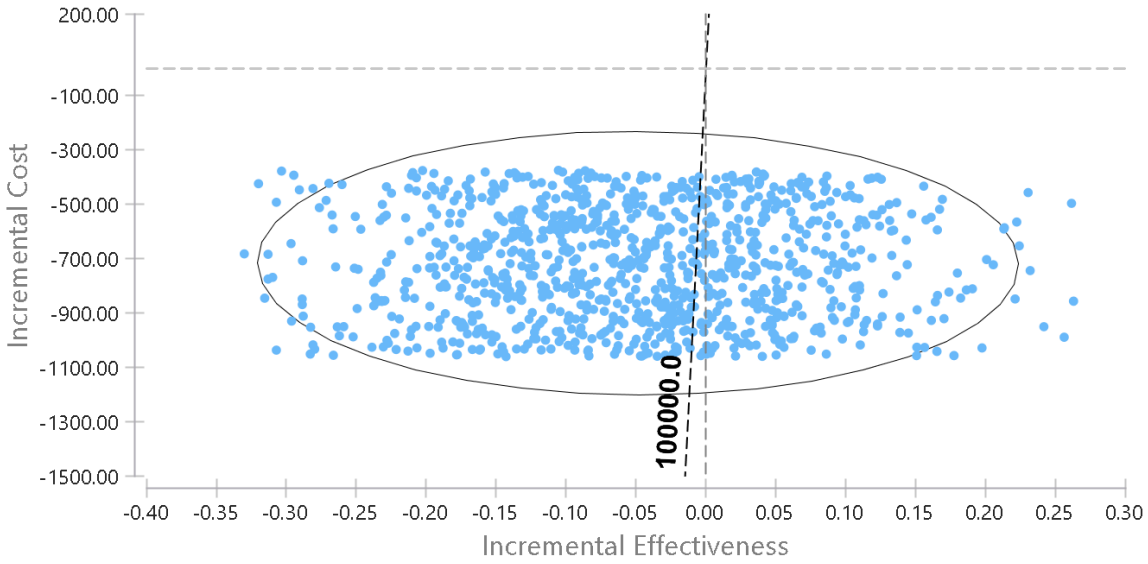

Figure 39 Incremental cost-effectiveness scatterplot (CS versus COX-2)

E0011 To what extent can differences in costs, outcomes, or 'cost-effectiveness' be explained by variations between any sub-groups using the technology and its comparator(s)?

The key drivers of the model include: (i) differences in the estimated utility for CS and COX-2 derived from the Pelletier[85] study; and (ii) differences in the estimated utility for CS versus placebo in Kahan[69], transformed to utilities by Bruyere[106]. Differences in utility for treatment arms are only observed in the short term and are relatively small. The limited evidence base hinders sub-group analysis, although differences seem to be less in mild to moderate osteoarthritis patients (e.g. Bruyere[106]). The longer-term impact of adverse events could not be estimated given that follow-up in trials included in the clinical evidence review was limited to two years. A longer-term extrapolation of 20 years was included in the economic analysis of NSAIDs, no treatment and paracetamol for osteoarthritis in the study by Latimer.[115] The exclusion of these costs is likely to favour the comparator given the high adverse event rates estimated for NSAIDs in the Latimer[115] study.

9.6 Results: Budget Impact

Budget impact analysis is undertaken to examine the financial implications of withdrawing an existing technology from mandatory health insurance. The economic analysis presented in the previous section examines the cost-effectiveness of the intervention (i.e. costs compared to health outcomes), whereas budget impact investigates financial cost implications from the introduction, or withdrawal of an intervention. This section addresses the questions regarding how the technology modifies the need for other technologies and resources, and what the likely budget impacts are of implementing/withdrawing the technologies being compared. Key sub-questions addressed in this section are outlined in ***Table 10***.

The budgetary impact of the substitution of CS for selective COX-2 inhibitors plus PPIs, paracetamol, and ns-NSAIDs plus PPIs is explored from a payer perspective (i.e. health insurance providers) for three scenarios. Scenarios of substitution are included as there is no readily available public data relating to the price and volume implications of delisting CS. The first scenario assumes that delisting CS would result in 25% of current CS users substituting CS for health insurance provider-supported selective COX-2 inhibitors plus PPIs, ns-NSAIDs plus PPIs or paracetamol. Of those patients substituting from CS to other osteoarthritis treatments, it is estimated that selective COX-2 inhibitors plus PPIs, ns-NSAIDs plus PPIs and paracetamol, would be taken-up equally (i.e. 33% for each sub-group). This assumption is also adopted due to the lack of information about price and volume relationships driving potential uptake of alternate medicines in the event that CS were to be delisted. The second scenario assumes that delisting of CS would result in 50% of current CS patients substituting with selective COX-2 inhibitors plus PPI, ns-NSAIDs plus PPI or paracetamol. The third scenario assumes 75% of current CS users would substitute with the above medical treatments.

The data sources used to estimate the number of osteoarthritis patients and those being treated with CS, selective COX-2 inhibitors and ns-NSAIDs in Switzerland, are provided in ***Table 63.*** Expected changes in health insurance provider costs, such as resources involved in technologies needed to supplement its use, are considered, e.g. additional use of selective COX-2 inhibitors plus PPI, paracetamol and ns-NSAIDs plus PPI using the three hypothetical scenarios.

D0023 How does the technology modify the need for other technologies and use of resources?

The data sources used to estimate the number of osteoarthritis patients and those being treated with CS in Switzerland are provided in ***Table 63.*** The scoping report noted that the incidence and prevalence of osteoarthritis in Switzerland could not be ascertained via published literature. The Swiss Health Survey in 2012[116] asked what proportion of people (over age 15) had sought medical treatment for osteoarthritis and rheumatic arthritis in the last 12 months, to which 7.3% of respondents provided a

positive answer. This proportion is equivalent to more than half a million patients. The Global Burden of Disease Study[117] reports osteoarthritis prevalence, and in 2017 it estimated 6,645 per 100,000 suffer osteoarthritis, or 581,920 people in 2020 (when the rate is applied to the projected Swiss population for this year). None of these estimates provide specific information about the number of osteoarthritis patients in Switzerland using different medicines.

The value of CS, ns-NSAIDs and selective COX-2 medicines sales (at the public price supported by health insurance providers) are reported by the FOPH. In the case of CS, a total of CHF 33.9 million was reported in 2018, with Condrosulf® 800 (Tabs 800mg 90 tablets) accounting for 87% of total value. Structum® 500 accounted for less than 5% of CS value in 2018. The volumes of Condrosulf® and Structum® were 34.6 and 2.5 million grams, respectively in 2018. The number of patients is difficult to determine as annual mg per patient varies with adherence and severity of osteoarthritis. The number of patients using Condrosulf® and Structum® at trial dosing (800mg and 1,000mg per day) is estimated in ***Table 63.***

The equivalent of 125,000 patients per year are using CS based on trial dosing per year.

Table 63 Budget impact assumptions

Description	2020	2021	2022	2023	2024	Source
Epidemiology assumptions						
Total Swiss population	8,757,650	8,838,980	8,919,990	9,000,580	9,080,650	Swiss population projections.[118]
Swiss population 15+ years	7,531,579	7,601,523	7,671,191	7,740,499	7,809,359	86% over age 15 in 2012[119]
Osteoarthritis prevalence per 100,000 total Swiss population	6,645	6,645	6,645	6,645	6,645	Prevalence per 100,000 from Global Burden of Disease Study.[25]
Osteoarthritis cases in Switzerland	581,920	587,324	592,707	598,062	603,382	Calculated
Medical treatment for arthritis						
Medical treatment for arthritis (osteoarthritis and rheumatic arthritis)	7.3%	7.3%	7.3%	7.3%	7.3%	Last 12 months among age 15+ in 2012 [120]
Swiss patients seeking medical treatment for arthritis	549,805	554,911	559,997	565,056	570,083	Calculated

Description	2020	2021	2022	2023	2024	Source
(osteoarthritis and rheumatic arthritis)						
CS use assumptions						
Condrosulf® values per year CHF	32,358,423	32,658,927	32,958,249	33,256,019	33,551,867	FOPH data assume 2018 volume indexed at population growth
Structum® value per year CHF	1,563,719	1,578,241	1,592,706	1,607,096	1,621,393	FOPH data assume 2018 volume indexed at population growth
Condrosulf® grams per year	34,607,264	34,928,652	35,248,776	35,567,241	35,883,650	FOPH data assume constant 2018 volume
Structum® grams per year	2,505,253	2,528,519	2,551,693	2,574,747	2,597,652	FOPH data assume constant 2018 volume
Total CS grams/year	37,112,517	37,457,171	37,800,469	38,141,988	38,481,302	Calculated
Condrosulf® grams per patient per year	292	292	292	292	292	365 days at 800mg/day
Structum® grams per patient per year	365	365	365	365	365	365 days at 1,000mg/day
Condrosulf® patients per year	118,518	119,619	120,715	121,806	122,889	Calculated based on 292,000mg per patient per year (800mg/day)
Structum® patients per year	6,864	6,927	6,991	7,054	7,117	Calculated based on 365,000mg per patient per year (1,000mg/day)
Projected CS patients without withdrawal	125,382	126,546	127,706	128,860	130,006	Calculated
Chondroitin Sulfate substitution assumptions (for 50% substitution scenario)						
Increase in patients using ns-NSAID plus PPI per year	20,897	21,091	21,284	21,477	21,668	Increase in patients using ns-NSAID plus PPI per year
Increase in patients using COX-2 plus PPI per year	20,897	21,091	21,284	21,477	21,668	Increase in patients using COX-2 plus PPI per year
Increase in patients using Paracetamol per year	20,897	21,091	21,284	21,477	21,668	Increase in patients using Paracetamol per year

Abbreviations

COX-2 = cyclooxygenase-2 inhibitors, **CS** = chondroitin sulfate, **FOPH** = Federal Office of Public Health, **mg** = milligrams, ns-**NSAIDs** = non-selective non-steroidal anti-inflammatory drugs.
Source
This study.

There is a great degree of uncertainty surrounding osteoarthritis patient numbers and how many patients would substitute from CS to ns-NSAIDs plus PPI, paracetamol, or COX-2 selective inhibitors plus PPI in the event of delisting. Many patients currently using CS may not substitute at all.

As noted, three scenarios provide differing assumptions about the degree of CS substitution to alternate medicines. The first assumes that delisting of CS would result in 25% of current CS users substituting to health insurance provider-supported COX-2 selective inhibitors plus PPI, ns-NSAIDs plus PPI or paracetamol, with uptake split equally among the subgroups (i.e. 33% each). The second assumes 50% substitution and the third assumes 75% substitution. The numbers of patients using each of these medicines under the 50% (second) substitution scenario are presented in ***Table 63.*** It is evident that half of current CS patients substitute to other medicines (i.e. 62,691 in 2020), with patients using COX-2 selective NSADIs + PPI, ns-NSAIDs + PPI and paracetamol in this year increasing by 20,897 for each sub-group. The other two scenarios (25% and 75% substitution) are presented in the sensitivity analysis in ***Table 65***.

Financial Implications

The five-year budget impact of the above assumptions is presented in ***Table 64***. The decrease in CS use is offset by increased ns-NSAIDs, paracetamol and COX-2 selective inhibitors usage. CS would not be supported by health insurance providers in the case of delisting, however, the net cost saving would be impacted by increased ns-NSAIDs, paracetamol and COX-2 selective NSAID usage. In 2020, it is estimated that delisting CS would result in health insurance provider savings of around CHF 33.9 million, while the financial value of increased NSAID, paracetamol and COX-2 usage amounts to CHF 31.5 million in 2020. Medical services and GP costs do not vary considerably, as similar general doctor use is assumed for all treatments.

Table 64 Scenario 2: Projected chondroitin sulfate uptake among osteoarthritis patients in Switzerland, 2020—2024

Change in osteoarthritis patient medicine usage		2020	2021	2022	2023	2024	Source
Change in osteoarthritis patients using CS and substituting other medicines	Number	-62,691	-63,273	-63,853	-64,430	-65,003	Assumption about adoption due to delisting
Change in osteoarthritis patients using ns-NSAIDs + PPI	Number	20,897	21,091	21,284	21,477	21,668	Assumption about substitution
Change in osteoarthritis patients using COX-2 + PPI	Number	20,897	21,091	21,284	21,477	21,668	Assumption about substitution
Change in osteoarthritis patients using paracetamol	Number	20,897	21,091	21,284	21,477	21,668	Assumption about substitution
Change in health insurance provider medicines costs							
Change in insurance provider costs for CS	CHF	-33,922,142	-34,237,168	-34,550,955	-34,863,114	-35,173,260	Calculated
Change in insurance provider costs for ns-NSAIDs + PPI	CHF	9,545,677	9,634,325	9,722,625	9,810,466	9,897,741	Calculated
Change in insurance provider costs for COX-2 + PPI	CHF	14,865,781	15,003,835	15,141,347	15,278,145	15,414,061	Calculated
Change in insurance provider costs for paracetamol	CHF	7,093,472	7,159,347	7,224,963	7,290,239	7,355,093	Calculated
Change in insurance provider medicines costs	CHF	-2,417,213	-2,439,661	-2,462,020	-2,484,264	-2,506,364	Calculated
Summary							
Change in osteoarthritis patients using CS and taking up other medicines	Number	-62,691	-63,130	-63,572	-64,017	-64,465	Calculated

Change in osteoarthritis patient medicine usage		2020	2021	2022	2023	2024	Source
Change in insurance provider medicines costs	CHF	-2,417,213	-2,439,661	-2,462,020	-2,484,264	-2,506,364	Calculated
Total net insurance provider costs	**CHF**	**-2,417,213**	**-2,439,661**	**-2,462,020**	**-2,484,264**	**-2,506,364**	**Calculated**

Abbreviations
CHF = Swiss Francs, **COX-2** = cyclooxygenase-2 inhibitors, **CS** = chondroitin sulfate, **GP** = general practitioner, ns-**NSAIDs** = non-selective non-steroidal anti-inflammatory drugs, **PPI** = proton pump inhibitor.
Source
This study.

G0007 What are the likely budget impacts of implementing/withdrawing the technologies being compared?

The health insurance provider cost savings associated with delisting CS in 2020 are CHF 33.9 million in this year (equivalent to current CS sales). Total savings of CS being delisted are offset by 62,691 patients estimated to substitute ns-NSAIDs plus PPI, COX-2 selective inhibitors plus PPI and paracetamol for osteoarthritis treatment. The net medicines cost saving is CHF 2.4 million in 2020. There are minor cost differences for GP and medical services as patients are still assumed to see a GP at current frequencies for non-complicated treatment despite CS being delisted.

Sensitivity Analysis

The budget impact model presented in this section provided a base case. Key base assumptions are included in sensitivity analyses in ***Table 65***. The budget impact is most sensitive to the numbers of patients who would use substitute medicines (or no medicines) in the event of CS delisting. It is evident that if only 25% of CS patients substituted to other osteoarthritis medicines, savings to the health insurance provider would be CHF 18.2 million in 2020. If, however, 75% of CS patients substituted to other health insurance provider-supported medicines, this would result in a net cost to providers of CHF 13.3 million due to the higher costs of ns-NSAIDs and COX-2 selective NSAIDs with PPIs compared to CS.

Table 65 Net health insurance provider cost sensitivity analysis

	2020	2021	2022	2023	2024
Base case net insurance provider cost (CHF)	-2,417,213	-2,439,661	-2,462,020	-2,484,264	-2,506,364
25% of CS patients substituting other osteoarthritis medicines upon CS delisting	-18,169,677	-18,338,414	-18,506,487	-18,673,689	-18,839,812

	2020	2021	2022	2023	2024
75% of CS patients substituting other osteoarthritis medicines upon CS delisting	13,335,252	13,459,093	13,582,447	13,705,161	13,827,083
Reduced CS patients substituted 0:50:50 by ns-NSAIDs, paracetamol and COX-2	-983,264	-992,395	-1,001,490	-1,010,538	-1,019,528
Reduced CS patients substituted 50:0:50 by ns-NSAIDs, paracetamol and COX-2	2,695,045	2,720,073	2,745,003	2,769,803	2,794,443
Reduced CS patients substituted 50:50:0 by ns-NSAIDs, paracetamol and COX-2	-8,963,419	-9,046,660	-9,129,573	-9,212,057	-9,294,008

Abbreviations

CHF = Swiss Francs, **COX-2** = cyclooxygenase-2 inhibitors, **CS** = chondroitin sulfate, ns-**NSAIDs** = non-selective non-steroidal anti-inflammatory drugs, **PPI** = proton pump inhibitor.

10. Legal Issues

10.1 Summary Statement on Legal Issues

Delisting CS is unlikely to result in substantial legal issues. Should CS be delisted from the Spezialitätenliste, it would retain its regulatory status as a prescription medication.

10.2 Methods

As noted in the scoping report, there are no important legal issues related to the potential disinvestment of CS from the reimbursement list in Switzerland. The only question from the EUnetHTA Core Model related to legal aspects relevant to CS is outlined in ***Table 11***.[121] Literature to address this question was sourced through targeted searches of the Swissmedic,[122] the FOPH,[123] the European Medicine's Agency,[124] and the European Parliament's websites.[125] As this search strategy was not systematic, a PRISMA chart is not provided.

10.3 Results

I001 What authorisations and register listings does the technology have?

The market authorisations for the two prescription formulations of CS available in Switzerland, Condrosulf® and Structum®, are presented in ***Section 4.4***. These products are registered as prescription medications. The registration of these products will not change should CS be disinvested, and it would remain available to consumers as an out-of-pocket prescription medication.

11. Social Issues

11.1 Summary Statement on Social Issues

There is limited literature evaluating the social aspects of delisting CS. Patients tend to hold a positive outlook towards CS. Treatment options are primarily explained by primary care physicians with an emphasis on pharmacological management, owing to uncertainties with non-pharmacological treatment strategies.

Feedback from targeted patient and physician groups suggests that Swiss patients view CS as an effective drug to reduce pain and slow the progression of osteoarthritis. Patient advocates estimate that 50% of patients currently taking CS will continue to pay out-of-pocket if it is disinvested, and the remaining patients will either stop or substitute CS due to financial concerns.

11.2 Methods

Sub-questions related to patient and social aspects of the potential disinvestment of CS are outlined in ***Table 12***.[121] Two methods were used to address these research questions: literature review, and targeted patient and physician feedback:

i. Literature was identified during the systematic literature review detailed in ***Section 7***. In addition, targeted searches were conducted in an additional database (Psychinfo) using combined keywords “chondroitin” and “osteoarthritis”. The supplementary literature searches were conducted by a single reviewer and did not identify any additional relevant studies.

ii. Patient and prescriber views are critical to the evaluation of patient and social issues related to the use of CS for osteoarthritis. Input from patient and physician groups was obtained through the FOPH’s formal engagement processes. A short list of questions was sent to targeted umbrella organisations representing patients with osteoarthritis, and physicians treating osteoarthritis. Questions were based around the specific EUnetHTA Core Model questions related to social, ethical and organisational aspects. The survey questions are presented in ***Appendix G***.

The results of the questionnaires and literature searches are summarised using narrative synthesis.[126]

11.3 Evidence Tables

Sixteen studies were included in the assessment of social issues.[127-142] The studies consisted of primary (survey or interviews) and secondary research (systematic reviews), and generally asked questions regarding the perception and utilisation of complementary and alternative medicines (CAMs), and patient and/or physician attitudes regarding osteoarthritis management and barriers in current osteoarthritis practice.

Studies were predominately from the US (k = 6), Australia (k = 3) and Canada (k = 2). No studies were performed in Switzerland. Participants were mostly recruited from community practices or hospitals and encompassed individuals with osteoarthritis or medical practitioners (including GPs, surgeons and nurses). The number of surveyed participants ranged from 11 to 2,679. Two studies utilised patient data from the Osteoarthritis initiative cohort, a National Institutes of Health-sponsored study of individuals with osteoarthritis. For further information regarding study characteristics refer to ***Table 69***.

In Switzerland, two formulations of CS are registered as prescription drugs. In countries such as the US or UK, CS is considered a CAM or dietary supplement. Given there is an absence of direct evidence evaluating the social impact of prescription CS, studies evaluating CS in the context of CAMs will be evaluated. It is important to note that the applicability of these studies to the Swiss context is uncertain, as the quality of CS may differ owing to its classification as a CAM or prescription medication.

Table 66 Characteristics of included studies for social issues

Author, year; country	Indication; Sample size	Design; Follow-up; Setting	Interview/survey topics	Sub-question addressed Key outcomes
Brienza 2002[130] USA	Female patients who visited the community practices n = 220	Survey NA Three community practices	CAM use, source of health news, costs, delay in care	H0006 Influence of patient demographic or CAM use on delay in obtaining conventional care
Herman 2004[137] USA	Osteoarthritis, rheumatoid arthritis, fibromyalgia patients n = 612	Survey, NA Six primary care clinics	CAM use, treatments for managing osteoarthritis	H0006 Influence of patient demographic on CAM use

Author, year; country	Indication; Sample size	Design; Follow-up; Setting	Interview/survey topics	Sub-question addressed Key outcomes
Fraenkel 2004[134] USA	Knee osteoarthritis patients n = 100	Survey NA Multiple community practices	Medication use, characteristics influencing patient choice	H0006 Influence of cost and purported benefit of medication on patient choice, patient preferences consistent with current practice
Grindrod 2010[136] Canada	Osteoarthritis patients n = 190	Survey, Six months Multiple community pharmacies	Treatments for managing osteoarthritis, WOMAC, SF-36, PAT-5D-QoL, HUI-3	H0006, H0202 Health service utilisation and osteoarthritis progression
Alami 2011[127] France	Medical practitioners and knee osteoarthritis patients n = 81	Interview, NA, Community practices	Osteoarthritis management	H0202 Views on osteoarthritis management and barriers
Glauser 2011[135] USA	Physicians, physician assistants and nurse practitioners n = 251	Survey NA Hospital, community practices	Management of osteoarthritis, attitudes towards guidelines and educational tools	H0202 Attitudes and practice patterns of primary care health workers for osteoarthritis
Jawahar 2012[138] USA	Knee osteoarthritis patients n = 2679	Survey NA Participants enrolled in the osteoarthritis initiative	CAM use, treatments for managing osteoarthritis	H0006 Influence of patient demographic on CAM use
Kingsbury 2012[139] UK	GPs n = 232	Survey NA Community practices	Attitudes relating to assessment and treatment of osteoarthritis	H0202 Factors influencing osteoarthritis management and barriers to treatments
Lapane 2012[140] USA	Knee osteoarthritis patients n = 2,679	Survey NA Participants enrolled in the osteoarthritis initiative	CAM use, treatments for managing osteoarthritis	H0006 Influence of patient demographic on CAM use
Tsui 2012[142] Canada	Osteoarthritis patients n = 25	Interview, NA, Senior and community centres	CAM use, information used to make disease management decisions	H0202 How/why individuals select CAMs

Author, year; country	Indication; Sample size	Design; Follow-up; Setting	Interview/survey topics	Sub-question addressed Key outcomes
Paskins 2014[141] NA	GPs and patients with osteoarthritis k = 22	SR NA	Patients' experiences with consultations, GP attitudes towards osteoarthritis management	H0202 Identify areas of patient-physician interactions that could be improved
Austine 2016[128] India	Orthopaedists n = 15	Interview NA Single tertiary hospital	Quality of life, pain management, precautions, adverse events, barriers, counselling	H0006 Perspectives on pain management for patients with osteoarthritis
Dimitrelis 2017[132] Australia	Nurses, midwives n = 5,041	Survey NA Hospital, community, GP, outpatient clinics, residential care, other	CAM use, health characteristics	H0006, H0202 Influence of demographic, work-related characteristics, health behaviour on CAM use
Basedow 2018[129] Australia	GPs n = 79	Survey NA Community practices	Management of osteoarthritis	H0202 Compare treatment management approaches to 2006 survey results
Corp 2018[131] NA	Non-traumatic musculoskeletal injury patients k = 169	SR NA Surveys	Qualitative and quantitative surveys of CAM use	H0006, H0202 Justification of CAM use
Egerton 2018[133] Australia	GPs n = 11	Interview NA Community practices	Attitudes relating to assessment and treatment of osteoarthritis	H0202 Behavioural drivers for managing patients with knee osteoarthritis

Abbreviations

CAM = complementary and alternative medicine, **GP** = general practitioner, **HUI** = health utilities index mark 3, **k** = number of studies, **n** = number of patients, **NA** = not applicable, **PAT-5D-QoL** = Paper adaptive test for five dimensions of health-related quality of life.

11.4 Results

There was limited literature addressing social implications of CS. Rather, most studies considered the broader context of CAMs. As such, studies pertaining to CAMs will be presented with the understanding that the generalisability of the results to CS is unclear.

H0006 How do patients perceive the technology under assessment?

Literature Review

No literature from the Swiss context was identified to answer this research question.

Utilisation of Complementary and Alternative Medicine

Overall, approximately 6.2% to 75.0% of patients with osteoarthritis report using, or have used, CAMs within the past year.[132 134 136] Glucosamine in combination with CS was generally the most frequently used supplement (range 16.1%—75%[132 134]) with approximately 17.9% to 53.6% of CAM users utilising CS.[137 138 140]

Perceived Advantages

No studies specifically addressed the perceived advantages or disadvantages of CS.

CAMs are perceived to improve pain and function in osteoarthritis patients, with approximately 50% of surveyed users stating that nutritional supplements were helpful in managing their condition.[136 137] Further perceived advantages of CAMs include, lower barrier for entry compared to conventional medicine as they are typically easier, cheaper and less time consuming to obtain; increased autonomy over an individual's healthcare; safety, with minimal to no side effects; provision of a 'natural' alternative; and ease of use or discontinuation of use.[128 131 136 137]

Perceived Disadvantages

Patients who did not, or have not used CAMs frequently reported satisfaction with their current level of care; disinterest in the product; inability to afford them; belief in CAMs being unsafe or lacking in scientific evidence [130]; or that CAMs were ineffective or had a slow, mild effect.[131]

Patient and Physician Feedback

Perceived Advantages

The patient organisations' response suggested that Swiss patients view CS as a "very effective" treatment that improves strength and mobility, stabilises or slows disease progression, relieves pain and leads to a higher quality of life. They also reported that CS is a safe drug with a favourable adverse

event profile. Similarly, physician responses suggest patients are likely to expect CS to reduce their pain and slow cartilage degeneration. Respondents' views do not align with the clinical data described in ***Section 6,*** which found no significant benefit of CS regarding pain reduction beyond six months compared to placebo.

Perceived Disadvantages

The patient organisations reported that CS is most useful in patients with early-stage disease, and that CS becomes less effective past Kellgren & Lawrence stage four. No other perceived disadvantages were reported by the patient or physician organisations.

Limitations

Patient and physician feedback should be interpreted with several limitations in mind. Questions were sent to targeted organisations, but it is unclear how well the received feedback represents the opinion of individual physicians and patients. Patient advocacy organisations may also have a different understanding than the Swiss public of the benefits and disadvantages of CS medications. Thus, their responses may not be generalisable to the broader Swiss population of patients with osteoarthritis or physicians that treat patients with osteoarthritis.

H0201 Are there groups of patients who currently don't have good access to available therapies?

In the context of the current policy question, this question should be framed around whether delisting CS will impact patients' access to available therapies.

Literature Review

No literature from the Swiss context was identified to answer this research question.

Austine[128] noted patients in India who have financial difficulties, do not have insurance, or have to travel far to healthcare facilities may not have access to needed therapies. Given the healthcare and demographic differences between India and Switzerland, it is unlikely these findings are applicable to the current context.

Patient and Physician Feedback

As discussed in ***Section 7***, the patient organisation feedback estimated that 50% of patients currently taking CS to treat osteoarthritis will not be able to afford payment for the medicine out-of-pocket if it is disinvested. In such circumstances, alternative medications indicated for this patient group include

paracetamol, ns-NSAIDs and COX-2 selective NSAIDs. This estimate is based on one returned questionnaire on behalf of the patient organisations and as such is subject to a high degree of uncertainty.

H0202 How are treatment choices explained to patients?

Literature Review

No literature from the Swiss context was identified to answer this research question.

Patients obtain information relating to the management and treatment of osteoarthritis from a variety of sources including their primary care physician, family and friends, or media sources such as the internet or magazines.[131] [142] There was limited information exploring the type and quality of information provided by friends and media sources. Most studies focused on the patient or physician perspective.

The treatments offered to patients include non-pharmacological options such as exercise, diet or walking aids. However, both physicians and patients note reluctance to offer and utilise these treatment options owing to a lack of current information, patient motivation and embarrassment.[127] Pharmacological treatment options include paracetamol, topical and oral NSAIDs, opioids and intra-articular injections.[139] Arthroplasty is reserved for patients who have failed or are contraindicated for pharmacological treatments, however, many patients and physicians view this treatment as an inevitable consequence of osteoarthritis.[133] It is unclear how closely GPs follow their respective countries' guidelines for osteoarthritis management, with physicians reporting general adherence[139], a lack of awareness of contemporary guidelines[135], or providing slightly different treatment options reflecting patient need for greater pain relief.[129]

Both physicians and patients report frustration regarding current management of osteoarthritis. The frustration of patients is derived from complex needs, expectations, perspective and misunderstanding about osteoarthritis.[141] For example, patients report pain and fear of disability as priorities during consultation and often hope for a more curative treatment option. However, when physicians present only 'palliative' treatment options, it can cause patients to question the efficacy of contemporary pharmacological therapies.[127] Patient frustration is further exacerbated if the pathological process underlying osteoarthritis and treatment options are not clearly explained and concerns validated (from their perspective) during consultations.[127] Consequently, patients disenfranchised with conventional medical practice often try CAMs as an alternative.[131] Patients which felt validated, believed their care was individualised, and that their doctor behaved in a competent and ethical manner were more likely to report feelings of satisfaction regarding their treatment management.[127]

For physicians, inadequate consultation time and patient-related factors (for example, unwillingness to change their lifestyle) contribute to their frustration at managing the condition.[133] Importantly, inadequate education resources for physicians and patients, and the unclear applicability and relevance of osteoarthritis assessment tools further hinder the physician's ability to inform patients about efficacious treatment choices.[133 135] Consequently, many surveyed physicians believed they were not managing patients with osteoarthritis effectively.[139] Collectively, these factors strain the physician-patient relationship, which may hinder the effective communication and explanation of treatment choices.

CAMs including SYSADOA are referred by GPs, pharmacists, family members and media sources.[136] Specifically, decision on supplementation with glucosamine and/or CS was made by the individual alone in 44% of cases and on advice by friends and family in 20% of cases.[136] Surveyed physicians provide conflicting recommendations of supplements, with some noting they may be useful between flare-ups but their efficacy has not been established, to others not recommending their use.[127 139] Doctors are more likely to hold negative attitudes towards CAMs, while nurses and midwives tend to be more supportive.[132]

Patient and Physician Feedback

The patient and physician organisations both report that patients play an active role in determining their choice of medication for osteoarthritis in Switzerland. Should CS be disinvested, this is likely to impact management decisions made by patients, in consultation with their treating physician. The patient organisations indicated that patients are informed about medication options through package leaflets that come with medications, advice from their treating physician, and advice from family and friends. While not stated, it is presumed that patients source information from the internet to inform their decision. From a disinvestment perspective, it is understood that Swiss patients will play an active role in decisions to change treatments should CS be disinvested. Given the nature of the intervention and comparators as primarily pain relievers, the ability of patients to understand the available treatment options is not a significant issue in this context.

12. Ethical Issues

12.1 Summary Statement on Ethical Issues

Delisting CS is unlikely to result in substantive ethical issues. Ethical concerns relate to whether patients will be able to differentiate between pharmaceutical and non-pharmaceutical grade CS, and whether patients are able to afford the drug if it is no longer reimbursed. Ethical issues concerning a patient's ability to manage the disease in accordance with their wishes is minimised as CS will remain available as an over-the-counter medication.

12.2 Methods

The ethical analysis utilises the methodological framework of principlism to address the moral and ethical concerns regarding the disinvestment of CS. In brief, principlism consists of four domains that consider the benefits, harms, individual autonomy and justice associated with healthcare utilisation. The four domains will be discussed in the context of CS using a systematic search strategy described in ***Section 7***, and supplemented by targeted searches of ethics databases listed in ***Appendix A***. The supplementary searches were conducted using combinations of keywords "chondroitin sulfate", "autonomy", "disinvestment", "patient preference*" and "principlism". Supplementary searches were conducted by one review author. No literature specific to CS supplementation was identified. Therefore, the literature used to inform the ethical analysis was based on theoretical principles and ethical papers on CAMs. Ethical sub-questions addressed in this section are outlined in ***Table 13***.

12.3 Evidence Tables

Two studies evaluating ethical issues associated with osteoarthrosis were included (***Table 70***).[143] [144] Both studies conducted interviews or surveys of osteoarthritis patients to ascertain how the disease affects quality of life. The number of participants varied substantially (n = 10—380) with only one study reporting how participants were identified and recruited.[144]

Table 67 Characteristics of included studies for ethical issues

Author, year; country	Indication; Sample size	Design; Setting	Key outcomes
Kabel 2014[143] USA	Knee osteoarthritis patients n = 10	Interview and survey NR	Impact of osteoarthritis on pain and embarrassment
Castro 2016[144] Puerto Rico	Osteoarthritis patients n = 380	Survey Primary care clinics	Relationship between osteoarthritis and quality of life

Abbreviations
n = number of patients, **NR** = not reported.

12.4 Results

F0010 What are the perceived benefits and harms for patients when implementing or not implementing the technology?

Non-maleficence: a norm of avoiding the causation of harm

Minimising the potential for, and amount of, harm to patients is a key ethical concern when considering an intervention. Harm is multifaceted and includes physical and psychological domains.

In terms of physical harm, CS had an unclear safety profile relative to placebo and NSAIDs owing to the limited sample size in the included studies. Side effects reported in patients treated with CS were typically mild, with severe adverse events and withdrawals due to adverse events reported in approximately 5% of patients treated with CS. It is acknowledged that product information listed on Swissmedic for comparator interventions does include adverse events not captured in the included RCTs (e.g. gastrointestinal/renal/cardiovascular events associated with NSAIDs[145], renal/hepatic events associated with paracetamol[146] etc.); however, no equivalent data for CS evaluating long-term safety exists beyond the RCT evidence. Therefore, it is unclear if consuming CS is likely to cause additional physical harm to the individual, but CS is less likely to alleviate pain attributable to osteoarthritis when compared to NSAIDs for periods greater than six months. Thus, using CS instead of a more efficacious treatment may prolong osteoarthritis-related pain.

Any medication may cause psychological distress if an individual's expectations regarding pain relief are not met. Alternatively, if the individual believes CS improves their condition then removing the reimbursement may impede access to the drug, which may result in psychological distress if the desired medication cannot be obtained. This harm is minimised as CS will remain available as an over-the-counter medication if it is disinvested.

Beneficence: a group of norms for providing benefits and balancing benefits against risks and costs

The ageing population, increasing prevalence of chronic diseases, and ineffective practices place economic strain on the healthcare system. This is particularly problematic in Switzerland, which has among the highest healthcare expenditure per capita in Europe.[147] Further, osteoarthritis has a considerable economic burden, with approximately one third of expenditure attributable to medication.[148] To reduce costs and maximise outcomes, disinvestment of low-value healthcare should be considered.[147] If CS is not efficacious, and healthcare costs could be reduced or re-allocated towards a high-value procedure/medicine, disinvestment from a societal perspective is beneficial.

However, without government intervention to regulate and negotiate the cost of CS on behalf of the consumer, the manufacturer is free to set the market price. Thus, an individual may end up paying more for the product than if it were reimbursed by the government. This may place additional economic hardship on patients, combined with the fact that chronic conditions like osteoarthritis impair the economic welfare of individuals with the condition, and healthcare costs are high.[144] Individuals with osteoarthritis already have high health care costs and potentially reduced income owing to the nature of the disease.[144]

F0004 Will the withdrawal of the technology affect the patient´s capability and possibility to exercise autonomy?

The transition from medical paternalism to shared decision-making has notable implications for the utilisation of health services.[149] Increasing emphasis is placed on patient preferences for disease management, and consequently this is a necessary consideration when evaluating in respect of autonomy.[149] This gains further importance owing to the chronic nature of, and limited treatment options for, osteoarthritis, which is a debilitating disease often resulting in a loss of independence. Individuals are unable to perform daily tasks, engage in meaningful activities and are often isolated.[143] [144] Independence and personal autonomy enables individuals to feel useful in society and improves quality of life in individuals with osteoarthritis.[144] As autonomy is reduced in other aspects of life, additional consideration should be given to an individual's opinion and autonomy in health-related decision-making. If CS is currently part of the management plan, and because of disinvestment a patient can no longer afford the drug, autonomy in terms of treatment management is reduced. This affects patients' ability to manage the disease in accordance with their wishes. However, as noted, any potential harm is minimised as CS will remain available as an over-the-counter medication (albeit for an out-of-pocket cost). As such, the potential consequences to human autonomy from disinvesting CS are limited.

F0008 Will the withdrawal of the technology affect human dignity?

No ethical issues were identified in the literature or through critically applying the principlist framework to the current policy decision. The withdrawal of CS reimbursement is not expected to affect human dignity. It is not expected to impact stigma surrounding osteoarthritis, disease labelling or work capability.

F0014 Will the withdrawal of the technology affect the realisation of basic human rights?

The withdrawal of CS reimbursement is not expected to affect the realisation of basic human rights. One aspect of human rights that could be perceived to be impacted is justice, which concerns equality and equitable aspects of principlism. In terms of equal access to treatment, disinvesting in CS may limit access for those with financial hardship, which individuals with chronic diseases are more likely to experience.[148] Patients will still have access to CS if they can afford to pay for it out-of-pocket. Patients unable to pay will have access to other osteoarthritis medications reimbursed by the government, such as paracetamol, NSAIDs and other anti-inflammatory drugs. Given that NSAIDs are associated with long-term adverse events (not captured by the evidence base) the utilisation of these drugs may potentially increase long-term harm.[150]

13. Organisational Issues

13.1 Summary Statement on Organisational Issues

The included studies did not identify a significant difference in concomitant paracetamol or NSAID use, or adverse events, between patients taking CS, placebo, paracetamol or NSAIDs, however, the lack of difference in adverse events may reflect the limited follow-up duration of the included trials. If CS is disinvested, patient advocates estimate that 50% of patients currently taking CS will cease taking it either with or without substitute therapy. (Substitutions with analgesics and NSAIDs come with the additional adverse events beyond 24 months.) The number of patients likely to substitute CS for other medications is unknown.

13.2 Methods

Organisational sub-questions addressed in this section are outlined in ***Table 14***. There are few organisational issues involved in the potential disinvestment of CS. The main issue that may arise relates to the need for other substitute technologies. If CS is disinvested, patients will either continue to pay for CS out-of-pocket, substitute CS with another medication, or stop CS medication without a substitute. Patients who substitute CS for more invasive medications may lead to organisational impacts through the treatment of adverse events. The likelihood of this happening was addressed via a systematic literature review (method described in ***Section 7***, results in ***Section 8***), and targeted patient and physician input from organisations representing patients with osteoarthritis and physicians treating osteoarthritis (method described in ***Section 7***, questions presented in ***Appendix G***). The results are described narratively.

13.3 Results

D0023 How does the technology modify the need for other technologies and use of resources?

Literature Review

Question D005 in ***Section 8.5*** and ***Section 8.6*** investigated concomitant medication usage in patients taking CS compared to placebo, paracetamol and NSAIDs. Overall, the reported meta-analysis did not report a significant difference in the need for concomitant paracetamol or NSAID use compared to placebo or NSAIDs. This finding suggests that there may be adverse event rates associated with

concomitant medication usage in CS patients, but these are no worse than for patients taking paracetamol or NSAIDs. Therefore, there is no relative organisational impact of CS use on adverse event rates associated with concomitant medication usage.

Patient and physician feedback provided during the scoping phase of this project indicated that CS is associated with lower adverse event rates than comparator interventions. The analyses presented in ***Section 8.6*** did not identify a significant difference in adverse event rates between the CS, NSAIDs or paracetamol, although long-term NSAID usage is known to be associated with gastrointestinal adverse events, which may not be captured in the trials due to the length of follow-up not exceeding 24 months.[3]

Patient and Physician Feedback

There was no data identified in the literature to inform which patients are likely to substitute CS. Therefore, Swiss patient and physician organisations were contacted to try and address this issue. Data supplied by the organisations provides limited information to inform this research question:

i. Patient advocates estimated that approximately 50% of patients currently prescribed CS are likely to pay for it out of pocket if it is disinvested. It was suggested that patients may replace CS with non-prescription medications and therapies such as knee wraps, ointments or green-lipped mussel extract. However, details about which therapeutic products would be used were not provided in sufficient detail to answer this question.
ii. Physician organisations provided estimates for the number of medications prescribed for osteoarthritis, but did not indicate whether patients are likely to substitute CS if it is disinvested.

Based on the literature review and patient and physician feedback, it is unclear whether patients that discontinue CS due to disinvestment (estimated 50% of CS patients) will substitute CS for another medication. The estimates for the number of people that will pay for CS out of pocket were provided by only one patient advocate, and as such is subject to a high degree of uncertainty.

14. Additional Issues

Eight clinical practice guidelines or recommendations were identified from the literature. There is no clear consensus regarding the clinical usefulness of CS. Organisations from Australia, USA and the UK do not recommend the use of CS, whereas European and Pan-American bodies either recommend its use or are uncertain about its benefits. A high-level summary of the organisation position is presented in ***Table 68***.

Table 68 Summary of clinical guidelines and recommendations regarding chondroitin sulfate

Organisation	Area affected	Recommendation	Strength of recommendation
Recommend use			
ESCEO 2019[26]	Knee	Recommend the use of CS	Strong
PANLAR 2016[39]	Hand	Recommend the use of CS	Evidence from RCTs or meta-analyses
EULAR 2018[27]	Hand	CS may be used in patients for pain relief and improvement in functioning	A, 7.3/10
EULAR 2003[8]	Knee	Recommend its use	A
Do not recommend use			
AAOS 2013[1]	Knee	Do not recommend the use of CS	Strong
ACR 2012[2]	Knee	Do not recommend the use of CS	Conditionally recommend
NICE 2014[4]	NR	Do not recommend the use of CS	NR
RACGP 2018[5]	Knee and hip	Do not recommend the use of CS	Conditional against recommendation
NCCC-CC 2008[3]	NR	Do not recommend the use of CS	NR
Unclear recommendation			
EULAR 2005[37]	Hip	No recommendation provided for hip osteoarthritis	NR
OsteoArthritis Research International 2014[41]	Knee	Unclear whether CS provides pain relief. Do not recommend CS as a disease modifying agent in knee osteoarthritis	NR Quality of evidence: good
PANLAR 2016[39]	Knee	Beneficial effect on symptoms	Evidence from RCTs or meta-analyses

Abbreviations

A = category 1 evidence (meta-analysis or at least one RCT), **AAOS** = American Academy of Orthopaedic Surgeons, **ACR** = American College of Rheumatology, **CS** = chondroitin sulfate, **ESCEO** = European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Disease, **EULAR** = European League Against Rheumatism, **NCCC-CC** = National Collaborating Centre for Chronic Conditions. **NICE** = National Institute for Health and Care Excellence, **NR** = not reported, **PANLAR** = Panamerican League of Associations for Rheumatology, **RACGP** = The Royal Australian College of General Practitioners.

15. Discussion

The objective of this HTA is to assess the clinical and economic effectiveness of CS, and consider legal, ethical, social and organisational issues relating to its delisting/defunding. To address the clinical and economic impact of CS a systematic search of the literature is presented. The clinical evaluation includes 26 RCTs that varied substantially in size, follow-up duration, risk of bias and outcomes reported. The knee was the most commonly studied indication, with relatively few studies on the hand and hip. The quality of the evidence for different outcomes ranges from moderate to very low.

Findings of the Clinical Evaluation

The relative safety of CS compared to placebo, paracetamol and NSAIDs is uncertain due to the low number of reported events in the included RCTs. Reported adverse events associated with CS use are generally mild; however, most studies do not provide detailed assessments of adverse events, and the results are likely underpowered to detect differences between groups. Further, the limited follow-up may miss adverse events associated with chronic NSAID use, namely peptic ulcers, renal failure and myocardial infarction.[150] One study excluded patients with existing gastrointestinal disorders,[85] which may additionally contribute to the lack of adverse events noted among trials utilising NSAIDs. Thus, the included studies do not represent the long-term, real-world comparative safety of CS. No additional evidence for the safety of CS—of any study design—was identified. As a consequence, it was not appropriate to conduct an expanded analysis of safety for the comparator interventions, as there is no available data from CS to compare against. Therefore, known side effects of comparator interventions (e.g. gastrointestinal/cardiac events related to NSAID use) are not reflected in this report as they were not captured in the included RCTs.

For efficacy outcomes, CS and placebo groups statistically differ for the critical outcomes of pain, Lequesne index and OMERAT-OARSI responder rate at six months. However, it is unclear whether the statistical differences translate to clinically meaningful differences. The effect sizes for most pain outcomes are small, as inferred by Cohen's effect thresholds for interpreting SMDs.[68] Pain outcomes at later time points, 'functional' and quality of life outcomes generally do not differ between CS and placebo groups. In addition, there is no statistical difference between NSAIDs and CS groups for any outcome.

Sub-group analyses show that studies utilising IBSA-manufactured CS exhibit statistically significant differences between groups for pain, Lequesne index and any adverse events. The effect size in the sub-group is greater than the effect size in the overall analysis.

Sensitivity analysis of studies that have unclear randomisation, allocation concealment and blinding of outcome assessors or participants have statistically significant differences between CS and placebo

groups for pain and Lequesne index outcomes at six months. The effect size in the sensitivity groups was similar to the overall effect. However, it is worth noting that studies were often unclear in multiple risk of bias domains, and therefore the statistical differences may be due to systematic under-reporting of methodology across studies, rather than specific risk of biases.

Comparison to Previous Literature

The results of the current meta-analysis generally align with recently published articles.[30 151 152] However, the effect sizes for pain and the Lequesne index were larger in Singh[30] and Honvo[151]. The difference in magnitude may relate to differences in the included studies, use of herbal medicines as a comparator intervention, stratification of follow-up duration, and combining the results from the hand and knee. Of importance are the differences in included studies. For example, both Honvo[151] and Singh[30] included studies with shorter trial duration (3 months), and Singh included Russian language studies and studies with active comparators (diclofenac).[30] Further, the present study included three large trials published after the completion of Singh[30] (Reginster[94], Pelletier[85], Fransen[28]). Similar to previously published meta-analyses, there was considerable heterogeneity and inconsistency among several outcomes (pain and function). Honvo[151] noted that larger studies and performing intention-to-treat analysis produced the lowest heterogeneity. By contrast, Singh reported that differences in risk of bias or sample size may not adequately explain the heterogeneity in the published trials.

Regarding the sub-group analysis, Honvo[151] determined that IBSA CS exhibited a greater reduction in pain and the Lequesne index compared to CS from other manufacturers. This difference was partly credited to potential differences in CS quality (pharmacological compared to non-pharmacological) and thus therapeutic activity.[35]

Quality and Applicability of the Clinical Evidence

The quality of the reported outcomes was generally low or very low as determined by GRADE. Common causes of downgrading related to inconsistency and imprecision of outcomes. For example, studies often have moderate/large variance and heterogeneity, inconsistent direction of effects and small number of patients/events. Analyses that included studies by Bucsi[74], Uebelhart[59] and Michel[82] were at the greatest risk of inconsistency and imprecision owing to the large effect sizes reported in these trials. Risk of bias parameters could adequately explain the heterogeneity attributable to these outcomes, owing to under-reporting of their methods—a finding echoed by Singh.[30] However, the larger effect size in Michel[82] may be attributed to the use of “per cent change from baseline” to measure pain score, which may inflate or depress the measure. Aside from joint space width, most outcomes did not have serious concerns with indirectness. Publication bias was suspected for several outcomes including

quality of life, function, paracetamol intake and walk test as baseline, and no follow-up data was reported. No unpublished studies or unpublished results from published studies were identified. In total, 16 out of 26 studies declared conflicts of interest relating to manufacturers of CS. IBSA (k = 9) was the most commonly reported sponsor followed by Bioiberica (k = 4) and Pierre Fabre (k = 3).

Most studies evaluated CS in the context of knee osteoarthritis, with limited studies evaluating the hip or hands. The EMA cautions against extrapolating the findings of interventions targeting the knee and/or hip osteoarthritis to the hand,[20] since compounds having demonstrated efficacy in the knee and hip may not be an efficacious treatment for hand osteoarthritis owing to pathophysiological and functional differences between the joints. However, the EMA suggests that extrapolating findings from knee to hip is appropriate owing to perceived similarities between the two joints (weight bearing).[20]

The efficacy and safety in hand osteoarthritis was informed by one[77] and two studies, respectively.[77 91] Like for the knee, CS was well tolerated among patients with limited adverse events. CS improved self- or doctor-reported pain and functional outcomes such as VAS or duration of morning stiffness, however physical outcomes such as grip strength or paracetamol intake did not differ between CS and placebo groups. Owing to the limited number of trials the conclusions and results from the trials are uncertain. Additional trials are required.

The methodological concerns and lack of evidence for the hand and hip are unlikely to be addressed in the near future. A search of clinical trial databases did not reveal any ongoing trials evaluating the safety, efficacy or effectiveness of CS for osteoarthritis. The only ongoing trial utilising CS (in combination with glucosamine) for knee osteoarthritis, has passed its estimated completion date (March 2019).[153]

There was no statistical difference in measures of joint space width or cartilage volume when CS was compared to placebo at 24 months. Changes in joint space width are considered a primary outcome by FDA[154] and EMA[20] when assessing the efficacy and effectiveness of disease-modifying osteoarthritis drugs. The change in joint space width is an indirect marker of cartilage volume.[155] However, a decrease in joint space width may reflect additional degenerative changes to other surrounding structures.[67] Further, there is conjecture regarding its clinical utility with studies demonstrating a weak correlation,[156] or lack thereof, to functional outcomes.[157] This may be attributable to the multifactorial nature of joint pain, which is unlikely solely attributable to differences in joint space width.[156] Consequently, its utility to measure the efficacy of disease-modifying drugs such as CS is unclear.

Limitations of the Economic Analysis

This health economic analysis has some limitations. The costs of each intervention are limited to medicines and a general doctor visit for annual prescription of medicines. This limitation was also noted in the NC-CC[3] study, where other costs: "such as adverse event costs, or decreased use of other medical resources because of increased well-being are not included" (p. 333). The placebo arm for Kahan[69] involved daily administration of a placebo sachet, which is assumed to incur no cost in the economic model. In practice, placebo is likely to incur some costs. This bias favours the comparator. When reviewing the Michel[82] and Clegg[75] studies, the NCC-CC[3] review noted that no adverse event costs were assumed and papers suggesting cuts in other medication use were not found.

Patients entering key trials were included with osteoarthritis knee scores of 1—3 on the Kellgren & Lawrence scale. Swissmedic advises CS is indicated for the treatment of osteoarthritis, without requiring a Kellgren & Lawrence scale score of 1—3 prior to use. Thus, patients with less severe osteoarthritis may be using CS. The direction of this bias is not clear. However, differences in total WOMAC appear to be less pronounced in patients having no or mild symptoms (e.g. Bruyere[106]).

The clinical evidence base is limited, as trials do not consistently report WOMAC outcomes and a maximum follow-up of two years is identified. The conclusion of the clinical effectiveness is that CS has significant pain reduction benefits over placebo at six months, however, no significant differences were found for total WOMAC. CS was non-significantly inferior (except at three months, which was not reported in the clinical effectiveness review) to COX-2 total WOMAC score.

Utility gains are included in a PSA as most likely, low and high values. High and low utility values are specified in triangular distributions by assuming they are three standard deviations from the average utility values. Pelletier[85] presented standard deviation for changes in total WOMAC scores from baseline, which is used to generate high and low total WOMAC scores for the CS versus COX-2 analysis (subsequently transformed to utility using the Barton[107] model). Standard deviations are not reported for total WOMAC at each period of follow-up, which creates uncertainty around distribution assumptions. The PSA health economic analyses however, show a wide range in ICER results either side of willingness-to-pay thresholds. These results reflect the relatively small short-term clinical benefits of CS over placebo and COX-2 over CS.

Two studies in the clinical evidence review were identified that provided evidence on gastrointestinal-related severe adverse events[75 85], and both were included in the meta-analysis. Overall, there was no statistically significant difference between the CS and NSAIDs groups (RR 0.93, 95% CI 0.60, 1.45, p = 0.75). The adverse event rates in Pelletier[85] and Kahan[69] were found to be similar for both arms, so no costs are included for adverse events. In the longer-term, adverse rates could be higher for NSAIDs,

which favours the comparator. No differences were found in the rates of joint narrowing in the short term. Correspondingly, the delisting of CS is not considered to lead to more arthroplasty.

Legal, Ethical, Social and Organisational Considerations

Minor legal, ethical, social and organisational issues were identified if CS were to be removed from the Spezialitätenliste. Key concerns relate to patients' ability to afford the drug if it is no longer reimbursed and to manage the disease in accordance with their wishes. This concern was echoed in the feedback from Swiss patient and physician organisations. These groups further claimed that CS relieves pain and leads to a higher quality of life—a finding not readily shown by the meta-analyses of efficacy and effectiveness.

16. Conclusion

The clinical findings of this report are extracted from a substantial body of evidence of low to moderate quality. Minor gastrointestinal-related adverse events are the most frequently reported CS safety concern in the available studies. However, the relative safety of CS compared to placebo, paracetamol and NSAIDs is uncertain, due to the low number of reported events in the included RCTs. No studies could be identified that report the safety of CS beyond the included RCTs.

CS reports significant improvements in pain, the Lequesne index and OMERACT-OARSI responder rate at six months compared to placebo, however, the significant difference did not persist beyond six months and the clinical relevance of the result is unclear. There was no difference in minimum joint space width between CS and placebo at 24 months. Quality of life, function and progression to joint replacement were infrequently reported. There was no significant difference between CS and NSAIDs for any effectiveness outcome. The quality of reported outcomes, as determined by GRADE, ranged from moderate to very low. Further, the limited long-term follow-up is unlikely to capture risk and cost of long-term adverse events associated with NSAIDs.

CS was found to be relatively cost-effective compared to placebo. Compared to COX-2, CS was estimated to be less effective with lower costs. Differences in the estimated utility for CS and COX-2 are derived from a single study, affecting the certainty of these results. The impact that delisting CS will have on the overall healthcare budget will depend on the number of patients that change to alternative medications reimbursed through mandatory health insurance. Assuming 50% of patients substitute CS for another reimbursed medication (e.g. paracetamol, ns-NSAIDs plus PPIs, COX-2 selective NSAIDs plus PPIs), the delisting of CS would result in an overall reduction in medicine costs for health insurance providers of CHF 2.4 million per year. Lower rates of substitution would result in additional cost savings (25% substitution = CHF 18.2 million savings pear year), and higher rates of substitution would result in higher overall costs (75% substitution = CHF 13.3 million additional costs per year).

No major social, legal, ethical or organisational issues relating to CS were identified from the literature. Should CS be de-listed, it will still be available to patients wishing to pay (estimated annual out-of-pocket costs range CHF 322—381). Patients unable or unwilling to pay out of pocket will have access to alternative medications reimbursed through mandatory health insurance (e.g. paracetamol, ibuprofen, COX-2).

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177. Mease PJ, Woolley JM, Bitman B, et al. Minimally important difference of Health Assessment Questionnaire in psoriatic arthritis: relating thresholds of improvement in functional ability to patient-rated importance and satisfaction. *J Rheumatol* 2011;38(11):2461-5.

18. Appendices

18.1 Appendix A: Sources of Literature (databases and websites)

Table 69 Databases searched and number of search results

Source	Location	Initial search	Updated search
PubMed	https://www.ncbi.nlm.nih.gov	1,097	27
Embase	https://www.embase.com/	889	167
The Cochrane Library (inc. CENTRAL)	https://www.cochranelibrary.com/	235	68
CINAHL	https://www.ebscohost.com/nursing/products/cinahl-databases/cinahl-complete	659	4
York CRD (inc. HTA, NHS EED, DARE)	https://www.crd.york.ac.uk/CRDWeb/	25	0
CEA Registry	http://healtheconomics.tuftsmedicalcenter.org/cear4/home.aspx	1	0
Econlit	https://www.aeaweb.org/econlit/	7	0
ETHMED	http://www.ethicsweb.eu/search_ets	3	0
Total		**2,916**	**266**

Notes
Initial searches ran from inception to 28 September 2018; updated searches ran from 28 September 2018—23 April 2019.

Table 70 Sources of literature for targeted, non-systematic searches (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 (CAHSPR)	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
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
Legal	
European Medicines Agency	https://www.ema.europa.eu/

Search strategy, PubMed

Osteoarthritis[Text Word]

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

18.2 Appendix B: List of Excluded Studies

Studies Excluded at Full-Text Review

Wrong Study Design

1. Barnhill JG, Fye CL, Williams DW, Chondroitin product selection for the glucosamine/chondroitin arthritis intervention trial. *J Am Pharm Assoc* (2003) 2006;46(1):14-24.
2. Morita M, Efficacy of Chondroitin Sulfate for Painful Knee Osteoarthritis: A One-Year, Randomized, Double-Blind, Multicenter Clinical Study in Japan. *Biol Pharm Bull*. 2018;41(2): 163-171.
3. Fardellone P, Comparative efficacy and safety study of two chondroitin sulfate preparations from different origin (avian and bovine) in symptomatic osteoarthritis of the knee. *Open Rheumatol*. 2013;7:1-12.
4. 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.
5. Morreale P, Manopulo R, Galati M, et al. Comparison of the antiinflammatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis. *J Rheumatol* 1996;23(8):1385-91.

Wrong Intervention

6. Alekseeva LI, Benevolenskaia LI, Nasonov EL, [Structum® (chondroitin sulfate)--a new agent for the treatment of osteoarthrosis]. *Ter Arkh* 1999;71(5):51-3.
7. Kubovy P, Mensikova L, Kurkova E, Influence of SYSADOA group chemicals on progression of human knee joint osteoarthritis: new objective evaluation method—measuring of rheological properties in vivo. *Neuro Endocrinol Lett* 2012;33(6):651-9.
8. L D, ache IEL, Izaguirre LB, The proposal to drop coverage for diacerein: Economic impact in the Basque Country (Spain). *Gaceta Medica de Bilbao* 2013;110(3):70-73.
9. Yang S, Dube CE, Eaton CB, Longitudinal use of complementary and alternative medicine among older adults with radiographic knee osteoarthritis. *Clin Ther* 2013;35(11):1690-702.

Wrong Outcomes

10. Alekseeva LI, Mednikov BL, Piiavskii SA, [Pharmacoeconomic aspects of use of structum® in osteoarthrosis]. *Ter Arkh* 2001;73(11):90-2.

11. Conrozier T. [Chondroitin sulfates (CS 4&6): practical applications and economic impact]. *Presse Med* 1998;27(36):1866-8.

12. Moller I, Gharbi M, Martinez Serrano H, Effect of chondroitin sulfate on soluble biomarkers of osteoarthritis: a method to analyze and interpret the results from an open-label trial in unilateral knee osteoarthritis patients. *BMC Musculoskelet Disord* 2016;17(1):416.

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14. Rubio-Terres C, Grupo del estudio V. [An economic evaluation of chondroitin sulfate and non-steroidal anti-inflammatory drugs for the treatment of osteoarthritis. Data from the VECTRA study]. *Reumatol Clin* 2010;6(4):187-95.

15. Rubio-Terres C, Rubio-Rodriguez D. Economic Evaluation of Chondroitin Sulfate and Non-Steroidal Antiinflammatory Drugs for The Treatment of Osteoarthritis. *Value Health* 2015;18(7):A640

16. Rubio-Terrés C, Rubio-Rodríguez D, Möller I. Estimation of the health and economic impact of chondroitin sulfate prescription in the treatment of knee and hand osteoarthritis compared to non-steroidal anti-inflammatory drugs in Catalonia. Pharmacoeconomics—*Spanish Research Articles* 2017;14(1):19-25.

Wrong Population

17. Brasky TM, Lampe JW, Slatore CG, 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

18. Clynes M, Wong W, Dennison E. How common is complementary and alternative medicine use in rheumatology? *Rheumatology (United Kingdom)* 2015;54:i183.

19. Demehri S, Hafezi Nejad N, Roemer F, 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.

20. Dreiser RL, Guillaume M. Quality of life (QOL) and lower limbs osteoarthritis (OA): A European rheumatologists study. *Annals of the Rheumatic Disease* 2013;71

21. EU Clinical Trials Register Efficacy and safety assessment of 6 months (24 weeks) treatment with Structum® 500 mg capsule bid in hip osteoarthritis: multicenter randomised double blind parallel group and placebo controlled study. Retrieved from: Http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2005-000508-15-cz pub type

22. EU Clinical Trials Register. A multicentre, comparative, randomised, double-blind clinical trial on the equivalence of the efficacy and the safety of CHONDROSULFATE 1,200 mg, oral gel in sachet, once daily, versus CHONDROSULFATE 400 mg, capsules, 3 capsules per day, and a placebo in the treatment of knee osteoarthritis. 2006: Retrieved from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01822673/full

23. EU Clinical Trials Register. Efficacy and tolerability of chondroitin sulphate 1,000mg, twice daily in patients with symptomatic knee osteoarthritis. 2009: Retrieved from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01843642/full

24. Fardellone P, Zaim M, Maheu E, Efficacy and safety of 2 proprietary based Chondroitin Sulfate medicinal products: Structum® 1000mg (500 mg BID) and Chondrosulf® 1200mg (400 mg TID) in 837 patients with symptomatic knee osteoarthritis (KOA). *Osteoarthritis and Cartilage* 2010;18:S144-S45.

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29. Gregori D, Giacovelli G, Minto C, Barbetta B, Gualtieri F, Azzolina D, Vaghi P, Rovati L. Association of Pharmacological Treatments with Long-term Pain Control in Patients with Knee Osteoarthritis: A Systematic Review and Meta-analysis. *JAMA* 2018:320(24); 2564-2579.

30. Gross D. Oral chondrosulfate treatment of arthroses. *Zeitschrift fur Rheumatologie* 1982;41(4):No.130.

31. Honvo G, Bruyere O, Geerinck A, Reginster J Symptomatic efficacy of oral chondroltin sulfate in knee osteoarthritls. A systematic review and meta-analysls of randomized, placebo-controlled trials. *Osteoarthritis and Cartliage* 2019;27(0):s498-499.

32. Honvo G, Bruyere O, Geerinck A, Veronese N, Reginster J. Efficacy of Chondroitin Sulfate in Patients with Knee Osteoarthritis: A Comprehensive Meta-Analysis Exploring Inconsistencies in Randomized, Placebo-Controlled Trials. *Advances in therapy* 2019;16(10):019-00921.

33. Honvo G, Reginster J, Geerinck A, Bruyere O. Safety of oral chondroitin sulfate in the management of knee osteoarthritis: results of a new meta-analysis of randomized, placebo-controlled trials. *Osteoarthritis and Cartilage* 2019;27(0):s499.

34. ISRCTN. Efficacy and safety of two Chondroitin Sulfate preparations in patients with symptomatic osteoarthritis of the knee. 2011 Retrieved from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01823192/full

35. ISRCTN. Chondroitin sulphate for hand osteoarthritis: a randomised, placebo-controlled trial in primary care. 2016 Retrieved from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01816409/full

36. Japan Primary Registries Network. A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Comparison Study on Effect of Daily Low Molecular Chondroitin Sulfate Origosaccharides Ingestion for Improvements in Knee Joint Function. 2016 Retrieved from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01828030/full

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47. Pavelka K, Coste P, Géher P, Erratum: Efficacy and safety of piascledine 300 versus chondroitin sulfate in a 6 months treatment plus 2 months observation in patients with osteoarthritis of the knee (Clinical Rheumatology DOI: 10.1007/s10067-010-1384-8). *Clinical Rheumatology* 2010;29(7):821.

48. Pelletier J, Raynauld J, Beaulieu A, In a two-year double-blind randomized controlled multicenter study, chondroitin sulfate was significantly superior to celecoxib at reducing cartilage loss with similar efficacy at reducing disease symptoms in knee osteoarthritis patients. *Osteoarthritis and Cartilage* 2016;24:S189-S90.

49. Pelletier JP, Beaulieu A, Bessette L, Twenty-four-month clinical trial on the effects of chondroitin sulfate on structural changes in knee osteoarthritis patients as assessed by MRI. *Basic and Clinical Pharmacology and Toxicology* 2011;109:48-49.

50. Pelletier JP, Beaulieu AD, Bessette L, Clinical trial of 24 months on the effects of chondroitin sulfate on structural changes in knee osteoarthritis patients as assessed by MRI. *Basic and Clinical Pharmacology and Toxicology* 2013;113:17.

51. Pelletier JP, Raynauld JP, Beaulieu A, In a 2-year double-blind randomized controlled multicenter study, chondroitin sulfate was significantly superior to celecoxib at reducing cartilage loss with similar efficacy at reducing disease symptoms in knee osteoarthritis patients. *Basic and Clinical Pharmacology and Toxicology* 2015;117:4.

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56. Reginster J, Tajana E. Single oral dose of (1200 MG) sachet of chondroitin 4&6 sulfate (CS4&6-chondrosulf®) relieves pain and improves function. Results of a double blind study, versus placebo and an active treatment in knee OA patients. *Osteoarthritis and Cartilage* 2011;19:S226-S27.

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64. Taieb C, Pibourdin JM. Economy of NSAIDs in the management of osteoarthritis: Sodium chondroitin sulfate vs. control group. *Value in Health* 2010;13(7):A316.

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66. Verbruggen G, Goemaere S, Veys EM. Chondroitin sulfate: S/DMOAD (structure/disease modifying anti-osteoarthritis drug) in the treatment of finger joint OA. *Osteoarthritis Cartilage* 1998;6 Suppl A:37-8.

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68. Zagaria MAE. Osteoarthritis of the Hand: Focus on Individualized Multimodal Therapy. *US Pharmacist* 2011;36(10):22-26.

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Non-English language

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18.3 Appendix C: Sub-Group and Sensitivity Analysis Results and Funnel Plots

Table 71 Studies reporting both VAS and WOMAC scores and the effect on the meta-analysis (knee)

Author year	VAS Chondroitin	VAS Placebo/NSAID	WOMAC Chondroitin sulfate	WOMAC Placebo/NSAID	Effect of omitted measure on meta-analysis
Kahan 2009[69]	12m -22.8 ± 25.7	12m -21.2 ± 20.1	12m -11.6 ± 22.7	12m -9.0 ± 20	-0.19 [-0.37, 0.00] p = 0.05, SC
Wildi 2011[92]	6m 14.8 ± 23.7 12m -21.0 ± 27.1	6m -20.3 ± 22.1 12m -24.7 ± 25.0	6m -79.7 ± 105.6 12m -99.2 ± 96.7	6m -94.4 ± 96.9 12m -124.4 ± 85.3	-0.29 [-0.49, -0.08] p = 0.005, NC -0.17 [-0.37, 0.03] p = 0.10, NC
Fransen 2015[28]	12m 4.0 ± 2.6	12m 4.1 ± 2.5	12m 4.8 ± 3.9	12m 4.7 ± 3.8	-0.17 [-0.36, 0.03] p = 0.10, NC
Pelletier 2016[85]	6m -22.5 ± 6.2 12m -27.4 ± 7.6 24m -24.4 ± 6.3	6m -26.9 ± 5.3 12m -28.2 ± 5.0 24m -26.1 ± 5.8	6m -9.1 ± 2.6 12m -10.6 ± 3.1 24m -8.8 ± 2.7	6m -11.0 ± 2.6 12m -11.2 ± 2.8 24m -11.1 ± 2.8	-0.27 [-1.01, 0.46] p = 0.47, NC 0.14 [-0.08, 0.37] p = 0.21, NC 0.14 [-0.08, 0.36] p = 0.20, NC

Abbreviations
m = month, **ND** = no difference, **NC** = no change in overall conclusion, **NR** = not reported, **SC** = significant change from p = 0.07 to p = 0.05, **VAS** = visual analogue scale, **WOMAC** = Western Ontario and McMaster Osteoarthritis.

Table 72 Chondroitin sulfate compared to placebo: mean joint space width at 24 months (knee)

Author year	Chondroitin sulfate mean ± SD	Placebo mean ± SD	p-value
Michel 2005	0.00 ± 0.53 mm	-0.14 ± 0.61 mm	0.04

Sub-Group and Sensitivity Analysis

Efficacy

Table 73 Chondroitin sulfate vs placebo: Sub-group and sensitivity analyses of pain at six months (knee)

Pain 6 months	Number of studies	Heterogeneity	Chondroitin sulfate number of participants	Placebo number of participants	Standard mean difference (95% CI)
Overall					
	9 [9 59 69 74 75 80 86 90 92]	Chi² = 31.85 p < 0.0001 I² = 75%	1,112	1,133	-0.28 (-0.47, -0.09) Z = 2.91 p = 0.004
Sub-group analyses					
Measure of pain					
WOMAC	1 [75]	NA	318	313	-0.01 (-0.15, 0.16) Z = 0.08 p = 0.94
VAS	8 [59 69 75 80 86 90 92 94]	Chi² = 20.80 p = 0.002 I² = 71%	794	820	-0.36 (-0.62, -0.09) Z = 2.67 p = 0.008
Inclusion criteria minimum pain score					
⩾ 40mm or % of total score	3 [80 104 158]	Chi² = 5.19 p = 0.07 I² = 61%	348	360	-0.18 (-0.45, 0.08) Z = 1.39 p = 0.16
⩽ 40mm or % of total score	2 [69 86]	Chi² = 0.73 p = 0.39 I² = 0%	330	335	-0.26 (-0.41, -0.10) Z = 3.30 p = 0.001
Not specified or below and above 40mm	4 [59 74 75 90]	Chi² = 25.00, p < 0.0001 I² = 88%	434	438	-0.53 (-1.05, -0.01) Z = 1.99 p = 0.05
Manufacturer					
Bioberica	2 [75 104]	Chi² = 0.81 p = 0.36 I² = 0%	353	347	-0.03 (-0.12, 0.18) Z = 0.38 p = 0.70
IBSA	5 [59 69 74 90 94]	Chi² = 13.11 p = 0.01 I² = 69%	585	610	-0.49 (-0.74, -0.24) Z = 3.87 p = 0.0001
Pierre Fabre	2 [80 86]	Chi² = 0.40 p = 0.52 I² = 0%	174	176	-0.19 (-0.40, 0.02) Z = 1.74 p = 0.08
TSI Health	0	NA	0	0	NA

Pain 6 months	Number of studies	Heterogeneity	Chondroitin sulfate number of participants	Placebo number of participants	Standard mean difference (95% CI)
Dose					
1,200mg/day	1 [75]	NA	318	313	0.01 (-0.15, 0.16) Z = 0.08 p = 0.94
1,000mg/day	2 [80 86]	Chi² = 0.40 p = 0.52 I² = 0%	174	176	-0.19 (-0.40, 0.02) Z = 1.74 p = 0.08
800mg/day	6 [59 69 74 90 92 94]	Chi² = 19.08 p = 0.002 I² = 74%	620	644	-0.40 (-0.66, -0.15) Z = 3.06 p = 0.002
Sensitivity analyses					
Risk of bias funding declared					
Yes	9 [9 59 69 74 75 80 86 90 92]	Chi² = 31.85 p < 0.0001 I² = 75%	1,112	1,133	-0.28 (-0.47, -0.09) Z = 2.91 p = 0.004
No	0	NA	0	0	NA
Unclear	0	NA	0	0	NA
Risk of bias randomisation					
Yes	4 [75 69 80 86]	Chi² = 6.74 p = 0.08 I² = 56%	801	802	-0.15 (-0.31, 0.02) Z = 1.73 p = 0.08
No	0	NA	0	0	NA
Unclear	5 [59 74 90 92 94]	Chi² = 17.89 p = 0.001 I² = 78%	311	331	-0.46 (-0.83, -0.08) Z = 2.39 p = 0.02
Risk of bias allocation					
Yes	3 [69 75 104]	Chi² = 8.36 p = 0.02 I² = 76%	662	660	-0.07 (-0.32, 0.19) Z = 0.51 p = 0.61
No	0	NA	0	0	NA
Unclear	6 [59 74 80 86 90 94]	Chi² = 15.03 p = 0.01 I² = 67%	662	660	-0.44 (-0.69, -0.18) Z = 3.35 p = 0.0008
Risk of bias blinding of participants					
Yes	2 [69 75]	Chi² = 6.14 p = 0.01 I² = 84%	627	626	-0.13 (-0.41, 0.14) Z = 0.95 p = 0.34
No	0	NA	0	0	NA

Pain 6 months	Number of studies	Heterogeneity	Chondroitin sulfate number of participants	Placebo number of participants	Standard mean difference (95% CI)
Unclear	7 [59 74 80 86 90 92 94]	Chi² = 20.80 p = 0.002 I² = 71%	485	507	-0.36 (-0.62, -0.09) Z = 2.67 p = 0.008
Risk of bias blinding of outcomes					
Yes	5 [69 74 80 90 92]	Chi² = 12.78 p = 0.01 I² = 69%	590	603	-0.28 (-0.52, -0.05) Z = 2.33 p = 0.02
No	3 [75 86 158]	Chi² = 7.46 p = 0.02 I² = 73%	499	507	-0.14 (-0.43, 0.15) Z = 0.95 p = 0.34
Unclear	1 [59]	NA	23	23	-1.13 (-1.76, -0.50) Z = 3.53 p = 0.0004
Intention-to-treat analysis					
Yes	7 [69 74 75 80 86 90 94]	Chi² = 20.17 p = 0.003 I² = 70%	1,054	1,076	-0.27 (-0.44, -0.09) Z = 2.98 p = 0.003
No	2 [59 104]	Chi² = 11.63 p = 0.0007 I² = 91%	58	57	-0.43 (-1.77, 0.91) Z = 0.63 p = 0.53
Unclear	0	NA	0	0	NA

Abbreviations

CI = confidence interval, **mg** = milligram**, mm** = millimetre, **NA** = not applicable, **VAS** = visual analogue scale, **WOMAC** = The Western Ontario and McMaster Universities Osteoarthritis Index.

Table 74 Chondroitin sulfate vs placebo: Sub-group and sensitivity analyses of pain at 12 months (knee)

Pain 12 months	Number of studies	Heterogeneity	Chondroitin sulfate number of participants	Placebo number of participants	Standard mean difference (95% CI)
Overall					
	7 [28 59 69 86 88 90 92]	Chi² = 13.33 p = 0.04 I² = 55%	669	662	-0.18 (-0.37, 0.01) Z = 1.82 p = 0.07
Sub-group analyses					
Measure of 'pain'					
WOMAC	1 [88]	NA	80	78	-0.06 (-0.37, 0.25) Z = 0.37 p = 0.71
VAS	6 [28 59 69 86 90 104]	Chi² = 13.185 p = 0.02 I² = 62%	589	584	-0.21 (-0.44, 0.02) Z = 1.80 p = 0.07
Inclusion criteria minimum pain score					
⩾ 40mm or % of total score	2 [28 92]	Chi² = 0.44 p = 0.51 I² = 0%	183	177	-0.02 (-0.23, 0.19) Z = 0.20 p = 0.85
⩽ 40mm or % of total score	2 [69 86]	Chi² = 0.43 p = 0.51 I² = 0%	331	330	-0.08 (-0.24, 0.07) Z = 1.06 p = 0.29
Not specified or below and above 40mm	3 [59 88 90]	Chi² = 8.58 p = 0.01 I² = 77%	155	155	-0.46 (-0.97, 0.05) Z = 1.77 p = 0.08
Manufacturer					
Bioberica	2 [88 104]	Chi² = 0.411 p = 0.52 I² = 0%	112	104	-0.01 (-0.27, 0.26) Z = 0.05 p = 0.96
IBSA	3 [59 69 90]	Chi² = 11.172 p = 0.004 I² = 82%	384	386	-0.45 (-0.94, 0.05) Z = 1.75 p = 0.08
Pierre Fabre	1 [86]	NA	22	21	-0.28 (-0.88, 0.32) Z = 0.90 p = 0.37
TSI Health	1 [28]	NA	151	151	-0.05 (-0.28, 0.17) Z = 0.44 p = 0.66
Dose					

Pain 12 months	Number of studies	Heterogeneity	Chondroitin sulfate number of participants	Placebo number of participants	Standard mean difference (95% CI)
1,200mg/day	1 [88]	NA	80	78	-0.06 (-0.37, 0.25) Z = 0.37 p = 0.71
1,000mg/day	1 [86]	NA	22	21	-0.28 (-0.88, 0.32) Z = 0.90 p = 0.37
800mg/day	5 [28 59 69 90 104]	Chi² = 11.913 p = 0.008 I² = 75%	535	537	-0.28 (-0.57, 0.01) Z = 1.87 p = 0.06
Sensitivity analyses					
Risk of bias funding declared					
Yes	5 [59 69 86 90 104]	Chi² = 12.604 p = 0.01 I² = 68%	438	433	-0.29 (-0.62, 0.04) Z = 1.73 p = 0.08
No	2 [28 88]	Chi² = 0.001 p = 0.97 I² = 0%	231	229	-0.05 (-0.24, 0.13) Z = 0.58 p = 0.56
Unclear	0	NA	0	0	NA
Risk of bias randomisation					
Yes	2 [69 86]	Chi² = 0.431 p = 0.51 I² = 0%	331	330	-0.08 (-0.24, 0.07) Z = 1.06 p = 0.29
No	1 [88]	Chi² = 12.033 p = 0.007 I² = 75%	258	254	-0.30 (-0.71, 0.11) Z = 1.45 p = 0.15
Unclear	4 [28 59 90 104]	NA	80	78	-0.06 (-0.37, 0.25) Z = 0.37 p = 0.71
Risk of bias allocation					
Yes	3 [28 69 104]	Chi² = 0.572 p = 0.75 I² = 0%	492	486	-0.05 (-0.18, 0.07) Z = 0.80 p = 0.42
No	1 [88]	NA	80	78	-0.06 (-0.37, 0.25) Z = 0.37 p = 0.71
Unclear	3 [59 86 90]	Chi² = 4.092 p = 0.13 I² = 51%	97	98	-0.56 (-1.00, -0.12) Z = 2.50 p = 0.01
Risk of bias blinding of participants					

Pain 12 months	Number of studies	Heterogeneity	Chondroitin sulfate number of participants	Placebo number of participants	Standard mean difference (95% CI)
Yes	2 [28 69]	Chi² = 0.021 p = 0.90 I² = 0%	469	469	-0.06 (-0.19, 0.07) Z = 0.96 p = 0.34
No	1 [88]	NA	80	78	-0.06 (-0.37, 0.25) Z = 0.37 p = 0.71
Unclear	4 [59 86 90 104]	Chi² = 8.823 p = 0.03 I² = 66%	129	124	-0.39 (-0.84, 0.06) Z = 1.70 p = 0.09
Risk of bias blinding of outcomes					
Yes	3 [69 90 104]	Chi² = 3.642 p = 0.16 I² = 45%	395	391	-0.13 (-0.38, 0.13) Z = 0.98 p = 0.33
No	2 [86 88]	Chi² = 0.401 p = 0.53 I² = 0%	102	99	-0.11 (-0.38, 0.17) Z = 0.75 p = 0.46
Unclear	2 [28 59]	Chi² = 9.061 p = 0.003 I² = 89%	172	172	-0.54 (-1.57, 0.50) Z = 1.01 p = 0.31
Intention-to-treat analysis					
Yes	5 [28 69 86 88 90]	Chi² = 3.404 p = 0.49 I² = 0%	616	615	-0.10 (-0.21, 0.01) Z = 1.77 p = 0.08
No	2 [59 104]	Chi² = 8.661 p = 0.003 I² = 88%	53	47	-0.47 (-1.70, 0.76) Z = 0.75 p = 0.45
Unclear	0	NA	0	0	NA

Abbreviations

CI = confidence interval, **mg** = milligram**, mm** = millimetre, **NA** = not applicable, **VAS** = visual analogue scale, **WOMAC** = The Western Ontario and McMaster Universities Osteoarthritis Index.

Table 75 Chondroitin sulfate vs placebo: Sub-group and sensitivity analyses of pain at 24 months (knee)

Pain 24 months	Number of studies	Heterogeneity	Chondroitin sulfate number of participants	Placebo number of participants	Standard mean difference (95% CI)
Overall					
	4 [28 69 82 88]	Chi² = 31.57 p < 0.00001 I² = 90%	679	680	-0.24 (-0.61, 0.13) Z = 1.29 p = 0.20
Sub-group analyses					
Measure of 'pain'					
WOMAC	3 [69 82 88]	Chi² = 29.03 p < 0.00001 I² = 93%	528	529	-0.31 (-0.82, 0.21) Z = 1.16 p = 0.24
VAS	1 [28]	NA	151	151	-0.06 (-0.28, 0.17) Z = 0.49 p = 0.63
Inclusion criteria minimum pain score					
⩾ 40mm or % of total score	1 [28]	NA	151	151	-0.06 (-0.28, 0.17) Z = 0.49 p = 0.63
⩽ 40mm or % of total score	1 [69]	NA	309	313	-0.07 (-0.23, 0.08) Z = 0.90 p = 0.37
Not specified or below and above 40mm	2 [82 88]	Chi² = 14.62 p = 0.0001 I² = 93%	219	216	-0.43 (-1.21, 0.36) Z = 1.06 p = 0.29
Manufacturer					
Bioberica	1 [88]	NA	69	66	-0.02 (-0.35, 0.32) Z = 0.09 p = 0.93
IBSA	2 [69 82]	Chi² = 26.62 p < 0.00001 I² = 96%	459	463	-0.44 (-1.17, 0.29) Z = 1.18 p = 0.24
Pierre Fabre	0	NA	0	0	NA
TSI Health	1 [28]	NA	151	151	-0.06 (-0.28, 0.17) Z = 0.49 p = 0.63
Dose					
1,200mg/day	1[88]	NA	69	66	-0.02 (-0.35, 0.32) Z = 0.09 p = 0.93
1,000mg/day	0	NA	0	0	NA

Pain 24 months	Number of studies	Heterogeneity	Chondroitin sulfate number of participants	Placebo number of participants	Standard mean difference (95% CI)
800mg/day	3 [28 69 82]	Chi² = 30.04 p < 0.00001 I² = 93%	610	614	-0.31 (-0.77, 0.15) Z = 1.33 p = 0.18
Sensitivity analyses					
Risk of bias funding declared					
Yes	1 [69]	NA	309	313	-0.07 (-0.23, 0.08) Z = 0.90 p = 0.37
No	2 [28 88]	Chi² = 0.01 p = 0.91 I² = 0%	460	464	-0.07 (-0.20, 0.06) Z = 1.02 p = 0.31
Unclear	1 [82]	NA	150	150	-0.82 (-1.05, -0.58) Z = 6.80 p < 0.00001
Risk of bias randomisation					
Yes	2 [69 82]	Chi² = 26.62 p < 0.00001 I² = 96%	459	463	-0.44 (-1.17, 0.29) Z = 1.18 p = 0.24
No	1 [88]	NA	69	66	-0.02 (-0.35, 0.32) Z = 0.09 p = 0.93
Unclear	1 [28]	NA	151	151	-0.06 (-0.28, 0.17) Z = 0.49 p = 0.63
Risk of bias allocation					
Yes	2 [28 69]	Chi² = 0.01 p = 0.91 I² = 0%	460	464	-0.07 (-0.20, 0.06) Z = 1.02 p = 0.31
No	1 [88]	NA	69	66	-0.02 (-0.35, 0.32) Z = 0.09 p = 0.93
Unclear	1 [82]	NA	150	150	-0.82 (-1.05, -0.58) Z = 6.80 p < 0.00001
Risk of bias blinding of participants					
Yes	2 [28 69]	Chi² = 0.01 p = 0.91 I² = 0%	460	464	-0.07 (-0.20, 0.06) Z = 1.02 p = 0.31
No	1 [88]	NA	69	66	-0.02 (-0.35, 0.32) Z = 0.09 p = 0.93

Pain 24 months	Number of studies	Heterogeneity	Chondroitin sulfate number of participants	Placebo number of participants	Standard mean difference (95% CI)
Unclear	1 [82]	NA	150	150	-0.82 (-1.05, -0.58) Z = 6.80 p < 0.00001
Risk of bias blinding of outcomes					
Yes	1 [69]	NA	309	313	-0.07 (-0.23, 0.08) Z = 0.90 p = 0.37
No	1 [88]	NA	69	66	-0.02 (-0.35, 0.32) Z = 0.09 p = 0.93
Unclear	2 [28 82]	Chi^2 = 20.96 p < 0.00001 I^2 = 95%	301	301	-0.44 (-1.18, 0.31) Z = 1.15 p = 0.25
Intention-to-treat analysis					
Yes	4 [28 69 82 88]	Chi^2 = 31.57 p < 0.00001 I^2 = 90%	679	680	-0.24 (-0.61, 0.13) Z = 1.29 p = 0.20
No	0	NA	0	0	NA
Unclear	0	NA	0	0	NA

Abbreviations
CI = confidence interval, **mg** = milligram**, mm** = millimetre, **NA** = not applicable, **VAS** = visual analogue scale, **WOMAC** = The Western Ontario and McMaster Universities Osteoarthritis Index.

Table 76 Chondroitin sulfate vs placebo: Sub-group and sensitivity analyses of paracetamol intake at six months (knee)

Paracetamol intake 6 months	Number of studies	Heterogeneity	Chondroitin sulfate number of participants	Placebo number of participants	Standard mean difference (95% CI)
Overall					
	4 [69 74 75 78]	Chi² = 2.40 p = 0.49 I² = 0%	729	734	0.01 [-0.10, 0.11] Z = 0.11 p = 0.91
Sub-group analyses					
Manufacturer					
Bioberica	1 [75]	NA	318	313	0.05 [-0.10, 0.21] Z = 0.68 p = 0.50
IBSA	3 [69 74 78]	Chi² = 1.75 p = 0.42 I² = 0%	411	421	-0.03 [-0.17, 0.11] Z = 0.44 p = 0.66
Pierre Fabre	0	NA	0	0	NA
TSI Health	0	NA	0	0	NA
Dose					
1,200mg/day	2 [75 78]	Chi² = 0.08 p = 0.78 I² = 0%	381	375	0.05 [-0.10, 0.19] Z = 0.62 p = 0.54
1,000mg/day	0	NA	0	0	NA
800mg/day	2 [69 74]	Chi² = 1.72 p = 0.19 I² = 42%	348	369	-0.08 [-0.35, 0.18] Z = 0.62 p = 0.54
Sensitivity analyses					
Risk of bias funding declared					
Yes	3 [69 74 75]	Chi² = 2.39 p = 0.30 I² = 16%			0.00 [-0.12, 0.12] Z = 0.02 p = 0.99
No	0	NA	0	0	NA
Unclear	1 [78]	NA	63	62	0.00 [-0.35, 0.35] Z = 0.00 p = 1.00
Risk of bias randomisation					
Yes	2 [69 75]	Chi² = 0.23 p = 0.63 I² = 0%	627	626	0.03 [-0.08, 0.14] Z = 0.48 p = 0.63
No	0	NA	0	0	NA

Paracetamol intake 6 months	Number of studies	Heterogeneity	Chondroitin sulfate number of participants	Placebo number of participants	Standard mean difference (95% CI)
Unclear	2 [74 78]	Chi² = 1.17 p = 0.28 I² = 14%	102	108	-0.13 [-0.42, 0.17] Z = 0.84 p = 0.40
Risk of bias allocation					
Yes	2 [69 75]	Chi² = 1.17 p = 0.28 I² = 14%	102	108	-0.13 [-0.42, 0.17] Z = 0.84 p = 0.40
No	0	NA	0	0	NA
Unclear	2 [74 78]	Chi² = 0.23 p = 0.63 I² = 0%	627	626	0.03 [-0.08, 0.14] Z = 0.48 p = 0.63
Risk of bias blinding of participants					
Yes	3 [69 75 78]	Chi² = 0.25 p = 0.88 I² = 0%	690	688	0.02 [-0.08, 0.13] Z = 0.46 p = 0.65
No	0	NA	0	0	NA
Unclear	1 [74]	NA	39	46	-0.31 [-0.73, 0.12] Z = 1.40 p = 0.16
Risk of bias blinding of outcomes					
Yes	2 [69 74]	Chi² = 1.72 p = 0.19 I² = 42%	348	359	-0.08 [-0.35, 0.18] Z = 0.62 p = 0.54
No	1 [75]	NA	318	313	0.05 [-0.10, 0.21] Z = 0.68 p = 0.50
Unclear	1 [78]	NA	63	62	0.00 [-0.35, 0.35] Z = 0.00 p = 1.00
Intention-to-treat analysis					
Yes	3 [69 74 75]	Chi² = 2.39 p = 0.30 I² = 16%	666	672	0.00 [-0.12, 0.12] Z = 0.02 p = 0.99
No	1 [78]	NA	63	62	0.00 [-0.35, 0.35] Z = 0.00 p = 1.00
Unclear	0	NA	0	0	NA

Abbreviations
CI = confidence interval, **mg** = milligram**, NA** = not applicable.

Table 77 Chondroitin sulfate vs placebo: Sub-group and sensitivity analyses of Lequesne index at six months (knee)

Lequesne index 6 months	Number of studies	Heterogeneity	Chondroitin sulfate number of participants	Placebo number of participants	Standard mean difference (95% CI)
Overall					
	6 [64 74 80 86 90 94]	Chi² = 7.55 p = 0.18 I² = 34%	491	516	-0.26 (-0.42 -0.09) Z = 3.08 p = 0.002
Sub-group analyses					
Manufacturer					
Bioberica	0	NA	0	0	NA
IBSA	3 [74 90 94]	Chi² = 6.61 p = 0.04 I² = 70%	253	274	-1.54 (-2.93, -0.15) Z = 2.17 p = 0.03
Pierre Fabre	3 [64 80 86]	Chi² = 1.22 p = 0.54 I² = 0%	238	242	-0.60 (-1.26, 0.06) Z = 1.79 p = 0.07
TSI Health	0	NA	0	0	NA
Dose					
1,200mg/day	0	NA	0	0	NA
1,000mg/day	3 [64 80 86]	Chi² = 1.22 p = 0.54 I² = 0%	238	242	-0.60 (-1.26, 0.06) Z = 1.79 p = 0.07
800mg/day	3 [74 90 94]	Chi² = 6.61 p = 0.04 I² = 70%	253	274	-1.54 (-2.93, -0.15) Z = 2.17 p = 0.03
Sensitivity analyses					
Risk of bias funding declared					
Yes	6 [64 74 80 86 90 94]	Chi² = 9.45 p = 0.09 I² = 47%	491	516	-1.02 (-1.73, -0.31) Z = 2.81 p = 0.005
No	0	NA	0	0	NA
Unclear	0	NA	0	0	NA
Risk of bias randomisation					
Yes	3 [64 80 86]	Chi² = 1.22 p = 0.54 I² = 0%	238	242	-0.60 (-1.26, 0.06) Z = 1.79 p = 0.07
No	0	NA	0	0	NA
Unclear	3 [74 90 94]	Chi² = 6.61 p = 0.04 I² = 70%	253	274	-1.54 (-2.93, -0.15) Z = 2.17 p = 0.03

Lequesne index 6 months	Number of studies	Heterogeneity	Chondroitin sulfate number of participants	Placebo number of participants	Standard mean difference (95% CI)
Risk of bias allocation					
Yes	0	NA	0	0	NA
No	0	NA	0	0	NA
Unclear	6 [64 74 80 86 90 94]	Chi² = 9.45 p = 0.09 I² = 47%	491	516	-1.02 (-1.73, -0.31) Z = 2.81 p = 0.005
Risk of bias blinding of participants					
Yes	0	NA	0	0	NA
No	0	NA	0	0	NA
Unclear	6 [64 74 80 86 90 94]	Chi² = 9.45 p = 0.09 I² = 47%	491	516	-1.02 (-1.73, -0.31) Z = 2.81 p = 0.005
Risk of bias blinding of outcomes					
Yes	2 [74 90]	Chi² = 5.12 p = 0.02 I² = 80%	93	102	-2.08 (-4.72, 0.57) Z = 1.54 p = 0.12
No	2 [86 94]	Chi² = 0.75 p = 0.39 I² = 0%	182	193	-0.78 (-1.56, 0.00) Z = 1.95 p = 0.05
Unclear	2 [64 80]	Chi² = 0.74 p = 0.39 I² = 0%	216	221	-0.67 (-1.35, 0.01) Z = 1.92 p = 0.06
Intention-to-treat analysis					
Yes	6 [64 74 80 86 90 94]	Chi² = 9.45 p = 0.09 I² = 47%	491	516	-1.02 (-1.73, -0.31) Z = 2.8 p = 0.005
No	0	NA	0	0	NA
Unclear	0	NA	0	0	NA

Abbreviations
CI = confidence interval**, mg** = milligram**, NA** = not applicable.

Safety

Table 78 Chondroitin sulfate vs placebo: Sub-group and sensitivity analyses of withdrawal due to adverse events (knee)

Withdrawal due to adverse events	Number of studies	Heterogeneity	Chondroitin sulfate n/N	Placebo n/N	Relative difference RR (95% CI)
Overall					
	17 [28 59 64 69 73-75 80-83 86 90 92-94]	Chi^2 = 5.54 p = 0.99 I^2 = 0%	104/1,950	86/1,970	1.21 (0.92, 1.61) Z = 1.35 p = 0.18
Sub-group analyses					
Manufacturer					
Pierre Fabre	4 [64 80 81 86]	Chi^2 = 0.99 p = 0.80 I^2 = 0%	19/296	13/299	1.49 (0.75, 2.96) Z = 1.15 p = 0.25
IBSA	10 [59 69 73 74 79 82 90 93 94 104]	Chi^2 = 2.92 p = 0.97 I^2 = 0%	58/1,124	53/1,142	1.10 (0.76, 1.58) Z = 0.51 p = 0.61
Bioberica	3 [75 83 104]	Chi^2 = 1.11 p = 0.29 I^2 = 10%	21/417	13/416	1.54 (0.66, 3.63) Z = 0.99 p = 0.32
Dose					
1,200mg/day	3 [73 75 93]	Chi^2 = 1.56 p = 0.46 I^2 = 0%	28/480	20/479	1.39 (0.79, 2.46) Z = 1.13 p = 0.26
1,000mg/day	3 [64 80 86]	Chi^2 = 0.04 p = 0.98 I^2 = 0%	19/238	12/243	1.61 (0.80, 3.25) Z = 1.33 p = 0.18
800mg/day	10 [13 28 59 69 74 79 83 90 94 104]	Chi^2 = 2.04 p = 0.98 I^2 = 0%	57/1,110	53/1,128	1.08 (0.75, 1.56) Z = 0.42 p = 0.68
Length of follow-up					
$\leqslant$ 6 months	8 [64 73-75 81 83 93 94]	Chi^2 = 2.48 p = 0.87 I^2 = 0%	41/903	30/918	1.39 (0.87, 2.21) Z = 1.38 p = 0.17
> 6 months	9 [28 59 69 79 82 86 90 104]	Chi^2 = 2.56 p = 0.96 I^2 = 0%	63/1,047	56/1,052	1.12 (0.79, 1.60) Z = 0.65 p = 0.51
Sensitivity analyses					
Risk of bias funding declared					

Withdrawal due to adverse events	Number of studies	Heterogeneity	Chondroitin sulfate n/N	Placebo n/N	Relative difference RR (95% CI)
Yes	13 [59 64 69 73-75 80 83 86 90 93 94 104]	Chi² = 4.00 p = 0.97 I² = 0%	75/1,441	58/1,463	1.30 (0.93, 1.82) Z = 1.52 p = 0.13
No	1 [28]	NA	11/151	8/151	1.38 (0.57, 3.32) Z = 0.71 p = 0.48
Unclear	3 [79 81 82]	Chi² = 0.45 p = 0.80 I² = 0%	18/358	20/356	0.91 (0.49, 1.68) Z = 0.30 p = 0.76
Risk of bias randomisation					
Yes	8 [69 75 80-83 86 93]	Chi² = 3.31 p = 0.77 I² = 0%	66/1,193	53/1,193	1.24 (0.87, 1.77) Z = 1.20 p = 0.23
No	0	NA	0	0	NA
Unclear	9 [28 59 64 73 74 79 90 94 104]	Chi² = 2.18 p = 0.97 I² = 0%	38/757	33/777	1.17 (0.74, 1.84) Z = 0.66 p = 0.51
Risk of bias allocation					
Yes	4 [28 69 75 104]	Chi² = 2.34 p = 0.50 I² = 0%	48/813	38/816	1.26 (0.83, 1.92) Z = 1.09 p = 0.27
No	0	NA	NA	NA	NA
Unclear	13 [59 64 73 74 79-83 86 90 93 94]	Chi² = 3.13 p = 0.99 I² = 0%	56/1,137	48/1,154	1.17 (0.81, 1.71) Z = 0.83 p = 0.40
Risk of bias blinding of participants					
Yes	5 [28 69 75 81 93]	Chi² = 2.60 p = 0.63 I² = 0%	53/955	43/955	1.23 (0.83, 1.83) Z = 1.03 p = 0.30
No	0	NA	NA	NA	NA
Unclear	12 [59 64 73 74 79 80 82 83 86 90 94 104]	Chi² = 2.93 p = 0.98 I² = 0%	51/995	43/1,015	1.20 (0.80, 1.78) Z = 0.88 p = 0.38
Risk of bias blinding of outcomes					
Yes	6 [69 74 79 80 90 104]	Chi² = 1.66 p = 0.89 I² = 0%	41/740	39/753	1.06 (0.69, 1.79) Z = 0.41 p = 0.68
No	3 [79 81 82]	Chi² = 0.03 p = 0.99 I² = 0%	30/539	17/544	1.77 (0.99, 3.18) Z = 1.93 p = 0.05

Withdrawal due to adverse events	Number of studies	Heterogeneity	Chondroitin sulfate n/N	Placebo n/N	Relative difference RR (95% CI)
Unclear	8 [28 59 64 73 80-83 93]	Chi² = 1.71 p = 0.94 I² = 0%	33/671	30/673	1.11 (0.68, 1.85) Z = 0.52 p = 0.60
Intention-to-treat analysis					
Yes	15 [28 64 69 73-75 79-83 86 90 93 94 159]	Chi² = 6.84 p = 0.94 I² = 0%	102/1,921	87/1,940	1.20 (0.90, 1.59) Z = 1.24 p = 0.22
No	2 [59 104]	Chi² = 0.83 p = 0.36 I² = 0%	2/58	2/57	0.93 (0.14, 6.14) Z = 0.60 p = 0.55
Unclear	0	NA	NA	NA	NA

Abbreviations
CI = confidence interval, **n** = number of patients, **N** = total number of participants, **NA** = not applicable, **RR** = risk ratio.

Table 79 Chondroitin sulfate vs placebo: Sub-group and sensitivity analyses of severe adverse events (knee)

Severe adverse events	Number of studies	Heterogeneity	Chondroitin n/N	Placebo n/N	Relative difference RR (95% CI)
Overall					
	5 [64 80 88 93 104]	Chi² = 4.94 p = 0.29 I² = 19%	23/496	25/504	0.97 (0.49, 1.95) Z = 0.07 p = 0.94
Sub-group analyses					
Manufacturer					
Bioberica	2 [88 104]	Chi² = 0.28 p = 0.60) I² = 0%	7/161	15/164	0.48 (0.20, 1.16) Z = 1.63 p = 0.10
IBSA	1 [93]	NA	4/119	2/117	1.97 (0.37, 10.53) Z = 0.79 p = 0.43
Pierre Fabre	2 [64 80]	Chi² = 0.83 p = 0.36 I² = 0%	12/216	8/222	1.42 (0.60, 3.37) Z = 0.79 p = 0.43
Dose					
1,200mg/day	2 [88 93]	Chi² = 2.31 p = 0.13 I² = 57%	10/245	16/248	0.79 (0.19, 3.25) Z = 0.33 p = 0.74
1,000mg/day	2 [64 80]	Chi² = 0.83 p = 0.36 I² = 0%	12/216	8/222	1.42 (0.60, 3.37) Z = 0.79 p = 0.43
800mg/day	1 [104]	NA	1/35	1/34	0.97 (0.06, 14.91) Z = 0.02 p = 0.98
Length of follow-up					
⩽ 6 months	2 [64 93]	Chi² = 0.33 p = 0.56 I² = 0%	6/182	2/185	2.50 (0.58, 10.82) Z = 1.22 p = 0.22
> 6 months	3 [80 88 104]	Chi² = 2.51 p = 0.28 I² = 20%	17/314	23/319	0.77 (0.36, 1.62) Z = 0.69 p = 0.49
Sensitivity analyses					
Risk of bias funding declared					
Yes	4 [64 80 93 104]	Chi² = 1.04 p = 0.79 I² = 0%	17/370	11/373	1.47 (0.70, 3.08) Z = 1.02 p = 0.31

Severe adverse events	Number of studies	Heterogeneity	Chondroitin n/N	Placebo n/N	Relative difference RR (95% CI)
No	1 [88]	NA	6/126	14/131	0.45 (0.18, 1.12) Z = 1.71 p = 0.09
Unclear	0	NA	NA	NA	NA
Risk of bias randomisation					
Yes	2 [80 93]	Chi² = 0.21, p = 0.65 I² = 0%	14/272	10/271	1.39 (0.63, 3.08) Z = 0.81 p = 0.42
No	1 [88]	NA	6/126	14/131	0.45 (0.18, 1.12) Z = 1.71 p = 0.09
Unclear	2 [64 104]	Chi² = 0.70 p = 0.40 I² = 0%	3/98	1/102	2.10 (0.28, 15.92) Z = 0.72 p = 0.47
Risk of bias allocation					
Yes	1 [104]	NA	1/35	1/34	0.97 (0.06, 14.91) Z = 0.02 p = 0.98
No	1 [88]	NA	6/126	14/131	0.45 (0.18, 1.12) Z = 1.71 p = 0.09
Unclear	3 [64 80 93]	Chi² = 0.95 p = 0.62 I² = 0%	16/335	10/339	1.52 (0.70, 3.27) Z = 1.07 p = 0.29
Risk of bias blinding of participants					
Yes	1 [93]	NA	4/119	2/117	1.97 (0.37, 10.53) Z = 0.79 p = 0.43
No	1 [88]	NA	6/126	14/131	0.45 (0.18, 1.12) Z = 1.71 p = 0.09
Unclear	3 [64 80 104]	Chi² = 0.90 p = 0.64 I² = 0%	13/251	9/256	1.37 (0.60, 3.12) Z = 0.75 p = 0.45
Risk of bias blinding of outcomes					
Yes	2 [80 104]	Chi² = 0.03 p = 0.86 I² = 0%	11/188	9/188	1.23 (0.52, 2.89) Z = 0.47 p = 0.64
No	1 [88]	NA	6/126	14/131	0.45 (0.18, 1.12) Z = 1.71 p = 0.09

Severe adverse events	Number of studies	Heterogeneity	Chondroitin n/N	Placebo n/N	Relative difference RR (95% CI)
Unclear	2 [64 93]	Chi² = 0.33 p = 0.56 I² = 0%	6/182	2/185	2.50 (0.58, 10.82) Z = 1.22 p = 0.22
Intention-to-treat analysis					
Yes	4 [64 80 88 93]	Chi² = 4.93 p = 0.18 I² = 39%	22/461	24/470	1.03 (0.44, 2.39) Z = 0.07 p = 0.95
No	1 [104]	NA	1/35	1/34	0.97 (0.06, 14.91) Z = 0.02 p = 0.98
Unclear	0	NA	0	0	NA

Abbreviations
CI = confidence interval, **n** = number of patients, **N** = total number of participants, **NA** = not applicable, **RR** = risk ratio.

Table 80 Chondroitin sulfate vs placebo: Sub-group and sensitivity analyses of treatment-related severe adverse events (knee)

Treatment-related severe adverse events	Number of studies	Heterogeneity	Chondroitin n/N	Placebo n/N	Relative difference RR (95% CI)
Overall					
	5 [64 75 80 88 104]	$Chi^2 = 0.25$ p = 0.62 $I^2 = 0\%$	1/695	2/705	0.64 (0.08, 5.15) Z = 0.42 p = 0.67
Sub-group analyses					
Manufacturer					
Bioberica	3 [75 88 104]	NA	0/479	1/483	0.35 (0.01, 8.43) Z = 0.65 p = 0.52
IBSA	0	NA	0	0	NA
Pierre Fabre	2 [64 80]	NA	1/216	1/222	1.01 (0.06, 15.95) Z = 0.00 p = 1.00
Dose					
1,200mg/day	2 [75 88]	NA	0/444	1/449	0.35 (0.01, 8.43) Z = 0.65 p = 0.52
1,000mg/day	2 [64 80]	NA	1/216	1/222	1.01 (0.06, 15.95) Z = 0.00 p = 1.00
800mg/day	1 [104]	NA	0/35	0/34	Not estimable
Length of follow-up					
$\leqslant$ 6 months	2 [64 75]	NA	0/381	0/386	Not estimable
> 6 months	3 [80 88 104]	$Chi^2 = 0.25$ p = 0.62 $I^2 = 0\%$	1/314	2/319	0.64 (0.08, 5.15) Z = 0.42 p = 0.67
Sensitivity analyses					
Risk of bias funding declared					
Yes	4 [64 75 80 104]	NA	1/569	1/574	1.01 (0.06, 15.95) Z = 0.00 p = 1.00
No	1 [88]	NA	0/126	1/131	0.35 (0.01, 8.43) Z = 0.65 p = 0.52
Unclear	0	NA	0	0	NA
Risk of bias randomisation					

Treatment-related severe adverse events	Number of studies	Heterogeneity	Chondroitin n/N	Placebo n/N	Relative difference RR (95% CI)
Yes	2 [75 80]	NA	1/461	1/472	1.01 (0.06, 15.95) Z = 0.00 p = 1.00
No	1 [88]	NA	0/126	1/131	0.35 (0.01, 8.43) Z = 0.65 p = 0.52
Unclear	2 [64 104]	NA	0/98	0/102	Not estimable
Risk of bias allocation					
Yes	2 [75 104]	NA	0/353	0/352	Not estimable
No	1 [88]	NA	0/126	1/131	0.35 (0.01, 8.43) Z = 0.65 p = 0.52
Unclear	2 [80 81]	NA	1/216	1/222	1.01 (0.06, 15.95) Z = 0.00 p = 1.00
Risk of bias blinding of participants					
Yes	1 [75]	NA	0/318	0/318	Not estimable
No	1 [88]	NA	0/126	1/131	0.35 (0.01, 8.43) Z = 0.65 p = 0.52
Unclear	3 [64 80 104]	NA	1/251	1/256	1.01 (0.06, 15.95) Z = 0.00 p = 1.00
Risk of bias blinding of outcomes					
Yes	2 [80 104]	NA	1/188	1/188	1.01 (0.06, 15.95) Z = 0.00 p = 1.00
No	2 [75 88]	NA	0/444	1/449	0.35 (0.01, 8.43) Z = 0.65 p = 0.52
Unclear	1 [64]	NA	0/63	0/68	Not estimable
Intention-to-treat analysis					
Yes	4 [64 75 80 88]	$Chi^2 = 0.25$ p = 0.62 $I^2 = 0\%$	1/660	2/671	0.64 (0.08, 5.15) Z = 0.42 p = 0.67
No	1 [104]	Not estimable	0/35	0/34	Not estimable
Unclear	0	NA	NA	NA	NA

Abbreviations
CI = confidence interval, **n** = number of patients, **N** = total number of participants, **NA** = not applicable, **RR** = risk ratio.

Table 81 Chondroitin sulfate vs placebo: Sub-group and sensitivity analyses of any adverse events (knee)

Any adverse events	Number of studies	Heterogeneity	Chondroitin n/N	Placebo n/N	Relative difference RR (95% CI)
Overall					
	8 [64 73 78 80-83 86]	Chi² = 7.83 p = 0.35 I² = 11%	258/616	288/619	0.93 (0.81, 1.05) Z = 1.17 p = 0.24
Sub-group analyses					
Manufacturer					
Bioberica	1 [83]	NA	31/64	31/64	1.00 (0.70, 1.43) Z = 0.00 p = 1.00
IBSA	3 [73 78 82]	Chi² = 1.84 p = 0.40 I² = 0%	106/256	130/256	0.84 (0.71, 0.99) Z = 2.07 p = 0.04
Pierre Fabre	4 [64 80 81 86]	Chi² = 3.79 p = 0.29 I² = 21%	121/296	127/299	1.00 (0.81, 1.25) Z = 0.02 p = 0.99
Dose[a]					
1,200mg/day	2 [73 78]	Chi² = 0.89, p = 0.35 I² = 0%	19/106	29/106	0.67 (0.40, 1.12) Z = 1.54 p = 0.12
1,000mg/day	3 [64 80 86]	Chi² = 0.55 p = 0.46 I² = 0%	114/238	117/243	1.03 (0.81, 1.30) Z = 1.49 p = 0.14
800mg/day	2 [82 83]	Chi² = 2.65 p = 0.45 I² = 0%	118/214	132/214	0.89 (0.76, 1.04) Z = 1.24 p = 0.21
Length of follow-up					
≤ 6 months	5 [64 73 78 81 83]	Chi² = 2.92 p = 0.57 I² = 0%	78/291	98/294	0.86 (0.65, 1.07) Z = 1.42 p = 0.15
> 6 months	3 [80 82 86]	Chi² = 4.10 p = 0.13 I² = 51%	180/325	190/325	0.99 (0.80, 1.21) Z = 0.14 p = 0.89
Sensitivity analyses					
Risk of bias funding declared					
Yes	5 [64 73 80 83 86]	Chi² = 3.15 p = 0.37 I² = 5%	124/281	129/287	1.01 (0.84, 1.22) Z = 0.12 p = 0.90
No	0	NA	0	0	NA

Any adverse events	Number of studies	Heterogeneity	Chondroitin n/N	Placebo n/N	Relative difference RR (95% CI)
Unclear	3 [78 81 82]	Chi² = 2.13 p = 0.34 I² = 6%	96/213	118/212	0.81 (0.66, 1.01) Z = 1.87 p = 0.06
Risk of bias randomisation					
Yes	5 [80-83 86]	Chi² = 4.75 p = 0.31 I² = 16%	218/447	231/445	0.96 (0.83, 1.11) Z = 0.57 p = 0.57
No					
Unclear	3 [64 73 78]	Chi² = 1.20 p = 0.55 I² = 0%	40/169	57/174	0.74 (0.53, 1.04) Z = 1.71 p = 0.09
Risk of bias allocation					
Yes	0	NA	0	0	NA
No	0	NA	0	0	NA
Unclear	8 [64 73 78 80-83 86]	Chi² = 7.83 p = 0.35 I² = 11%	258/616	288/619	0.93 (0.81, 1.07) Z = 1.17 p = 0.24
Risk of bias blinding of participants					
Yes	2 [78 81]	Chi² = 0.20 p = 0.66 I² = 0%	16/121	27/118	0.58 (0.33, 1.02) Z = 1.90 p = 0.06
No	0	NA	0	0	NA
Unclear	6 [64 73 80 82 83 86]	Chi² = 4.74 p = 0.45 I² = 0%	242/495	261/501	0.94 (0.84, 1.06) Z = 1.02 p = 0.31
Risk of bias blinding of outcomes					
Yes	1 [80]	NA	75/153	76/154	0.99 (0.79, 1.25) Z = 0.06 p = 0.95
No	1 [86]	NA	18/22	13/21	1.32 (0.90, 1.95) Z = 1.41 p = 0.16
Unclear	6 [64 73 78 81-83]	Chi² = 2.93 p = 0.71 I² = 0%	165/441	199/444	0.85 (0.74, 0.98) Z = 2.18 p = 0.03
Intention-to-treat analysis					
Yes	7 [64 73 80-83 86]	Chi² = 5.28 p = 0.51 I² = 0%	249/553	271/557	0.94 (0.83, 1.05) Z = 1.12 p = 0.26

Any adverse events	Number of studies	Heterogeneity	Chondroitin n/N	Placebo n/N	Relative difference RR (95% CI)
No	1 [78]	NA	9/63	17/62	0.52 (0.25, 1.08) Z = 1.76 p = 0.08
Unclear	0	NA	0	0	NA

Abbreviations
CI = confidence interval, **n** = number of patients, **N** = total number of participants, **NA** = not applicable, **RR** = risk ratio.
Notes
a = Mazieres 1992 did not report the dose of chondroitin sulfate administered in this trial.

Table 82 Chondroitin sulfate vs placebo: Sub-group and sensitivity analyses of treatment-related adverse events (knee)

Treatment-related adverse event	Number of studies	Heterogeneity	Chondroitin n/N	Placebo n/N	Relative difference RR (95% CI)
Overall					
	7 [73 74 80 82 86 90 104]	Chi² = 2.43 p = 0.79 I² = 0%	30/496	36/505	0.82 (0.52, 1.30) Z = 0.84 p = 0.40
Sub-group analyses					
Manufacturer					
Bioberica	1 [104]	NA	0/35	0/34	Not estimable
IBSA	4 [73 74 82 90]	Chi² = 1.77 p = 0.62 I² = 0%	14/286	19/296	0.73 (0.39, 1.38) Z = 0.97 p = 0.33
Pierre Fabre	2 [80 86]	Chi² = 0.39 p = 0.53 I² = 0%	16/175	17/175	0.94 (0.49, 1.80) Z = 0.20 p = 0.84
Dose					
1,200mg/day	1 [73]	NA	8/43	12/44	0.94 (0.49, 1.80) Z = 0.95 p = 0.34
1,000mg/day	1 [80 86]	Chi² = 0.39 p = 0.53 I² = 0%	16/175	17/175	0.83 (0.29, 2.38) Z = 0.20 p = 0.84
800mg/day	4 [74 82 90 104]	Chi² = 1.69 p = 0.43 I² = 0%	6/278	7/286	0.66 (0.31, 1.42) Z = 0.35 p = 0.72
Length of follow-up					
⩽ 6 months	2 [73 74]	Chi² = 0.11 p = 0.74 I² = 0%	8/82	13/90	0.66 (0.31, 1.42) Z = 1.06 p = 0.29
> 6 months	5 [80 82 86 90 104]	Chi² = 1.83 p = 0.61 I² = 0%	22/414	23/415	0.93 (0.53, 1.63) Z = 0.26 p = 0.80
Sensitivity analyses					
Risk of bias funding declared					
Yes	6 [73 74 80 86 90 104]	Chi² = 1.02 p = 0.91 I² = 0%	28/346	36/355	0.79 (0.50, 1.25) Z = 1.00 p = 0.32
No	0	NA	0	0	NA
Unclear	1 [82]	NA	2/150	0/150	5.00 (0.24, 103.28) Z = 1.04 p = 0.30

Treatment-related adverse event	Number of studies	Heterogeneity	Chondroitin n/N	Placebo n/N	Relative difference RR (95% CI)
Risk of bias randomisation					
Yes	3 [80 82 86]	Chi² = 1.54 p = 0.46 I² = 0%	18/325	17/325	1.01 (0.53, 1.91) Z = 0.03 p = 0.98
No	0	NA	0	0	NA
Unclear	4 [73 74 90 104]	Chi² = 0.12 p = 0.94 I² = 0%	12/171	19/180	0.67 (0.35, 1.28) Z = 1.22 p = 0.22
Risk of bias allocation					
Yes	1 [104]	NA	0/35	0/34	Not estimable
No	0	NA	0	0	NA
Unclear	6 [73 74 80 82 86 90]	Chi² = 2.43 p = 0.79 I² = 0%	30/461	36/471	0.82 (0.52, 1.30) Z = 0.84 p = 0.40
Risk of bias blinding of participants					
Yes	0	NA	0	0	NA
No	0	NA	0	0	NA
Unclear	7 [73 74 80 82 86 90 104]	Chi² = 2.43 p = 0.79 I² = 0%	30/496	36/505	0.82 (0.52, 1.30) Z = 0.84 p = 0.40
Risk of bias blinding of outcomes					
Yes	4 [74 80 90 104]	Chi² = 0.33 p = 0.85 I² = 0%	18/281	23/290	0.81 (0.45, 1.45) Z = 0.71 p = 0.48
No	1 [86]	NA	2/22	1/21	1.91 (0.19, 19.52) Z = 0.55 p = 0.59
Unclear	2 [73 82]	Chi² = 1.62 p = 0.20 I² = 38%	10/193	12/194	1.08 (0.20, 5.81) Z = 0.09 p = 0.93
Intention-to-treat analysis					
Yes	6 [73 74 80 82 86 90]	Chi² = 2.43 p = 0.79 I² = 0%	30/461	36/471	0.82 (0.52, 1.30) Z = 0.84 p = 0.40
No	0	NA	0	0	NA
Unclear	1 [104]	NA	0/35	0/34	NA

Abbreviations
CI = confidence interval, **n** = number of patients, **N** = total number of participants, **NA** = not applicable, **RR** = risk ratio.

Table 83 Chondroitin sulfate vs placebo: Sub-group and sensitivity analyses of gastrointestinal-related adverse events (knee)

Gastrointestinal-related adverse events	Number of studies	Heterogeneity	Chondroitin n/N	Placebo n/N	Relative difference RR (95% CI)
Overall					
	9 [69 73-75 78 80 81 86 90 104]	Chi² = 3.18 p = 0.92 I² = 0%	62/1,094	77/1,104	0.81 (0.59, 1.11) Z = 1.32 p = 0.19
Sub-group analyses					
Manufacturer					
Bioberica	2 [75 104]	NA	7/353	7/352	0.97 (0.38, 2.48) Z = 0.06 p = 0.95
IBSA	5 [69 73 74 78 90]	Chi² = 4.86 p = 0.30 I² = 18%	37/508	50/772	1.08 (0.68, 1.73) Z = 0.33 p = 0.74
Pierre Fabre	3 [80 81 86]	Chi² = 0.04 p = 0.98 I² = 0%	18/223	20/231	0.88 (0.49, 1.60) Z = 0.41 p = 0.68
Dose[a]					
1,200mg/day	3 [73 75 104]	Chi² = 0.53 p = 0.47 I² = 0%	14/424	25/424	0.57 (0.31, 1.03) Z = 1.86 p = 0.06
1,000mg/day	2 [80 86]	Chi² = 0.01 p = 0.91 I² = 0%	12/175	13/175	0.91 (0.44, 1.90) Z = 0.24 p = 0.81
800mg/day	4 [69 74 90 104]	Chi² = 0.70 p = 0.87 I² = 0%	30/437	32/449	0.95 (0.60, 1.53) Z = 0.19 p = 0.85
Length of follow-up					
⩽ 6 months	5 [73-75 78 81]	Chi² = 1.00 p = 0.80 I² = 0%	20/521	33/526	0.62 (0.37, 1.03) Z = 1.86 p = 0.06
> 6 months	5 [69 80 86 90 104]	Chi² = 0.43 p = 0.98 I² = 0%	42/573	44/578	0.96 (0.64, 1.43) Z = 0.22 p = 0.82
Sensitivity analyses					
Risk of bias funding declared					
Yes	8 [69 73-75 80 86 90 104]	Chi² = 1.04 p = 0.98 I² = 0%	49/973	55/986	0.90 (0.63, 1.29) Z = 0.58 p = 0.56
No	0				

Gastrointestinal-related adverse events	Number of studies	Heterogeneity	Chondroitin n/N	Placebo n/N	Relative difference RR (95% CI)
Unclear	2 [78 81]	Chi² = 0.77 p = 0.38 I² = 0%	13/121	22/118	0.58 (0.30, 1.10) Z = 1.67 p = 0.10
Risk of bias randomisation					
Yes	5 [69 75 80 81 86]	Chi² = 0.22 p = 0.97 I² = 0%	37/860	38/862	0.97 (0.63, 1.49) Z = 0.15 p = 0.88
No	0	NA	NA	NA	NA
Unclear	5 [73 74 78 90 104]	Chi² = 1.55 p = 0.82 I² = 0%	25/234	39/242	0.66 (0.42, 1.05) Z = 1.77 p = 0.08
Risk of bias allocation					
Yes	3 [69 75 104]	Chi² = 0.03 p = 0.87 I² = 0%	26/662	25/665	1.04 (0.62, 1.75) Z = 0.14 p = 0.89
No	0				
Unclear	7 [73 74 78 80 81 86 90]	Chi² = 1.64 p = 0.90 I² = 0%	36/432	52/439	0.70 (0.47, 1.04) Z = 1.77 p = 0.08
Risk of bias blinding of participants					
Yes	4 [69 75 78 81]	Chi² = 2.57 p = 0.28 I² = 11%	32/748	40/749	0.78 (0.46, 1.31) Z = 0.95 p = 0.34
No	0				
Unclear	6 [73 74 80 86 90 104]	Chi² = 0.60 p = 0.99 I² = 0%	30/346	37/355	0.82 (0.53, 1.28) Z = 0.86 p = 0.39
Risk of bias blinding of outcomes					
Yes	5 [69 74 80 90 104]	Chi² = 0.73 p = 0.95 I² = 0%	37/590	40/603	0.94 (0.61, 1.44) Z = 0.28 p = 0.78
No	2 [75 86]	NA	5/340	5/339	0.95 (0.32, 2.83) Z = 0.08 p = 0.93
Unclear	3 [73 78 81]	Chi² = 0.92 p = 0.63 I² = 0%	20/164	32/162	0.62 (0.37, 1.05) Z = 1.79 p = 0.07
Intention-to-treat analysis					
Yes	8 [69 73-75 80 81 86 90]	Chi² = 1.03 p = 0.98 I² = 0%	48/996	55/1,008	0.88 (0.61, 1.27) Z = 0.69 p = 0.49

Gastrointestinal-related adverse events	Number of studies	Heterogeneity	Chondroitin n/N	Placebo n/N	Relative difference RR (95% CI)
No	2 [78] [104]	Chi² = 1.39 p = 0.24 I² = 28%	14/98	22/96	0.65 (0.31, 1.34) Z = 1.17 p = 0.24
Unclear	0	NA	0	0	NA

Abbreviations
CI = confidence interval, **n** = number of patients, **N** = total number of participants, **NA** = not applicable, **RR** = risk ratio.
Notes
a = Mazieres 1992[160] did not report the dose of chondroitin sulfate administered in this trial.

Funnel Plots

Efficacy

No outcome had ten or more studies so assessment of publication bias using a funnel plot was deemed inappropriate.

Effectiveness

No outcome had ten or more studies so assessment of publication bias using a funnel plot was deemed inappropriate.

Safety

Two outcomes met the threshold for assessment of publication bias (***Figure 40*** and ***Figure 41***). Visual inspection of ***Figure 40*** indicates relative symmetry around the effect summary estimate. By contrast, ***Figure 41*** displays relative asymmetry around the effect summary estimate. Publication bias was not assessed for the remaining safety outcomes.

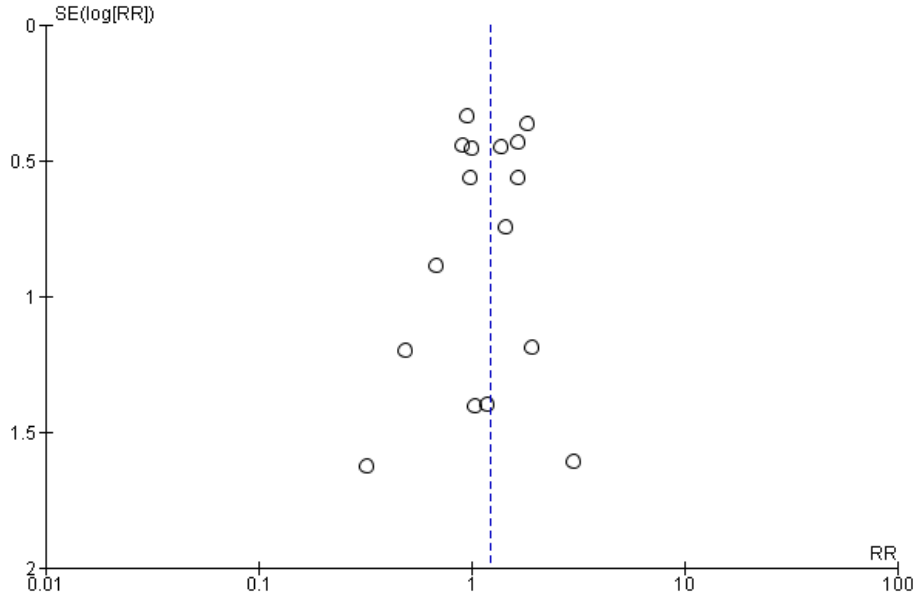

Figure 40 Chondroitin sulfate vs placebo: Funnel plot of withdrawal due to adverse events

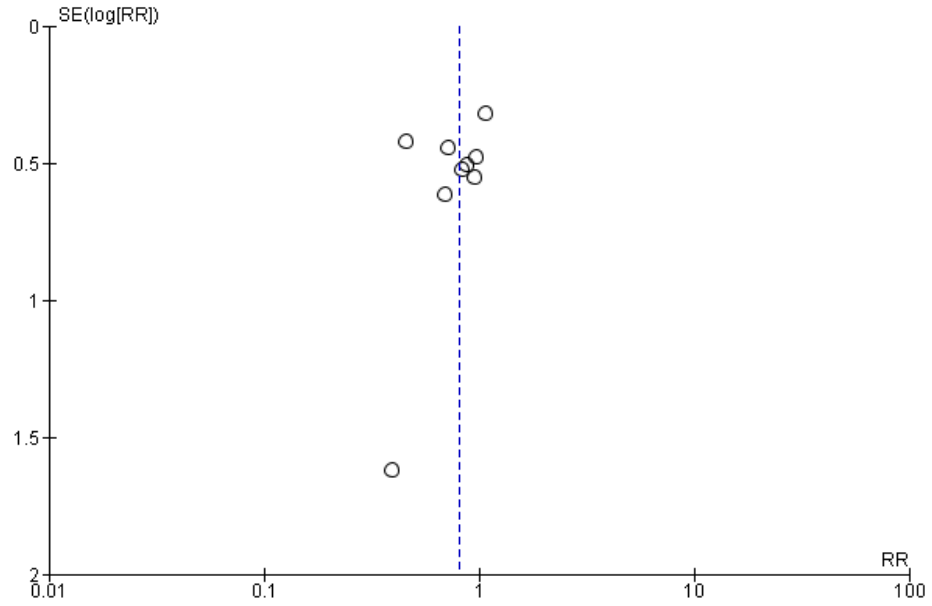

Figure 41 Chondroitin sulfate vs placebo: Funnel plot of gastrointestinal-related adverse events

18.1 Appendix D: Minimal Clinically Important Differences (MCIDs) and Improvements (MCII) for Outcomes of Interest

A non-systematic search was conducted to identify MCIDs and minimum clinically important improvement (MCII) for the outcomes of interest. The identified MCIDs were intended to act as a guide and were not a comprehensive assessment of the literature. The MCIDs generally relate to VAS or WOMAC scores for the hip or knee, with limited studies evaluating quality of life domains, Lequesne index or hand-related outcomes. The variability in the MCIDs relates to the use of anchor- or distribution-based methods, and differences in patient demographic and the type of intervention.

The applicability of the MCIDs and MCIIs to the current report is uncertain. There are differences with respect to population demographics and the interventions so caution should be taken when extrapolating the MCIDs to the outcomes listed in this report.

Table 84 Minimal clinically important differences/improvements for outcomes of interest

Outcome	MCID/MCII	Study type	Applicability	Reference
Hand				
Grip strength (kg/m^2)	5.0—6.5kg/m^2	I Systematic review	Intervention: Surgical repair, IV IG Demographic: Stroke, fracture, neuropathies, myotonic dystrophy	Bohannon 2019[161]
Pain VAS (0—100mm)	Relative -21% (95% CI, -24, -19%) Absolute 17mm (95% CI 18, 15)	IV Prospective Multicentre	Intervention NSAIDs Demographics Similar age, BMI	Tubach 2012[70]
Hip				
Pain VAS (0—100mm)	Relative -32.0% (95% CI -38.5, -24.0) Absolute -15.3mm (95% CI, -17.8, -12.5)	IV Prospective NR	Intervention: Onset of treatment or switching from NSAI Demographics: Similar age, BMI, gender	Tubach 2005[162]
	-18.6 mm	IV Prospective Single centre	Intervention: THA Demographic: Similar age, BMI, ethnicity and SF-12 scores	Danoff 2018[163]

Outcome	MCID/MCII	Study type	Applicability	Reference
WOMAC pain (100-point scale)	−29.26 to 35.8	I Systematic review	Intervention: NR Demographic: NR	Doganay 2016[164]
	8.3—41.0	I Systematic review	Intervention: THA Demographic: Similar age, gender, more severe osteoarthritis	MacKay 2019[165]
WOMAC function (100-point scale)	Relative -21.1% (95% CI -24.8, -17.0%) Absolute -7.9 (95% CI, -8.8, -5.0)	IV Prospective NR	Intervention: Onset of treatment or switching from NSAI Demographics: Similar age, BMI, gender	Tubach 2005[162]
	−26.54 to −9.42	I Systematic review	Intervention: NR Demographic: NR	Doganay 2016[164]
	9.7—34.0	I Systematic review	Intervention: THA Demographic: Similar age, gender, more severe osteoarthritis	MacKay 2019[165]
Joint space width	-0.2 to 0.4mm cut off values	IV Prospective Single centre	Intervention: NA Demographic: Similar age, BMI	Maillefert 2002a and b[166 167]
	0.22 to 0.78mm cut off values	I Systematic review	Intervention: NA Demographic: NA	Ornetti 2009[168]
Knee				
Lequesne index	0.5 SD	NR	Intervention: NR Demographic: NR	Singh 2015[30]
	0.7 points	I Pooled analysis of 3 trials	Intervention: NR Demographic: NR	Eberle & Ottillinger 1999[169]

Outcome	MCID/MCII	Study type	Applicability	Reference
Pain VAS (0—100mm)	Relative -40.8% (95% CI -44.87, -36.1) Absolute -19.9mm (95% CI, -21.6, -17.9)	IV Prospective NR	Intervention: Onset of treatment or switching from NSAI Demographics: Similar age, BMI, gender	Tubach 2005[162]
	−22.6 mm	IV Prospective Single centre	Intervention: TKA Demographic: Similar age, BMI, ethnicity and SF-12 scores	Danoff 2018[163]
WOMAC Pain (100-point scale)	−29.9 to −7.5 n = 3	I Systematic review	Intervention: NR Demographic: NR	Doganay 2016[164]
	13.3—36.0	I Systematic review	Intervention: TKA Demographic: Similar age, gender, more severe osteoarthritis	MacKay 2019[165]
	22.87—36.00	I Systematic review	Intervention: NSAIDs Demographic: NR	Collins 2011[170]
WOMAC function (100-point scale)	Relative -26.0% (95% CI, 28.6%, -23.3%) Absolute -9.1 (95% CI -10.5, -7.5)	IV Prospective NR	Intervention: Onset of treatment or switching from NSAI Demographics: Similar age, BMI, gender	Tubach 2005[162]
	−33.5 to −5.3 n = 6	I Systematic review	Intervention: NR Demographic: NR	Doganay 2016[164]
	1.8—33.0	I Systematic review	Intervention: TKA Demographic: Similar age, gender, more severe osteoarthritis	MacKay 2019[165]
	9.1	I Systematic review	Intervention: NSAIDs Demographic: NR	Collins 2011[170]

Outcome	MCID/MCII	Study type	Applicability	Reference
	19.01—33.00	I Systematic review	Intervention: TKA Demographic: NR	Collins 2011[170]
Joint space width	≥0.5mm cut off values	I Systematic review (ESCEO guidelines)	Intervention: NA Demographic: NA	Reginster 2015[9]
SF-12 Physical	5.0	IV Prospective Single centre	Intervention: TKA Demographic: Similar age, gender and BMI	Blevins 2019[171]
	1.8	IV Prospective Single centre	Intervention: TKA Demographic: Similar age, BMI	Clement 2019[172]
	4.3 (95% CI, 3.8, 4.8)	IV Prospective Single centre	Intervention: TKA Demographic: Similar age, gender	Clement 2014[173]
	1.7—4.2	IV Retrospective Single centre	Intervention: OAT Demographic: Different age, previous treatments	Ogura 2018[174]
SF-12 Mental	5.4	IV Prospective Single centre	Intervention: TKA Demographic: Similar age, gender, BMI	Blevins 2019[171]
	1.5 (NS)	IV Prospective Single centre	Intervention: TKA Demographic: similar	Clement 2019[172]
	1.8—4.6	IV Retrospective Single centre	Intervention: OAT Demographic: Different age, previous treatments	Ogura 2018[174]
HAQ disability	-0.57 (95% CI, -1.01, -0.12)	IV Retrospective Single centre	Intervention: None Demographic: Similar age, gender, different pathology (RA)	Pope 2009[175]

Outcome	MCID/MCII	Study type	Applicability	Reference
	-0.36 (95% CI, -0.55, -0.17)	IV Retrospective Single centre	Intervention: None Demographic: Similar age, gender, different pathology (PsA)	Kwok & Pope 2010[176]
	0.586	IV Prospective	Intervention: Etanercept Demographic: Different age, gender, different pathology (PsA)	Mease 2011[177]

Abbreviations:
BMI = body mass index, **CI** = confidence interval, **HAQ** = health assessment questionnaire**, IV IG** = intravenous immunoglobulin, **mm** = millimetre, **NA** = not applicable, **NR** = not reported, **NSAIDs** = non-steroidal anti-inflammatory drugs, **OAT** = osteochondral allograft transplantation, **PsA** = psoriatic arthritis, **RA** = rheumatoid arthritis, **SF-12** = 12-item short form survey, **THA** = total hip arthroplasty, **TKA** = total knee arthroplasty, **VAS** = visual analogue scale, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index.

18.2 Appendix E: GRADE Evidence Profile Tables

Efficacy

Table 85 GRADE evidence profile table for chondroitin sulfate vs placebo for knee osteoarthritis

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chondroitin sulfate	Placebo	Relative (95% CI)	Absolut (95% CI)		
Pain (follow-up 6 months; assessed with VAS and WOMAC)												
9	randomised trials	not serious	serious [a,b,c]	not serious	serious [d]	none	1,112	1,133	-	SMD 0.28 SD lower (0.47 lower to 0.09 lower)	⨁⨁◯◯ LOW	CRITICAL
Pain (follow-up 12 months; assessed with VAS and WOMAC)												
7	randomised trials	not serious	serious [a,b,e]	not serious	serious [d]	none	669	666	-	SMD 0.17 lower (0.37 lower to 0.02 higher)	⨁⨁◯◯ LOW	CRITICAL
Pain (follow-up 24 months; assessed with WOMAC, 10-point scale)												
4	randomised trials	not serious	serious [a,b,c]	not serious	serious [d]	none	679	680	-	SMD 0.24 lower (0.61 lower to 0.13 higher)	⨁⨁◯◯ LOW	CRITICAL
Paracetamol utilisation (follow-up 6 months; assessed with tablets/day)												

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chondroitin sulfate	Placebo	Relative (95% CI)	Absolut (95% CI)		
4	randomised trials	not serious	not serious [g]	serious [h]	not serious	publication bias strongly suspected [i]	729	734	-	MD 0.01 SD lower (0.07 lower to 0.04 higher)	⊕⊕◯◯ LOW	IMPORTANT
Paracetamol utilisation (follow-up 12 months; assessed with tablets/day, number of patients)												
2	randomised trials	serious [o]	not serious [n]	serious [h]	serious [k]	publication bias strongly suspected [i]	One study reported a statistically significant difference between CS and placebo groups and one study did not.				⊕◯◯◯ VERY LOW	IMPORTANT
Paracetamol utilisation (follow-up 24 months; assessed with tablets/day)												
1	randomised trials	not serious	not serious [n]	serious [h]	serious [k]	none	CS vs placebo 1.3 ± 1.6 vs 1.3 ± 1.8, p = NR				⊕⊕◯◯ LOW	IMPORTANT
NSAID utilisation (follow-up 6 months; assessed with units per month, number of patients, number of days used)												
3	randomised trials	serious [p]	serious [g]	serious [h]	serious [q]	none	One study reported a statistically significant difference between CS and placebo groups and two studies did not.				⊕◯◯◯ VERY LOW	IMPORTANT
NSAID utilisation (follow-up 24 months; assessed with number of patients, cumulative dose)												
2	randomised trials	not serious	not serious [n]	serious [h]	not serious	none	There was no statistically significant difference between CS and placebo groups in both studies.				⊕⊕⊕◯ MODERATE	IMPORTANT
OMERACT-OASRI responder rate (follow-up 6 months; assessed with % above or equal to OMERACT-OASRI threshold)												
3	randomised trials	not serious	not serious [g]	not serious	not serious	none	444/670 (66.3%)	377/672 (56.1%)	RR 1.08 (1.08 to 1.29)	86 more per 1,000 (from 35 more to 144 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Function (follow-up 6 months; assessed with VAS and WOMAC)												

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chondroitin sulfate**	**Placebo**	**Relative (95% CI)**	**Absolut (95% CI)**		
3	randomised trials	not serious	serious [b]	not serious	serious [d]	none	422	429	-	SMD 0.02 lower (0.24 lower to 0.21 higher)	⨁⨁◯◯ LOW	CRITICAL
Function (follow-up 12 months; assessed with VAS and WOMAC)												
3	randomised trials	not serious	serious [a b]	not serious	serious	none	252	250	-	SMD 0.17 (0.25 lower to 0.58 higher)	⨁⨁◯◯ LOW	CRITICAL
Function (follow-up 24 months; assessed with WOMAC)												
2	randomised trials	not serious	not serious	not serious	serious [d]	none	220	217	-	SMD 0.04 lower (0.23 lower to 0.14 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Lequesne index score (follow-up 6 months; assessed with Lequesne index)												
6	randomised trials	not serious	very serious [a,b,e]	not serious	serious [d]	none	491	516	-	MD 1.02 units lower (1.73 lower to 0.31 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Lequesne index score (follow-up 12 months; assessed with Lequesne index)												

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chondroitin sulfate	Placebo	Relative (95% CI)	Absolut (95% CI)		
2	randomised trials	serious [j]	not serious [f]	not serious	serious [d,k]	none	76	77	-	MD 0.89 SD lower (2.11 lower to 0.34 higher)	⊕⊕◯◯ LOW	CRITICAL
Function walk time (follow-up 6 months; assessed with 20m walk test)												
2	randomised trials	serious [m]	not serious [f]	not serious	serious [k]	none	93	102	-	MD 2.08 lower (4.37 lower to 0.2 higher)	⊕⊕◯◯ LOW	CRITICAL
Function walk time (follow-up 12 months; assessed with 20m walk test)												
2	randomised trials	not serious	serious [b]	not serious	serious [d,k]	none	205	207	-	SMD 0.17 lower (0.45 lower to 0.12 higher)	⊕⊕◯◯ LOW	CRITICAL
Function walk time (follow-up 24 months; assessed with 20m walk test)												
1	randomised trials	not serious	not serious	not serious	serious [k]	publication bias strongly suspected [l]	CS vs placebo 8.4 ± 1.7 vs 8.4 ± 1.9, p = 0.61				⊕⊕◯◯ LOW	CRITICAL
Quality of life (follow-up 6 months; assessed with SF-12)												
1	randomised trials	not serious	serious [g]	not serious	serious [k]	publication bias strongly suspected [i,l]	Statistically significant difference between CS and placebo groups with respect to the physical domain (p = 0.021) but not mental health domain (p = 0.72).				⊕◯◯◯ VERY LOW	CRITICAL
Quality of life (follow-up 12 months; assessed with SF-12)												
1	randomised trials	not serious	not serious [n]	not serious	serious [k]	publication bias strongly suspected [i]	There was no statistically significant difference between CS and placebo groups with respect to the physical or mental health domains.				⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chondroitin sulfate	Placebo	Relative (95% CI)	Absolut (95% CI)		
Quality of life (follow-up 24 months; assessed with SF-12)												
1	randomised trials	not serious	not serious [n]	not serious	serious [k]	none [i]	There was no statistically significant difference between CS and placebo groups with respect to the physical health domains. However, there was a difference between the groups in the mental health domain (p = 0.05).				⊕⊕⊕◯ MODERATE	CRITICAL
Health Assessment Questionnaire score (follow-up 6 months; assessed with HAQ)												
1	randomised trials	not serious	serious [g]	not serious	serious [k]	none	There was no statistically significant difference between CS and placebo groups with respect to the pain or disability domains.				⊕⊕◯◯ LOW	CRITICAL
Minimum joint space width (follow-up 24 months; assessed with joint space width)												
3	randomised trials	not serious	not serious [b]	serious [r]	serious [d]	none	576	584	-	SMD 0.19 higher (0.06 lower to 0.45 higher)	⊕⊕◯◯ LOW	IMPORTANT
Mean joint space width (follow-up 24 months; assessed with joint space width)												
1	randomised trials	not serious	not serious	serious [r]	serious [k]	none	CS vs placebo 0.00 ± 0.53 vs-0.14 ± 0.61 mm p = 0.04				⊕⊕◯◯ LOW	IMPORTANT

Abbreviations

CI = confidence interval, **CS** = Chondroitin sulfate, **GRADE** = Grading of Recommendations, Assessment, Development and Evaluations**, mm** = millimetre, **MD** = mean difference, **NSAID** = non-steroidal anti-inflammatory drugs, **OMERACT-OASRI** = Outcome Measures in Rheumatology Osteoarthritis Research Society International, **RR** = risk ratio, **SMD** = standardised mean difference, **VAS** = visual analogue scale, **vs** = versus, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index.

Notes

a = confidence intervals do not overlap in one or more studies.
b = measures of heterogeneity are moderate/considerable.
c = effect explained by manufacturer sub-group.
d = variance (95% CI) is moderate/large.

e = heterogeneity is not adequately explained by sub-group analysis.
f = measures of heterogeneity are low.
g = measure of variance within individual studies was moderate/large.
h = indirect measure of pain.
i = values not reported in text, results narratively surmised.
j = studies had notable drop-out, unclear whether per protocol or intention-to-treat analysis was performed.
k = small number of studies/participants.
l = baseline data reported only.
m = half the evidence base poorly reported randomisation, blinding and concealment.
n = measure of variance from individual studies was low.
o = half the evidence base had notable drop-out; performed per-protocol analysis; provided limited information on blinding method.
p = 2/3 studies poorly reported blinding, randomisation or concealment information.
q = variance not reported in one study.
r = surrogate outcome/indirect measure.

Table 86 GRADE evidence profile table for chondroitin sulfate vs placebo for hand osteoarthritis

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chondroitin sulfate	Placebo	Relative (95% CI)	Absolute (95% CI)		
Duration of morning stiffness (follow-up 6 months; assessed by self-reported)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	CS vs placebo 11.4 ±16.6 vs 12.0 ± 12.7, p = 0.031				⊕⊕⊕◯ MODERATE	IMPORTANT
Functional index hand osteoarthritis (follow-up 6 months; assessed with FIHOA)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	CS vs placebo 8.2 ± 5.9 vs 9.6 ± 5.6, p = 0.008				⊕⊕⊕◯ MODERATE	IMPORTANT
Grip strength (follow-up 6 months; assessed with grip test kg/m^2)												
1	randomised trials	not serious	not serious	not serious	not serious	none	CS vs placebo 26.5 ± 10.8 vs 25.6 ± 9.9, p = 0.132				⊕⊕⊕⊕ HIGH	IMPORTANT
Pain (follow-up 6 months; assessed with global assessment of hand pain, VAS)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	CS vs placebo 34.9 ± 25.3 vs 42.3 ± 24.9, p = 0.016				⊕⊕⊕◯ MODERATE	CRITICAL
Paracetamol utilisation (follow-up 6 months; assessed with tablets/week)												
1	randomised trials	not serious	not serious	serious [b]	serious [a]	none	CS vs placebo 1.9 ± 2.8 vs 2.0 ±4.2, p = NS				⊕⊕◯◯ LOW	IMPORTANT
Anatomical lesion progression score (follow-up 36 months; anatomical lesion progression score mm)												
1	randomised trials	not serious	not serious	serious [c]	serious [d]	none	There was no statistically significant difference between CS and placebo groups with respect to any joint.				⊕⊕◯◯ LOW	IMPORTANT

Abbreviations

CI = Confidence interval, **CS** = Chondroitin sulfate, **FIHOA** = functional index hand osteoarthritis**, GRADE** = Grading of Recommendations, Assessment, Development and Evaluations**, kg/m^2** = kilograms per metres squared, **mm** = millimetre, **NS** = not significant, **VAS** = visual analogue scale, **vs** = versus.

Notes

a = Measure of variance moderate/large.

b = Indirect measure of pain.

c = surrogate outcome/indirect measure.

d = measure of variance not reported.

Table 87 GRADE evidence profile table for chondroitin sulfate vs placebo for hip osteoarthritis

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chondroitin sulfate	Placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (follow-up 6 months; assessed with VAS)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,c,d]	strong association	CS vs placebo -42.6 ± NR vs -2 ± NR p < 0.0001				⨁⨁◯◯ LOW	Critical
Lequesne index score (follow-up 6 months; assessed with Lequesne index)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,c,d]	strong association	CS vs placebo -36 ± NR vs -6 ± NR p < 0.0001				⨁⨁◯◯ LOW	Critical
Maximum walking distance (follow-up 6 months; assessed with walking distance)												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	CS vs placebo 1727.3 ± 848.5 vs 1015.2 ± 454.5 p = NS				⨁⨁◯◯ LOW	Critical

Abbreviation

CI = confidence interval, **CS** = Chondroitin sulfate, **GRADE** = Grading of Recommendations, Assessment, Development and Evaluations**, m** = metres **mm** = millimetre, **NR** = not reported, **NS** = not significant, **vs** = versus.

Notes

a = notable drop-outs; unclear whether intention-to-treat analysis was performed; randomisation methods not reported.

b = measure of variance not reported.

c = small number of studies/participants.

d = measure of variance not reported.

Effectiveness

Table 88 GRADE evidence profile table for chondroitin sulfate vs NSAIDs for knee osteoarthritis

Certainty assessment							Number of patients			Effect	Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chondroitin sulfate	NSAIDs	Relative (95% CI)	Absolute (95% CI)		
Pain (follow-up 6 months; assessed with VAS and WOMAC)												
3	randomised trials	not serious	serious [a,b]	not serious	serious [c]	none	558	569	-	SMD 0.25 lower (0.13 lower to 0.64 higher)	⊕⊕◯◯ LOW	CRITICAL
Pain (follow-up 12 months; assessed with WOMAC)												
2	randomised trials	not serious	not serious [a,d]	not serious	serious [e]	none	149	160	-	SMD 0.19 higher (0.03 lower to 0.42 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Pain (follow-up 24 months; assessed with WOMAC)												
2	randomised trials	not serious	serious [a,b]	not serious	serious [c,e]	none	160	166	-	SMD 0.52 higher (0.11 lower to 1.15 higher)	⊕⊕◯◯ LOW	CRITICAL
OMERACT-OARSI responder rate (follow-up 6 months; assessed with % above or equal to OMERACT-OASRI threshold)												
3	randomised trials	serious [f]	not serious [d]	not serious	not serious	none	340/517 (65.8%)	347/517 (67.1%)	RR 0.98 (0.90 to 1.07)	13 fewer per 1,000 (from 67 fewer to 47 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							Number of patients			Effect	Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chondroitin sulfate	NSAIDs	Relative (95% CI)	Absolute (95% CI)		
Paracetamol Utilisation (follow-up 6 months; assessed with tablets/day)												
1	randomised trials	not serious	not serious	serious [g]	serious [e]	none	The number of tablets/days was similar between CS and NSAIDs in two studies p = NR				⨁⨁◯◯ LOW	IMPORTANT
Paracetamol Utilisation (follow-up 24 months; assessed with tablets/day)												
2	randomised trials	not serious	not serious	serious [g]	serious [e,h]	none	The number of tablets/days was similar between CS and NSAIDs in two studies p = NR				⨁⨁◯◯ LOW	IMPORTANT
Pain on loading (follow-up 6 months; assessed with 4-point ordinal scale (absent, light, moderate, intense))												
1	randomised trials	serious [i]	not serious [j]	not serious	serious [e]	none	CS vs NSAIDs 1.1 ± 0.5 vs 2.0 ± 0.5, p < 0.01				⨁⨁◯◯ LOW	IMPORTANT
Function (follow-up 6 months; assessed with WOMAC)												
2	randomised trials	not serious	serious [a,b]	not serious	serious [c]	none	398	396	-	SMD 0.40 higher (0.20 lower to 1.01 higher)	⨁⨁◯◯ LOW	CRITICAL
Function (follow-up 12 months; assessed with WOMAC)												
2	randomised trials	not serious	not serious	not serious	serious [c,e]	none	149	160	-	SMD 0.18 higher (0.05 lower to 0.40 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Function (follow-up 24 months; assessed with WOMAC)												

Certainty assessment							Number of patients			Effect	Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chondroitin sulfate	NSAIDs	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	not serious	serious [c,e]	none	160	166	-	SMD 0.18 higher (0.04 lower to 0.39 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Lequesne index (follow-up 6 months; assessed with Lequesne index)												
1	randomised trials	serious [f]	not serious	not serious	serious [c,e]	none	CS vs NSAIDs 7.1 ± 3.8 vs 7.0 ± 3.9 p = NR				⊕⊕◯◯ LOW	CRITICAL
Health Assessment Questionnaire (follow-up 6 months; assessed with HAQ)												
1	randomised trials	not serious	not serious	not serious	serious [e]	none	There was no difference between CS and NSAIDs in either the pain or disability domains p = NR				⊕⊕⊕◯ MODERATE	CRITICAL
Cartilage volume (follow-up 24 months; assessed with cartilage volume mm^3)												
1	randomised trials	not serious	not serious	serious [g]	serious [e]	none	CS vs NSAIDs Lateral -4.6 ± 3.0 vs -4.4 ± 2.8, p = 0.75 Medial -6.6 ± 3.3 vs -8.4 ± 4.2, p = 0.02				⊕⊕◯◯ LOW	IMPORTANT
Synovial membrane thickness (follow-up 24 months; assessed with Synovial membrane mm)												
1	randomised trials	not serious	not serious	serious [g]	serious [e]	none	CS vs NSAIDs 0.15 ± 0.26 vs 0.15 ± 0.24, p = 0.73				⊕⊕◯◯ LOW	IMPORTANT

Abbreviations

CI = confidence interval, **CS** = chondroitin sulfate, **GRADE** = Grading of Recommendations, Assessment, Development and Evaluations**, HAQ** = health assessment questionnaire, **NR** = not reported**, SMD** = standardised mean difference, **RR** = risk ratio, **MD** = mean difference, **NSAIDs** = non-steroidal anti-inflammatory drugs, **VAS** = visual analogue scale, **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index.

Notes

a = confidence intervals do not overlap in one or more studies.
b = measures of heterogeneity are moderate/considerable.
c = variance (95% CI) is moderate/large.
d = measures of heterogeneity are low.

e = small number of studies/participants.
f = notable drop-outs; performed per-protocol analysis and provided limited information regarding the randomisation process and blinding of treatments.
g = surrogate outcome/indirect measure.
h = variance was not reported in one study.
i = small number of studies/participants; notable drop-outs; per-protocol analysis.
j = measure of variance from individual studies was low.

Table 89 GRADE evidence profile table for chondroitin sulfate vs paracetamol for knee osteoarthritis

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chondroitin sulfate**	**Paracetamol**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pain (follow-up 6 months; assessed with VAS)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,c]	none	CS vs placebo 40.8 ± 22.0 vs 38.9 ± 27.7, p = 0.92				⨁⨁◯◯ LOW	CRITICAL
Lequesne index (follow-up 6 months; assessed with Lequesne index)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,c]	none	CS vs placebo 7.7 ± 3.3 vs 8.5 ± 4.6, p = 0.22				⨁⨁◯◯ LOW	CRITICAL

Abbreviations
CI = confidence interval, **CS** = chondroitin sulfate, **GRADE** = Grading of Recommendations, Assessment, Development and Evaluations**, mm** = millimetre, **VAS** = visual analogue scale.
Notes
a = single-blinded; per protocol analysis.
b = measure of variance moderate/large.
c = small number of studies/participants.

Safety

Table 90 GRADE evidence profile table for chondroitin sulfate vs placebo for knee osteoarthritis

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chondroitin sulfate	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up range 3 months to 24 months; assessed by total number of patients)												
3	randomised trials	not serious	not serious	not serious	not serious [a]	none	1/467 (0.2%)	1/472 (0.2%)	not pooled	-	⊕⊕⊕⊕ HIGH	CRITICAL
Withdrawal due to adverse events (follow-up range 3 to 24 months; assessed by total number of patients)												
17	randomised trials	not serious	not serious	not serious	serious [a,b]	none	104/1,950 (5.3%)	86/1,970 (4.4%)	RR 1.21 (0.92 to 1.61)	9 more per 1,000 (from 3 fewer to 27 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Severe adverse events (follow-up range 3 to 24 months; assessed by total number of patients)												
5	randomised trials	not serious	not serious	not serious	serious [a,b]	none	23/496 (4.6%)	25/504 (5.0%)	RR 0.97 (0.49 to 1.95)	1 fewer per 1,000 (from 25 fewer to 47 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Treatment-related severe adverse events (follow-up range 6 to 24 months; assessed by total number of patients)												
5	randomised trials	not serious	not serious	not serious	serious [a,b]	none	1/695 (0.1%)	2/705 (0.3%)	RR 0.64 (0.08 to 5.15)	1 fewer per 1,000 (from 3 fewer to 12 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Any adverse event (follow-up range 3 to 24 months; assessed by total number of patients)												
8	randomised trials	not serious	not serious	not serious	serious [a,b]	none	258/616 (41.9%)	288/619 (46.5%)	RR 0.93 (0.81 to 1.05)	33 fewer per 1,000 (from 88 fewer to	⊕⊕⊕◯ MODERATE	IMPORTANT

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chondroitin sulfate	Placebo	Relative (95% CI)	Absolute (95% CI)		
										23 more)		
Treatment-related adverse event (follow-up range 3 to 24 months; assessed by total number of patients)												
7	randomised trials	not serious	not serious	not serious	serious [a,b]	none	30/496 (6.0%)	36/505 (7.1%)	RR 0.82 (0.52 to 1.30)	13 fewer per 1,000 (from 34 fewer to 21 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Gastrointestinal-related adverse event (follow-up range 3 months to 24 months; assessed by total number of patients)												
10	randomised trials	not serious	not serious	not serious	serious [b]	none	62/1,094 (5.7%)	77/1,104 (7.0%)	RR 0.81 (0.59 to 1.11)	13 fewer per 1,000 (from 29 fewer to 8 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

Abbreviations

CI = confidence interval, **GRADE** = Grading of Recommendations, Assessment, Development and Evaluations**, RR** = risk ratio, **SMD** = standardised mean difference.

Notes

a = variance (95% CI) is moderate/large.

b = small number of studies, participants or events.

Table 91 GRADE evidence profile table for chondroitin sulfate vs placebo for hand osteoarthritis

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chondroitin sulfate	Placebo	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow-up range 6 to 36 months; assessed by total number of patients)												
2	randomised trials	not serious	not serious	not serious	serious [a,b]	none	4/124 (3.2%)	8/130 (6.2%)	RR 0.67 (0.11 to 4.28)	20 fewer per 1,000 (from 55 fewer to 202 more)	⊕⊕◯◯ LOW	CRITICAL
Severe adverse events (follow-up 6 months; assessed by total number of patients)												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	2/80 (2.5%)	2/82 (2.4%)	not estimable	-	⊕⊕⊕◯ MODERATE	CRITICAL
Treatment-related severe adverse events (follow-up 6 months; assessed by total number of patients)												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	0/80 (0.0%)	1/82 (1.2%)	not estimable	-	⊕⊕⊕◯ MODERATE	CRITICAL
Any adverse event (follow-up 6 months; assessed by total number of patients)												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	34/80 (42.5%)	34/82 (41.5%)	not estimable	-	⊕⊕⊕◯ MODERATE	IMPORTANT
Treatment-related adverse event (follow-up 6 months; assessed by total number of patients)												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	13/80 (16.3%)	19/82 (23.2%)	not estimable	-	⊕⊕⊕◯ MODERATE	IMPORTANT

Abbreviations

CI = confidence interval, **GRADE** = Grading of Recommendations, Assessment, Development and Evaluations**, RR** = risk ratio.

Notes

a = variance (95% CI) is moderate/large.

b = small number of studies, participants or events.

Table 92 GRADE evidence profile table for chondroitin sulfate vs placebo for hip osteoarthritis

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chondroitin sulfate	Placebo	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events (follow-up 6 months; assessed by total number of patients)												
1	randomised trials	serious	not serious	not serious	serious [a]	none	0/29 (0.0%)	3/27 (11.1%)	not estimable	-	⨁⨁⨁◯ MODERATE	CRITICAL

Abbreviations
CI = confidence interval, **GRADE** = Grading of Recommendations, Assessment, Development and Evaluations.
Notes
a = small number of studies, participants or events.

Table 93 GRADE evidence profile table for chondroitin sulfate vs NSAIDs for knee osteoarthritis

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chondroitin sulfate	NSAIDs	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up range 6 months to 24 months; assessed by total number of patients)												
3	randomised trials	not serious	not serious	not serious	not serious	none	0/541 (0.0%)	0/557 (0.0%)	not pooled	-	⊕⊕⊕⊕ HIGH	CRITICAL
Withdrawal due to adverse events (follow-up range 6 to 24 months; assessed by total number of patients)												
3	randomised trials	not serious	not serious	not serious	serious [b]	none	26/614 (4.2%)	41/614 (6.7%)	RR 1.51 (0.81 to 2.84)	22 more per 1,000 (from 85 fewer to 78 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Severe adverse events (follow-up 24 months; assessed by total number of patients)												
2	randomised trials	not serious	serious [c]	not serious	serious [b]	none	16/223 (7.2%)	29/239 (12.1%)	RR 0.69 (0.13 to 3.80)	38 fewer per 1,000 (from 106 fewer to 340 more)	⊕⊕◯◯ LOW	CRITICAL
Treatment-related severe adverse events (follow-up range 6 to 24 months; assessed by total number of patients)												
3	randomised trials	not serious	not serious	not serious	serious [b]	none	1/541 (0.2%)	5/557 (0.9%)	RR 0.40 (0.07 to 2.19)	5 fewer per 1,000 (from 8 fewer to 11 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Any adverse event (follow-up 24 months; assessed by total number of patients)												
1	randomised trials	not serious	not serious	not serious	very serious [b,d]	none	78/97 (80.4%)	77/97 (79.4%)	RR 1.01 (0.88 to 1.17)	8 more per 1,000 (from 95 fewer to 135 more)	⊕⊕◯◯ LOW	IMPORTANT
Treatment-related adverse events (follow-up range 6 to 24 months; assessed by total number of patients)												

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chondroitin sulfate**	**NSAIDs**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	not serious	serious [d]	none	27/97 (27.8%)	24/97 (24.7%)	RR 1.13 (0.70 to 1.80)	36 more per 1,000 (from 84 fewer to 223 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Gastrointestinal adverse event (follow-up range 6 to 24 months; assessed by total number of patients)												
2	randomised trials	not serious	not serious	not serious	not serious	none [e]	29/415 (7.0%)	27/415 (6.5%)	RR 0.93	5 fewer per 1,000 (from 28 fewer to 31 more)	⨁⨁⨁⨁ HIGH	IMPORTANT

Abbreviations

CI = confidence interval, **GRADE** = Grading of Recommendations, Assessment, Development and Evaluations**, NSAIDs** = non-steroidal anti-inflammatory drugs, **RR** = Risk ratio.

Notes

b = variance (95% CI) is moderate/large.

c = heterogeneity measures were moderate/large.

d = small number of studies, participants or events.

e = short follow-up unlikely to sufficiently capture adverse events associated with long-term NSAID use.

Table 94 GRADE evidence profile table for chondroitin sulfate vs paracetamol for knee osteoarthritis

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chondroitin sulfate	Paracetamol	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse event (follow-up 6 months; assessed by total number of patients)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	0/35 (0.0%)	0/33 (0.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
Any adverse event (follow-up 6 months; assessed by total number of patients)												
1	randomised trials	not serious	not serious	not serious	serious [a]	strong association	1/35 (2.9%)	12/33 (36.4%)	not estimable		⊕⊕⊕◯ MODERATE	IMPORTANT
Treatment-related adverse event (follow-up 6 months; assessed by total number of patients)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	0/35 (0.0%)	0/33 (0.0%)	not estimable		⊕⊕⊕◯ MODERATE	IMPORTANT

Abbreviations

CI = confidence interval, **GRADE** = Grading of Recommendations, Assessment, Development and Evaluations.

Notes

a = small number of studies, participants or events.

18.3 Appendix G: Patient and Physician Organisation Surveys

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Eidgenössisches Departement des Innern EDI
Bundesamt für Gesundheit BAG
Direktionsbereich Kranken- und Unfallversicherung

Fragebogen für Ärztinnen und Ärzte: "Chondroitinsulfat bei Arthrose"

Das Bundesamt für Gesundheit (BAG) führt eine Evaluation von Chondroitinsulfat zur Behandlung von Patientinnen und Patienten mit Arthrose in Knien, Hüften und Händen durch.

Im Rahmen dieser Evaluation sammelt das BAG Meinungen von Ärztinnen und Ärzten zum Einsatz von Chondroitinsulfat, zum Umgang mit Arthrose-Patientinnen und -Patienten und zu den möglichen Auswirkungen eines Wegfalls der Vergütung von Chondroitinsulfat durch die obligatorische Krankenpflegeversicherung (OKP).

Diese Umfrage richtet sich nicht an Einzelpersonen, sondern soll von Ärztegruppen oder Fachorganisationen beantwortet werden.

Wir danken Ihnen für Ihre Teilnahme.

Fragen:

1. **Wie werden den Patientinnen und Patienten die Behandlungsmöglichkeiten gegen Arthrose erklärt?**

2. **Spielen die Patientinnen und Patienten eine aktive Rolle bei der Entscheidung, welche Medikamente ihnen verschrieben werden?**

3. **Wie viel Prozent der Patientinnen und Patienten mit Arthrose werden die folgenden Medikamente verschrieben?**

(Hinweis: bestmögliche Schätzung, verbindliche Zahlen sind möglicherweise nicht verfügbar; das Total kann mehr als 100% betragen, wenn Patientinnen und Patienten mehr als ein Medikament erhalten)

- o Chondroitinsulfat ..... ___%
- o Paracetamol ..... ___%
- o Nicht-selektive, *nicht-steroidale* Entzündungshemmer (z.B. Ibuprofen) ..... ___%
- o COX-2-selektive NSAR (z.B. Celecoxib)..... ___%
- o Opiate..... ___%

- Andere (bitte mittels Klick hier angeben) Physiotherapie (nicht-medikamentös)___%

4. **Was – falls überhaupt – würde sich für die Medikamente, die bei Patientinnen und Patienten mit Arthrose verschrieben werden, in Bezug auf die in Frage 3 angegebenen Prozentsätze ändern, wenn Chondroitinsulfat nicht von der OKP vergütet würde?**

5. **Welche Auswirkungen hätte eine Medikationsänderung (z.B. durch den Wegfall der Vergütung von Chondroitinsulfat) auf Patientinnen und Patienten mit Arthrose und/oder deren Familien und Pflegepersonal?**

6. **Ist es wahrscheinlich, dass Patientinnen und Patienten Chondroitinsulfat aus eigener Tasche bezahlen, wenn es nicht von der OKP vergütet wird?**

7. **Könnte der Wegfall der Vergütung von Chondroitinsulfat das Arzt-Patienten-Verhältnis beeinträchtigen? Wenn ja, beschreiben Sie bitte, wie.**

8. **Haben Sie weitere Anmerkungen zur Behandlung von Arthrose mit Chondroitinsulfat?**

9. **Haben Sie Anmerkungen zu dieser Umfrage? Bitte geben Sie Kommentare ab oder unterbreiten Sie Vorschläge dazu, wie dieser Prozess verbessert werden könnte.**

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Direktionsbereich Kranken- und Unfallversicherung

Fragebogen für Patientinnen und Patienten: "Chondroitinsulfat bei Arthrose"

Das Bundesamt für Gesundheit (BAG) führt eine Evaluation von Chondroitinsulfat zur Behandlung von Patientinnen und Patienten mit Arthrose in Knien, Hüften und Händen durch.

Im Rahmen dieser Evaluation sammelt das BAG Meinungen von Patientinnen und Patienten zum Einsatz von Chondroitinsulfat, zum Umgang mit Arthrose-Patientinnen und -Patienten und zu den möglichen Auswirkungen einer Medikationsänderung.

Diese Umfrage richtet sich nicht an Einzelpersonen, sondern soll von Patientengruppen oder Patientenorganisationen beantwortet werden.

Wir danken Ihnen für Ihre Teilnahme.

Fragen:

1. **Wie werden den Patientinnen und Patienten die Behandlungsmöglichkeiten gegen Arthrose erklärt?**

2. **Spielen die Patientinnen und Patienten eine aktive Rolle bei der Entscheidung, welche Medikamente ihnen verschrieben werden?**

3. **Welche wahrgenommenen Vorteile bietet Chondroitinsulfat für Patientinnen und Patienten mit Arthrose und/oder deren Familien und Pflegepersonal (z.B. Schmerzlinderung, Mobilität, Lebensqualität)?**

4. **Welche wahrgenommenen Nachteile hat Chondroitinsulfat für Patientinnen und Patienten mit Arthrose und/oder deren Familien und Pflegepersonal (z.B. Nebenwirkungen)?**

5. **Wenn Chondroitinsulfat nicht von der obligatorischen Krankenpflegeversicherung (OKP) vergütet würde, welche anderen Möglichkeiten hätten Patientinnen und Patienten zur Behandlung ihrer Arthrose-Symptome?**

6. **Wie würde sich ein Behandlungswechsel zu einer der unter Frage 5 aufgeführten alternativen Behandlungsmöglichkeiten auf die Patientinnen und Patienten und/oder deren Familien und Pflegepersonal auswirken?**

7. **Würden Patientinnen und Patienten das Chondroitinsulfat aus eigener Tasche bezahlen, wenn es nicht aus der OKP vergütet würde? Falls ja, welcher Prozentsatz der Patientinnen und Patienten würde das tun?**

8. **Haben Sie weitere Anmerkungen zur Behandlung von Arthrose mit Chondroitinsulfat?**

9. **Haben Sie Anmerkungen zu dieser Umfrage? Bitte geben Sie Kommentare ab oder unterbreiten Sie Vorschläge dazu, wie dieser Prozess verbessert werden könnte.**