

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal determination

**Collagenase clostridium histolyticum for
treating Dupuytren's contracture**

1 Recommendations

- 1.1 People who meet the inclusion criteria for the ongoing clinical trial ([HTA-15/102/04](#)), comparing collagenase clostridium histolyticum (CCH) to limited fasciectomy, are encouraged to participate in the study.
- 1.2 For people not taking part in the ongoing clinical trial, CCH is recommended as an option for treating Dupuytren's contracture with a palpable cord in adults only if all of the following apply:
- There is evidence of moderate disease (functional problems and metacarpophalangeal joint contracture of 30° to 60° and proximal interphalangeal joint contracture of less than 30° or first web contracture) plus up to 2 affected joints.
 - Percutaneous needle fasciotomy (PNF) is not considered appropriate, but limited fasciectomy is considered appropriate by the treating hand surgeon.
 - The choice of treatment (CCH or limited fasciectomy) is made on an individual basis after discussion between the responsible hand surgeon and the patient about the risks and benefits of the treatments available.
 - 1 injection is given per treatment session by a hand surgeon in an outpatient setting.

- 1.3 These recommendations are not intended to affect treatment with CCH that was started in the NHS before this guidance was published. Adults having treatment outside this recommendation may continue their current course without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Collagenase clostridium histolyticum reduces hand contracture compared with placebo in randomised controlled trials. But there were no randomised trials comparing the clinical effectiveness of CCH with current NHS treatment for Dupuytren's contracture (surgery with PNF or limited fasciectomy), which made the results of the cost-effectiveness analysis very uncertain.

CCH is the first pharmacological treatment to get a marketing authorisation for treating Dupuytren's contracture. Although there are uncertainties in the available evidence, it has the potential to offer benefits compared with current treatments, including avoiding a general anaesthetic and a shorter recovery time.

For people with moderate disease (plus up to 2 affected joints), CCH is a potentially cost effective option when 1 injection per treatment session is given in an outpatient setting and when PNF is not appropriate but limited fasciectomy is an option. However, there is a risk to the NHS in funding a treatment that may not prove to be cost effective when further data become available.

Additional research is needed before a broader recommendation for CCH can be made. A [multicentre trial](#) starting in 2017 will provide more clinical and cost effectiveness evidence for CCH compared with limited fasciectomy. There were concerns that if CCH is recommended for people with moderate Dupuytren's

contracture, people may choose to have treatment with CCH rather than take part in the clinical trial, even though there is no evidence to show CCH has better or worse outcomes than limited fasciectomy. CCH is therefore recommended under very specific conditions to allow access to CCH in a way that supports the ongoing trial and manages risk to the NHS while further clinical and cost effectiveness data are collected.

If recruitment to the ongoing clinical trial falls below predicted levels, the guidance will be considered for early review.

2 The technology

Collagenase clostridium histolyticum (Xiapex; Sobi)	
Marketing authorisation	Collagenase clostridium histolyticum (CCH) is indicated for treating Dupuytren's contracture in adults with a palpable cord.
Recommended dose and schedule	<p>The recommended dose of CCH is 0.58 mg per injection into a palpable Dupuytren's cord. The volume of solvent needed and the volume of reconstituted CCH to be administered into the cord differs depending on the type of joint being treated.</p> <ul style="list-style-type: none"> • For cords affecting metacarpophalangeal joints, each dose is administered in an injection volume of 0.25 ml. • For cords affecting proximal interphalangeal joints, each dose is administered in an injection volume of 0.20 ml. <p>Injections in up to 2 cords or 2 affected joints in the same hand can be given during a treatment visit. Two palpable cords affecting 2 joints may be injected or 1 palpable cord affecting 2 joints in the same finger may be injected at 2 locations during a treatment visit. Each injection contains a 0.58 mg dose. If the disease has resulted in multiple contractures, additional cords may be treated at other treatment visits approximately 4 weeks apart.</p>
Price	<p>CCH proposed list price is £572 per 0.90 mg vial excluding VAT.</p> <p>Costs may vary in different settings because of negotiated procurement discounts.</p>

3 Committee discussion

The appraisal committee (see section 7) considered evidence from a number of sources. See the [committee papers](#) for full details of the evidence.

Current treatment

Patients and clinicians would welcome effective new treatments for moderate and severe Dupuytren's contracture

3.1 The clinical experts explained that people with mild disease are not usually offered treatment because there is a risk of making the condition worse. The committee recognised that, in the NHS, the most common treatment for moderate or severe disease is limited fasciectomy and fewer people have percutaneous needle fasciotomy (PNF) or collagenase clostridium histolyticum (CCH). It heard that the choice of treatment is made on an individual basis and is influenced by disease severity, patient preference and the clinician's expertise. The committee heard from the clinical experts that CCH and PNF are most suitable for people with moderate disease when a fast recovery time is important. It also heard that limited fasciectomy is used for both moderate and severe disease, but it is a more invasive treatment with a longer recovery time. The committee was aware that its remit was to appraise CCH, and therefore it could not make recommendations about the use of other treatments. It was also aware that the multiple technology appraisal process had been used because of the difficulty in comparing the effectiveness of CCH and surgery. The committee recognised that contractures often recur, even after successful treatment, and the choice of treatment after recurrence varies. It understood that people prefer to have a choice of treatments. The committee concluded that effective new treatments for moderate and severe Dupuytren's contracture would be welcomed by both patients and clinicians.

The population

CCH may be more clinically and cost effective for some groups of people with moderate disease

- 3.2 The committee recalled that the scope covered a broad population of adults with Dupuytren's contracture and did not specify disease severity or the number of affected joints. The committee accepted that people with mild disease are not usually offered treatment and therefore it was not necessary to include this group in the appraisal. It heard from the company and the clinical experts that there are subgroups of people for whom CCH may be more clinically effective and cost effective, such as those with moderate disease and few affected joints. The committee concluded that the appraisal should consider a population of people with moderate and severe Dupuytren's contracture but that it was appropriate to explore subgroups within this population.

Comparators

PNF and limited fasciectomy are relevant comparators for CCH

- 3.3 The committee was aware that the company had excluded PNF as a comparator, despite its inclusion in the scope, because in the company's opinion PNF is rarely used in England. Nonetheless, the committee heard from the clinical experts that PNF is part of established practice in the NHS. It noted that NICE interventional procedures guidance on [needle fasciotomy for Dupuytren's contracture](#) states that the evidence supports the use of PNF with normal arrangements for consent, audit and clinical governance. The committee concluded that PNF and limited fasciectomy are the relevant comparators for this appraisal.

Subgroups

There is no clear definition of the people for whom PNF would not be suitable

- 3.4 The committee discussed whether there was a subgroup of people for whom PNF would not be suitable, and therefore not a relevant comparator. It noted that there was no consensus regarding a subgroup of patients with Dupuytren's contracture for whom CCH would be a suitable treatment but PNF would not be suitable. Having reviewed the submissions, expert advice and responses to consultation, the committee considered that there was a lack of agreement about the clinical characteristics that would make CCH but not PNF suitable for treating the contracture. The committee was also aware that it had not been presented with any evidence of the clinical and cost effectiveness of CCH in these people. The committee concluded that although it had not been presented with a clear definition of the people whose disease is unsuitable for PNF, it acknowledged that this group may exist in clinical practice.

Availability of PNF

PNF is an established treatment in the NHS, making it a relevant comparator

- 3.5 The committee heard from the clinical experts and the patient expert that PNF is not available in some regions of England because some clinicians choose not to do PNF, or may not be trained in PNF. The committee noted that this advice was supported by the responses to consultation. It heard that, based on hospital episode statistics in England between 2012 and 2013, PNF accounted for approximately 8% of all procedures for Dupuytren's contracture. However, it noted that this estimate was based on the overall population of people with Dupuytren's contracture. It agreed that a higher proportion of people with moderate disease may have PNF, because clinical experts advised that PNF is most suitable for

this subgroup. The committee observed that there were different opinions about the level of skill needed to do PNF. A clinical expert advised that a clinician who was able to administer CCH would also have the skills needed to do PNF. The committee noted that this implied that patients for whom CCH was available would also have access to PNF. However, it was aware that this advice was contradicted by responses to consultation which stated that it is easier to use CCH than to do PNF. The committee considered that it was beyond the scope of this appraisal to make recommendations on the use of PNF or to address the reasons for geographical variation in its use. It concluded that the use of PNF was sufficiently established within the NHS to make it a relevant comparator for this appraisal.

Clinical evidence

CCH is clinically effective and the evidence is relevant to the NHS

3.6 The committee considered that the randomised controlled CORD trials used appropriate methods and the results were likely to be generalisable to the NHS. The committee noted that the assessment group's meta-analysis, which was based largely on the CORD trials, showed that CCH was more effective than placebo in reducing contracture. The committee concluded that, compared with placebo, CCH is a clinically effective treatment for Dupuytren's contracture.

There is limited evidence comparing CCH with current NHS practice

3.7 The committee was aware that no randomised trials had directly compared CCH with PNF or limited fasciectomy. An indirect comparison was not possible because the published trials did not share a common comparator; the CCH trials were against placebo, and the surgical trials compared 2 types of surgery. The committee was aware of responses to consultation that called for further

research into the comparative clinical effectiveness of treatments for Dupuytren's contracture. It also noted that the National Institute for Health Research had called for applications in 2015 for research funding to examine the clinical effectiveness of CCH compared with surgery. The committee was aware that a pragmatic multicentre non-inferiority trial will start in 2017 comparing injections of CCH with surgical correction for treating moderate Dupuytren's in adults (see section 3.37). The committee noted that the success rates seen in clinical studies varied widely for all treatments. It heard from the clinical experts that success rates depended on the skill of the clinician and the severity of disease, with higher success rates for moderate than for severe disease. The committee observed that this advice was supported by post hoc subgroup analyses of the CORD studies and POINT X trial. In the CORD studies success was seen in 46/57 (81%) people with moderate disease and 51/95 (54%) of people with severe disease. The POINT X analysis showed a success rate of 66% in the moderate-disease subgroup. Given the lack of data comparing CCH with the treatments currently used in the NHS, the committee concluded that further research was needed to establish whether CCH was more or less effective than PNF and limited fasciectomy.

Recurrence rates in the trials and clinical practice

The recurrence rates for current care are uncertain

3.8 The committee was aware that the CORDLESS study (of CCH) and the post hoc analyses by Van Rijssen et al. (2012; of limited fasciectomy and PNF) used the same definition of recurrence, that is, an increase in contracture of at least 20° in a successfully treated joint. These studies indicated that recurrence was lowest with limited fasciectomy and highest with CCH, with PNF in between. In contrast, the committee heard from the clinical experts that recurrence was typically lowest with limited fasciectomy and

highest with PNF, with CCH in between. The committee considered possible explanations for the discrepancy between the trial results and clinical experience. It recalled that the trials included different populations: people in the Van Rijssen et al. trial had not previously had surgery for Dupuytren's contracture, in contrast to 38% and 53% of people in the CORD I and II studies respectively. The committee was not presented with data on whether people in CORDLESS had previously had surgery but, because CORDLESS included people from CORD I and II, it is likely that some people in CORDLESS had previously had surgery. The committee heard from the clinical experts that people with a history of recurrence had a higher risk of further recurrence. The committee considered that the difference in population may partly explain why recurrence was lower in the Van Rijssen et al. trial than in CORDLESS. The committee also heard from the company that the recurrence rate for limited fasciectomy from the Van Rijssen et al. trial was lower than in many other studies. The committee accepted the clinical experts' views that recurrence was typically lowest with limited fasciectomy and highest with PNF, with CCH in between. The committee concluded that there was substantial uncertainty about the recurrence rates likely to be seen in clinical practice for each of these treatments.

Study populations

The different populations made the trials difficult to compare

3.9 The committee had noted that some trials recruited different populations, making it difficult to compare the results. It discussed the company's analysis of CORDLESS, POINT X and Van Rijssen et al., from which the company concluded that 'the differences in the study populations [did] not affect the comparability of the efficacy results.' Having discussed the evidence, the committee agreed with the assessment group's advice that the company's

analysis only included a subgroup of the people in CORDLESS and POINT X, and therefore the results did not imply that differences between complete trial populations can be ignored. The committee also noted that the aim of the company's analysis was to assess the potential bias in the comparison, rather than to re-estimate the success and recurrence rates. The committee concluded that the company's comparison of the trial populations did not alter its conclusions in section 3.7.

Recovery

Recovery time after CCH is shorter than after limited fasciectomy

3.10 The committee noted that there was a lack of evidence on recovery time from randomised controlled trials comparing CCH with surgery. It was aware that, in response to consultation, patient experts and clinical experts advised that recovery time is longer after limited fasciectomy than after CCH. The committee discussed the additional evidence submitted by the company in response to consultation, which showed that some people report that their hand function has not fully recovered 12 months after limited fasciectomy. The committee noted that these results came from the Engstrand et al. (2014) study, which appeared to recruit a population with more severe contracture than the CORD studies. It also noted that most people in Engstrand et al. reported that hand function was much better, or fully recovered, only 3 months after surgery. The committee concluded that recovery time after limited fasciectomy was likely to be longer than after CCH, but was unlikely to extend to 12 months for most people.

Adverse events

The risk of adverse events after CCH treatment is low and comparable to current care

- 3.11 The committee noted that almost all people had at least 1 adverse event after having CCH, and the adverse events were normally mild or moderate. The committee heard from the clinical experts that the clinical trials of CCH used stringent definitions of adverse events, and if the same definitions were applied to surgery, then as many people would have mild or moderate adverse events after surgery as after treatment with CCH. The committee noted that a small number of serious adverse events had occurred after treatment with CCH, but the risk was low and comparable to surgery. The committee concluded that CCH had an acceptable safety profile.

Administering CCH

CCH should be given by clinicians with advanced knowledge of hand anatomy who have done the company's training

- 3.12 The committee discussed the level of competency needed to give CCH safely. It heard from the clinical experts that CCH must be given correctly to minimise the risk of adverse events. The committee also heard from the clinical experts that clinicians are expected to complete a training programme provided by the company before using CCH. The committee concluded that CCH should only be given by suitably qualified clinicians who have an advanced knowledge of the anatomy of the hand and have completed the company's training.

The company's economic model

The company's economic model is not suitable for decision-making

- 3.13 The committee discussed the company's cost–minimisation model noting that the analysis excluded PNF, which is a relevant comparator (see section 3.3). It was aware that a cost–minimisation analysis assumes equal efficacy for all clinical outcomes of the included treatments (that is, CCH and limited fasciectomy), and that

there was no evidence from randomised controlled trials to support that assumption. It was also aware that the NICE [guide to the methods of technology appraisal](#) recommends cost–utility analysis. The committee concluded that a cost–minimisation analysis was not an appropriate method of assessing the cost effectiveness of CCH and that the analysis was further limited because it excluded PNF.

The assessment group's economic model

The assessment group's economic model is based on the best available evidence

3.14 The committee discussed the assessment group's cost–utility model, which was based on a naive indirect comparison. It was aware that this comparison did not maintain randomisation and made no adjustment for differences between studies. It understood that, with this type of comparison, the data are observational and the results are associated with increased uncertainty. However, the committee recognised that a naive indirect comparison was necessary since there were no head-to-head trials comparing CCH with surgery. An indirect comparison was not possible because the trials did not include a common comparator arm (the CCH trials were against placebo and the surgical trials compared 2 types of surgery). It concluded that the assessment group's model was based on the best available evidence. It also concluded that, given the uncertainty in the results of the naive indirect comparison, it was appropriate to ask clinical and patient experts whether the model used appropriate success rates, recurrence rates and rates of adverse events.

The population in the economic model

Separate analyses for moderate and severe disease are needed

- 3.15 The committee discussed the modelled population. It noted that the assessment group's original model included people with moderate or severe Dupuytren's contracture in 1 hand, and the committee agreed that this reflected the overall population in the appraisal. The committee heard from the company and the clinical experts that there are subgroups of people for whom CCH may be more clinically effective and cost effective, such as those with moderate disease and few affected joints. The committee therefore requested additional analyses from the assessment group to include patients with moderate disease and up to 2 affected joints and, separately, patients with severe disease and up to 2 affected joints.

The treatment pathway in the economic model

The assessment group's pathway is preferred for the economic model

- 3.16 The committee noted that the treatment pathways in the assessment group's model were based on the Van Rijssen et al. and CORDLESS trials supplemented by clinical advice. The committee heard from the company that the Van Rijssen et al. study was done some years ago at a single centre in the Netherlands, and CORDLESS was done in the USA before CCH got its marketing authorisation. As a result, in the company's opinion, these studies may not represent treatment pathways in the NHS. The committee considered the company's additional evidence, which presented an alternative treatment pathway proposed by 1 hand surgeon and endorsed by 4 others. The new pathway increased the probability of having further treatment after recurrence: 72% for CCH, 72% for PNF and 56% for limited fasciectomy. The committee asked how the company selected these experts, and it heard that they were known by the company's field team or were attendees at a conference. The committee noted that the new pathway was written by a surgeon in Birmingham, and a response to consultation had identified this hospital as the largest

NHS user of CCH. It also heard from the company that this individual surgeon uses PNF very rarely. Accordingly, the committee was concerned that the company's new pathway may not represent the wider NHS. The committee acknowledged the company's concerns about the generalisability of trial data, but nonetheless stated that it prefers treatment pathways in economic models to be based on trial data unless there is evidence that this is inappropriate. Overall, the committee agreed that it had not been presented with convincing evidence that the company's new treatment pathway was more representative of the NHS than the assessment group's pathway. The committee considered that it preferred to use the assessment group's treatment pathway in the economic model. It was aware of the company's additional evidence, stating that it was illogical to include CCH as an option for treatment after PNF because this meant CCH was being compared with itself. The committee concluded that it was appropriate to consider analyses in which CCH was not an option after PNF.

Success rates in the economic model

Success rates of CCH are uncertain for moderate and severe disease

3.17 The committee noted that the analyses of the overall population in the assessment group's model used a 63% success rate based on the meta-analysis of randomised trials. The committee concluded that the assessment group's analysis of the overall population used the best available data to estimate the success rate for CCH. For the moderate-disease subgroup, the committee noted that some analyses used a success rate of 81% (based on the moderate subgroup in the CORD trials) whereas other analyses used 66% (based on the moderate subgroup in POINT X). The committee was aware that analyses of the severe-disease subgroup used 54%, based on the severe subgroup in the CORD trials. It noted

that, for all subgroup analyses, the success rates for CCH were based on post hoc analyses of a small number of patients. The committee concluded that the success rates for subgroups were uncertain and, for the moderate-disease subgroup, it was appropriate to consider analyses using success rates of both 81% and 66%.

Success rates of PNF and limited fasciectomy in the moderate and severe subgroups are uncertain

3.18 The committee noted that most analyses in the assessment group's model used success rates of 41% for PNF and 71% for limited fasciectomy, based on Van Rijssen et al. which recruited patients with moderate or severe disease. The committee concluded that the assessment group's analysis of the overall population used the best available data to estimate surgical success rates. The committee was aware that the assessment group's modelling for the moderate and severe subgroups used success rates for PNF and limited fasciectomy from the overall population, because Van Rijssen et al. did not report subgroup analyses. The committee noted that, because of the limitations of the data, the subgroup modelling did not reflect the advice from clinical experts that all treatments were more effective in moderate than in severe disease. It noted that one of the assessment group's sensitivity analyses for the moderate subgroup tried to address this limitation, by using higher estimated success rates for PNF (55%) and limited fasciectomy (95%). The committee concluded that the assessment group's subgroup analyses should be interpreted with caution because the success rates for PNF and limited fasciectomy were uncertain.

Recurrence rates in the economic model

The assessment group's model used the preferred 5-year recurrence rates

3.19 The committee noted that the recurrence rates in the original assessment group's model were taken from CORDLESS and Van Rijssen et al., and that these results did not reflect clinical practice, in which recurrence was typically lowest with limited fasciectomy and highest with PNF, with CCH in between (see section 3.8). The committee identified 5-year recurrence rates that it agreed were plausible: 25.0% for limited fasciectomy (the midpoint of published estimates); 42.8% for CCH (the lower limit of the 95% confidence interval from CORDLESS); and 52.5% for PNF (the midpoint of published estimates). The committee concluded that these recurrence rates were broadly consistent with: the evidence base; the advice from the clinical experts that recurrence was lowest with limited fasciectomy and highest with PNF; and the comment from the company that recurrence after limited fasciectomy was lower in Van Rijssen et al. than in other studies.

The company's revised recurrence rates are uncertain

3.20 The committee noted that the assessment group's model defined recurrence as an increase in contracture of at least 20°. It was aware that the company's evidence, submitted after the final appraisal determination, defined recurrence as an increase of at least 30°. The committee heard that the company had written to the lead author of Van Rijssen et al. and she had described the post hoc analysis of 20° recurrence as 'unstable'. The committee noted that the correspondence was not in the company's submission, so it could not read the detailed advice. The committee observed that, by moving from a 20° to a 30° definition of recurrence, the 5-year recurrence rates in Van Rijssen et al. increased from 23% to 85% for PNF and from 5% to 21% for limited fasciectomy. For comparison, for CCH the 20° recurrence rate was 46.7% and the 30° recurrence rate was lower at 28.5%. In the committee's opinion, using a more severe definition of recurrence should decrease the recurrence rate, as was the case for CCH. The

committee observed that using a more severe definition of recurrence had increased the recurrence rates substantially for PNF and limited fasciectomy. It noted that this unexpected result could have occurred because, for the 30° analyses, CORDLESS and Van Rijssen et al. may have used different definitions of recurrence by excluding patients who needed re-treatment. It also heard from the assessment group that the 20° recurrence rates were defined in a way that fitted the structure of the model. The committee concluded that it had not been presented with convincing evidence that the company's revised recurrence rates were more appropriate than the committee's preferred recurrence rates identified in section 3.19.

Utility values in the economic model

The assessment group's utility values should be adjusted for age

3.21 The committee was aware that in the assessment group's economic model for the overall population, at baseline, patients were assumed to have Tubiana stage 3 contracture in 3 fingers. The committee heard from the clinical experts that this degree of contracture is more severe than is typically seen in clinical practice. The committee concluded that the assessment group's model used a baseline level of contracture that was too severe. The committee noted that successful treatment had a utility value of 1 in the assessment group's model, but it is unlikely that an average utility value of 1 is appropriate for a sample of the population aged over 63 years. The committee concluded that it was appropriate to adjust the utility values by the average utility value for the modelled age group.

The recovery time was uncertain in the revised utility analyses

3.22 The committee noted that the revised utility values represented a less severe contracture than in the original model and were

adjusted by the average utility value for the modelled age group. The committee agreed that the revised utility values represented a plausible degree of contracture for people with up to 2 affected joints and either moderate or severe disease. However, the committee noted that the utility values were based on a discrete-choice experiment scaled on to EQ-5D utilities, and therefore did not follow the NICE reference case. The committee also noted that, informed by the company's additional evidence submitted after consultation, the assessment group's sensitivity analyses applied a utility decrement to some patients to reflect recovery time after treatment (for 12 weeks after limited fasciectomy and 2 weeks after CCH and PNF). The committee concluded that, given the limited evidence base, the utility values in the assessment group's subgroup analyses were reasonable but uncertainty remained about the duration of recovery time.

Assumptions in the economic model

The assessment group's model used the best available data

3.23 The committee discussed the assumptions about the number of injections of CCH and the number of treated joints in the assessment group's model, noting that these parameters had a substantial effect on the total costs of CCH. It was aware that the original model for the overall population assumed 1.6 injections per joint and 3 treated joints, based on the CORD trials. It noted that, for the severe-disease subgroup, the model assumed 1.6 injections per joint and 1.43 treated joints, based on the subgroup with severe disease and up to 2 affected joints in the CORD trials. The committee concluded that the assessment group's model used the best available data to estimate the number of injections and number of treated joints for the overall population and the severe-disease subgroup.

The effect of different assumptions should be explored for the moderate-disease subgroup

3.24 The committee discussed the assumptions about the number of injections of CCH and the number of treated joints in the assessment group's analyses of the moderate-disease subgroup. It noted that the analyses initially assumed 1.6 injections per joint and 1.47 treated joints, based on the subgroup with moderate disease and up to 2 affected joints in the CORD trials. After consultation on the assessment report, the committee was aware of 2 observational studies which found that patients needed fewer injections per joint in clinical practice than in the CORD trials (Peimer et al. 2013 and POINT X). The committee was also aware of responses to consultation, stating that UK audit data show the average number of injections per joint is 1.03 to 1.30. The clinical experts explained that this is because local anaesthetic is used before finger straightening in clinical practice (whereas anaesthetic was not used in the trials) and, as a result, acceptable results are sometimes achieved after only 1 injection in clinical practice. However, the committee was aware of a submission from a clinical expert which suggested that the recurrence rate may be higher if patients have fewer injections, because not all of the diseased tissue would be broken down by the CCH. The committee noted that the assessment group provided additional analyses for the moderate subgroup, assuming 1.22 injections per joint and 1.17 treated joints based on POINT X. The committee concluded that it was appropriate to explore the impact of alternative assumptions for the moderate-disease subgroup and that, when doing so, it was logical to take the number of injections and the CCH success rate from the same trial. Accordingly, analyses based on the CORD moderate-disease subgroup should use 1.6 injections, 1.47 treated joints and a CCH success rate of 81%. Analyses based on the POINT X moderate-disease subgroup

should use 1.22 injections, 1.17 treated joints and a CCH success rate of 66%.

Assuming no vial sharing is appropriate in the economic model

3.25 The committee noted that the assessment group's model assumed no vial sharing of CCH whereas the company's model had allowed vial sharing, and it questioned which approach was most appropriate. It heard from the clinical experts and the company that there is no vial sharing of CCH in clinical practice. It also noted that the summary of product characteristics states that CCH is provided in a single-use vial and any unused product must be discarded. The committee concluded that it was appropriate to assume no vial sharing of CCH in the economic model.

Costs in the economic model

The proportion of limited fasciectomy procedures done as inpatient procedures is uncertain

3.26 The committee considered the costs of limited fasciectomy, noting that the assessment group assumed 26% were inpatient procedures whereas the company's model assumed 37.8%. The committee observed that these estimates were for the overall population and the percentage would probably be lower for a moderate-disease subgroup; the company representative acknowledged that this was possible. The committee heard from the clinical experts that, in their specialist centres, no limited fasciectomy procedures were carried out as inpatient procedures. In contrast, the committee heard from a patient expert that some people did have limited fasciectomy as inpatients. The committee had previously considered sensitivity analyses that showed that lowering the proportion of inpatient limited fasciectomy procedures lowered the cost of limited fasciectomy. The committee concluded

that the true proportion of inpatient limited fasciectomy procedures was likely to be above 0% and below 26%.

Using NHS reference costs is appropriate for calculating costs in the model

3.27 The committee noted that the assessment group's model and the company's model used NHS reference costs. The committee considered the company's new evidence, which presented alternative cost estimates using the payment by results tariff (recently renamed the national tariff payment system). The committee was aware of correspondence from a clinical commissioning group, which recommended using the national tariff to estimate costs in the model because the tariff represents the costs paid by NHS commissioners. The committee noted that the NICE [guide to the methods of technology appraisal](#) supports the use of NHS reference costs. The committee understood that the national tariff is based on reference costs but the tariff can be adjusted up or down to encourage providers to use certain treatments or to permit better quality care. Because of this, in the committee's experience the national tariff does not always reflect the costs of a procedure. The committee also understood that, across government departments, there is a preference for using costs rather than charges in economic models. It agreed that it had not been presented with a compelling argument as to why the model for CCH should depart from this principle. The committee was also aware of concerns raised by a clinical commissioning group that the assessment group had used inappropriate healthcare resource group (HRG) codes for limited fasciectomy and PNF. The committee accepted that the choice of HRG codes varies between areas, and it noted that it had not been presented with evidence that the codes used by this clinical commissioning group were nationally representative. Overall, the committee concluded

that it preferred to use the cost estimates developed by the assessment group as the basis for its decision.

Cost-effectiveness conclusions before the appeal

For the overall population, CCH is unlikely to be cost effective

3.28 The committee discussed the cost-effectiveness results for the overall population of people with moderate or severe Dupuytren's contracture. It noted that CCH was dominated by limited fasciectomy in the assessment group's base case, meaning that CCH was more costly and less effective than limited fasciectomy (incremental costs £2,931 and incremental quality-adjusted life year [QALY] gain -0.08). It noted that the analysis was not ideal because the model did not use appropriate utility values (see section 3.21). However, the committee considered that changes to the utility values would be unlikely to substantially alter the results for the overall population. The committee concluded that, for the overall population of people with moderate or severe contracture, the incremental cost-effectiveness ratio (ICER) for CCH was unlikely to fall into the range usually considered to be a cost-effective use of NHS resources.

More robust data on the relative clinical effectiveness of CCH would be welcomed

3.29 The committee discussed whether CCH could be considered a cost-effective use of NHS resources for the subgroup of patients with moderate disease and up to 2 affected joints. In the previous final appraisal determination issued, the committee concluded that the ICER for CCH compared with PNF for the moderate-disease subgroup was likely to be around £31,100 per QALY gained. Based on the evidence it considered at the time, the committee had concluded it could not recommend CCH as an appropriate use of NHS resources for treating Dupuytren's contracture in adults with a

palpable cord, except in the context of research. The committee had agreed that the research should be designed to generate robust evidence about the benefits of CCH compared with current treatments for people with moderate Dupuytren's contracture. The main areas of uncertainty identified by the committee were the success rates, recurrence rates and impact on health-related quality of life associated with each treatment. The committee concluded that they would welcome more robust data on the relative clinical effectiveness of CCH and supported the call for further research by the National Institute for Health Research.

After the appeal

The company propose reducing the price of CCH and using it only when PNF is not appropriate

3.30 After an appeal, the committee met to consider 2 upheld points of the appeal decision. These were:

- It was unreasonable for the committee not to reach a conclusion on the use of CCH (either to recommend or not recommend it) for the subgroup of patients for whom PNF was not clinically appropriate.
- It was unreasonable for the committee to use a cost of £225.00 for PNF.

In addition, the company submitted a new value proposition for people with moderate Dupuytren's contracture (and up to 2 affected joints), which included reducing the list price and using CCH only for people for whom PNF is not considered clinically appropriate. The company stated its support for the ongoing trial (DISC: Dupuytren's interventions surgery versus collagenase; HTA-15/102/04) and using CCH in the NHS that does not interfere with the trial recruitment. The committee noted the Decision Support

Unit's analyses with the reduced price, which superseded the analyses previously considered.

People for whom PNF is unsuitable are considered in decision-making

3.31 The committee considered the first upheld appeal point (see section 3.30), which stated that it was unreasonable for the committee not to make recommendations for CCH in the subgroup of people for whom PNF was not appropriate. It considered that its original recommendation included people eligible for CCH but for whom PNF may not be considered suitable on an individual basis (for clinical- or disease-related reasons). The committee recalled that there was a lack of agreement about the clinical characteristics that would make contracture suitable for CCH but unsuitable for PNF, and that there was no clear definition of which people had disease that was unsuitable for PNF (see section 3.4). However, it acknowledged that in clinical practice, around 90% of patients have limited fasciectomy and only 10% or less have PNF (see section 3.5). It therefore accepted that the NHS has in practice defined this subset based on the treating hand surgeon's assessment of the disease and suitability of treatment. The committee recognised that the company proposes using CCH only for those patients for whom PNF is not considered appropriate and as an alternative to limited fasciectomy. The committee concluded that it would consider this group in its decision-making.

Increasing the unit cost of CCH and PNF increases the ICERs for CCH

3.32 The committee considered the second upheld appeal point (see section 3.30), which referred to its unreasonable use of £225.00 for the cost of PNF. It noted the Decision Support Unit's report stated that, based on the activity levels for HRG codes and their respective NHS reference costs (2012/13), the weighted cost of an outpatient attendance for PNF is estimated to be £164.11, whereas the weighted cost of a day-case attendance for PNF is estimated to

be £1,184.23. The committee noted that the weighted outpatient cost is actually lower than the figure of £225.00 originally used by the assessment group, and that the day-case cost was reasonably close to the updated costs presented for PNF and CCH by the company. The committee understood from the Decision Support Unit's analyses that if administration costs are assumed to be the same for PNF and CCH, increasing the unit cost from the assessment group's original outpatient cost estimate (£225.00) would increase the ICERs, making CCH a less cost-effective option.

CCH is most likely to be used as an outpatient treatment

3.33 The committee considered the setting in which CCH and PNF are administered. Given the uncertainty about this, the Decision Support Unit gathered expert opinion from clinicians experienced in using CCH or in doing PNF. Information was sought about the time and resource use associated with CCH and PNF and the setting in which each procedure is administered. Among the respondents, 2 were surgeons who had experience of doing PNF but not of using CCH, one was a surgeon who uses CCH but does not do PNF, whereas the fourth respondent had experience of both PNF and CCH. Based on the information the committee considered, it concluded that the most likely setting for CCH treatment is the outpatient setting.

The company's price reduction affects the cost effectiveness of CCH

3.34 The committee discussed the new analyses from the Decision Support Unit which incorporated the reduced list price. It noted that in the severe subgroup CCH was dominated in all scenarios. Therefore, the committee acknowledged that these analyses confirmed that CCH was unlikely to be considered a cost-effective use of NHS resources for the severe disease group. It noted that, when applying the reduced list price in the moderate subgroup

analyses, the cost effectiveness varied greatly. It noted that the ICERs for CCH within this subgroup were mostly in a range from £10,000 to £34,000 per QALY gained. The committee also acknowledged that in a few scenarios the ICER was higher than £34,000 per QALY gained or CCH was dominated. Conversely, CCH dominated limited fasciectomy in some scenarios; particularly when CCH is given in an outpatient setting and PNF is given in a 100% day-case setting. However, the committee acknowledged the small differences in the costs and QALYs in the analyses which were having a large effect on the ICERs, as well as the uncertainty. The committee therefore concluded that the company's price reduction could modify the cost effectiveness of CCH for moderate disease, but that the cost effectiveness varied greatly.

CCH could be a cost-effective option for the population with moderate disease

3.35 The committee recognised that, in the NHS, the most common treatment for moderate or severe disease is limited fasciectomy and a smaller number of people have PNF or CCH. It was aware that no trials had directly compared CCH with PNF or limited fasciectomy, and an indirect comparison was not possible because the published trials did not share a common comparator. It agreed that the assessment group's model was based on the best available evidence but given the uncertainty in the naive indirect comparison, several parameters in the model were highly uncertain. The committee focused on the population with moderate disease with up to 2 affected joints, for whom CCH is most likely to be clinically and cost effective (see section 3.34). The committee noted that the estimates of cost effectiveness for this group varied greatly because of the uncertainty in the data (from less than £20,000 to more than £20,000 per QALY gained). The committee recognised that the new analyses identified a wider set of scenarios in which CCH could be considered cost effective. It also noted that

although the reduced list price would affect the cost effectiveness of CCH, it would not reduce the clinical uncertainty underpinning the analyses. The committee agreed that, because of the considerable uncertainty that remained in the clinical and cost effectiveness, it was unable to conclude that the true value of the ICER was within or outside a range in which CCH could be considered a cost-effective use of NHS resources compared with current clinical practice.

CCH is innovative and all benefits have been included in the analyses

3.36 The committee considered whether there were additional benefits of CCH that had not been captured in the QALY calculation. It acknowledged that CCH is the first pharmacological treatment to get a marketing authorisation for treating Dupuytren's contracture and patients wished to encourage industry to develop new treatments. The committee heard from the patient expert that a benefit of CCH was avoiding general anaesthetic, but it also heard from the clinical experts that other treatment options such as PNF and limited fasciectomy can be carried out under local or regional anaesthetic. It heard from the patient expert and the clinical experts that recovery time is shorter after CCH than after limited fasciectomy. The committee acknowledged the view of patient organisations that CCH offers a treatment option at an earlier stage of disease progression, and may permit a greater number of repeat treatments than is possible with surgery. The committee also acknowledged the view of some NHS professionals, whose response to consultation advised that treating recurrence may be cheaper and more successful if the initial treatment is CCH rather than limited fasciectomy. The committee concluded that CCH was innovative, but that it had not been presented with any evidence of demonstrable and distinctive benefits that had not been captured in the reference-case measure of QALYs.

CCH is recommended for use in the NHS under specific circumstances until further evidence becomes available

3.37 The committee reiterated that several parameters in the model were very uncertain because there was a lack of high-quality evidence comparing the clinical effectiveness of treatments for Dupuytren's contracture. The committee agreed that additional research was necessary to address these uncertainties. It was aware that the pragmatic multicentre non-inferiority trial ([HTA-15/102/04](#)) will start recruitment in 2017, comparing CCH with surgical correction for treating moderate Dupuytren's in adults. It acknowledged that this trial may provide evidence of clinical and cost effectiveness for patients for whom PNF is not considered suitable. The committee was aware of the risk to the NHS of funding a treatment that may not prove to be cost effective when further data are available. However, the committee acknowledged the innovative aspects of CCH, its potential to offer benefits to patients compared with current treatments, and the potential value of CCH to the NHS. It carefully considered whether there were circumstances in which it could recommend CCH as a treatment option in the NHS while the research is ongoing. The committee was concerned that if it recommended CCH for people with moderate Dupuytren's contracture, they may choose to have treatment with CCH rather than take part in the clinical trial; even though there is no evidence to show CCH has better or worse outcomes than limited fasciectomy. The committee did not want to affect recruitment into the trial given the importance of the trial outcomes in resolving the uncertainty for the NHS on the clinical benefit of CCH compared with current clinical practice. Taking this into account, the committee recommended CCH as a treatment option under very specific conditions for a group of adults with moderate Dupuytren's contracture (see section 1), to allow access to CCH in a way that supports the ongoing trial and appropriately

manages risk to the NHS while further data are collected. It further agreed that, for people not taking part in the ongoing trial, the choice of treatment between CCH and limited fasciectomy should be made on an individual basis after discussion between the responsible hand surgeon and the patient about the risks and benefits of the treatments available, considering the available evidence.

4 Implementation

- 4.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- 4.3 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has Dupuytren’s contracture and the doctor responsible for their care thinks that CCH is the right treatment, it should be available for use, in line with NICE’s recommendations.

5 Recommendations for further research

- 5.1 The committee noted that a [multicentre non-inferiority trial](#) will start recruiting in 2017 and that it did not want to affect trial recruitment with its recommendation (see section 3.37). The principal investigator has informed NICE that recruitment will be piloted in 6 centres and that the number of participants who are eligible for the trial but do not want to take part will be monitored. NICE will be told of any increase in this group so that an early review of the guidance can be considered.

6 Review of guidance

The guidance on this technology will be considered for review 3 years after publication of the guidance or sooner if recruitment to the clinical trial ([HTA-15/102/04](#)) falls below predicted levels. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Gary McVeigh
Chair, appraisal committee
June 2017

7 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee D](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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