Final appraisal determination

Collagenase clostridium histolyticum for treating Dupuytren's contracture

This guidance was developed using the multiple technology appraisal (MTA) process.

1 Guidance

1.1 Collagenase clostridium histolyticum is not recommended for treating Dupuytren’s contracture with a palpable cord, except in the context of research.

1.2 Such research should be designed to generate robust evidence about the benefits of collagenase clostridium histolyticum compared with limited fasciectomy and percutaneous needle fasciotomy in people with moderate Dupuytren’s contracture. The Committee identified that success rates, recurrence rates and effects on health-related quality of life were the main areas of uncertainty in the current research. The Committee heard from patient and clinical experts that recovering hand function was more important to patients than reducing contracture.

1.3 People whose treatment with collagenase clostridium histolyticum is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue their current course of collagenase clostridium histolyticum until they and their NHS clinician consider it appropriate to stop.
2 Clinical need and practice

2.1 Dupuytren’s disease is a benign, slowly progressive condition that can restrict hand function. The disease is characterised by a build-up of collagen in the connective tissues in the palm. The collagen forms nodules and fibrous bands called cords. The cords gradually contract as the disease progresses, causing the fingers to become fixed in a bent position. When the fingers cannot be straightened, the disease is called Dupuytren’s contracture.

2.2 People with Dupuytren’s contracture often have impaired hand function, which can limit normal activities at home (such as washing and dressing), in the workplace (especially for people who work with their hands), and in recreational and social interactions (such as sports and shaking hands). The condition can be painful. The little finger and ring finger are most commonly affected and some people have contracture in both hands. The contracture typically affects the metacarpophalangeal joints (where the phalanges of the finger attach to the metacarpal bones of the hand) and/or the proximal interphalangeal joints (the joints between the proximal and middle phalanges of the finger). The cause of Dupuytren’s contracture is unknown, but there is a clear genetic component. Further risk factors include drinking alcohol, smoking, diabetes, epilepsy, thyroid disorders and trauma.

2.3 Approximately 2 million people in the UK have Dupuytren’s disease, most of whom do not seek or need treatment. The number of people with Dupuytren’s contracture is unknown. Hospital episode statistics show that there were 18,222 hospital admissions for Dupuytren’s contracture in England between April 2012 and March 2013.

2.4 There is no cure for Dupuytren’s contracture and the goal of treatment is to restore hand function. Surgical treatments such as limited fasciectomy, dermofasciectomy and fasciotomy are widely
used. Limited fasciectomy involves removing the connective tissues from the affected area. Dermofasciectomy involves removing both the connective tissues and the overlying skin followed by a skin graft. Fasciotomy involves cutting the connective tissue to relieve the contraction and it can be carried out using a scalpel, or percutaneously using a needle (known as percutaneous needle fasciotomy [PNF]). Limited fasciectomy and dermofasciectomy are done in an operating theatre and an anaesthetist must be present. PNF can be carried out in a clinic room with local anaesthetic and an anaesthetist is not needed. If several joints are affected in the same hand, they can all be treated in 1 surgery. Hospital episode statistics show that, of the procedures for Dupuytren’s contracture carried out in England between 2012 and 2013, 87% involved fasciectomy, 8% fasciotomy and 5% dermofasciectomy.

2.5 After surgery, hand therapy and splints are often needed and recovery can take several weeks. The recovery time is usually shorter for PNF than for other types of surgery. Complications of surgery include nerve injury, artery injury, problems with wound healing, pain and abnormal sensitivity to touch. A recurrence of contracture is common, even after successful treatment.

2.6 The British Society for Surgery of the Hand classifies Dupuytren’s disease as:

- **Mild** – no functional problems, no contracture or metacarpophalangeal joint contracture of less than 30°.
- **Moderate** – functional problems, metacarpophalangeal joint contracture of 30° to 60°, proximal interphalangeal joint contracture of less than 30°, or first web contracture.
- **Severe** – severe contracture of both metacarpophalangeal joint (greater than 60°) and proximal interphalangeal joint (greater than 30°).
2.7 NICE's interventional procedure guidance on needle fasciotomy for Dupuytren's contracture recommends PNF as a treatment option for Dupuytren's contracture, particularly for older people for whom major surgery may not be suitable. NICE's interventional procedure guidance on radiation therapy for early Dupuytren's disease recommends that radiation therapy for early Dupuytren's disease should only be used with special arrangements for clinical governance, consent and audit or research.

3 The technology

3.1 Collagenase clostridium histolyticum (Xiapex, Swedish Orphan Biovitrum AB) is a mixture of 2 purified collagenase enzymes isolated from the bacterium Clostridium histolyticum. Collagenase clostridium histolyticum (CCH) has a marketing authorisation in the UK for treating Dupuytren's contracture in adults with a palpable cord. It is given by injection into the cord. The enzymes break up the collagen fibres, which weakens and disrupts the cord. Approximately 24 hours after injection, a finger extension procedure may be performed, if necessary, to facilitate cord disruption. The summary of product characteristics states that, if a satisfactory response has not been achieved, the injection and finger extension procedures may be repeated after approximately 4 weeks. Injections may be given up to 3 times per cord and only 1 cord must be treated at a time. If the person has multiple contractures, each cord must be treated sequentially.

3.2 The summary of product characteristics lists the following adverse reactions experienced by at least 10% of people having CCH: swollen lymph nodes, itching, pain, swelling, injection site bleeding, tenderness and bruising. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.3 CCH costs £650.00 per 0.9 mg vial excluding VAT (British national formulary edition 68). The recommended dose for treating
Dupuytren’s contracture is 0.58 mg per injection. The company estimates that the average cost of a course of treatment is £1248.00, assuming an average of 1.92 injections per patient and no vial sharing. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (section 9) considered evidence from a number of sources (section 10).

Clinical effectiveness

Collagenase clostridium histolyticum

4.1 The Assessment Group’s systematic review did not find any randomised controlled trials that compared collagenase clostridium histolyticum (CCH) with surgery. The review identified 5 randomised controlled trials that compared CCH with placebo, 2 non-randomised studies that compared CCH with surgery, and 15 case series that assessed the effects of CCH.

4.2 The CORD I randomised controlled trial was carried out in the USA; 204 patients were randomised to have CCH and 104 to have placebo. The treatment groups were similar in age (CCH mean 62.3 years, placebo mean 63.3 years), percentage of men (CCH 83.8%, placebo 79.5%), number of affected joints per patient (mean 3.0 joints for both groups) and total contracture index (mean 149° for both groups). The total contracture index is the sum of all contractures of at least 20° across all 16 metacarpophalangeal and proximal interphalangeal joints in the 2 hands. Across both treatment groups, 38% of patients had already had surgery for Dupuytren’s contracture. The CORD II randomised controlled trial was carried out in Australia; 45 patients were randomised to have CCH and 21 to have placebo. The treatment groups were similar in age and percentage of men, but the CCH group had slightly more...
affected joints per patient (CCH mean 3.4, placebo mean 3.0) and a higher total contracture index (CCH mean 174.7°, placebo mean 150.1°). Across both treatment groups, 53% of patients had already had surgery for Dupuytren’s contracture. Patients remained in the CORD I and II trials for 90 days of double-blind follow-up (that is, the patients and healthcare providers did not know which treatment the patients had). Patients and healthcare providers were then told which group the patient was in and patients remained in the study for an additional 9 months.

4.3 The remaining 3 randomised controlled trials were carried out in the USA and included 49 patients (Badalamente et al. 2002), 35 patients (Badalamente and Hurst 2005) and 35 patients (Badalamente and Hurst 2007).

4.4 The Assessment Group assessed the risk of bias in the randomised trials for CCH, except for Badalamente and Hurst (2005) which was published only as an abstract. CORD I and II were at low risk of bias for both sequence generation (the method used to generate the random allocation) and allocation concealment. The risk of these types of bias was unclear in the other 2 randomised controlled trials. All 4 trials assessed were double-blind and analysed results on the basis of intention to treat.

4.5 The company’s submission included unpublished 5-year results from CORDLESS, an open-label follow-up study that recruited patients who previously had treatment with CCH in clinical trials including CORD I and II. CORDLESS was carried out in the USA, Australia and Europe. The study enrolled 645 patients (mean age 65.9 years, 84.4% were men), of whom 451 completed 5 years of follow-up.

4.6 The Assessment Group conducted a meta-analysis of randomised controlled trials that used the same definition of clinical success (that is, contracture of less than 5° in the primary treated joint...
measured 30 days after the last injection). The trials were CORD I, CORD II and Badalamente and Hurst (2007). The meta-analysis showed clinical success in 171/271 (63%) primary joints treated with CCH and 8/136 (6%) primary joints treated with placebo; the difference between treatments was statistically significant (risk ratio 10.2, 95% confidence interval [CI] 5.3 to 19.7).

4.7 The company submitted post hoc analyses of 2 subgroups in CORD I and II: patients with moderate disease and up to 2 affected joints, and patients with severe disease and up to 2 affected joints (moderate and severe disease were defined using the classification in section 2.6). The moderate-disease subgroup had 1.47 affected joints on average and treatment success was seen in 46/57 (81%) patients. The severe-disease subgroup had 1.43 affected joints on average and treatment success was seen in 51/95 (54%) patients. Patients in both subgroups had an average of 1.6 injections per joint.

4.8 Across all studies of CCH (including randomised trials, non-randomised studies and case series), the percentage of joints in which contracture recurred ranged from 0% to 67% for metacarpophalangeal joints and from 0% to 100% for proximal interphalangeal joints. Recurrence rates at 5 years’ follow-up were reported in CORDLESS. Recurrence was defined as an increase in contracture of at least 20°, in the presence of a palpable cord, in a joint that had been successfully treated (that is, with contracture of less than 5° measured 30 days after the last injection of CCH). After 5 years, recurrence had occurred in 291/623 (47%) joints and 105/623 (17%) joints had received further treatment.

4.9 The Assessment Group examined the adverse events associated with CCH using a meta-analysis of randomised controlled trials. A total of 265/272 (97%) patients who had CCH had at least 1 adverse event compared with 39/137 (28%) patients who had
placebo; this difference was statistically significant (risk ratio 2.5, 95% CI 1.1 to 5.5). Adverse events were generally mild or moderate. The most common adverse events were peripheral oedema (73% of people who had CCH), contusion (55%), extremity pain (35%), injection-site pain (39%) and injection-site haemorrhage (38%). Across the randomised trials, there were 4 serious adverse events affecting patients who had CCH: 1 patient had complex regional pain syndrome, 2 patients had tendon rupture and 1 patient had flexion pulley rupture.

Surgical treatments

4.10 The Assessment Group’s systematic review identified 3 randomised controlled trials and 5 non-randomised studies that compared 2 surgical procedures. An indirect comparison with CCH was not carried out because the published trials did not include a common comparator arm.

4.11 A randomised controlled trial by Van Rijssen et al. (2012) was carried out at a single site in the Netherlands and compared PNF (n=57) with limited fasciectomy (n=56). The 2 groups were similar in age (mean 64 years for both groups), percentage of men (PNF 84%, limited fasciectomy 82%) and baseline contracture (for both groups, the mean was close to 43° in metacarpophalangeal joints and 34° in proximal interphalangeal joints). None of the patients had previously had surgery for Dupuytren’s contracture. The length of follow-up was 5 years. The Assessment Group commented that there was a low risk of bias for both sequence generation and allocation concealment, but there was no blinding of patients or healthcare providers. Data were analysed on the basis of intention to treat. The 2 other randomised controlled trials compared dermofasciectomy with fasciectomy (Ullah et al. 2009) or compared 2 fasciectomy techniques (Citron and Nunez 2005); these comparisons are not the focus of this appraisal.
4.12 The non-randomised studies included a retrospective chart review of 3286 European patients who had PNF, fasciotomy, fasciectomy or dermofasciectomy (Dias et al. 2013). Although Dias et al. did not compare the effectiveness of the different surgical procedures, they did report the incidence of adverse events. The Assessment Group advised that all the non-randomised surgical studies were at high risk of bias or the risk was unclear.

4.13 The randomised controlled trial by Van Rijssen et al. reported the percentage of joints with clinical success, defined as contracture of less than 5° measured 6 weeks after surgery. Results were reported for 93 patients (84% of those enrolled in the trial) who had recurrence or completed 5 years of follow-up. For the 52 patients who had PNF, 55% of metacarpophalangeal joints and 26% of proximal interphalangeal joints reached clinical success; for the 41 patients who had limited fasciectomy, the results were 94% and 47% respectively. The success rates were not compared using a test of statistical significance.

4.14 Across all surgical studies (including randomised trials and non-randomised studies), the recurrence rate ranged from 0% to 85%. The studies varied in their duration of follow-up and definition of recurrence. The Van Rijssen et al. study included a post hoc analysis that used the same definition of recurrence as CORDLESS (see section 4.8). After 5 years of follow-up, recurrence had occurred in 21.8% of the metacarpophalangeal joints and 23.5% of the proximal interphalangeal joints successfully treated with PNF; for limited fasciectomy, recurrence was 5.3% for both joints.

4.15 The retrospective study by Dias et al. found that 6.2% of patients had an adverse event during fasciectomy and 25.4% had an adverse event after fasciectomy; the results for PNF were 2.6% and 0.8% respectively. Among patients who had an adverse event
during fasciectomy, the event was: nerve damage (55% of patients); artery damage (24%); volar-plate damage (15%); tendon damage (4%); bleeding (1%); or ischaemia (1%). Among patients who had an adverse event during PNF, the event was: nerve damage (14% of patients); artery damage (43%); volar-plate damage (29%); or tendon damage (14%). For both fasciectomy and PNF, the most common adverse events after surgery were haematoma, pain, delayed healing and inflammation.

Additional evidence submitted after the appraisal consultation document

4.16 In response to consultation, the company submitted additional evidence from POINT X, an open-label observational study of 254 European patients who had CCH. A post hoc analysis showed that the moderate-disease subgroup had a success rate of 66.1%, the mean number of joints treated was 1.17 and there was a mean of 1.22 CCH injections per treated joint. For comparison, the subgroup with moderate disease and up to 2 affected joints in the CORD studies had a success rate of 81%, a mean of 1.47 joints treated and 1.6 injections per joint (see section 4.7). The Assessment Group commented that POINT X is likely to reflect the use of CCH in clinical practice. The Assessment Group compared the populations in POINT X and Van Rijssen et al. to assess whether it was appropriate to compare the success rates in these studies. It noted that the populations in POINT X and Van Rijssen et al. had a similar gender and age distribution, but that the patients in Van Rijssen et al. appeared to have more severe disease. For example, in the overall study population, the mean number of joints treated per patient was 1.44 in POINT X and 3.14 in Van Rijssen et al.

4.17 In response to consultation, the company submitted additional evidence on recovery time after limited fasciectomy, taken from a Swedish prospective cohort study (Engstrand et al. 2014). The
study recruited 90 patients with Dupuytren’s contracture with a total active extension deficit of at least 60° in 1 finger. All patients had limited fasciectomy. The percentage of patients who reported that they had ‘fully recovered’ hand function was 18%, 32% and 37% at 3, 6 and 12 months after surgery, respectively. The percentage with ‘much better’ hand function was 60%, 60% and 50% at 3, 6 and 12 months after surgery respectively.

4.18 The Assessment Group noted that Engstrand et al. reported data on post-operative treatment (for events such as swelling, pain and scarring) during only the first 3 months after surgery, so the study did not provide information about whether longer-term treatment for recovery problems was needed. The Assessment Group advised that most of the patients in Engstrand et al. appeared to have severe disease, in contrast to the Van Rijssen et al. and CORD studies which recruited a population with both moderate and severe disease. The Engstrand et al. study also included patients with contracture in distal interphalangeal joints; the Assessment Group noted that these joints are typically difficult to treat and were excluded from the Van Rijssen et al. and CORD studies.

Additional evidence submitted after the final appraisal determination

4.19 Following release of a FAD, NICE suspended the appraisal and accepted new evidence because consultees raised concerns about errors in the model (see section 4.37). In its new evidence, the company acknowledged the concerns raised by the Assessment Group and the Committee that differences in study populations made it difficult to compare the results of studies of CCH and surgery. To address this concern, the company used data from the subgroup with moderate or severe disease in CORDLESS and POINT X. The company built statistical models to predict success and recurrence with CCH from baseline characteristics. It then used the average baseline parameters from Van Rijssen et al. as inputs to the statistical model, to predict success and recurrence.
rates if the Van Rijssen et al. patients had CCH. The predicted success and recurrence rates were within the 95% confidence intervals of the observed results in CORDLESS and POINT X. From this, the company ‘concluded that the differences in the study populations [did] not affect the comparability of the efficacy results.’ The company’s analysis aimed to demonstrate that it was fair to compare the results from the studies of CCH and surgery; the aim was not to re-estimate success and recurrence rates. The Assessment Group advised that the company’s analysis showed there was a subgroup of patients in CORDLESS and POINT X with the same disease severity as the overall population in Van Rijssen et al. In the Assessment Group’s opinion, the company’s analysis did not imply that differences between the complete study populations can be ignored.

**Clinical-effectiveness summary**

4.20 The Assessment Group concluded that CCH was significantly more likely than placebo to achieve clinical success for people with Dupuytren’s contracture. Almost all patients had a mild or moderate adverse event after CCH. 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). Therefore, the Assessment Group concluded that there was no evidence that CCH was clinically better or worse than surgical treatments.

**Cost effectiveness**

**Company’s model**

4.21 The company submitted a cost-minimisation analysis that compared CCH with limited fasciectomy over a 5-year time horizon. This analysis assumed that both treatments were equally effective, so only costs were compared. The modelled population comprised
patients with moderate or severe contracture who had up to 2 joints affected in the same hand. The company’s rationale for choosing this subgroup was that mild disease is not usually treated. Also, the company advised that CCH is likely to be used in patients with only a few affected joints. The company did not include PNF as a comparator because it advised that this procedure is used for only 10% of patients.

4.22 Patients in the company’s model had a first course of therapy with either CCH or fasciectomy. If the first course of therapy was unsuccessful, no further costs were accumulated. If the initial therapy was successful, patients were at risk of recurrence and some patients with recurrence had a second course of therapy with either CCH or fasciectomy. The company assumed that success rates, recurrence rates and the costs of treating recurrence were equivalent for CCH and fasciectomy. In the base case, the company assumed that patients received a mean of 1.6 injections of CCH per joint and each patient had 1.4 affected joints on average. It also assumed that 37.8% of fasciectomies were done on an inpatient basis and there was no wastage of CCH when a vial was opened (that is, there was vial sharing).

4.23 The Assessment Group advised that a cost-minimisation analysis may not be appropriate because there is no evidence from randomised controlled trials to support the assumption that CCH and limited fasciectomy are equally effective. In addition, the assessment report noted that cost-minimisation analysis is not in line with the NICE reference case, which recommends cost–utility analysis. In the opinion of the Assessment Group, PNF is a relevant comparator because it is used in clinical practice in the UK, it was included in the scope, and previous economic analyses identified PNF as the most cost-effective treatment strategy. The Assessment Group also noted concerns about assumptions made by the company such as the number of affected joints, the number
of hand therapy appointments, assuming no treatment after treatment failure, and possibly underestimating the cost of treating recurrence.

**Assessment Group’s model**

4.24 The Assessment Group developed a cost–utility Markov model that compared CCH, PNF and limited fasciectomy. The model included 4 health states: treatment, treatment success, treatment failure and recurrence. The model had a lifetime time horizon and a cycle length of 6 months. A half-cycle correction was used and costs and outcomes were discounted at 3.5% per year. The analysis was from the perspective of the NHS and personal and social services.

4.25 The economic model was based on a naive indirect comparison, meaning that the estimates of efficacy for each treatment were taken from separate studies without maintaining randomisation and without any adjustment for differences between studies. The Assessment Group noted that there were differences in patient characteristics between studies and it is likely that there were differences in patient treatment history and the skill of the clinician. As a result, the Assessment Group advised that the results from the economic model should be considered with caution.

4.26 The modelled population comprised patients with moderate or severe Dupuytren’s contracture in 1 hand for whom surgery was considered suitable. The Assessment Group defined this group as patients with total passive extension deficit of at least 30° in any finger and a clearly defined palmar cord. The modelled cohort was 84% men, had a starting age of 63 years and a mean of 3 affected joints in the base case.

4.27 The Assessment Group’s model compared 3 treatment strategies defined by the choice of initial treatment: CCH, PNF or limited fasciectomy. After treatment, some patients had treatment
complications, which incurred additional costs and a utility decrement for 6 weeks. Patients then entered a treatment success or treatment failure health state. Treatment success had a higher utility value and patients could either remain in that health state or have recurrence. Recurrence had a lower utility value and patients could either remain in that health state or have further treatment. Treatment failure had the lowest utility value and patients could either remain in that health state or have further treatment. The model permitted up to 3 courses of therapy in total. A course of therapy with CCH involved a series of injections, whereas a course of therapy with PNF or limited fasciectomy involved only 1 surgery. Death could occur from any health state.

4.28 The Assessment Group defined treatment success as a reduction in contracture to within 5° of full extension. The probability of success was 63% for CCH, based on the meta-analysis of randomised trials of CCH. The base-case probability of success was 41% for PNF and 71% for limited fasciectomy, based on Van Rijssen et al. averaged across metacarpophalangeal and proximal interphalangeal joints. The same success rates were used for first, second and third courses of therapy.

4.29 The model included only those treatment complications that needed treatment. The probability of complications was 0 for CCH (based on clinical opinion), 0.01 for PNF (from Dias et al.) and 0.05 for limited fasciectomy (from Dias et al.). The same probabilities were used for first, second and third courses of therapy.

4.30 The Assessment Group defined recurrence as a return of contracture of at least 20° in a joint that had been successfully treated. It chose this definition because it matched the primary outcome measure in CORDLESS; moreover, recurrence rates using this definition were available from Van Rijssen et al. for PNF and limited fasciectomy. The 5-year probability of recurrence after
CCH was 46.7%, after PNF was 22.7% and after limited fasciectomy was 5.3%. The same recurrence rates were used for first, second and third courses of therapy.

4.31 The Assessment Group assumed that the probability of having treatment after recurrence or treatment failure depended on the preceding therapy. The probability of having treatment after recurrence was 40% following CCH, 73% following PNF and 40% following limited fasciectomy. The probabilities in the model were based on Van Rijssen et al. and clinical opinion. The Assessment Group assumed that the choice of the second course of treatment also depended on the preceding therapy. The probabilities were based on the CORDLESS data used in the company’s model and clinical opinion.

4.32 The model included costs associated with initial treatment, treatment complications, and further treatment after recurrence or treatment failure. Costing was done for the financial year 2012/13 from sources including NHS reference costs, Unit Costs of Health and Social Care and the British national formulary.

4.33 Each injection of CCH incurred the cost of 1 vial of CCH, an outpatient appointment for administration, an appointment for finger extension and a session of physiotherapy. The base-case model assumed that patients would have 1.6 injections per joint, based on the patients in CORD I and II who had moderate or severe disease and up to 2 affected joints. Each treated joint also incurred the cost of a splint. The total cost of a course of CCH, assuming 3 affected joints per patient and no vial sharing, was £4814 in the base case. Treatment with CCH after recurrence or treatment failure was assumed to be for a single joint and incurred a cost of £1605 in the base case. Treatment with PNF incurred the cost of an outpatient appointment and a session of physiotherapy. Treatment with limited fasciectomy incurred the cost of surgery (assuming 26% of
procedures were carried out as an inpatient procedure), a follow-up outpatient appointment and 5 sessions of physiotherapy. The total cost of a course of treatment was £255 for PNF and £2290 for limited fasciectomy; for both procedures, treatment after recurrence or treatment failure cost the same as initial therapy.

4.34 In the Assessment Group’s model, the severity of contracture in each health state was based on the Tubiana staging system, which classifies contracture in a finger as follows (the sum of contracture includes metacarpophalangeal and proximal interphalangeal joints):

- Stage 0: no contracture.
- Stage 1: the sum of contracture is between 0° and 45°.
- Stage 2: the sum of contracture is between 46° and 90°.
- Stage 3: the sum of contracture is between 91° and 135°.
- Stage 4: the sum of contracture is between 136° and 180°.

4.35 The utility values in the Assessment Group’s model were derived from a discrete-choice experiment conducted in the UK (Gu et al. 2013). This study calculated an indirect utility weight for different configurations of contracture, and these weights were scaled onto EQ-5D utilities. The utility values in the Assessment Group’s base-case model were:

- 0.776 for a hand with Tubiana stage 3 contracture in 3 fingers (baseline and treatment failure health states)
- 0.965 for a hand with Tubiana stage 1 contracture in 1 finger (recurrence health state)
- 1 for a hand with no contracture (treatment success health state).

4.36 After NICE released a final appraisal determination in February 2015, the company advised that the Assessment Group’s model had applied discounting incorrectly. This guidance presents the Assessment Group’s corrected analyses.
4.37 The Assessment Group’s base-case results for the overall population showed that PNF was the least costly treatment option, followed by limited fasciectomy and CCH. CCH was dominated by limited fasciectomy, meaning that CCH was more costly (incremental costs £2931) and less effective (incremental QALY gain −0.082) than limited fasciectomy. The Assessment Group considered that the results of its model were primarily driven by treatment effectiveness. The results were also affected by the cost of initial treatment, recurrence rates and the cost of subsequent courses of treatment.

Assessment Group’s subgroup analyses

4.38 After the first Appraisal Committee meeting, the Committee requested cost-effectiveness analyses for the subgroup of patients with moderate disease and up to 2 affected joints, and for the subgroup with severe disease and up to 2 affected joints. Based on the subgroup results for CORD I and II (see section 4.7), the Assessment Group’s analyses for the moderate-disease subgroup assumed that the CCH success rate was 81% and the cost of the first course of CCH was £2359 (based on 1.47 affected joints and 1.6 injections per joint). The Assessment Group’s analyses for the severe-disease subgroup assumed that the CCH success rate was 54% and the cost of the first course of CCH was £2295 (based on 1.43 affected joints and 1.6 injections per joint). After a request from the Committee (see section 4.71), for both subgroup analyses the Assessment Group used recurrence rates at 5 years of 25.0% for limited fasciectomy (the midpoint of published estimates), 42.8% for CCH (the lower limit of the 95% confidence interval from the CORDLESS study) and 52.5% for PNF (the midpoint of published estimates). For both subgroup analyses, the success rates for surgery were the same as for the analyses of the overall population (41% for PNF and 71% for limited fasciectomy).
After a request from the Committee, the Assessment Group revised its method of calculating utility values. For each subgroup, the Assessment Group identified 5 plausible configurations of contracture and used the equations from Gu et al. to calculate an EQ-5D utility value for each configuration, assuming 67% of patients were affected in the dominant hand (Bainbridge et al. 2012). The Assessment Group took the average utility value for the 5 configurations and multiplied it by the average utility value for people in the general population aged 65–74 years, or aged over 75 years. Thus, the model used lower utility values when the modelled population became older than 75 years (table 1).

Table 1 Revised utility values in the Assessment Group’s analyses

<table>
<thead>
<tr>
<th>Health state</th>
<th>Moderate disease and up to 2 affected joints</th>
<th>Severe disease and up to 2 affected joints</th>
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</thead>
<tbody>
<tr>
<td>Younger than 75 years</td>
<td></td>
<td></td>
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<tr>
<td>Treatment success</td>
<td>0.780</td>
<td>0.780</td>
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<tr>
<td>Baseline, treatment failure and recurrence</td>
<td>0.743</td>
<td>0.725</td>
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<tr>
<td>75 years and above</td>
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<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>0.730</td>
<td>0.730</td>
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<tr>
<td>Baseline, treatment failure and recurrence</td>
<td>0.695</td>
<td>0.678</td>
</tr>
</tbody>
</table>

The Assessment Group’s analysis for the subgroup of patients with moderate disease and up to 2 affected joints showed that limited fasciectomy was extendedly dominated by CCH and PNF. A treatment is ‘extendedly dominated’ when its incremental cost-effectiveness ratio (ICER) is higher than that of the next, more effective, option – in this case CCH – when compared with a common baseline (PNF). Treatments that are extendedly dominated are normally removed from consideration in an incremental analysis. The ICER for CCH compared with PNF was £32,201 per quality-adjusted life year (QALY) gained. Total costs were £1425 for PNF and £2788 for CCH, giving an incremental cost of £1363; total QALYs were 8.418 for PNF and 8.460 for CCH, giving an incremental QALY gain of 0.042. After the final appraisal
determination, the company submitted additional evidence stating that it was illogical to include CCH as an option for second-line treatment in the PNF arm of the model, because this meant CCH was being compared with itself. After a request from the Committee, the Assessment Group provided a revised analysis in which the options for further treatment after PNF were limited fasciectomy (60% of patients) and PNF (40% of patients). In this analysis, limited fasciectomy was extendedly dominated and the ICER for CCH compared with PNF was £31,084 per QALY gained (incremental cost £1337; incremental QALY gain 0.043).

4.41 The Assessment Group’s analyses for the subgroup of patients with severe disease and up to 2 affected joints showed that CCH was dominated by both PNF and limited fasciectomy, meaning that CCH was more costly and less effective than these treatments. Compared with limited fasciectomy, CCH cost £462 more and gained 0.116 fewer QALYs.

Additional evidence submitted after the appraisal consultation document

4.42 In response to consultation, consultees identified some health-related benefits of CCH that were not included in the QALY calculation, specifically: avoiding a general anaesthetic, the possibility of treatment at an earlier stage of disease progression and the potential for more repeat treatments than are possible with surgery.

4.43 In response to consultation the company provided data from the moderate-disease subgroup in POINT X, showing a mean of 1.22 injections per joint, 1.17 joints treated per patient and a success rate of 66.1% for CCH (see section 4.16). Using these parameters and the recurrence rates from section 4.38, the Assessment Group’s analysis for the moderate-disease subgroup
showed that CCH was extendedly dominated by PNF and limited fasciectomy (table 2).

4.44 The Assessment Group noted that, in POINT X, the success rate for CCH for patients with moderate disease (66.1%) was higher than that for patients with moderate or severe disease (49.2%). The Assessment Group's economic analyses of the moderate-disease subgroup had previously used success rates for PNF (41%) and limited fasciectomy (71%) from the Van Rijssen et al. study, which recruited a broad population with moderate or severe disease and did not report subgroup analyses. The Assessment Group advised that the Van Rijssen et al. results may underestimate the success rates when PNF and limited fasciectomy are used to treat moderate disease. Accordingly, an exploratory analysis by the Assessment Group estimated the success rates for limited fasciectomy and PNF for a moderate-disease subgroup, based on the proportional increase in CCH success rates for the moderate compared with the moderate-severe subgroup in POINT X. The estimated success rates were 55% for PNF and 95% for limited fasciectomy. Using these success rates, the Assessment Group's model showed that CCH was dominated by PNF (treatment with CCH cost £650 more and gained 0.024 fewer QALYs; table 2).

4.45 The Assessment Group conducted a further sensitivity analysis that applied a utility decrement to reflect the recovery time after treatment. After limited fasciectomy, a utility decrement was applied to 22% of patients for 12 weeks. After CCH and PNF, a utility decrement was applied to 14% of patients for 2 weeks. The success rates were 66.1% for CCH, 41% for PNF and 71% for limited fasciectomy. The ICER for CCH compared with PNF was £36,540 per QALY gained (table 2).
Table 2  Assessment Group’s analyses (based on POINT X results) for the subgroup with moderate disease and up to 2 affected joints

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Total discounted cost</th>
<th>Incremental cost</th>
<th>Total discounted QALYs</th>
<th>Incremental QALYs</th>
<th>ICER – incremental analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.22 CCH injections per joint, 1.17 joints per patient. Success rates: CCH 66.1%, PNF 41%, limited fasciectomy 71%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNF</td>
<td>£1408</td>
<td>-</td>
<td>8.416</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CCH</td>
<td>£1931</td>
<td>£523</td>
<td>8.428</td>
<td>0.012</td>
<td>Extendedly dominated</td>
</tr>
<tr>
<td>Limited fasciectomy</td>
<td>£2529</td>
<td>£1121</td>
<td>8.446</td>
<td>0.030</td>
<td>£37,221</td>
</tr>
<tr>
<td><strong>1.22 CCH injections per joint, 1.17 joints per patient. Success rates: CCH 66.1%, PNF 55%, limited fasciectomy 95%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNF</td>
<td>£1282</td>
<td>-</td>
<td>8.467</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CCH</td>
<td>£1932</td>
<td>£650</td>
<td>8.442</td>
<td>-0.024</td>
<td>Dominated</td>
</tr>
<tr>
<td>Limited fasciectomy</td>
<td>£2583</td>
<td>£1301</td>
<td>8.533</td>
<td>0.067</td>
<td>£19,455</td>
</tr>
<tr>
<td><strong>1.22 CCH injections per joint, 1.17 joints per patient. Success rates: CCH 66.1%, PNF 41%, limited fasciectomy 71%, with utility decrements to reflect recovery time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNF</td>
<td>£1408</td>
<td>-</td>
<td>8.412</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CCH</td>
<td>£1931</td>
<td>£523</td>
<td>8.426</td>
<td>0.014</td>
<td>£36,540</td>
</tr>
<tr>
<td>Limited fasciectomy</td>
<td>£2529</td>
<td>£598</td>
<td>8.438</td>
<td>0.011</td>
<td>£52,283</td>
</tr>
</tbody>
</table>

Abbreviations. CCH, collagenase clostridium histolyticum; ICER, incremental cost-effectiveness ratio; PNF, percutaneous needle fasciotomy.

A treatment is extendedly dominated when its ICER is higher than that of the next, more effective, option. A treatment is dominated when it costs more and is less effective than the comparator.

Additional evidence submitted after the final appraisal determination

4.46 In its new evidence, the company stated that the costs in the Assessment Group’s model did not reflect the costs incurred by the NHS. The company used hospital episode statistics data to assess which healthcare resource group (HRG) codes were used in the NHS for PNF and limited fasciectomy. The company then used the Payment by Results tariff to calculate an average cost for CCH, PNF and limited fasciectomy. For CCH, the company assumed that the administration visit costs the same as for PNF, and that there were 1.17 joints treated and 1.22 injections per joint. The company’s estimate of the cost of 1 course of treatment (including
follow-up appointments and physiotherapy) was £2764 for CCH, £1186 for PNF and £5342 for limited fasciectomy. For comparison, the Assessment Group’s estimates were £1434 for CCH, £255 for PNF and £2290 for limited fasciectomy.

4.47 The Assessment Group advised that its model and the company’s original submission both used the same HRG codes and NHS reference costs for limited fasciectomy and CCH, and it was not clear why the company had changed its approach. The Assessment Group noted that the use of NHS reference costs was supported by section 5.5.5 of the NICE guide to the methods of technology appraisal (2013). The Assessment Group also advised that the Payment by Results tariff reflects resource use plus additional accounting elements, and is often not an accurate representation of resource use in the NHS. Lastly, the Assessment Group was concerned that the company’s new cost estimates used data from the overall population rather than from the relevant subgroup of people with moderate disease and up to 2 affected joints.

4.48 In its new evidence, the company also commented that the treatment pathways in the Assessment Group’s model were not evidence-based and led to results that were biased against CCH. The company created a new treatment pathway based on advice from a hand surgeon working in Birmingham. The company’s submission stated that the new pathway had been ‘validated’ by 4 other clinical experts in England. The new pathway increased the probability of having further treatment after recurrence (table 3) because the company’s clinical expert advised that the Assessment Group’s probabilities were too low. The company’s expert also stated that the probability of further treatment should be similar after CCH and PNF because the patient experience was similar. The new pathway also altered the choice of further treatment (table 4). The Assessment Group had included CCH as an option after
PNF, but the company felt this was illogical because it meant that CCH was being compared with itself. The company stated that its clinical expert advised that most patients who had CCH would have further treatment with CCH, and most patients who had PNF would have further treatment with limited fasciectomy.

4.49 In its critique of the new evidence, the Assessment Group observed that the company had not provided any details of how it had selected and surveyed the clinical experts, and the company’s proposed treatment pathway was substantially different from the pathway in the company’s original model.

Table 3 The probability of having further treatment after recurrence

<table>
<thead>
<tr>
<th>Preceding treatment</th>
<th>Assessment Group’s model</th>
<th>Company’s new pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCH</td>
<td>40%</td>
<td>72%</td>
</tr>
<tr>
<td>PNF</td>
<td>73%</td>
<td>72%</td>
</tr>
<tr>
<td>Limited fasciectomy</td>
<td>40%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Abbreviations: CCH, collagenase clostridium histolyticum; PNF, percutaneous needle fasciotomy.

Table 4 The choice of the second course of treatment after recurrence

<table>
<thead>
<tr>
<th>First treatment</th>
<th>Second treatment</th>
<th>Assessment Group’s model</th>
<th>Company’s new pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCH</td>
<td>CCH</td>
<td>19%</td>
<td>62.5%</td>
</tr>
<tr>
<td></td>
<td>PNF</td>
<td>19%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Limited fasciectomy</td>
<td>62%</td>
<td>37.5%</td>
</tr>
<tr>
<td>PNF</td>
<td>CCH</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>PNF</td>
<td>40%</td>
<td>12.5%</td>
</tr>
<tr>
<td></td>
<td>Limited fasciectomy</td>
<td>50%</td>
<td>87.5%</td>
</tr>
<tr>
<td>Limited fasciectomy</td>
<td>Limited fasciectomy</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Abbreviations: CCH, collagenase clostridium histolyticum; PNF, percutaneous needle fasciotomy.

4.50 In its new evidence submitted after the final appraisal determination, the company changed the recurrence rates in the
Assessment Group’s model. The Assessment Group had defined recurrence as an increase in contracture of at least 20°, because this was the primary outcome measure in CORDLESS and results using this definition were available from a post hoc analysis by Van Rijssen et al. (see section 4.30). However, in its new evidence, the company commented that it was not appropriate to use the Van Rijssen et al. 20° analysis because it excluded patients who needed re-treatment. To address this, the company used the main analysis of Van Rijssen et al., which defined recurrence as an increase in contracture of at least 30°; 5-year recurrence rates were 84.9% for PNF and 20.9% for limited fasciectomy. The company also presented a new analysis of CORDLESS using the 30° definition of recurrence, producing a 5-year recurrence rate of 28.5%. The Assessment Group’s critique of the new evidence commented that, in the model, patients who needed immediate re-treatment moved to the treatment failure health state and could not have recurrence. Accordingly, in the Assessment Group’s opinion it was appropriate to use the Van Rijssen et al. 20° analysis that excluded patients who needed re-treatment. The Assessment Group was also concerned that, in the company’s 30° analyses, the results of CORDLESS and Van Rijssen et al. may not be comparable because:

- Van Rijssen et al. examined recurrence in the hand whereas CORDLESS examined recurrence in the joint; and
- Van Rijssen et al. included all patients whereas CORDLESS only included those whose treatment was successful.

4.51 In its new evidence, the company presented analyses using the Assessment Group’s model with the revised cost estimates, treatment pathways and recurrence rates described in sections 4.46–4.50.
Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of CCH, having considered evidence on the nature of Dupuytren’s contracture and the value placed on the benefits of CCH by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.52 The Committee discussed the current treatments available for Dupuytren’s contracture. It heard from clinical experts 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 a smaller number of people have PNF, CCH or dermofasciectomy. The Committee 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. It heard from 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 recurrence of contracture is common, 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 Committee discussed the relevant population for the appraisal. It 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 broad population of people with moderate and severe Dupuytren's contracture but that it was appropriate to explore subgroups within this population.

The Committee considered the relevant comparators for CCH. It heard from the clinical experts that dermofasciectomy is used for contractures that involve the skin and CCH would not be used for this type of disease. It 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. The Committee 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 were the relevant comparators for this appraisal.

The Committee discussed whether there was a subgroup of people for whom PNF would not be a suitable treatment and therefore not a relevant comparator. It heard from a clinical expert that all people with disease that was suitable for CCH would also be suitable for PNF. The Committee noted that this advice was contradicted by some responses to the appraisal consultation document, which
stated that a subgroup of patients with moderate disease would be suitable for treatment with CCH but not with PNF. The Committee considered carefully whether this subgroup exists and how it could be defined. Having reviewed the submissions, expert advice and responses to consultation, the Committee considered that there was a lack of consensus about the clinical characteristics that would make contracture suitable for CCH but unsuitable for PNF. The Committee agreed that there was no clear definition of which patients had disease that was unsuitable for PNF, and it was aware that it had not been presented with any evidence of the clinical and cost effectiveness of CCH in these patients. Therefore, the Committee concluded that it would not be appropriate to consider this subgroup separately from the rest of the population.

4.56 The Committee discussed the availability of PNF in different areas and whether it was a relevant comparator. 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 to do PNF. The Committee noted that this advice was supported by the responses to consultation. It was aware that PNF accounts for approximately 8% of hospital procedures for Dupuytren’s contracture (see section 2.4). 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 may be treated with PNF within the subgroup of patients with moderate disease, because clinical experts advised that PNF is most suitable for this subgroup. The Committee observed that there were differing opinions about the level of skill required to perform PNF. A clinical expert advised that the procedure is similar for CCH and PNF, meaning that a clinician who was able to administer CCH would also have the skills needed to perform PNF. The Committee observed that this implied that patients for whom CCH was available would also have access to
PNF. However, the Committee was aware that this advice was contradicted by responses to consultation which stated that CCH is easier to administer than PNF. The Committee considered that it was beyond the scope of this technology 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 effectiveness

4.57 The Committee discussed the clinical effectiveness of CCH relative to placebo. It considered that the CORD trials used appropriate methods and the results were likely to generalise 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 was a clinically effective treatment for Dupuytren’s contracture.

4.58 The Committee considered the clinical effectiveness of CCH relative to PNF and limited fasciectomy. It was aware that no randomised 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 (see section 4.20). The Committee was aware of responses to the appraisal consultation document that called for further research into the comparative clinical effectiveness of treatments for Dupuytren’s contracture, and it also noted that the National Institute for Health Research had issued a call for applications for research funding to examine the clinical effectiveness of CCH compared with surgery. 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 (see sections 4.7 and 4.16). 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.

The Committee explored the rate of recurrence of contracture after successful treatment. It was aware that the CORDLESS study (of CCH) and the post hoc analyses by Van Rijssen et al. (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 people in the Van Rijssen et al. trial had not previously had surgery for Dupuytren's contracture, in contrast to 38% and 53% of patients in the CORD I and II studies respectively. The Committee was not presented with data on whether patients in CORDLESS had previously had surgery but, because CORDLESS included patients from CORD I and II, it is likely that some patients in CORDLESS had previously had surgery. The Committee heard from the clinical experts that patients with a history of recurrence had a higher risk of further recurrence than previously untreated patients. The Committee considered that a 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 views of the clinical experts that the recurrence rate 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 observed in clinical practice for each of these treatments.

4.60 The Committee had noted that some trials recruited different populations, making it difficult to compare the results (see section 4.59). It discussed the company’s analysis of CORDLESS, POINT X and Van Rijssen et al. (see section 4.19), 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 patients 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 the conclusions summarised in sections 4.58 and 4.59.

4.61 The Committee discussed the recovery time after treatment for Dupuytren’s contracture, noting that there was a lack of evidence 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 the appraisal consultation document, which showed that some patients report that hand function is not fully recovered 12 months after limited fasciectomy. The Committee noted that these results came
from the Engstrand et al. study, which appeared to recruit a population with more severe contracture than the CORD studies. It also noted that most patients 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 patients.

4.62 The Committee considered the adverse events associated with treatment for Dupuytren's contracture. It noted that almost all patients had at least 1 adverse event after treatment with 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 patients 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.

4.63 The Committee discussed the level of competency needed to give CCH safely. It heard from the clinical experts that CCH must be given correctly in order 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 training provided by the company.

Cost effectiveness

4.64 The Committee discussed the company’s cost-minimisation model, noting that the analysis excluded PNF which is a relevant
comparator (see sections 4.53–4.55). 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.

4.65 The Committee discussed the Assessment Group’s cost–utility model, which was based on a naive indirect comparison. The Committee was aware that this indirect 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 in nature and the results are associated with increased uncertainty. However, the Committee recognised that a naive indirect comparison was necessary for the reasons stated in section 4.20. 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.

4.66 The Committee discussed the modelled population. It noted that the Assessment Group’s original model included patients 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.

4.67 The Committee discussed the treatment pathways in the Assessment Group’s model, noting that they 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 conducted some years ago at a single centre in the Netherlands, and CORDLESS was conducted in the USA before CCH gained a marketing authorisation. Consequently, in the company’s opinion, these studies may not be representative of 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 (see section 4.48). 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 the appraisal consultation document 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 be representative of 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 concluded that it preferred to use the Assessment Group’s treatment pathway in the economic model.

4.68 The Committee further discussed the treatment pathways in the Assessment Group’s 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.

4.69 The Committee discussed the success rates for CCH in the Assessment Group’s model, noting that analyses of the overall population used 63% 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%.

4.70 The Committee discussed the success rates for PNF and limited fasciectomy in the Assessment Group’s model. It noted that most analyses used 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 1 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.

4.71 The Committee considered the recurrence rates in the Assessment Group’s model. It noted that the rates in the original 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 4.59). 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 Committee further discussed the recurrence rates, noting 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 the rates increased from 5% to 21% for limited fasciectomy (see sections 4.30 and 4.50). 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, counterintuitively, using a more severe definition of recurrence had increased the recurrence rates substantially for PNF and LF. 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 (see section 4.50). 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 4.71.

The Committee considered the utility values in the Assessment Group’s economic model for the overall population. It was aware that, 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.

4.74 The Committee discussed the revised utility values in the Assessment Group’s subgroup analyses. It noted that these 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.

4.75 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.

4.76 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 the appraisal consultation document, stating that UK audit data show the average number of injections per joint is 1.03–1.30. 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%.

4.77 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.

4.78 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 an inpatient. 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%.

4.79 The Committee discussed the costs of treatment, noting 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 (2013) 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 of 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 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.
4.80 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 £2931 and incremental QALY gain −0.08). It noted that the analysis was not ideal because the model did not use appropriate utility values (see section 4.73). However, the Committee considered that changes to the utility values would be unlikely to substantially alter the results for the overall population, because the results were mainly driven by treatment effectiveness and treatment costs rather than utility values (see section 4.37). The Committee was aware of a response to consultation from a professional group, which stated that NHS commissioners in 1 region estimated that treating 60 patients with CCH saved more than £65,000. It was also aware of responses to consultation from NHS professionals, stating that CCH was a cost-saving intervention. Although it values input from professionals and commissioners, the Committee noted that it had no information about how these figures had been calculated and they were not cost-effectiveness analyses. The Committee concluded that, for the overall population of people with moderate or severe contracture, the ICER for CCH was unlikely to fall into the range usually considered to be a cost-effective use of NHS resources.

4.81 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. It discussed the Assessment Group’s analysis using: the Committee’s preferred recurrence rates; parameters from the CORD trials (CCH success rate of 81%, 1.47 affected joints and 1.6 injections of CCH per joint); and excluding CCH as an option after PNF. The ICER for CCH compared with PNF was £31,100 per QALY gained.
(incremental costs £1337 and incremental QALY gain 0.04). An intervention is ‘extendedly dominated’ when it is more costly and less effective than a combination of 2 comparators. In this analysis, limited fasciectomy was extendedly dominated by CCH and PNF. The Committee had agreed that it was appropriate to consider analyses that assumed fewer injections of CCH (see section 4.76). Accordingly, the Committee discussed the Assessment Group’s analysis using parameters from the POINT X study (CCH success rate of 66%, 1.2 affected joints and 1.2 injections of CCH per joint) and the Committee’s preferred recurrence rates. CCH was extendedly dominated by PNF and limited fasciectomy. The Committee considered that these analyses probably underestimated the ICER for CCH because the success rates for limited fasciectomy and PNF were likely to be higher in the moderate-disease subgroup than in the overall population, but the model used success rates from the overall population for these treatments. The Committee discussed the Assessment Group’s exploratory analysis that assumed a higher success rate for limited fasciectomy and PNF; this analysis showed that CCH was dominated by PNF (CCH cost £650 more and gained 0.02 fewer QALYs). The Committee then discussed the Assessment Group’s analysis that assumed a longer recovery time after limited fasciectomy than after CCH. The ICER for CCH compared with PNF was £36,500 per QALY gained; compared with limited fasciectomy, CCH gained fewer QALYs at lower cost. The Committee recalled that the proportion of inpatient limited fasciectomy procedures could be lower than the 26% assumed by the Assessment Group, and noted that implementing this change in the model would lower the cost of limited fasciectomy. The Committee acknowledged the lack of research comparing the clinical effectiveness of CCH with PNF and limited fasciectomy, and it observed that the lack of data made the results of the economic analysis very uncertain. Taking all of the available evidence into
account, the Committee concluded that the ICER for CCH compared with PNF for the moderate-disease subgroup was likely to be at least £31,100 per QALY gained, and so the ICER did not fall within the range usually considered cost effective.

4.82 The Committee discussed whether CCH could be considered a cost-effective use of NHS resources for the subgroup of people with severe disease and up to 2 affected joints. It noted that CCH was dominated by both PNF and limited fasciectomy in the Assessment Group’s analysis. The Committee concluded that CCH cost more and gained fewer QALYs (that is, was less effective) than alternative treatments and so could not be considered a cost-effective treatment for the subgroup of patients with severe disease and up to 2 affected joints.

4.83 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 gain 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 noted that the Assessment Group’s sensitivity analyses included a longer recovery time after limited fasciectomy, but nonetheless the ICER for CCH did not fall within the range usually considered cost effective. 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 the appraisal consultation document advised that treatment of recurrence may be cheaper and more successful if the initial treatment is CCH rather than limited fasciectomy. Although it valued the input from patients and professionals, the Committee noted that it had not been presented with evidence that these potential benefits were realised in practice or how these benefits might affect cost effectiveness. 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.

4.84 The Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS Payment Mechanism, when appraising CCH for Dupuytren’s contracture. The Committee noted NICE’s position statement in this regard, and accepted the conclusion ‘that the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines’. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of CCH for Dupuytren’s contracture. It therefore concluded that the PPRS Payment Mechanism was not applicable for the consideration of cost effectiveness of CCH for Dupuytren’s contracture.

4.85 The Committee noted that the ICERs for CCH were above the range usually considered a cost-effective use of NHS resources, for both the overall population and subgroups within that population. The Committee also noted that several parameters in the model were very uncertain because there was a lack of high-quality evidence that compared the clinical effectiveness of treatments for Dupuytren’s contracture. However, the Committee acknowledged
that CCH had the potential to offer benefits to patients compared with current treatments, and it was supportive of the National Institute for Health Research’s call for research into the clinical effectiveness of CCH. The Committee considered whether it should recommend CCH for use in the NHS while additional research is conducted. It was mindful of the NICE Social Value Judgements which state that an intervention should not be recommended if there is no evidence, or not enough evidence, on which to make a clear decision. It was also mindful of the health benefits that would be foregone by displacing other treatments in the NHS by recommending a technology for which the cost effectiveness had not been demonstrated, based on the evidence presented to it. The Committee therefore decided that it would not be appropriate to recommend CCH for routine use. The Committee 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 agreed that the research should be designed to generate robust evidence about the benefits of CCH compared with limited fasciectomy and PNF for people with moderate Dupuytren’s contracture (see section 6). 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.

**Summary of Appraisal Committee’s key conclusions**

<table>
<thead>
<tr>
<th>TAXXX</th>
<th>Appraisal title: Collagenase clostridium histolyticum for treating Dupuytren’s contracture</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key conclusion</td>
<td>Collagenase clostridium histolyticum (CCH) is not recommended for treating Dupuytren’s contracture in adults with a palpable cord, except in the context of research.</td>
<td>1.1</td>
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<td></td>
<td>Such research should be designed to generate robust evidence about the</td>
<td>1.2</td>
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benefits of CCH compared with limited fasciectomy and percutaneous needle fasciotomy (PNF) in people with moderate Dupuytren’s contracture.

The Committee concluded that CCH was more effective than placebo in reducing contracture, but further research was needed to establish whether CCH was more or less effective than PNF and limited fasciectomy.

The Committee was aware that the Assessment Group’s model was based on the best available evidence but that the success rates, recurrence rates and rates of adverse events in the model were highly uncertain. It noted that the incremental cost-effectiveness ratios (ICERs) for CCH were above the range usually considered a cost-effective use of NHS resources, for both the overall population and subgroups within that population. The Committee considered whether it should recommend CCH for use while additional research is conducted. It was mindful of the NICE Social Value Judgements which state that an intervention should not be recommended if there is no evidence, or not enough evidence, on which to make a clear decision. It was also mindful of the health benefits that would be foregone by displacing other treatments in the NHS by recommending a technology for which the cost effectiveness had not been demonstrated, based on the evidence presented to it. The Committee therefore decided that it would not be appropriate to recommend CCH for routine use. The Committee 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 that compares the clinical effectiveness of CCH with PNF and limited fasciectomy.

### Current practice

| Clinical need of patients, including the availability of alternative treatments | In the NHS, the most common treatment for moderate or severe disease is limited fasciectomy and a smaller number of people have PNF, CCH or dermofasciectomy. The Committee concluded that effective new treatments would be welcomed by patients and clinicians. | 4.52 |

4.57, 4.58

4.65, 4.85
### The technology

<table>
<thead>
<tr>
<th>Proposed benefits of the technology</th>
<th>The proposed benefits include a reduction in contracture, avoiding a general anaesthetic, shorter recovery time, the possibility of treatment at an earlier stage of disease progression and the potential for more repeat treatments than are possible with surgery. CCH is the first pharmacological treatment to gain a marketing authorisation for treating Dupuytren’s contracture. 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 quality-adjusted life years (QALYs).</th>
<th>4.57, 4.83</th>
</tr>
</thead>
<tbody>
<tr>
<td>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</td>
<td>Treatment with CCH is an alternative to treatment with PNF or limited fasciectomy.</td>
<td>4.52, 4.54–4.56</td>
</tr>
<tr>
<td>What is the position of the treatment in the pathway of care for the condition?</td>
<td>Almost all patients had at least 1 adverse event after treatment with CCH, and the adverse events were normally mild or moderate. The Committee concluded that CCH has an acceptable safety profile.</td>
<td>4.62</td>
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<tr>
<td>Adverse reactions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Evidence for clinical effectiveness

<table>
<thead>
<tr>
<th>Availability, nature and quality of evidence</th>
<th>The Committee considered evidence from the CORD I and II randomised controlled trials, which compared CCH with placebo. 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. The Committee also considered evidence from the Van Rijssen et al. trial that compared limited fasciectomy with PNF.</th>
<th>4.11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevance to general clinical practice in the NHS</td>
<td>The Committee considered that the results of the CORD trials were likely to generalise to the NHS.</td>
<td>4.57</td>
</tr>
<tr>
<td>Uncertainties generated by the evidence</td>
<td>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.</td>
<td>4.58</td>
</tr>
</tbody>
</table>
### Evidence for cost effectiveness

| Availability and nature of evidence | The Committee discussed the company’s cost-minimisation model and the Assessment Group’s cost–utility model. | 4.64, 4.65 |
| Uncertainties around and plausibility of assumptions and inputs in the economic model | The Committee concluded that a cost-minimisation analysis was not an appropriate method of assessing the cost effectiveness of CCH and that the company’s analysis was further limited because it excluded PNF as a comparator. | 4.64 |
| | The Committee was aware that the Assessment Group’s cost–utility model was based on a naive indirect comparison, which did not maintain randomisation and made no adjustment for differences between studies. It understood that, with this type of comparison, the data are observational in nature and the results are uncertain. It concluded that the Assessment Group’s model was based on the best available evidence. It also concluded that, given the uncertainty in 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. | 4.65 |
The Committee noted that assumptions about the number of injections of CCH and the number of treated joints had a substantial impact on the total costs. It heard that patients may need fewer injections in clinical practice than in clinical trials.

The Committee noted that the Assessment Group provided analyses for the moderate subgroup assuming fewer injections and fewer 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.

After the final appraisal determination, the company submitted new evidence and proposed changes to the Assessment Group’s model (specifically, the costs, treatment pathways and recurrence rates).

The Committee was concerned that the company’s revised cost estimates, based on the national tariff, may not reflect the true costs of a procedure. It noted that the Assessment Group’s approach of using NHS reference costs was in line with the Methods guide.

The Committee was concerned that the company’s new treatment pathways may not be representative of the NHS.

The Committee noted that the company’s new recurrence rates were counterintuitive and may not be comparable between treatments because of different definitions of recurrence.

The Committee chose to use the Assessment Group’s cost estimates and treatment pathways, and the Committee’s preferred recurrence rates identified in section 4.71.
| Incorporation of health-related quality-of-life benefits and utility values | The baseline utility value in the Assessment Group’s original model assumed that patients had Tubiana stage 3 contracture in 3 fingers. The Committee heard that this contracture is more severe than is typically seen in clinical practice. The Committee noted that the Assessment Group had not adjusted the utility values by the average utility value of the modelled population (that is, treatment success was associated with a utility of 1). It noted that the analysis was not ideal because the model did not use appropriate utility values. After the first Committee meeting, the Assessment Group submitted new subgroup analyses with revised utility values. In its sensitivity analyses, the Assessment Group applied a utility decrement to some patients to reflect recovery time after treatment. 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. | 4.73, 4.80 |
| Are there specific groups of people for whom the technology is particularly cost effective? | CCH may be more cost effective for people with moderate disease and few affected joints than for the overall population. | 4.66 |
| What are the key drivers of cost effectiveness? | The Assessment Group’s model was primarily driven by treatment effectiveness. The results were also affected by recurrence rates and costs. | 4.37, 4.80 |
| Most likely cost-effectiveness estimate (given as an ICER) | For the overall population, 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. The Committee concluded that the ICER for CCH was unlikely to fall into the range usually considered to be a cost-effective use of NHS resources. | 4.80 |
For the subgroup of patients with moderate disease and up to 2 affected joints, using the Committee's preferred recurrence rates and parameters from the CORD trials, the ICER was £31,100 per QALY gained for CCH compared with PNF. The Committee discussed alternative analyses that assumed fewer injections of CCH, a higher success rate for limited fasciectomy and PNF, or a longer recovery time after limited fasciectomy. These analyses did not result in a lower ICER. The Committee concluded that the ICER for CCH compared with PNF for the moderate-disease subgroup was likely to be at least £31,100 per QALY gained.

For the subgroup of patients with severe disease and up to 2 affected joints, CCH was dominated by both PNF and limited fasciectomy in the base case.

### Additional factors taken into account

| Patient access schemes (PPRS)                | Not applicable. |
| End-of-life considerations                  | Not applicable. |
| Equalities considerations and social value judgements | No equality issues relevant to the Committee’s recommendations were raised. |

### Implementation

#### 5.1

NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
• A costing statement explaining the resource impact of this guidance.
• Audit support for monitoring local practice.

5.2 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.

6 Recommendations for further research

6.1 The Committee recommended that further research should be done to assess the clinical effectiveness of collagenase clostridium histolyticum (CCH) compared with percutaneous needle fasciotomy and limited fasciectomy. The study should recruit people with moderate Dupuytren’s contracture. Outcomes should include measures of hand function and assessments of health-related quality of life using both a disease-specific measure and a generic preference-based measure.

6.2 The Committee agreed that further research was needed because there are no trials comparing CCH with percutaneous needle fasciotomy and limited fasciectomy. It was aware that the National Institute for Health Research had issued a call for applications for research funding to examine the clinical effectiveness of CCH. The Committee agreed that research should focus on patients with moderate disease (defined in section 2.6), because CCH cost less and was more clinically effective for these patients than for those with severe disease (see sections 4.79–81). The Committee identified that success rates, recurrence rates and effects on health-related quality of life were the main areas of uncertainty in the current research. It also noted that, in the opinion of patient and
clinical experts, the outcome of most importance to patients was recovery of hand function rather than reduction in contracture. No ongoing trials have been identified.

7 Related NICE guidance

Details are correct at the time of publication. Further information is available on the NICE website.

- Radiation therapy for early Dupuytren's disease (2010) NICE interventional procedure guidance 368
- Needle fasciotomy for Dupuytren's contracture (2004) NICE interventional procedure guidance 43

8 Review of guidance

8.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. 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
September 2015
9 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

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Professor of Cardiovascular Medicine, Queen’s University Belfast and Consultant Physician, Belfast City Hospital

Dr Lindsay Smith (Vice Chair)
General Practitioner, West Coker Surgery, Somerset

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Regulatory and Medical Affairs Director Europe and North America, Reckitt Benckiser

Dr Andrew Black
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Consultant Haematologist, Leeds Teaching Hospitals NHS Trust

Dr Matthew Bradley  
Vice President, Value Evidence & Outcomes, GlaxoSmithKline

Dr Ian Campbell  
Honorary Consultant Physician, Llandough Hospital, Cardiff

Ms Tracey Cole  
Lay Member

Dr Ian Davidson  
Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon  
Professor of Health Economics, University of Sheffield

Susan Dutton  
Senior Medical Statistician, Oxford Clinical Trials Research Unit

Dr Alexander Dyker  
Consultant Physician, Wolfson Unit of Clinical Pharmacology, Newcastle University

Christopher Earl  
Surgical Care Practitioner, Wessex Neurological Centre at University Hospital Southampton NHS Foundation Trust

Mrs Gillian Ells  
Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Professor Paula Ghaneh  
Professor and Honorary Consultant Surgeon, University of Liverpool

Dr Susan Griffin  
Research Fellow, Centre for Health Economics, University of York

National Institute for Health and Care Excellence  
Final appraisal determination – collagenase clostridium histolyticum for treating Dupuytren's contracture

Issue date: September 2015
Professor Carol Haigh
Professor of Nursing, Manchester Metropolitan University

Professor John Henderson
Professor of Paediatric Respiratory Medicine, University of Bristol and Bristol Royal Hospital for Children

Professor Steven Julious
Professor in Medical Statistics, University of Sheffield

Dr Tim Kinnaird
Lead Interventional Cardiologist, University Hospital of Wales

Dr Warren Linley
Independent Pharmacist and Health Economist

Dr Malcolm Oswald
Lay Member

Professor Femi Oyebode
Professor of Psychiatry and Consultant Psychiatrist, National Centre for Mental Health

Dr John Radford
Director of Public Health, Rotherham Clinical Commissioning Group and Metropolitan Borough Council

Dr Mohit Sharma
Consultant in Public Health, Public Health England

Dr Murray Smith
Associate Professor in Social Research in Medicines and Health, University of Nottingham

Professor Carolyn Young
Consultant Neurologist, Walton Centre for Neurology and Neurosurgery
**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.

**Dr Rosie Lovett and Boglarka Mikudina**  
Technical Leads

**Nicola Hay and Zoe Charles**  
Technical Advisers

**Kate Moore**  
Project Manager
10 Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by the Aberdeen Health Technology Assessment Group:

- Brazzelli M, Cruickshank M, Tassie E et al., Collagenase clostridium histolyticum for the treatment of Dupuytren’s contracture, May 2014.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I. Company:

- Swedish Orphan Biovitrum AB

II. Professional/specialist and patient/carer groups:

- British Dupuytren’s Society
- British Association of Hand Therapists
- British Society for Surgery of the Hand
- Royal College of Nursing

III. Other consultees:

- Department of Health
- NHS England
- NHS Herts Valley Clinical Commissioning Group (West)
- Welsh Government

IV. Commentator organisations (without the right of appeal):
C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee’s deliberations. They gave their expert personal view on collagenase clostridium histolyticum by providing oral evidence and a written statement to the Committee.

- Mr Christopher Bainbridge, Consultant Hand Surgeon, nominated by British Dupuytren’s Society – clinical expert
- Mr Henk Giele, Consultant Plastic Reconstructive and Hand Surgeon, nominated by British Dupuytren’s Society – clinical expert
- Ms Anna Schurer, nominated by British Dupuytren’s Society – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Swedish Orphan Biovitrium