NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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 between 17% and 59% of 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 are believed to 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. The choice of surgical technique is influenced by factors including the severity of disease, the patient’s age, the patient’s preference, comorbidities, and the surgeon’s preference and expertise. Hospital episode statistics show that, of the hospital 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 the treatment of 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 disease has resulted in 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

4.1 The Assessment Group conducted a systematic review of randomised controlled trials, non-randomised comparative studies and observational studies. The assessment report included case series that assessed the effects of collagenase clostridium histolyticum (CCH) but did not include case series that assessed the effects of surgical procedures.

Collagenase clostridium histolyticum

4.2 The Assessment Group’s systematic review did not find any randomised controlled trials that compared 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.

4.3 The CORD I randomised controlled trial was carried out at 16 sites in the USA. There were 204 patients 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. Almost all patients were white (99.7%) and 38% had already had surgery for Dupuytren’s contracture. Another randomised controlled trial (CORD II) was carried out at 5 sites in Australia. There were 45 patients randomised to have CCH and 21 patients randomised to have placebo. The CORD II treatment groups were similar in age (CCH mean 63.0 years, placebo mean 65.5 years) and percentage of men (CCH 86.7%, placebo 81.0%). 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°). All the patients in CORD II were white and 53% 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.

4.4 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). Across these 3 trials, the length of follow-up ranged from 1 to 5 years, patients’ mean age ranged from 60 to 65 years and the percentage of men ranged from 80% to 86%.

4.5 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. In all 4 trials assessed, patients and healthcare providers did not know what treatment the patient had (that is, they were blinded). It was not clear whether any trials blinded the outcome assessors. All trials analysed results on the basis of intention to treat.

4.6 A non-randomised retrospective study by Naam (2013) was carried out at a single site in the USA; 25 patients had CCH and 21 had fasciectomy. A non-randomised retrospective study by Nydick et al. (2013) was also carried out at a single site in the USA; 29 patients had CCH and 30 had percutaneous needle fasciotomy (PNF). The Assessment Group considered that both these studies were at high risk of bias because patients were allocated to treatments by patient or physician preference. In both studies, there was a lack of blinding and a high risk of confounding, performance bias and detection bias.

4.7 For the 15 case series of CCH, the number of patients ranged from 8 to 645 and the length of follow-up ranged from 4 weeks to 8 years. 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.

4.8 A range of outcome measures was used in trials of treatments for Dupuytren’s contracture. For CORD I and II, the primary outcome measure was the proportion of patients with clinical success, defined as contracture of less than 5° in the primary treated joint
measured 30 days after the last injection. The primary treated joint was chosen by the investigator before the start of treatment. The CORD trials also measured clinical improvement, defined as a reduction in contracture of at least 50% in the primary treated joint compared with baseline.

4.9 The Assessment Group conducted a meta-analysis that included end points that had been measured by more than 1 randomised controlled trial. Accordingly, the analysis included CORD I, CORD II and, for some measures, 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). Clinical improvement was shown in 207/248 (83%) primary joints treated with CCH and 15/124 (12%) primary joints treated with placebo; the difference between treatments was statistically significant (risk ratio 6.9, 95% CI 4.3 to 11.1).

4.10 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. Confidence intervals for the success rates were not reported. Patients in both subgroups had an average of 1.6 injections per joint.

4.11 The non-randomised study by Naam found that the mean post-treatment contracture for 25 patients who had CCH was 3.6° for metacarpophalangeal joints and 17.5° for proximal interphalangeal
joints. For 21 patients who had fasciectomy, the results were 3.7° and 8.1° respectively. Patients returned to normal activities 1.9 days after treatment with CCH on average, compared with 37.4 days after fasciectomy. The non-randomised study by Nydick et al. defined clinical success as a reduction in contracture to within 5° of full extension; this end point was reached by 19/34 (56%) joints treated with CCH and 35/50 (67%) joints treated with PNF. Both of these studies found that the reduction in contracture did not differ significantly between treatment groups.

4.12 The Assessment Group noted that it was difficult to compare the results of the CCH case series because studies used different definitions of success. When success was defined as a reduction in contracture to within 5° of full extension, success rates for CCH ranged from 51% to 88% for metacarpophalangeal joints and from 14% to 44% for proximal interphalangeal joints.

4.13 Across all studies of CCH (including randomised controlled trials, non-randomised comparative 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. The Assessment Group advised that it was difficult to compare recurrence rates because studies varied in their duration of follow-up and definition of recurrence. 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.

4.14 The Assessment Group examined the adverse events associated with CCH using a meta-analysis of CORD I, CORD II and, for some
events, Badalamente and Hurst (2007). 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 controlled 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**

4.15 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.

4.16 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, n=79) or
compared 2 fasciectomy techniques (Citron and Nunez 2005, n=100); these comparisons are not the focus of this appraisal.

4.17 The non-randomised studies included a retrospective chart review of 3286 patients at several sites in Europe (Dias et al. 2013) and 4 smaller studies. The study by Dias et al. included patients who had PNF, fasciotomy, fasciectomy and dermofasciectomy. The average age of patients was 61.9 years, 81% were men and the length of follow-up was 1 year. 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.

4.18 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.

4.19 The Assessment Group noted that it was difficult to compare results of the 5 non-randomised surgical studies because the studies used different outcome measures. None of the 5 studies reported the percentage of patients who had contracture of less than 5° after treatment.

4.20 Across all surgical studies (including randomised controlled trials and non-randomised studies), the recurrence rate ranged from 0% to 85%. The Assessment Group advised that it was difficult to compare recurrence rates for each surgical procedure because
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 4.13). 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.

4.21 The retrospective study by Dias et al. found that, across all surgical procedures, 4% of patients had at least 1 adverse event during surgery and 34% had at least 1 adverse event after surgery. Adverse events were more common for dermofasciectomy and fasciectomy than for less invasive procedures such as fasciotomy and PNF. For fasciectomy, 6.2% of patients had an adverse event during surgery and 25.4% had an adverse event after surgery; the results for PNF were 2.6% and 0.8% respectively. Among those 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 those 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 provided after consultation

4.22 After 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 mean of 1.22 CCH injections per treated joint. The company noted that this was lower than the mean of 1.6 injections needed for the subgroup with moderate
disease and up to 2 affected joints in the CORD studies (see section 4.10). For the moderate-disease subgroup in POINT X, the success rate was 66.1% and the mean number of joints treated was 1.17 (compared with 81% and 1.47 joints affected for the moderate-disease subgroup in the CORD studies). 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.

4.23 The company submitted additional evidence on recovery time after limited fasciectomy, taken from a prospective cohort study conducted in Sweden (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 (including metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints). 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. The company stated that the results showed that the majority of patients had hand dysfunction for up to 12 months after limited fasciectomy.

4.24 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.

Clinical-effectiveness summary
4.25 The Assessment Group concluded that CCH was significantly more likely than placebo to achieve clinical success and clinical improvement 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 and an indirect comparison was not possible. Therefore, the Assessment Group concluded that there was no evidence that CCH was clinically better or worse than surgical treatments.

Cost effectiveness

Previous economic evaluations
4.26 The Assessment Group identified 2 previous economic evaluations of treatments for Dupuytren’s contracture. Both were cost–utility analyses using a societal perspective and included CCH, PNF and limited fasciectomy. Chen et al. (2011) compared all interventions with no treatment. The study was carried out in the USA and utilities were obtained from 50 members of the public using the standard gamble method. The utility value for severe Dupuytren’s contracture was 0.987. Chen et al. reported that the incremental cost-effectiveness ratio (ICER) for CCH compared with no treatment was $166,268 per quality-adjusted life year (QALY) gained. Baltzer and Binhammer (2013) compared the interventions
with each other in an incremental analysis. The study was conducted in Canada and utilities were based on Chen et al. Baltzer and Binhammer reported that PNF was the most cost-effective treatment. The ICER for CCH compared with PNF was $284,383 per QALY gained. Limited fasciectomy was dominated because it was more costly and less effective than the other treatments.

The Assessment Group noted that both of the published economic evaluations used efficacy data from several studies with no adjustment for differences between studies. Neither of the economic evaluations included changes in quality of life or costs associated with recurrence or further treatment. The Assessment Group also advised that the standard gamble method may not fully capture the impact of Dupuytren’s contracture on health-related quality of life. This is because the disease is not life-threatening, so respondents may have been unwilling to accept an additional risk of death in order to have a greater probability of living in a better health state.

**Company’s model**

The company submitted a cost-minimisation analysis that compared CCH with fasciectomy. This analysis assumed that both treatments were equally effective, so only costs were compared. A 5-year time horizon was adopted with costs discounted at 3.5% per year. 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 in the UK. 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. The analysis was from the perspective of the NHS and personal and social services.
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. For CCH, a course of therapy involved a series of up to 3 injections. For fasciectomy, a course of therapy involved a single surgery. 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).

The base-case results of the company’s model showed that the total cost per hand was £1841 for CCH and £2784 for fasciectomy. Therefore, CCH was associated with a cost saving of £943. A series of 1-way sensitivity analyses showed that the results were sensitive to assumptions about the number of CCH injections per joint, the proportion of patients having fasciectomy as inpatients, and allowing for the waste of CCH when a vial is opened but not fully used (that is, assuming no vial sharing). CCH remained cost saving in all the company’s sensitivity analyses.

The Assessment Group advised that a cost-minimisation analysis may not be appropriate because there was no evidence from randomised controlled trials to support the assumption that CCH and fasciectomy are equally effective. The assessment report noted that the use of 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 (see section 4.26). The Assessment Group noted that the company assumed each patient had 1.4 affected joints, whereas in CORD I patients had 3 affected joints on average. The Assessment Group also noted concerns about some of the assumptions made by the company such as the number of hand therapy appointments, assuming no treatment after treatment failure, and possibly underestimating the cost of treating recurrence.

Assessment Group’s model

4.32 The Assessment Group developed a cost–utility Markov model that compared CCH, PNF and limited fasciectomy. The model included 4 main 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 a fully incremental analysis was reported. Costs and outcomes were discounted at 3.5% per year. The analysis was from the perspective of the NHS and personal and social services.

4.33 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 surgeon quality. As a result, the Assessment Group advised that the results from the economic model should be considered with caution.

4.34 The population for the economic evaluation 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, who were willing to be considered for surgery. The modelled cohort was 84% men, had a starting age of 63 years and a mean of 3 affected joints.

4.35 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. Within all health states, there was a risk of all-cause mortality, adjusted for gender and age based on interim UK life tables.

4.36 The Assessment Group defined treatment success as a reduction in contracture to within 5° of full extension. The probability of success was 0.63 for CCH, based on the Assessment Group’s meta-analysis (see section 4.9). The probability of success was 0.41 for PNF and 0.71 for limited fasciectomy, based on Van Rijssen et al. averaged across metacarpophalangeal and proximal interphalangeal joints (see section 4.18). The same success rates were used for first, second and third courses of therapy.

4.37 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.

4.38 The Assessment Group defined recurrence as a return of contracture of at least 20° in a joint that had been successfully treated. The 6-month probability of recurrence after CCH was 0.061 (from CORDLESS). The 6-month probability of recurrence after PNF was 0.025 and after limited fasciectomy was 0.005 (both from Van Rijssen et al.). In the base case, recurrence could occur only in the first 5 years after treatment. The same recurrence rates were used for first, second and third courses of therapy.

4.39 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 0.40 following CCH, 0.73 following PNF and 0.40 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 company’s model and clinical opinion.

4.40 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.

4.41 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 model assumed that patients would have 1.6 injections per joint, based on the subgroup of 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, was £4814. Treatment with CCH after recurrence or treatment failure was assumed to be for a single joint and incurred a cost of £1605. 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. For PNF and limited fasciectomy, the cost of complications was £1824.

4.42 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 (in which 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°.

In the model, patients at baseline were assumed to have stage 3 contracture in 3 fingers of the dominant hand. Patients who had treatment success were assumed to have no contracture. Patients who had treatment failure were assumed to have stage 3 contracture in the base case. Patients with recurrence were assumed to have stage 1 contracture until they progressed to further treatment, at which point they had stage 3 contracture for 1 model cycle.
The utilities 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. For example, Gu et al. reported that the utility value for a dominant hand with Tubiana stage 2 contracture in the ring and little fingers was 0.89.

The Assessment Group calculated the utility value associated with each Tubiana stage. Their method was explained using the example of Tubiana stage 3. First, the indirect utility weight for a hand with stage 3 contracture in the index finger was obtained from Gu et al. Second, this indirect utility weight was multiplied by 3 because patients in the model were assumed to have a mean of 3 affected joints. Third, the indirect utility weight was converted to an EQ-5D utility value using the equation published by Gu et al. for the dominant hand. This process was then repeated for the middle, ring and little fingers. Finally each utility value was multiplied by the probability of that finger being affected. This process led to a weighted average utility value of:

- 0.776 for a hand with Tubiana stage 3 contracture in 3 fingers (baseline and treatment failure health state)
- 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).

The Assessment Group’s base-case results 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 £2899) and less effective (incremental QALY gain −0.06) than limited fasciectomy.
The assessment report included deterministic sensitivity analyses that varied the number of injections of CCH, the success rates, the time period in which recurrences could occur, the probability of treatment after recurrence, the choice of the second course of therapy, the utility value for treatment failure, the treatment costs, the number of affected joints and the discount rate. Further sensitivity analyses applied a utility decrement to patients having limited fasciectomy, either at baseline (to reflect anxiety before the procedure) or after treatment (to reflect the recovery time). CCH was dominated in most of the analyses.

The Assessment Group conducted a probabilistic sensitivity analysis in which distributions were assigned to the unit costs of hospital-based procedures, recurrence rates, success rates, complication rates, the probability of further treatment and utility values. The results showed that, at £20,000 per QALY gained, the probability of being the most cost-effective treatment was 0.1% for CCH, 34.8% for PNF and 65.1% for limited fasciectomy. At £30,000 per QALY gained, the probability of being the most cost-effective treatment was 1.3% for CCH, 24.8% for PNF and 73.9% for 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.

The Assessment Group noted that their estimate of the cost of a course of CCH (£4814) was substantially higher than the company’s estimate (£1739). The Assessment Group observed that the company’s analysis was limited to a subgroup of the population and assumed that only 1.4 joints were treated, whereas the Assessment Group assumed that 3 joints were treated. A
further reason for the difference in cost was that the Assessment Group assumed there was no vial sharing.

4.50 Before the first Appraisal Committee meeting, the Assessment Group provided additional deterministic sensitivity analyses to test the sensitivity of the results to the success rate for CCH and alternative recurrence rates. Using the upper limit of the confidence interval for the success rate for CCH (0.69) resulted in an ICER for CCH compared with limited fasciectomy of £183,899 per QALY gained. When the 6-month probability of recurrence for CCH was set to the lower limit of the confidence interval (0.054), CCH was dominated by limited fasciectomy. When the 6-month probability of recurrence was assumed to be equal for all treatments (0.061), the ICER for CCH compared with limited fasciectomy was £117,596 per QALY gained. Finally, using the upper limit of the confidence interval for the success rate of CCH and equal recurrence rates for all treatments resulted in an ICER for CCH compared with limited fasciectomy of £25,793 per QALY gained.

Assessment Group’s analyses completed after the first Appraisal Committee meeting

4.51 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 company’s subgroup results (see section 4.10), the Assessment Group’s analyses for the moderate-disease subgroup assumed that the CCH success rate was 0.81 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 0.54 and the cost of the first course of CCH was £2295 (based on 1.43 affected joints and 1.6 injections per joint, see section 4.10).
For both subgroups, the cost of the second course of CCH was £1605.

4.52 After a request from the Committee, the Assessment Group revised its method of calculating utility values for the new subgroup analyses. For each subgroup, the Assessment Group identified 5 plausible configurations of contracture. An example configuration for the moderate-disease subgroup was Tubiana stage 1 contracture in both the ring and little fingers. The Assessment Group used the equations from Gu et al. (see section 4.43) to calculate an EQ-5D utility value for each configuration of contracture, assuming 67% of patients were affected in the dominant hand (based on 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. For the moderate-disease subgroup, the utility value for baseline, treatment failure and recurrence was 0.743 for patients younger than 75 years and 0.695 for older patients. For the severe-disease subgroup, the utility value for baseline, treatment failure and recurrence was 0.725 for patients younger than 75 years and 0.678 for older patients. For both subgroups, the utility value for treatment success was 0.780 for patients younger than 75 years and 0.730 for older patients. The Assessment Group corrected an error in the way the utility values were adjusted for age; this appraisal consultation document refers to the corrected analyses.

4.53 The Assessment Group did deterministic sensitivity analyses for both subgroups. The sensitivity analyses varied the number of injections of CCH, the success rate for CCH, the recurrence rates, the proportion of limited fasciectomies done as inpatient procedures, and the utility values. A further sensitivity analysis
applied a utility decrement after limited fasciectomy to reflect the recovery time.

4.54 The Assessment Group’s analysis for the subgroup of patients with moderate disease and up to 2 affected joints showed that CCH was dominated by limited fasciectomy (total costs were £2407 for limited fasciectomy and £2757 for CCH, giving an incremental cost of £350; total QALYs were 6.769 for limited fasciectomy and 6.753 for CCH giving an incremental QALY gain of −0.016). CCH was dominated in 9 of the 13 sensitivity analyses. There were 2 sensitivity analyses in which CCH had an ICER below £50,000 per QALY gained. Assuming the 6-month probability of recurrence was 0.061 for all treatments, the ICER for CCH compared with PNF was £44,374 per QALY gained (total costs were £1344 for PNF and £2785 for CCH, giving an incremental cost of £1441; total QALYs were 6.713 for PNF and 6.746 for CCH, giving an incremental QALY gain of 0.032). Assuming the 5-year recurrence rate was 25% for limited fasciectomy (the midpoint of published estimates), 42.8% for CCH (the lower limit of the 95% CI from CORDLESS) and 52.5% for PNF (the midpoint of published estimates) the ICER for CCH compared with PNF was £39,389 per QALY gained. In this analysis, total costs were £1349 for PNF and £2751 for CCH giving, an incremental cost of £1402; total QALYs were 6.720 for PNF and 6.756 for CCH giving an incremental QALY gain of 0.036. A probabilistic sensitivity analysis showed that, at £20,000 per QALY gained, the probability of being the most cost-effective treatment was 13.6% for CCH, 39.9% for limited fasciectomy and 46.5% for PNF.

4.55 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 limited fasciectomy (incremental costs £429 and incremental QALY gain −0.087 for CCH compared with limited fasciectomy). CCH was dominated in all the sensitivity analyses. A
probabilistic sensitivity analysis showed that, at £20,000 per QALY gained, the probability of being the most cost-effective treatment was 22.0% for CCH, 33.7% for PNF and 44.3% for limited fasciectomy.

4.56 Consultees identified some health-related benefits of CCH that were not included in the QALY calculation, including 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.

Additional evidence provided after consultation

4.57 After consultation, the company submitted an additional analysis using the Assessment Group’s economic model for the moderate-disease subgroup (see sections 4.51 and 4.52). Based on the post hoc analysis of POINT X (see section 4.22), the company assumed a mean of 1.22 injections per joint, a mean of 1.17 joints treated per patient and a success rate for CCH of 66.1%. The company used recurrence rates of 25% for limited fasciectomy, 42.8% for CCH and 52.5% for PNF. It presented the results as a series of pairwise comparisons. Compared with limited fasciectomy, treatment with CCH cost £678 less and gained 0.002 fewer QALYs. The ICER for CCH compared with PNF was £43,778 per QALY gained. The Assessment Group was unable to replicate the company’s results; it advised that this was probably due to a rounding error. Using the same assumptions as the company, the Assessment Group calculated the ICER for CCH compared with PNF as £47,926 per QALY gained (total costs were £1333 for PNF and £1895 for CCH giving an incremental cost of £561; total QALYs were 6.719 for PNF and 6.731 for CCH, giving an incremental QALY gain of 0.012). The Assessment Group calculated that the ICER for limited fasciectomy compared with PNF was £47,805 per QALY gained (total costs were £1333 for PNF and £2513 for limited fasciectomy, giving an incremental cost of £1179; total QALYs were 6.719 for...
PNF and 6.744 for limited fasciectomy, giving an incremental QALY gain of 0.025). In this analysis, CCH was extendedly dominated by limited fasciectomy and PNF (a treatment is ‘extendedly dominated’ when its ICER is higher than that of the next, more effective, option – in this case limited fasciectomy – when compared with a common baseline [PNF]).

4.58 The Assessment Group noted that, in POINT X, the success rate for CCH for patients with moderate disease (66.1%) was higher than for patients with moderate or severe disease (49.2%). It also noted that the company’s analyses 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 estimated the success rates for limited fasciectomy and PNF for a moderate 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. The Assessment Group applied these success rates in the economic model, with all other assumptions kept the same as in section 4.57. The results showed that CCH was dominated by PNF (treatment with CCH cost £689 more and gained 0.017 fewer QALYs).

4.59 The Assessment Group conducted a further sensitivity analysis that applied a utility decrement to reflect the recovery time after treatment (see sections 4.23 and 4.24). 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; all other assumptions were the same as in section 4.57. The ICER for CCH compared with PNF was £40,881 per QALY gained. The Assessment Group’s final sensitivity analysis combined the higher success rates for PNF and
limited fasciectomy (see section 4.58) with the utility decrements after treatment. CCH was dominated by PNF (treatment with CCH cost £689 more and gained 0.015 fewer QALYs). Compared with limited fasciectomy, treatment with CCH cost £665 less and gained 0.063 fewer QALYs.

**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.

4.60 The Committee discussed the current clinical pathway of care for people with 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. For this reason, limited fasciectomy is most suitable for severe or widespread disease. 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.

4.61 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.

4.62 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.

4.63 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 eligible for CCH would also be eligible for PNF. The Committee noted that this advice was contradicted by some responses to consultation, 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.

4.64 The Committee discussed whether there was a subgroup of patients for whom PNF is not available and for whom the relevant comparator would be limited fasciectomy. 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 perform the procedure. 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 (see section 4.60). 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, and that it would not be appropriate to consider separately a subgroup of patients for whom PNF may not be available.

Clinical effectiveness

4.65 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.

4.66 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. The Committee was aware of consultation responses 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. 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 and for metacarpophalangeal joints than for proximal interphalangeal joints. The Committee observed that this advice was supported by post hoc subgroup analyses of the CORD studies and POINT X, which found that the success rate for CCH was higher for a moderate subgroup than for the overall population (see sections 4.10 and 4.22). The Committee agreed with the advice of the clinical experts that CCH, PNF and limited fasciectomy were all clinically effective, but it concluded that further research was needed to establish which treatment was the most effective.

4.67 The Committee explored the recurrence of contracture after successful treatment. It was aware that the CORDLESS study (of CCH) and the Van Rijssen et al. trial (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 (see section 4.3). 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 Rijsen et al. trial than in CORDLESS. The Committee also noted a comment from the company that the recurrence rate for limited fasciectomy from the Van Rijsen et al. trial was lower than many estimates from 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 for each of these treatments.

4.68 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, which showed that some patients report that hand function is not fully recovered 12 months after limited fasciectomy (see sections 4.23 and 4.24). 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.

4.69 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 all treatments for Dupuytren’s contracture were associated with mild or moderate adverse events, and both CCH and surgery have an acceptable safety profile.

4.70 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 such as tendon damage. 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

4.71 The Committee discussed the company’s cost-minimisation model, noting that the analysis excluded PNF which is a relevant comparator (see sections 4.62–4.64). It was aware that a cost-minimisation analysis assumes equal efficacy of the included
treatments (that is, CCH and 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.

4.72 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 4.66. 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.

4.73 The Committee considered the assumptions in the Assessment Group’s base-case analysis of the overall population with moderate and severe Dupuytren’s contracture. It noted that recurrence rates were derived from CORDLESS and the Van Rijssen et al. trial, 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 4.67). The Committee noted that, in some sensitivity analyses, the Assessment Group assumed that all treatments had equal recurrence rates (see section 4.50). Based on advice from the clinical experts, the Committee agreed that the assumption of equal
recovery rates was not plausible. 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 the Van Rijssen et al. trial than in other studies.

4.74 The Committee considered the costs of CCH in the Assessment Group’s original model. It was aware that assumptions about the number of injections of CCH needed per joint had a substantial impact on the total costs (see section 4.30). The Committee noted that the base-case economic models from both the company and the Assessment Group assumed that patients would have 1.6 injections per joint on average, based on 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 clinical experts explained that this is because local anaesthetic is used before finger straightening in clinical practice (whereas local 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 noted that a submission from a clinical expert 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 was unsure whether success rates would be lower if patients had fewer injections. It noted that, in response to consultation, the company provided
additional evidence about the number of injections needed in clinical practice and the associated success rates (see section 4.82). The Committee concluded that the base case of the Assessment Group’s economic model should use the number of injections observed in clinical trials, but that it was appropriate to explore the sensitivity of the model to different assumptions about the number of injections of CCH.

4.75 The Committee noted that the Assessment Group had assumed no vial sharing of CCH in its model whereas the company 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.

4.76 The Committee considered the costs of limited fasciectomy in the Assessment Group’s model. It noted that the Assessment Group assumed 26% of procedures were inpatient procedures, whereas the company assumed 37.8%. 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 procedure. The Committee concluded that the true proportion of inpatient limited fasciectomy procedures was likely to be above 0% and below 26%, and that it was appropriate to vary this parameter in sensitivity analyses.

4.77 The Committee considered the utility values in the Assessment Group’s original economic model. It was aware that, at baseline, patients were assumed to have Tubiana stage 3 contracture in
3 fingers (see section 4.42). 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 may have 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. It heard from the Assessment Group that the utility values reflected impairments in health-related quality of life due to Dupuytren’s contracture only, with no adjustment to account for other conditions that may lower the average utility value for the modelled age group. The Committee considered that the utility values should be based on overall health-related quality of life, not just the impairment in health-related quality of life caused by Dupuytren’s contracture. The Committee concluded that it was appropriate to adjust the utility values by the average utility value for the modelled age group.

4.78 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 original base-case analysis, meaning that CCH was more costly and less effective than limited fasciectomy (incremental costs £2899 and incremental QALY gain −0.06 for CCH compared with limited fasciectomy). It also noted that CCH was dominated by limited fasciectomy in most of the sensitivity analyses, and that CCH had a very low probability of being the most cost-effective treatment strategy. The Committee was aware that the ICER for CCH did not fall below £20,000 per QALY gained even when implausible assumptions were made, such as equal recurrence rates for all treatments and a 69% success rate for CCH. It noted that the analyses were flawed
because the model did not use appropriate utility values (see section 4.77). 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 4.48). 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.

4.79 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. It also requested that the analyses incorporate revised utility values to address the limitations in the original model (see section 4.77) and that the recurrence rates were varied in line with its conclusions in section 4.73.

4.80 The Committee considered the Assessment Group’s subgroup analyses that were presented after the first Appraisal Committee meeting. It noted that the success rate for CCH was 80.7% for the moderate-disease subgroup and 53.7% for the severe-disease subgroup (compared with the original base-case value of 63% for the overall population), based on the subgroup analyses of the CORD trials (see section 4.10). It was aware that the success rates for limited fasciectomy and PNF were the same as the original base case because subgroup analyses were not available for the Van Rijssen et al. trial. The Committee heard from the clinical experts that all treatments were more effective in moderate than in severe disease, and it noted that the modelled success rates for limited
fasciectomy and PNF did not reflect this advice because of the limitations of the data. It noted that, after consultation, the Assessment Group estimated higher success rates for limited fasciectomy and PNF for a moderate subgroup (see section 4.83). It also noted that the success rates for CCH were based on post hoc subgroup analyses of a small number of patients. The Committee concluded that the results of the Assessment Group’s subgroup analyses should be interpreted with caution because the success rates for each treatment were uncertain.

4.81 The Committee considered the appropriateness of the revised utility values in the Assessment Group’s subgroup analyses. It agreed that the utility values represented a plausible degree of contracture for people with up to 2 affected joints and either moderate or severe disease. The Committee also agreed that it was appropriate to adjust the utility values by the average utility value for the modelled age group (see section 4.77). 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 concluded that, given the limited evidence base, the utility values in the Assessment Group’s subgroup analyses were reasonable.

4.82 The Committee discussed the company’s analyses for the moderate-disease subgroup, submitted in response to consultation. The company assumed a mean of 1.22 injections of CCH per joint, based on the POINT X study. The Committee noted that this assumption was consistent with expert clinical advice (see section 4.74) and with responses to consultation stating that the average number of injections per joint is 1.03–1.30 (based on UK audit data). The Committee concluded that it was appropriate to conduct sensitivity analyses that assumed a mean of 1.22 injections of CCH per joint and, in these analyses, it was
appropriate also to use the CCH success rate from POINT X (66.1%).

4.83 The Committee considered the Assessment Group’s sensitivity analyses for the moderate-disease subgroup, presented after consultation. It noted that the Assessment Group estimated the success rates for PNF and limited fasciectomy for the moderate subgroup, based on an extrapolation of the POINT X data. The Committee accepted that the success rates for a moderate subgroup were likely to be higher than for the overall population. The Committee noted that, informed by the company’s additional evidence (see section 4.23), the Assessment Group assumed that some patients experienced a utility decrement for 12 weeks after limited fasciectomy. The Committee concluded that the Assessment Group’s sensitivity analyses submitted after consultation were reasonable, but that they should be viewed as exploratory in nature because of a lack of robust comparative evidence about success rates and recovery times.

4.84 The Committee discussed the results of the Assessment Group’s sensitivity analysis for the moderate-disease subgroup, presented after consultation. The results showed that treatment with CCH gained fewer QALYs than with PNF, even though CCH had a higher success rate and a lower recurrence rate than PNF (see section 4.58). The Committee heard from the company that this result was counterintuitive and may indicate a mistake in the model. The Committee heard from the Assessment Group that the lower QALYs with PNF occurred because of differences between CCH and PNF in the probability of treatment after recurrence and in the choice of treatment after recurrence (see section 4.39). The Committee noted that the treatment pathways in the model were based on the best available evidence. The Committee concluded that the analyses reported in section 4.58 were unlikely to contain an error.
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. The Committee noted that the Assessment Group’s analysis using the Committee’s preferred recurrence rates (see section 4.73), a mean of 1.6 CCH injections per joint and a CCH success rate of 80.7% resulted in an ICER of £39,400 per QALY gained for CCH compared with PNF (incremental costs £1402 and incremental QALY gain 0.036). An intervention is ‘extendedly dominated’ when it is more costly and less effective than a combination of 2 comparators; that is, the ICER for the intervention is higher than that of the next more effective comparator when both are compared with another less effective comparator. In this analysis, limited fasciectomy was extendedly dominated by CCH and PNF, because the ICER for limited fasciectomy compared with PNF was higher than that of CCH compared with PNF. The Committee agreed that it was appropriate to consider analyses that assumed fewer injections of CCH (see section 4.82). Accordingly, the Committee discussed the company’s analysis that used the Assessment Group’s model, the preferred recurrence rates, a mean of 1.2 CCH injections and a CCH success rate of 66%. The ICER for CCH compared with PNF was £43,800 per QALY gained; compared with limited fasciectomy, CCH gained fewer QALYs at lower cost. The Committee considered that the company’s analysis 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 (see section 4.80). 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 extendedly dominated. The Committee then discussed the Assessment Group’s analysis that assumed a longer recovery time...
after limited fasciectomy than after CCH. In this analysis, the ICER for CCH compared with PNF was £40,900 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. Taking all of the 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 £39,400 per QALY gained, and so the ICER did not fall within the range usually considered cost effective.

4.86 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 base case for the severe-disease subgroup. It was also aware that CCH was dominated by either PNF or limited fasciectomy in all the sensitivity analyses. 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.

4.87 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. It 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 (see section 4.85). 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. However, 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.

4.88 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. Therefore, the Committee 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. 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>
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<tr>
<td></td>
<td>Key conclusion</td>
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<td></td>
<td>Collagenase clostridium histolyticum 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 benefits of collagenase clostridium histolyticum (CCH) compared with limited fasciectomy and percutaneous needle fasciotomy (PNF) in people with moderate Dupuytren’s contracture.</td>
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<td>The Committee agreed with the advice of the clinical experts that CCH, PNF and limited fasciectomy were all clinically effective, but it concluded that further research was needed to establish which treatment was the most effective.</td>
<td>4.66</td>
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<td></td>
<td>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. Therefore, the Committee 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.</td>
<td>4.72, 4.88</td>
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<td></td>
<td>Current practice</td>
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<td></td>
<td>Clinical need of patients, including the availability of alternative treatments</td>
<td>4.60</td>
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<td>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.</td>
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### The technology

| **Proposed benefits of the technology** | The proposed benefits include a reduction in contracture, 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. 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). | 4.65, 4.87 |
| **What is the position of the treatment in the pathway of care for the condition?** | Treatment with CCH is an alternative to treatment with PNF or limited fasciectomy. | 4.60, 4.62 |
| **Adverse reactions** | 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. | 4.69 |

### Evidence for clinical effectiveness

<p>| <strong>Availability, nature and quality of evidence</strong> | 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 trial that compared limited fasciectomy with PNF. | 4.65–4.66 |
| <strong>Relevance to general clinical practice in the NHS</strong> | The Committee considered that the CORD trials used appropriate methods and the results were likely to generalise to the NHS. | 4.65 |
| <strong>Uncertainties generated by the evidence</strong> | 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. | 4.66 |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
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<tr>
<td>The Committee noted that there was uncertainty about the rate of</td>
<td>The Committee noted that there was uncertainty about the rate of recurrence of contracture, and it was aware of a discrepancy between the trial results and clinical experience.</td>
<td>4.67</td>
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<tr>
<td>Are there any clinically relevant subgroups for which there is</td>
<td>Post hoc subgroup analyses of the CORD trials and POINT X showed that the success rate for CCH was higher for the subgroup with moderate disease and up to 2 affected joints than in the overall population.</td>
<td>4.79-80, 4.82</td>
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<tr>
<td>evidence of differential effectiveness?</td>
<td></td>
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<tr>
<td>Estimate of the size of the clinical effectiveness including strength</td>
<td>The Assessment Group’s meta-analysis showed that CCH was more effective than placebo in reducing contracture (success rate 63% compared with 6%).</td>
<td>4.9, 4.65</td>
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<tr>
<td>of supporting evidence</td>
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**Evidence for cost effectiveness**

<p>| Availability and nature of evidence                                   | The Committee discussed the company’s cost-minimisation model and the Assessment Group’s cost–utility model.                                                                                           | 4.71-2 |
| Uncertainties around and plausibility of assumptions and inputs in    | 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. | 4.71  |
| the economic model                                                   |                                                                                                                                                                                                         |      |
|                                                                         | The Committee discussed the Assessment Group’s cost–utility model. The 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 associated with increased uncertainty. 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. | 4.72  |</p>
<table>
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<tr>
<th>The Committee noted that the recurrence rates used in the base case did not reflect clinical experience. It identified a plausible recurrence rate for each treatment; these recurrence rates were consistent with the evidence base, advice from clinical experts, and a comment from the company. These recurrence rates were used in the Assessment Group’s sensitivity analyses.</th>
<th>4.73, 4.85–6</th>
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<tr>
<td>The Committee noted that assumptions about the number of injections of CCH needed per joint had a substantial impact on the total costs. It heard that patients may need fewer injections in clinical practice than in clinical trials. It noted that, in response to consultation, the company provided additional evidence about the number of injections needed in clinical practice and the associated success rates. The Committee concluded that the base case of the Assessment Group’s economic model should use the number of injections observed in clinical trials, but that it was appropriate to explore the sensitivity of the model to different assumptions about the number of injections of CCH.</td>
<td>4.74, 4.82</td>
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| 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 from the clinical experts that this degree of 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 concluded that the analyses were flawed because the model did not use appropriate utility values. After the first Committee meeting, the Assessment Group submitted new subgroup analyses that used a revised method of calculating utility values. The Committee noted that the utility values were based on a discrete-choice experiment and therefore did not follow the NICE reference case. However, it concluded that, given the limited evidence base, the utility values in the Assessment Group’s subgroup analyses were reasonable. | 4.77-8 |
| Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered? | 4.52, 4.81 |
### Are there specific groups of people for whom the technology is particularly cost effective?

The Committee heard from the company and the clinical experts that CCH may be more cost effective for people 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.

| 4.79 |

### What are the key drivers of cost effectiveness?

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.

| 4.48, 4.78 |

### 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 analysis and in most of the sensitivity analyses (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.

For the subgroup of patients with moderate disease and up to 2 affected joints, and using the Committee’s preferred recurrence rates and a mean of 1.6 CCH injections, the ICER was £39,400 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 £39,400 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. CCH was also dominated in all the sensitivity analyses.

| 4.85 |

### Additional factors taken into account

| 4.86 |

| Patient access schemes (PPRS) | Not applicable. |
5 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.

6 Recommendations for further research

6.1 The Committee agreed that further research would be of value to compare the clinical effectiveness of collagenase clostridium histolyticum, percutaneous needle fasciotomy and limited fasciectomy as treatments for Dupuytren’s contracture. The Committee agreed that research should focus on patients with moderate disease, because collagenase clostridium histolyticum cost less and was more clinically effective for these patients than for those with severe disease (see sections 4.84 and 4.85). It advised that the outcome measures should include assessments of health-related quality of life using both a disease-specific measure
and a generic preference-based measure. The Committee 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.

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
February 2015
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.

Professor Gary McVeigh (Chair)
Professor of Cardiovascular Medicine, Queen’s University Belfast and Consultant Physician, Belfast City Hospital

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

Dr Aomesh Bhatt
Regulatory and Medical Affairs Director Europe and North America, Reckitt Benckiser

Dr Andrew Black
General Practitioner, Mortimer Medical Practice
Professor David Bowen
Consultant Haematologist, Leeds Teaching Hospitals NHS Trust

Dr Matthew Bradley
Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline

Dr Ian Campbell
Honorary Consultant Physician, Llandough Hospital

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

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: February 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

Warren Linley BSc
Senior Research Fellow, Centre for Health Economics and Medicines Evaluation, Bangor University

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 Lead

Zoe Charles
Technical Adviser

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 Biovitrum