The DISC Trial was designed as a multicentre, pragmatic, parallel two-arm randomised controlled trial to evaluate whether collagenase injection is not inferior to limited fasciectomy (LF) surgery in the treatment of Dupuytren's Contracture (DC). A cost effectiveness evaluation and nested qualitative and photography sub studies were also included.

The objectives of the DISC Trial were successfully achieved.

## Results

In total 672 participants (64.6%) were recruited and randomised; 336 to receive collagenase injection and 336 to receive LF.

Baseline characteristics were similar across groups. Of the 672 randomised participants, 621 (92.4%) received treatment as part of the trial. Cross over was limited: one participant (0.3%) allocated to collagenase received LF; seven participants allocated to LF received collagenase (2.1%). On average participants received collagenase by 12.1 weeks (Standard deviation (SD) 13.7) and LF in 17.7 weeks (SD 16.5) after randomisation. Most participants (n=315, 95.2 %) had just one digit treated. No participants required an unplanned inpatient admission following treatment and 62.0% (n=201) collagenase participants and 78.3% (n=224) LF participants had full correction following treatment.

At 1-year (primary time-point) the difference in Patient Evaluation Measure (PEM) scores showed that collagenase was inferior to LF; Difference 5.95 (95% CI 3.12 to 8.77, p=0.49). The benefit of LF over collagenase continued to increase to 2 years (7.18, 95% CI: 4.18 to 10.88). Results did not significantly change when adjusted analyses were undertaken.

PEM Overall Assessment scores corresponded with the primary outcome analyses and participants in both groups reported positive experiences of treatment.

The estimated difference in Unité Rhumatologique des Affections de la Main (URAM) scores followed those of PEM, increasing in favour of LF over time from 3 months (0.82, 95% CI -0.21 to 1.84, p=0.12) to 5.37 (95% CI 3.85 to 6.88, p=<0.00005) at 2

years. At 1-year Michigan Hand Questionnaire (MHQ) scores were higher (better) in the LF group (1 year: -4.69, 95% CI -7.27 to -2.12, p=0.0004) and this continued at 2 years (2 years: -6.71, 95% CI -9.60 to -3.82, p=<0.00005).

Return to function was better in the short term for the collagenase group (Week 2: 14.93, 95% CI 11.66 to 18.19, p=<0.00005; 6 weeks: 5.00, 95% CI 2.29 to 7.70, p=0.003) but by 1 year function was superior after LF (-4.93, 95% CI -7.63 to -2.22, p=0.0004). At 1 year participants who received LF were more likely to respond as being “cured” or “much better” than participants who received collagenase (Odds Ratio (OR): 3.01, 95% 2.15 to 4.23, p=<0.00005).

Passive extension deficit was similar between the groups at Baseline (Mean: 45.8°; SD 17.0). Following collagenase treatment, extension deficit seemed to be worse at all timepoints ranging from a difference of 5.73° (95% CI 2.88 to 8.59, p=0.0001) at 3 months to 10.10° (95% CI 6.46 to 13.73, p=<0.00005) at 1 year and increasing again up to 2 years. Results when imputed data were included were similar. Increases in reference joint passive range of movement were similar between the two groups following treatment however from 6 months there was strong evidence that collagenase resulted in poorer passive range of movement (-7.42°, 95% CI -11.54 to -3.29, p=0.0004) and this difference increased further over time.

Measurements of active extension deficit were similar between the two groups at Baseline (Mean: 51.9°, SD 16.1). Like passive extension deficit, active extension deficit was worse following collagenase treatment at all timepoints, ranging from a difference at 3 months of 5.57° (95% CI 3.02 to 8.12, p=<0.00005) to 11.52° (95% CI 8.13 to 14.91, p<0.00005) at 1 year and increasing again up to 2 years. Results when imputed data were included were similar. Increases in active range of movement of the reference joint were similar between the two groups following treatment however from 6 months there was strong evidence that collagenase resulted in poorer active range of movement (-8.37°, 95% CI -11.99 to -4.75, p=<0.00005). Again, this difference increased further over time.

In total 54 participants (15.7%) experienced recurrence of DC. There was weak evidence to suggest that following collagenase treatment participants were more

likely to experience recurrence compared to participants who received LF (OR 1.39, 95% CI 0.74 to 2.63, p=0.31).

There were 267 complications (0.82 per participant) reported for the collagenase group, compared to 177 complications (0.60 per participant) reported for the LF group. Participants in the LF group experienced a higher proportion of “moderate” or “severe” complications (5% vs 2%).

In the 1 year following intervention, most participants did not require re-intervention (n=399, 64.3%), which dropped to 47.7% by 2 years. By 2 years, 10% of collagenase participants had re-intervention compared to 2.5% of LF participants.

Cost Effectiveness

The mean cost of surgery was estimated to be £2,510 (SD £818) per participant compared to £1008 (SD £94) for the collagenase group. The overall mean healthcare cost was slightly lower in the collagenase group compared to the LF group at 2 years (mean difference: -£28, 95% CI -£87 to £30). Baseline utility scores (EQ-5D-5L) were slightly higher in the LF group (Mean 0.794, SD 0.170) compared to the collagenase group (Mean 0.791, SD 0.174) but this was not statistically significant (95% CI -0.029 to 0.024).

For both groups, utility scores decreased immediately following treatment but by 3 months had reverted to baseline levels. The mean difference between groups at 2 years was -0.044 (95% CI -0.077 to -0.010).

After adjustment for baseline costs and utilities, participants who received collagenase showed a statistically insignificant decrease in quality-adjusted life year (QALY) gains at 1 year (-0.003, 95% CI -0.006 to 0.0004) and a reduced cost (-£1095, 95% CI -£1,139 to £1042) compared to LF participants. At 1 year the probability of collagenase being cost effective was over 99% for both willingness-to-pay thresholds of £20,000 and £30,000 per QALY and this finding was robust for the sensitivity analyses conducted. At 2 years collagenase continued to be both significantly less costly (-£1212, 95% CI -£1276 to -£1147) and less effective (-0.048, 95% CI-0.055 to -0.040). The probability of collagenase being cost effective was

72% at the £20,000 threshold and 37% at the £30,000 threshold. The longer-term Markov model indicated that collagenase became less cost effective than LF at the lifetime horizon, the probability of collagenase being cost effective ranged from 22% to 16%.

Qualitative

Semi-structured qualitative interviews were conducted with 45 patients, resulting in four core topics: Lived experience, Knowledge, Experience and Looking to the future. Participants reported living for extended periods with DC and only seeking medical advice when impacted by the difficulty in doing tasks or appearance of the hand. Most participants reported improvement in their contracture and function; some treated with collagenase noted that while the outcome was not perfect it was acceptable. More participants treated with collagenase reported preferring this in the future compared to LF participants preferring the same intervention again.

Photography Sub Study

The difference between goniometric measurements and participant taken photographs for active extension deficit was -9.7° (SD 16.2) for Metacarpophalangeal (MCP), 8.0° (SD 15.1) for Proximal interphalangeal (PIP) and 5° (SD 9.5) for Distal interphalangeal (DIP) joints. The limits of agreement were approximately +/- 30° for MCP from +/-12° to +/-30° for PIP and +/-18° for DIP joints. For flexion, differences were -0.8° (SD 19.3) for MCP, -1.6° (SD 14.5) for PIP and -2.7° (SD 13.5) for DIP joints. Limits of agreement were approximately +/- 36° for MCP, +/- 20° for PIP and a range of +/-33° to +/-24° for DIP joints.

## Conclusions

For adults with DC, the evidence suggests that at 1 year collagenase delivered in an outpatient setting is less effective but more cost effective than limited fasciectomy surgery. The DISC Trial followed participants for up to 2 years following treatment and therefore further research is required to better understand the longer-term trajectories for patients following initial contracture correction.