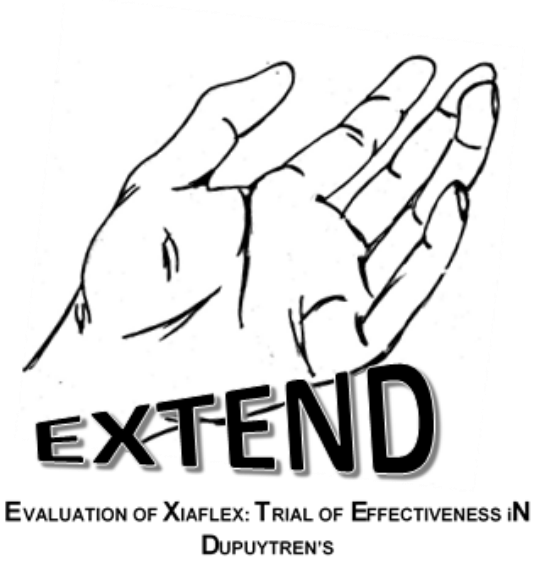
A Multi-center, Randomized Controlled Trial Comparing the Clinical Effectiveness and Cost-Effectiveness of Collagenase Injection (Xiaflex) and Palmar Fasciectomy in the Management of Dupuytren's Disease

Evaluation of Xiaflex: Trial of Effectiveness iN Dupuytren's (EXTEND)



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1 INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

1.1 Background Information

Dupuytren's Disease (DD) is a benign fibroproliferative condition, which although generally painless, it gradually causes flexion contractures to the digits and causes functional problems to those who have it. Although multiple etiologies have been implicated in this condition, it is thought to be mostly transmitted through autosomal dominant gene with variable penetrance affecting primarily patients with Northern European ancestry[1]. A recent systematic review and meta-analysis has shown that prevalence of DD in Western countries varies from 0.6% to 31.6% and increases steadily with increasing age [2]. Another recent review of prevalence and incidence in the United States found that prevalence ranged from 0.5% to 11% consistent with the 4-6% prevalence rates found in previous studies of general populations and concluded that there are a number of unmet medical needs particularly for better understanding, recognition and treatment of DD [3]. Many surgical approaches have been introduced over the years to deal with DD including percutaneous needle aponeurotomy, open fasciotomy, and commonly limited open palmar fasciectomy[4,5]. Non-surgical management options such as injections with steroids or verapamil have been previously proven ineffective and rejected clinically[6]. Limited palmar fasciectomy (LPF) has been the most common and widely accepted treatment for this condition. In the last 6 years however, collagenase injection (CI) has been making inroads as a legitimate treatment for DD. A multicentre double-blind RCT in 2009 (CORD I study) comparing collagenase to placebo has demonstrated its clinical safety and efficacy[7]. A second multicentre double-blind study also comparing collagenase to placebo (CORD II study) in 2010 confirmed that collagenase is effective and well tolerated in DD[8]. A number of adverse effects have been associated with collagenase injections but these are mostly well tolerated by patients. The most severe complication is tendon rupture which is rare, with an overall incidence at around 0.5% in previous randomized, double-blind, placebo-controlled studies[7–9]. Technical tips have been provided by a number of authors to avoid this complication[6–8]. A more recent study (CORDLESS study) in 2013 evaluated the long term efficacy and safety of collagenase treated patients in 5 previous clinical studies (which included both CORD RCTs in addition to 3 open-label trials) over a 3 year period and found that the recurrence rate was comparable to the surgical approaches to DD. Furthermore, they found no long term adverse effects[10]. This study has subsequently published 5 year follow-up results for the same cohort and has concluded that collagenase is an effective and safe treatment for DD with comparable recurrence rates after surgical treatments[11].

The two previous RCTs (CORD I and CORD II) have greatly influenced the adoption of collagenase, which now stands as a legitimate contender to palmar fasciectomy for DD.

The main methodological weakness of the CORD I and CORD II trials is that the comparative intervention was placebo. Many trial methodologists would be concerned with using a placebo when existing surgical techniques exist such as the commonly performed palmar fasciectomy. We believe that presently, we are uncertain if collagenase, a non-surgical treatment is superior to palmar fasciectomy, a surgical treatment. An RCT is warranted for a head-to-head comparison. Zhou et al. directly compared CI to LPF in a propensity score matched study and found that CI was not significantly different from LPF in reducing metacarpophalangeal joint contractures. CI was also inferior to LPF in correcting proximal interphalangeal joint contractures. On the positive side, CI provided a more rapid recovery of hand function than LPF and was associated with fewer serious adverse events [12]. However, their study evaluated only short-term clinical results at 12 weeks after surgery and included a minimal number of recurrent cases in their sample. They also acknowledge the limitation of propensity matching in terms of confounding and that a well-designed randomized trial would help eliminate some confounding factors. Their overall conclusion stated that long-term effectiveness trials are still needed in head-to-head comparison studies. Based on the available evidence we believe that there presently exists a state of equipoise, which is a precondition for an RCT comparing the effectiveness of these two approaches.

A previous cost-effectiveness study by Baltzer and Binhammer found that the collagenase injection was cost-effective from the societal perspective[5]. Our appraisal of the study however, identified some methodological weaknesses. That study used a decision analysis model which was not an ideal study design as it relies on secondary data. A trial-based cost-effectiveness analysis would be greatly strengthened by its access to individual patient level data collected directly from the trial cohort. In addition, Brazzelli et al has published a systematic review and economic evaluation in October 2015 [13] concluding that there is no evidence that CI is clinically better or worse than surgical treatments and that LPF appears to be the most cost-effective choice for moderate to severe contractures. However, the results of their cost-utility analysis were based on an indirect comparison of clinical effectiveness. The Markov model they used for the CUA was fraught with considerable uncertainty about the appropriateness of many assumptions and parameters used in the model. They conclude that a RCT is required to confirm or refute these findings.

1.2 Rationale

No study to-date has compared both the clinical effectiveness and cost-effectiveness of collagenase injection versus limited palmar fasciectomy with patient derived data in a prospective RCT study. Therefore, we do not know for certain if collagenase is, indeed, a superior treatment for DD as previous studies imply. Furthermore, the collagenase

injections are costly and therefore, we need to know if this novel medical intervention is cost-effective from the patient, Ministry of Health (MOH), and societal perspectives.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare the clinical effectiveness of collagenase injections (CI) versus limited palmar fasciectomy (LPF) as measured by the 12 month post-randomization Michigan Hand Questionnaire (MHQ) after adjusting for the pre-randomization MHQ score.

2.2 Secondary Objectives

Secondary objectives include the cost-effectiveness of CI versus LPF from the consumer (patient), payer (Ministry of Health) and societal perspectives and additional measures of clinical effectiveness.

3 STUDY DESIGN

3.1 General Design

This trial is a prospective, randomized, multicentre, parallel, pragmatic clinical trial to investigate the clinical effectiveness and cost-effectiveness of collagenase injection (CI) versus limited palmar fasciectomy (LPF) in the treatment of Dupuytren's disease.

3.2 Primary Outcome Measure

The primary outcome is Health-Related Quality of Life (HRQL) measured with the Michigan Hand Outcomes Questionnaire (MHQ), a hand-specific outcomes instrument [14], at one year post-treatment.

3.3 Secondary Outcome Measures

Secondary outcomes include:

(a) HRQL measured with the Health Utility Index Mark 3 (HUI3), a generic multi-attribute health-status classification instrument [15].
(b) HRQL measured with the Unité Rhumatologique des Affections de la Main (URAM), a disease-specific HRQL measure developed for Dupuytren's contracture [16].
(c) HRQL measured with the Southampton Dupuytren's Scoring Scheme (SDSS), a disease-specific scoring system developed for Dupuytren's contracture [17].
(d) Quality Adjusted Life Years (QALY) measured with the HUI3. QALY is an important component of Cost-Utility Analysis (CUA), a variant of Cost-Effectiveness Analysis

(CEA); therefore, we will be able to calculate incremental cost per QALY gained between the two treatments. Utility scores of HRQL derived from responses to the HUI3 questionnaire have the required measurement properties for calculating QALYs[18].

(e) Self-reported healthcare utilization (e.g. visits to hand surgeons, family physician, parking costs, etc.) and productivity loss (e.g. time lost from work and leisure activities by patient and caregiver).

(f) Range of motion (ROM) of hand joints measured with goniometry

(g) Recurrence rates defined as an increase in joint contracture in any treated joint of at least 20 degrees at one year post-treatment.

(h) Necessary Dupuytren's Disease treatments applied to the previously affected digit(s) (the digit(s) treated in the EXTEND trial) up to 4 years following their original (EXTEND trial) treatment.

4 STUDY ENROLLMENT AND WITHDRAWAL

Following receipt of verbal and written information about the study, the patient must provide **signed and dated informed consent** before any study related activity is carried out. Patients will be recruited from the practices of plastic hand surgeons in Ontario. Patients will be eligible for entry into this study if they meet all of the inclusion criteria and have no exclusion criteria present.

4.1 Inclusion Criteria

1. 18 years of age or older
2. Dupuytren's contracture of the metacarpophalangeal (MCP) joint or of the proximal interphalangeal (PIP) joint with a fixed flexion contracture of 20º or greater in at least 1 finger (not the thumb)
3. Demonstrated inability to simultaneously place the affected finger and palm flat on a table
4. Able to understand and communicate in English

4.2 Exclusion Criteria

1. Previous treatment of the primary joint within 90 days of study inclusion
2. Patients undergoing any concomitant procedure on the same hand (e.g. carpal tunnel release, stenosing tenosynovitis release)
3. Persistent extension deficit from a previous surgery of the same digit
4. Any chronic muscular or neuromuscular disorder affecting wrist or hand
5. Patient generally unfit for surgery
6. Patient with specific treatment preference
7. Bleeding disorder or recent stroke
8. Allergy to collagenase
9. Collagenase treatment or treatment with any investigational drug within 30 days of study inclusion

10. Use of a tetracycline derivative within 14 days of first dose of study drug (because tetracycline derivatives may inhibit the collagenolytic activity of mammalian collagenase homologs [i.e., matrix metalloproteinases])
11. Pregnant or breast feeding patients
12. Patients who do not have insurance coverage for collagenase injections
13. Patients who are unable to provide informed consent or are unable to complete quality of life questionnaires due to mental capacity or neuro-psychological problems.

4.3 Patient Screening Log

A Patient Screening Log will be used in this study to document all patients who have provided written informed consent and have been screened, including those who cannot be randomized.

4.4 Strategies for Recruitment and Retention

For the successful conduct and timely completion of the study, it is important that the collaborating surgeons see a high volume of patients with DD. We chose the participating surgeons as we know these practicing surgeons and their willingness to participate in the study. These practices in various cities represent the diversity of the general population in Ontario.

The surgeons involved in our study each perform LPF on an average of 60 patients per year. It is assumed that 50% of potential patients will either be ineligible or not enrolled due to refusal of consent. It is therefore anticipated that 50% of eligible patients will be recruited.

Assuming that at least 10 surgeons screen a total of 600 patients and 50% of patients screened will be enrolled it is likely that approximately 300 patients can be recruited over a 12 month period. Using the estimated sample size of 128, it is estimated that all the patients could be recruited over approximately a 6-month year period. If the actual rate of enrollment is better than predicted, the duration of patient recruitment will be shortened accordingly. If the actual rate of enrollment is worse than predicted, additional surgeons will be invited to participate in this trial.

Every reasonable effort will be made to follow all participants for the entire duration of the trial. We will collect contact information for a family member, name & address of workplace/business, email address, and any social media account details to make it easier to locate the participant. Patients will be contacted via telephone the week before each follow-up appointment as a reminder. We will try to coordinate the study-related

follow up visit with the regular clinical visit to avoid extra trips to the clinic. If this is not possible, we will provide the participants with a gift card and/or parking vouchers. Compromises will be made for participants who are unable or unwilling to come for a follow-up such as completing questionnaires via mail or email.

For the research staff, quarterly meetings or teleconferences will be organized to discuss the recruitment & retention issues and their troubleshooting options. A standard operations manual will be developed at the beginning of the trial, and this will be updated and circulated at regular intervals as necessary. We will try to hire study coordinators who can commit to the duration of the study. In any case, the coordinators will be required to maintain a log of all the participants and note any scheduling issues.

4.5 Treatment Assignment Procedures

4.5.1 Randomization Procedures

Eligible, consenting patients will be randomly allocated (1:1) to receive either CI or LPF using block randomization to ensure equal group sizes. Allocation will be determined in advance using a computer-based random number generator and stratified by primary joint type (MCP or PIP). We will use central randomization via a web-based system generated by the Biostatistics Unit at St Joseph's Healthcare—Hamilton. The randomization will be blocked within strata using randomly permuted blocks of various sizes. Approximately 2-3 months prior to their procedure, eligible, consenting patients will be randomized to one of the 2 treatments.

4.5.2 Masking Procedures

Blinding of patient and surgeon will not be possible. No or very minor scar is expected from collagenase injections. For palmar fasciectomy however, a noticeable scar is expected. As such, the patients will know which procedure they received. Outcome assessors will be hand occupational therapists or physiotherapists who will perform the goniometric measurements. Although they cannot be blinded for the same reason, they nevertheless work independent of the surgeon and therefore the risk of bias in the measurements will be mitigated. The statistician for the study however, can be blinded as he will be unaware of group allocation (Study A vs Study B).

As the palmar fasciectomy can be performed some weeks later there is a risk of cross-over but this can be avoided by obtaining the consent for palmar fasciectomy in the same clinic visit as the randomization.

4.6 Subject Withdrawal

Participants will be able to withdraw from the study at any point and for any reason, and without stating a reason. A 'consent to withdraw' with the permission to use/not use patient information will be signed by the patient. The reason for withdrawal will be documented and may include any of the following reasons: voluntary withdrawal, non-compliant patient, unable to contact patient (lost-to-follow-up), medical contraindication, adverse event(s), patient deceased, etc. In case of written withdrawal of consent for follow-up visits, and unless otherwise stated by the patient in the informed consent form, investigators will be encouraged to get information from the general practitioner, any other physician, or other medical-care provider, in order to follow the medical status of the patients (especially if they withdraw their consent after having experienced an AE/SAE). Investigators will also be expected to try as much as possible to re-contact those patients at the end of the trial, in order to obtain at least their vital status (dead or alive), as well as their health status (recurrence), and thus avoid lost to follow-up. For patients considered lost to follow-up, the CRF must be completed up to the last visit performed.

5 STUDY INTERVENTIONS

5.1 Collagenase Injection (CI) Group

This procedure will be performed either in a minor procedure room or the hand clinic as per surgeon's routine practice. Collagenase will be administered with or without local anesthesia. As this is a pragmatic study we may inject more than one digit at a time just as we operate on more than one digit at a time. A recently published study by Gaston et al confirmed that two concurrent injections of CI to 2 affected joints in the same hand are generally well tolerated and the frequency of most AEs is similar to those reported in studies that use single sequential injections [19].

The patient's affected hand will be prepped with antiseptic solution. Using a hubless syringe with 0.01 mL graduations and a permanently fixed 26- or 27-gauge ½ inch needle the required amount of reconstituted collagenase clostridium histolyticum will be withdrawn as follows: a) Cord affecting an MP joint, withdraw 0.25 mL of the reconstituted solution; b) Cord affecting a PIP joint: withdraw 0.20 mL of the reconstituted solution per published guidelines.

While applying tension to the cord in the hand to be treated, the needle will be placed into the cord while carefully ensuring that the tip stays within the cord and does not pass through the cord. After confirming the needle is placed correctly in the cord,

approximately one-third of the dose is injected. The needle tip is then withdrawn from the cord and repositioned in a slightly more distal location to the initial injection in the cord (approximately 2 to 3 mm) and another one-third of the dose is injected. Again, the needle tip is withdrawn from the cord and repositioned proximal to the initial injection (approximately 2 to 3 mm) and the final portion of the dose injected into the cord. When injecting a cord affecting the PIP joint of the fifth finger, the needle insertion should not be more than 2 to 3 mm in depth and injecting more than 4 mm distal to the palmar digital crease should be avoided.

After the injections are completed, the patient's treated hand will be wrapped with a soft, bulky gauze dressing and kept elevated for the remainder of the day. The patient will return to the surgeon's office/clinic 1-7 days post-injection to assess if the contracture has resolved. If a contracture remains, a passive finger extension procedure, with or without local anesthesia as determined by the surgeon, will be undertaken in an attempt to disrupt the cord. If residual contracture remains the patient will return for a 30-day follow-up when the cord may be reinjected and the finger extension procedure repeated.

5.2 Limited Palmar Fasciectomy (LPF) Group

The Dupuytren's cord will be excised under local anesthesia in a minor procedure room setting or main operating room under local or general anesthetic depending on the complexity of the disease and the surgeon's routine. As this is a pragmatic study we will be comparing CI (novel intervention) to LPF as it is actually presently performed in all settings academic or community (local in minor room or general/local anesthetic in the main operating room). The procedure will be performed according to the operating surgeon's preferred technique i.e. zig-zag Brunner incision or straight incision with z-plasty closure of the skin. Loupe magnification will be used in surgery to identify and protect the digital neurovascular bundles. The diseased Dupuytren's fascia (cords) causing the contracture will be excised. Contracted ligaments at the PIP joints may be released by passive stretching or with knife intraoperatively. A plaster splint will be applied at the discretion of the surgeon. Patients will be discharged home the same day as their surgery and will return within 1 week for assessment.

5.3 Concomitant Medications/Treatments

Medicines for pain control will be prescribed at the discretion of the operating surgeon.

5.4 Procedures for Training of Clinicians on the Interventions

As CI is the "novel" intervention in this RCT, we need to consider the learning curve. Participating surgeons will be expected to review the detailed description of the technique, by viewing the provided learning video (*http://www.xiaflexrems.com/video/dupuytren/Xiaflex_REMS.html*) and have performed at least 10 CI injections with successful correction of the extension deficit (less than 5°) without serious complication before they begin the enrollment in the study.

6 STUDY PROCEDURES /EVALUATIONS

6.1 Schedule of Study Procedures

Patients referred to the recruiting surgeons will be screened for eligibility during their initial consultation. Patients who meet the inclusion criteria with no exclusion criteria present will be invited to join the trial and asked to provide written informed consent. Patients will be randomized after eligibility has been confirmed; it is expected that their procedure will occur 2-3 months after randomization. For the CI group, collagenase will be ordered and the procedure scheduled for as soon as possible following randomization. For the LPF group, the procedure will be done sometime in the ensuing weeks, as the procedure needs to be booked by the participating surgeon's office with the OR of the appropriate hospital. Approximately 1 week prior to their scheduled procedure, eligible, consenting patients will have their baseline data collected.

Surgeons may maintain their standard care for follow-up to patients. All patients will be seen for their study-specific follow-up visits at 1, 3, 6, and 12 months after their procedure. Best efforts will be made to coordinate routine patient care with study follow-up visits. Patients will be encouraged to contact their surgeon's office if they have any complications, questions, or concerns. If they are experiencing difficulties outside of regular hours, they will return to the emergency room of their surgeon's hospital. Patients will be asked at their follow-up visits if they have seen a physician not associated with the trial regarding their affected hand, and if so, the record will be obtained. If a patient is unable to return for follow up, copies of the quality of life questionnaires will be mailed to the patients. Reminder telephone calls will also be made to help ensure complete follow up.

If any unscheduled visits occur, the number of visits will be recorded in the patient's study diary. If occupational or physiotherapists are required to administer treatment, this information will also be recorded in the patient's study chart and in the study diary.

Additional visits for each of the study groups may occur as follows:

Collagenase Injection Group:

Patients in the CI group will return to the surgeon's office within 1-7 days after receiving their injection to determine if the contracture has resolved. If a contracture remains, a passive finger extension procedure will be undertaken in an attempt to disrupt the cord. If residual contracture remains the patient will return for a 30-day follow-up when the cord may be reinjected and finger extension procedure repeated.

Limited Palmar Fasciectomy Group:

Patients in the LPF group will return to the surgeon's office 1 week following their procedure.

The schedule of study procedures is presented in the Appendix.

6.2 Baseline Assessment

Baseline demographic information will be collected approximately 1 week prior to the patient's procedure and will include age, height, weight, marital and employment status, income and education level, medical history and level of co-morbidities. ROM will also be collected.

In addition, 4 HRQL questionnaires will be administered at the baseline visit: MHQ, HUI3, URAM, and SDSS (see Health-related Quality of Life section below for further details). These questionnaires will be completed in the office/clinic and will take approximately 20-30 minutes to complete. The patient will also be given a diary to keep track of hospital and doctor visits, blood work, medications, and other health services related to their procedure as well as personal expenses incurred and time off from work.

6.3 Follow-up Assessment

All patients will be seen for their study-specific follow-up visits at 1, 3, 6, and 12 months after their procedure. This will involve repeat administration of the same 4 questionnaires as at the baseline assessment (MHQ, HUI3, URAM and SDSS) along with ROM assessment. Adverse events and recurrence will be monitored and documented throughout the follow-up period.

6.4 Health-related Quality of Life (HRQL)

HRQL will be assessed using the MHQ, a hand-specific outcomes instrument, at baseline and 12 months as the primary outcome measure. Secondary measures of HRQL include the HUI3, URAM and SDSS. All questionnaires will be scored using algorithms provided by the individual developers[14–17].

6.4.1 Michigan Hand Questionnaire (MHQ)

The MHQ is a thoroughly developed and sensitive hand-specific outcomes instrument which measures the health outcomes of patients with chronic hand conditions [14,20]. The MHQ contains six distinct scales: 1) overall hand function, 2) activities of daily living, 3) pain, 4) work performance, 5) aesthetics, and 6) patient satisfaction with hand function with scores ranging from 0 (poorest function) to 100 (best function). The MHQ takes approximately 15 minutes to complete and is self-administered. It can assess a patient's general hand function or if administered several times (i.e., pre- and post-operatively), it can be used to assess changes in hand function. The raw scale score

for each of the six scales is the sum of the responses of each scale item, which is converted to a score ranging from 0-100. For the pain scale, a higher score indicates more pain. For the other five scales, higher scores indicate better hand performance.

6.4.2 Health Utilities Index Mark 3 (HUI3)

The HUI3 is a generic multi-attribute health-status classification instrument composed of eight attributes or dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain with five or six levels per attribute [15,21,22]. The HUI3 produces health utilities anchored at 0 for equal to being dead and 1 for perfect health. Negative scores represent states of health considered worse than being dead. The HUI3 takes approximately 10 minutes to complete and is self-administered.

6.4.3 Unité Rhumatologique des Affections de la Main (URAM)

The URAM is a relatively new disease-specific HRQL measure developed for DD [16] and is composed of a 9-item patient-reported questionnaire. Each item is scored between 0 and 5 depending on the difficulty in performing that particular function with total scores for DD–associated disability ranging from 0 (best) to 45 (worst). High scores suggest high levels of disability and disturbance. The URAM scale is a 1-domain outcome measure postulated to be related to disability associated with DD. The questionnaire takes approximately 1 minute to complete and is self-administered.

6.4.4 Southampton Dupuytren's Scoring Scheme (SDSS)

The SDSS is also a new disease-specific scoring system developed for DD with 5 domains, each relevant to DD[17] and scored on a five-point scale (no problem, mild inconvenience, modest inconvenience, definitely troublesome, severe problem). The minimum score is 0 and maximum score is 20 with higher scores suggesting higher levels of disability. The SDSS takes approximately 1 minute to complete and is self-administered.

6.5 Healthcare Resource Utilization

We will identify and tabulate the costs for the two procedures under the purview of the patient, Ministry of Health and society. We will further classify these costs into two categories: surgery-related costs and costs incurred by the patient. These valuations will be calculated for the financial year of 2015 and in Canadian dollars. The methodology used for the economic evaluation will be as per Drummond et al.[23], A methodological guide to performing cost-utility study comparing surgical techniques Can J Plast Surg 2004;12:179-187[18] and Thoma et al. Cost-Effectiveness Analysis Parallel

to a Randomized Controlled Trial Comparing Vertical Scar Reduction and Inverted T-Shaped Reduction Mammaplasty PRS 134:1093, 2014[24].

Procedural-related costs:

Pre-operative and Operative costs

The plastic surgeon's fees will be obtained from the Ministry of Health Schedule for Benefits for Physician Services (http://www.health.gov.on.ca/en/pro/). The anaesthesiologist's fees will be calculated based on an arithmetic sum of the costs of preoperative consultation and time in the operating room (i.e., Basic and time units used in the operating room. The time units are calculated as: time × fee per time unit). According to the Ontario Health Insurance Plan fee code, one time unit corresponds to 15 minutes of anesthesiologist time. The operating room time units for the two procedures will be obtained from the surgeon case report form respectively. The costs for the nursing staff will be based on time required in the operating room and for inpatient services.

For palmar fasciectomy the services of 2 full-time nurses are required in the operating room or 1 nurse for the Minor Procedure Room (MPR). Direct costs for the surgery, including costs for the medications, bandages, haematological investigations, etc., will be obtained from the Finance Department at St. Joseph's HealthCare, Hamilton or from other participating hospitals. The amount and type of medication required by the patient during the procedure will be obtained from each patient's anaesthesia record, and the medication costs will be determined based on the Ministry of Health's Ontario Drug Benefit Formulary/Comparative Drug Index (Available online: https://www.healthinfo.moh.gov.on.ca/formulary/).

Post-operative costs

Postoperative costs (post-discharge from the hospital) and costs related to complications will include the costs to visit plastic surgeon and/or other health professional (family physician), walk-in clinics and emergency room visits and will be obtained from the Ministry of Health Schedule of Benefits for Physician Services. Costs pertaining to any kind of investigation (including pathology/haematological or radiographic) and/or overnight stay at the hospital will be obtained from the Finance Department of St. Joseph's Healthcare, Hamilton or from other participating hospitals. The costs for medications will be calculated in the manner similar to that given above and will be based on each patient's post-operative note and orders. If the patient requires a visit(s) from community nurse post-surgery, the costs will be obtained from a local community nursing program.

Lost productivity costs:

The information related to the time lost from work by the patient and care-giver will be obtained from the individual patient diaries. To estimate the costs, we will use the Human Capital method (i.e. obtain average market wages for skilled workers (2015) from Statistics Canada) [23]. This statistic is equal to $x/day and $y on a weekly basis. We will use unskilled labour wage rates to calculate the costs related to time lost from usual or volunteering activities by the patient and the caregiver.

Costs incurred by the patient:

These expenses will include transportation-related cost (fuel and/or parking expenses, public transportation, taxi services etc. for their physician visits) and costs to hire a babysitter, housekeeper, or other services as a result of being away from home during these visits. The cost to buy hand /finger splints and out of hospital physiotherapy treatments, etc. that are not reimbursed as a part of OHIP will be included in this category. These out of pocket expenditures will be obtained from the patient diary.

7 ASSESSMENT OF SAFETY

7.1 Adverse Events

An Adverse Event (AE) is broadly defined as any untoward medical occurrence in a patient or clinical investigation occurring after the patient has signed the study consent form. The AE does not necessarily have a causal relationship with the study treatment or study procedures. Consequently, AEs include adverse drug reactions, significant abnormal laboratory values and intercurrent diseases.

AEs are expected when their nature, severity or outcome are consistent with the latest version of the Investigator's Brochure for XIAFLEX®. At each patient visit, from the date the patient provides written informed consent until the end of the study, each patient will be asked non-leading questions regarding their well-being since the last visit. Any unintended and unfavourable sign (e.g. a clinically significant abnormal laboratory finding), symptom or disease described by the patient or noted by the site staff will be recorded as an AE in the source documents, on the study CRF and followed up with more specific questions or actions as required.

If a change in the patient's health status was noted prior to drug administration, it will be recorded in the patient's source documents and in the medical, surgical or physical screening CRF pages. Only medically qualified personnel must assess AEs. For the purpose of data collection, all untoward events that occur after informed consent

through 12 months of the study period are to be recorded on the CRF by the study site. This requirement includes AEs recorded from unscheduled visits as well as scheduled visits.

7.2 Reporting of Adverse Events

All AEs must be recorded on the study CRF and described using appropriate medical terminology. If a sign or symptom is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the CRF. Each event is to be evaluated for duration, severity, relationship to the investigational product/procedure and any action taken.

A pre-existing condition should not be reported as an AE at baseline but must be reported in the appropriate section of the baseline CRF. Medical conditions/diseases present at baseline before the study procedure are to be considered as an AE only in cases where they worsen after starting the study.

7.3 Serious Adverse Events

We define serious adverse events (SAEs) as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization or events that are believed with a reasonable level of certainty to be associated with participation in the trial . For such events research personnel will complete an SAE CRF and immediately fax or email it to the PI's office, who will then inform the necessary authorities.

7.4 Reporting of Serious Adverse Events

Any SAE, regardless of causal relationship, must be reported to the principal investigator's office immediately (i.e. within 24 hours of knowledge of the event) on the SAE CRF and should be accompanied by any relevant documents. All SAEs that have not resolved upon discontinuation of the patient's participation in the study must be followed until either the event resolves, stabilizes, or returns to baseline. Investigators are responsible for reporting SAEs to their local ethics committee according to local regulations.

8 STATISTICAL CONSIDERATIONS

8.1 General

Analysis of baseline characteristics will be performed using descriptive statistics reported by group as mean (standard deviation [SD]) or median (first quartile, third

quartile) for continuous variables and count (percent) for categorical variables. All analyses of primary and secondary outcomes will follow the intention-to-treat principles. We will use multiple imputation to handle missing data [25]. The results for comparisons between groups will be presented as mean difference (for continuous outcomes) and relative risk (for binary outcomes), corresponding 95% confidence intervals and associated p-values. P-values will be reported to four decimal places with p-values less than 0.001 reported as $p < 0.001$. All analyses will be performed using SAS software version 9.4 (Cary, NC, USA).

8.2 Sample Size Determination

The sample size will be based on the 12 month post-randomization MHQ score adjusted for baseline MHQ score. According to the paper by London, Stepan and Calfee [26] the MCID for the total MHQ score from an ROC analysis of patients from a population with multiple hand and forearm diagnoses is 8.7. The MCID for the total MHQ score falls between 8-13 points (depending on the method used to obtain an MCID) with a mean equal to 10.8. If we adopt an MCID of 8.7 it will be in the lower end of the range of estimates which will require a larger sample size than if the MCID were larger. For an estimate of the SD of the total MHQ score for patients with DD we obtain a value of 15.0 from the one week pre-operative assessment and 16.0 for the 12 month post-operative assessment based on the papers by Thoma et al [27,28]. The midpoint of these two estimates is 15.5.

If we use $\alpha=0.05$, $\beta = 0.80$, MCID=8.7 and SD=15.5 for the sample size calculation, assuming a correlation value of 0.0 between baseline and 12-month post-randomization MHQ scores, based on the method outlined in Borm et al[29] the required total sample is 102 patients, or 51 per group. If we account for a 20% loss to follow-up rate the required sample increases to 128 (64 per group). These calculations assume that the relationship between the baseline and 12 month post-randomization MHQ scores is linear and that the slopes of the best fit lines of the two groups are parallel.

8.3 Clinical Effectiveness Analysis

The clinical effectiveness of the collagenase will be assessed using the following HRQL instruments: MHQ, HUI3, URAM and SDSS (see section 6.4 for details). Objective measures of ROM will also be conducted and used to evaluate improvement and recurrence rates.

8.4 Cost-Utility Analysis (CUA)

Quality Adjusted Life Years (QALY) will be measured with the HUI3. QALY is an important component of Cost-Utility Analysis (CUA), a variant of Cost-Effectiveness Analysis (CEA); therefore, we will be able to calculate incremental cost per QALY gained between the two treatments. Of the available utility scales, the HUI3 is the most powerful as it can discriminate among close to one million different health states. Utility scores of HRQL derived from responses to the HUI3 questionnaire have the required measurement properties for calculating QALYs[18].

The methodology used for data analysis will be as per Drummond et al. Methods for the economic evaluation of health care programs, Oxford University Press, 2005 [23] and Thoma et al. A methodological guide to performing cost-utility study comparing surgical techniques, Can J Plast Surg 2004;12:179-187[18] and Thoma et al. Cost-Effectiveness Analysis Parallel to a Randomized Controlled Trial Comparing Vertical Scar Reduction and Inverted T-Shaped Reduction Mammaplasty PRS 134:1093, 2014[24].

Probabilistic sensitivity analysis will be undertaken to assess stochastic uncertainty using nonparametric bootstrapping to quantify the joined effect of uncertainty around the costs and the QALYs. Nonparametric bootstrapping will be used to estimate the confidence interval around the mean treatment effects and the incremental cost-effectiveness ratio[30]. This technique randomly draws with replacement samples of the original cost and quality-adjusted life-year data over a large number of times (1000 replications) [23]. These bootstrapped cost-QALY pairs are graphically represented on an incremental cost-effectiveness plane. The bootstrapped estimates will be further used to construct the cost-effectiveness acceptability curves. These will show the probability that collagenase injection is cost-effective compared to limited palmar fasciectomy across a selected set of cost-effectiveness threshold values when taking into consideration the uncertainty inherent in the estimates[31].

9 ETHICS/PROTECTION OF HUMAN SUBJECTS

9.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in Tri-Council Policy Statement-2: Ethical Conduct for Research Involving Humans (2010).

9.2 Research Ethics Board (REB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Research Ethics Board (REB) for review and approval.

Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the REB before the changes are implemented in the study.

9.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be REB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

Consent for the follow-up portion of the EXTEND trial will take the form of verbal consent over the telephone. The principal investigator's office administrator or the study coordinator will contact the patients to obtain consent using the script uploaded to the HiREB portal. The date that the patient was contacted, their consent decision and who obtained consent will be recorded on the form also uploaded to the HiREB portal.

10 DATA HANDLING AND RECORD KEEPING

10.1 Case Report Forms (CRFs)

Data will be recorded on study-specific paper-based CRFs by the site investigator or by designated staff authorized by the investigator and sent to the office of the principal investigator for central review and entry into the study database by the research assistant. The CRFs must be completed as soon as possible during or after any patient visit. Access to CRF data will be limited to personnel directly participating in the study. Data should be recorded on the CRF completely by the site investigator or by staff

authorized by the investigator. Completed CRFs will be shipped to the office of the PI by courier service.

10.2 Data Management Responsibilities

Paper-based CRFs and patient diary/quality of life questionnaires will be used for this study and managed centrally in the office of the principal investigator. Data collected will be reviewed and entered into the study database by the research assistant. Entered data will be statistically checked for coherency and outliers. Data from the patient diaries will be extracted and recorded on study CRFs by the research assistant. All CRF data and questionnaires will be stored in a locked cabinet in a locked office at each site.

Personal data shall be handled and processed in accordance with national legislation regulating privacy and data protection. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by written agreement between the PI and the study site investigator.

10.3 Archiving of Study Documents

The investigator at each study site must make arrangements to store the essential study documents, (as defined in Essential Documents for the Conduct of a Clinical Trial [ICH E6, Guideline for GCP]).

In addition, the investigator is responsible for archiving of all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from regulatory authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period.

11 PUBLICATION PLAN

Findings will be shared and discussed with all of the investigators for the study. An estimated timeline for creation of an abstract/manuscript will be defined at that time. The publication or presentation of any study results shall comply with all applicable privacy laws.

12 KEY ROLES AND CONTACT INFORMATION

Principal Investigator:	Dr. Achilles Thoma, Hamilton
Clinical Site Investigators:	Dr. Bimpe Ayeni, Newmarket Dr. Rodger Shortt, Oakville Dr. Nancy De Kleer, Oakville Dr. Yasser El-Sheikh, Toronto Dr. Tara Lynn Teshima, Toronto Dr. Carolyn Levis, Hamilton Dr. James Bain, Hamilton Dr. Bing Siang Gan, London Dr. Murray Allen, Ottawa
Other Key Personnel:	Jessica Murphy, Research Assistant Lorrie Costantini, Research Assistant Dr. Feng Xie, Health Economist Dr. Gary Foster, Biostatistician Dr. Lehana Thabane, Biostatistician

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14 APPENDIX. SCHEDULE OF ENROLMENT, INTERVENTIONS, AND ASSESSMENTS.

	STUDY PERIOD							
	Screening	Enrolment	Procedure	Post-allocation				Unscheduled visits
TIMEPOINT		*-1wk*	**0**	*1mo*	*3mo*	*6mo*	*12mo*	
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Randomization		X						
INTERVENTIONS:								
Collagenase Injection (CI)			X					
Limited Palmar Fasciectomy (LPF)			X					
ASSESSMENTS:								
In-hospital utilization			X					
Baseline demographics		X						
HRQL questionnaires		X		X	X	X	X	
Range of Motion		X		X	X	X	X	
Resource utilization				X	X	X	X	X
AE/SAE monitoring				X	X	X	X	X
Recurrence				X	X	X	X	X
Study completion							X	X