THE BRISBANE
HAND & UPPER LIMB
RESEARCH INSTITUTE

STUDY PROTOCOL

Conservative management of triangular fibrocartilage injuries

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Contents

1 PROJECT SUMMARY

TITLE	Conservative management of triangular fibrocartilage injuries
INVESTIGATORS	**Primary:** Dr Greg Couzens (Principal Investigator), Prof Mark Ross, Dr Libby Anderson, Ms Wilma Walsh, Ms Ruby Strauss **Associate:** Ms Anna Gore, Dr Timothy Gilmour, Dr Chris Jeffery
OBJECTIVES	**Primary Objective:** To determine the efficacy of splint immobilisation and cortisone injection, used in isolation or combination, for the non-operative management of triangular fibrocartilage complex injury. **Secondary Objective:** To determine the prevalence and factors associated with TFCC tears not benefitting from a course of conservative treatment.
STUDY DESIGN	Randomised control trial
SITES	Brisbane Private Hospital, Brisbane, Australia
NUMBER OF SUBJECTS	180 participants (45 per treatment group) will be recruited in this study
TARGET POPULATION	Adults presenting with clinical and MRI confirmation of isolated TFCC tear, no greater than 12 months from primary injury.
LENGTH OF CLINICAL INVESTIGATION	It is anticipated that this study will require 50 months from commencement of recruitment (24-month recruitment period) to final data collection and analysis. Study participants will be assessed at baseline (pre-intervention) and post intervention intervals. The **primary end point** of the study will be 12 weeks post initiation of conservative treatment to determine treatment effectiveness. The **secondary end point** of the study will be at 24 months to monitor long term outcomes and ascertain rates of re-injury or recurrence of symptoms.
OUTCOMES	**Primary Outcomes:** ▪ Pain and function using Patient Rated Wrist and Hand Evaluation (PRWHE) **Secondary Outcomes:** ▪ Improvement in symptoms and function using the global rating of change 15-point scale (GRC) ▪ Disability using the abbreviated version of the Disabilities of the Arm, Shoulder and Hand Score (QuickDASH) ▪ Pain and satisfaction using a visual analogue scale (VAS) ▪ Health-related quality of life using the EQ-5D-5L ▪ Grip strength measured using a hydraulic dynamometer ▪ Complications or adverse events

2 INTRODUCTION

Injury to the triangular fibrocartilage complex (TFCC) is recognised as a common cause of both short and long-term wrist pain and loss of wrist function, with a resultant impact on quality of life. At present, it is common practice in Australia and overseas for health care providers to initially recommend non-operative or 'conservative' treatments for patients. Studies of conservative management are limited despite being the first line of treatment for TFCC injury, with failure of non-operative management an indication for surgical treatment.

This study will investigate the efficacy of non-operative treatments in relieving symptoms and improving function in adults with TFCC tears. It will be conducted as a four-arm randomised trial which will compare routinely used combinations of non-operative interventions. Hand therapy used in isolation will be compared to therapy with splint immobilisation, therapy with corticosteroid injection and a combination of the three treatments, for TFCC injury management. It expected that the outcome of this study will have a substantial contribution to the evidence-base for the initial, non-operative management of TFCC injuries in standard practice worldwide.

2.1 LITERATURE REVIEW

Located at the distal radioulnar joint (DRUJ), the triangular fibrocartilage complex (TFCC) is an intricate anatomical structure which plays a significant role in wrist biomechanics. The TFCC is comprised of an articular disc of triangular fibrocartilage, meniscal homologue, the ulnar collateral ligament (UCL), volar/palmar and dorsal radioulnar ligaments, ulnolunate and ulnotriquetral carpal ligaments and extensor carpi ulnaris (ECU) subsheath. The cartilaginous ligament complex is recognised as a major stabiliser of the DRUJ and carries approximately 20% of the axial load of the wrist (Palmer, Glisson, & Werner, 1984; Palmer & Werner, 1981). In forearm pro-supination, the TFCC acts to inhibit dorsal displacement and when loading in extension, helps to distribute the load between the ulna and radius. Despite its role in protective wrist function in high stress conditions, the TFCC itself remains vulnerable to injury under torsional force and repetitious loading.

As per the Palmer Classification System (1989), injury to the TFCC is most often described in two major categories: Type 1 acute traumatic injury or Type 2 chronic degenerative conditions. This injury classification system further branches into subgroups A to D in Type 1 injury to indicate location of injury or involved structures, and A to E in Type 2, which sequentially increases with condition severity. Palmer classification of injury severity, with consideration to blood supply to the affected region, is often utilised to justify the suitability of surgical procedures for cases published in literature.

Vasculature of the TFCC is characterised by a well-supplied peripheral margin arising ulnarly from the dorsal and volar attachments, with a central avascular region (Bednar, Arnoczky, & Weiland, 1991). Type 1A central tears to the articular disc are thought to have a low potential for healing with surgical repair, due to poor vascularisation of the inner region (Atzei, Rizzo, Luchetti, & Fairplay, 2008; Rein et al., 2015). Type 1 B and C tears are situated at the well-vascularised periphery and thus are often repaired surgically if non-operative management in the acute period is unsuccessful. Despite Type 1D tears having varying degrees of blood supply due to the involvement of the avascular radial attachment, the peripheral blood supply often lends itself to operative treatment approaches also. In contrast, there is little research available relative to TFCC microvasculature and its relation to suitability of non-operative interventions. Even more so, literature is lacking concerning implications of vascularity to injury progression in the absence of intervention.

Degenerative TFCC injuries are influenced by age, gender, repetitious loading and positive ulnar variance (UV) of the DRUJ. Chronic TFCC lesions are a recurrent finding in cohorts of collegiate, elite or professional athletes who participate in sports which involve repetitively exerting force in wrist hyperextension, prosupination or deviation. Chronic ulnar-sided wrist pain, with crepitus or instability is often reported by gymnasts, basketball, golf and tennis players, particularly those with positive UV (Jarrett & Baratz, 2012; Ko & Wiedrich, 2012; Pang & Yao, 2017). Ulnar impaction is recognised as a primary contributor to central TFCC tears with absent damage to peripheral, dorsal and ulnar structures. The length of the ulnar, when compared to radial length at the DRUJ, has been found to have an inverse relationship with thinning of the TFCC, observable on MRI between the ulnar and lunate (Palmer et al., 1984; Roenbeck & Imbriglia, 2011). Yoshioka found a near linear decrease in TFCC thickness on MRI with increase in UV >1mm, with an average 1.56mm ulna positive variation in patients with substantial TFCC disruption in comparison to 0.05mm in asymptomatic volunteers (Yoshioka et al., 2007).

Initial treatment for clinically indicated and MRI confirmed TFCC tears typically begins with 4 weeks of splint or cast immobilisation with or without intra-articular corticosteroid injection, though this approach lacks a solid evidence base despite its routine prescription. Park (2010) reported that 57% of patients with clinically suspected (but radiologically unconfirmed) TFCC injury had complete resolution of symptoms after a 4-week course of wrist immobilisation, irrespective of splint or cast type used (Park, Jagadish, & Yao, 2010). Lee (2019) found that 15% of patients in their retrospective review progressed to surgical interventions following a course of extended splint wear (4-12 weeks) and 37% experienced worsening or no change in PRWHE scores (Lee, Hwang, Lee, & Kwon, 2019). Two case-studies have found benefits using prolonged non-operative management; one using a neoprene orthosis for 12 weeks after 4 weeks of

immobilisation and corticosteroid injection, and the other a 12-week sensorimotor therapy protocol 2 months initial post injury (Barlow, 2016; Chen, 2018). Both case studies found significant improvement in pain and function following the 3 months of extended non-operative management. In studies investigating other hand and wrist conditions, research has supported trials of early mobilisation and heat wrapping for short-term functional benefits, though evidence is lacking to demonstrate any potential long-term benefits (Michlovitz, Hun, Erasala, Hengehold, & Weingand, 2004; Roll & Hardison, 2017). A 13-15 year follow up on untreated, arthroscopically confirmed TFC tears associated with distal radius fractures found that the presence of TFCC abnormality did not significantly impact long-term recovery outcomes(Mrkonjic, Geijer, Lindau, & Tagil, 2012). There are noticeably fewer publications specific to non-operative interventions in comparison to those investigating surgical procedures and an even larger gap in the literature regarding the natural progression of untreated TFCC pathology.

The benefits of a prolonged period of non-operative management for recalcitrant ulnar-sided wrist pain is inconclusive. This randomised control trial will investigate routinely used non-operative interventions, hand therapy, splinting and corticosteroid injection, to determine their efficacy in resolving symptoms. The outcomes of this trial will help determine whether splinting or cortisone injections, in isolation or combination, provide any additional benefit compared to hand therapy alone for non-operative treatment. This will contribute to the literature regarding non-operative interventions for TFCC injury management, and may also offer a greater understanding of TFCC injury pathology in the absence of any treatment. It is our aim to develop an evidence-based treatment protocol for managing TFCC tears non-operatively, with the potential to increase rates of successful conservative intervention.

3 PURPOSE OF THE INVESTIGATION

The purpose of this investigation is to determine the clinical outcomes and efficacy of the various conservative treatments offered to patients who suffer from triangular fibrocartilage complex tears.

3.1 RESEARCH QUESTION

Do adults with acute tears to the triangular fibrocartilage complex receiving a combination of the hand therapy, thermoplastic splint immobilisation and a corticosteroid injection to the TFCC (Group D) have significantly greater improvement in pain and function, as compared to those receiving just one conservative treatment of either splinting (Group B), or corticosteroid injection (Group C), or the control treatment of hand therapy (Group A)?

3.2 OBJECTIVES

3.2.1 Primary Objective

To determine the efficacy of splint immobilisation and cortisone injection, used in isolation or combination, for the non-operative management of triangular fibrocartilage complex injury.

3.2.2 Secondary Objectives

To determine the prevalence and factors associated with triangular fibrocartilage complex tears not benefitting from a course of conservative treatment.

3.3 NULL HYPOTHESIS

Patients receiving a combination of hand therapy, splint immobilisation, and corticosteroid injection (Group D) will have no greater improvement in pain and function, compared to those receiving the splint immobilisation (Group B), or corticosteroid injection (Group C), or the active control treatment of hand therapy (Group A) in adults with triangular fibrocartilage complex tears. In testing the main effects, the null hypothesis is that the means of all groups for the corresponding effect are not significantly different.

4 STUDY INVESTIGATORS

4.1 INVESTIGATORY TEAM

Principal Investigator:

- Dr Greg Couzens (orthopaedic surgeon)

Primary Investigators:

- Professor Mark Ross (orthopaedic surgeon)
- Dr Libby Anderson (orthopaedic surgeon)
- Ms Wilma Walsh (hand therapist)
- Ms Ruby Strauss (HDR student/research manager)

Associate Investigators:

- Dr Benjamin Hope (orthopaedic surgeon)
- Dr Andrew Mayo (orthopaedic surgeon)
- Dr David Gilpin (orthopaedic surgeon)
- Ms Anna Gore (research assistant)
- Dr Tim Gilmour (junior doctor)
- Dr Paul McEniery (orthopaedic surgeon)
- Dr Chris Jeffery (orthopaedic surgeon)

MPhil student QUT Academic Supervisory Team: Dr Anjali Jaiprakash (Primary), Professor Ross Crawford, Professor Jonathan Roberts

4.2 INVESTIGATOR RESPONSIBILITIES

The Primary Investigators will be responsible for:

- Monitoring the conduct of the study and study processes in line with the study protocol;
- To report any adverse events to the ethical committee, and relevant persons.

All Investigators will be responsible for:

- Obtaining ethical clearance prior to the commencement of the study;
- Recruitment;
- Providing participants with informed consent prior to allocation of intervention;
- Random allocation of participants;
- Provision of intervention;
- Concise and comprehensive collection of clinical and radiological data from the participants (blinded for collection of clinical outcomes);
- Ensuring confidentiality of data collection forms and results;
- Ensuring data is kept in a safe, secure and lockable location, and electronic copies have been backed up on a secure server;
- Ensuring the study is conducted in a safe and ethical manner in line with Queensland Health policies and procedures, NHMRC guidelines and relevant laws;
- Maintaining the confidentiality of participant records and data collected, and abiding by the NHMRC guidelines for human research;
- Data input from paper into electronic format;
- Data analysis;
- Paper preparation and submission; and
- Adherence to the Good Clinical Practice Guidelines.

5 STUDY DESIGN

This study aims to determine if there are differences in the effectiveness and clinical outcomes of various conservative treatments offered to patients who suffer from triangular fibrocartilage complex (TFCC) tears. A four-arm (Section 2.4) factorial, randomised clinical trial will be implemented.

Participants will be randomly allocated to either an active control group or one of three intervention groups. Participants will be asked to complete an electronic questionnaire consisting of outcome measures designed for conditions specific to the hand and wrist. Outcome measures will be administered at baseline (pre-treatment); 6 and 12 weeks (primary end-point); and at 6, 12 and 24 months from baseline (secondary end-point). Compliance and complications will be recorded at all post-intervention intervals, including two weeks after treatment commencement.

5.1 INTERVENTION GROUPS

This study will have an active control group (Group A) and three intervention groups;

Group A: will receive hand therapy

Group B: will receive a thermoplastic wrist splint + hand therapy

Group C: will receive a corticosteroid injection to the TFCC + hand therapy

Group D: will receive a thermoplastic wrist splint + corticosteroid injection to the TFCC + hand therapy

Participants will be randomly allocated to a treatment group following informed consent and a baseline research assessment.

5.2 STUDY LOCATION

This investigation will be conducted at the Brisbane Hand and Upper Limb Research Institute at Brisbane Private Hospital, Brisbane, Australia. It is anticipated that the majority of the study participants will be recruited by surgeons with private consulting suites at the Brisbane Hand and Upper Limb Clinic.

5.3 STUDY DURATION

It is expected that participant recruitment will be carried out over a 24 months period, with data collection for the primary end-point anticipated to be finalised no later than 28 months from commencement. Data collection will continue for the secondary end-point, until the remaining participants are up to 24 months post baseline.

6 STUDY POPULATION

Adults presenting with a TFCC tear, no greater than 12 months from primary injury will be invited to participate in the research study. As per standard care, clinical presentation of TFCC localised ulnar-sided wrist pain in addition to radiological confirmation of tear, will be considered by the treating surgeon to determine eligibility and suitability for conservative management *(Screening and Recruitment, 8.1.1).*

6.1 ELIGIBILTY CRITERIA

6.1.1 Inclusion Criteria

Participants will be eligible for inclusion in the study if they:

1. Aged 18 years and over;
2. Have a clinical diagnosis of TFCC localised, ulnar-sided wrist pain
3. Are ≤12 months post initial injury;
4. Have MRI confirmation of isolated TFCC tear;

6.1.2 Exclusion Criteria

Participants will be excluded from the study if they present with:

1. Frank instability of the distal radioulnar joint (DRUJ);
2. Arthritis of the distal radioulnar joint (DRUJ);

3. Concomitant injury (e.g. scaphoid fracture) in addition to TFCC tear;
4. Splint immobilisation or steroid injection within the last 3 months, to treat current injury;
5. Pregnancy due to risks associated with the corticosteroid injections;
6. Known allergies or adverse reactions to hydrocortisone and local anaesthetic (HCLA) injections;
7. Medical dependency that may interfere with ability to complete assessments or compliance;

6.2 RISKS TO PARTICIPANTS

All treatments offered in this trial are available to patients outside of study participation. No substantial evidence exists to suggest if any of the treatments offered as part of this trial are more or less effective than other treatments available. Participants who experience no improvement in their symptoms during the study may discuss study withdrawal with their study surgeon or other health care provider to seek further treatment. As none of the study interventions differ to those that would be recommended to eligible patients as treatment options, there are no perceivable study-specific health risks to participants.

Health risks associated with the treatments offered in this study include adverse reactions to the therapy exercise, thermoplastic splint or cortisone injection. Potential risks involved with injection of Marcain and or Celestone Chronodose as with any injection include infection, bruising or bleeding or a reaction to the medication. Adverse reactions to Celestone Chronodose may include fluid and electrolyte disturbances, musculoskeletal, gastrointestinal, dermatologic, neurologic, endocrine, ophthalmic, metabolic and psychiatric issues. Adverse reaction to Marcain may be of a cardiovascular, haemodynamic, neurologic or allergic nature. Although the mentioned reactions have been documented, the likelihood of occurrence is extremely rare. Any adverse reaction from the use of the thermoplastic wrist splint, including allergic contact dermatitis (redness, itching, skin eruptions, raised temperature, swelling); milaria rubra/prickly heat (small red elevated inflammatory papules with tingling/burning sensation); pressure or friction related complications and skin maceration from retained moisture caused by sweating or getting the splint wet and not drying properly.

Risks specific to study participation include risks relating to the collection and storage of personal data for data analysis *(Data storage, Management and Confidentiality, 9.2).*

7 STUDY OUTCOMES

Patient-reported pain and function questionnaires will be administered at baseline, 6 and 12 weeks; and 6, 12 and 24 months post baseline. Compliance and adverse events will be recorded at all post-intervention intervals, including 2 weeks after treatment initiation.

7.1 PRIMARY OUTCOME

7.1.1 Patient Rated Wrist and Hand Evaluation (PRWHE)

The Patient Rated Wrist and Hand Evaluation (PRWHE) is a patient-reported questionnaire, comprised of pain and function elements specific to wrist conditions. The 15-item questionnaire consists of two subscales designed to measure wrist pain and difficulty in activities of daily living (ADL), to give an overall score of wrist disability. It is one of the most widely used and validated instruments specific for this population.

Patients are asked to rate their pain on four items from 0 (no pain) to 10 (worst pain) and function on 10 items from 0 (no difficulty) to 10 (unable to do), including four broad ADL questions. Questions are specific to the affected wrist and can be used to calculate a total PRWHE score, in which pain and function are equally weighted. The PRWHE has been used to assess wrist-related pain and disability in various populations and its reliability, validity, and responsiveness have been extensively researched and publicized (MacDermid, Wessel, Humphrey, Ross, & Roth, 2007). A change of 14 points will be considered the minimum change to detect a difference with clinical relevance for the population.

7.2 SECONDARY OUTCOMES

7.2.1 Global Rating of Change (GRC)

The Global Rating of Change (GRC) scale provides a tool for measuring self-perceived change in health status in a quick and uncomplicated way (Kamper, Maher, & Mackay, 2009). It quantifies the extent to which the patient discerns their own improvement or deterioration over time on a 15-point scale, where 0 is no change. The GRC will be used in this study to measure change in symptoms and function between baseline and post-intervention assessment intervals. The instrument has the advantages of clinical relevance, adequate re-producibility, and sensitivity to change and is intuitively easy to understand by the patient and the person administering. Test-retest reliability is high (ICC 0.9) and face validity is supported by strong association between GRC and patient ratings of the importance of change (Pearson's r = 0.90) (Kamper et al., 2009). A change in symptoms or function of at least 5 points will be used to indicate a significant clinical change, perceivable to the patient.

7.2.2 Disabilities of the Arm, Shoulder and Hand, Short Form (QuickDASH)

The QuickDASH is a shortened version of the Disabilities of the Arm, Shoulder and Hand (DASH) Outcome Measure, and scoring is highly correlated to the DASH score. Both the DASH and the QuickDASH Outcome measure are valid, reliable and responsive and can be used for clinical and research purposes relating to upper limb disability (MacDermid et al., 2007; Mintken, Glynn, &

Cleland, 2009). The QuickDASH uses 11 items to measure physical function and symptoms in people with disorders of the upper limb, but questions are not specific to the affected joint. The survey is intended to be answered irrespective of the arm used to complete the activity in order to accurately capture limitations experienced whilst acknowledging adaptations made to perform activities. The QuickDASH also has two optional modules intended to measure symptoms and function in athletes, performing artists and other workers whose jobs require a high degree of physical performance.

7.2.3 Pain and Satisfaction Visual Analogue Scale (VAS)

A five-question visual analogue scale (VAS) will be used to assess wrist pain and satisfaction. These patient-reported scales are a commonly used tool for measuring pain intensity in clinical and research setting, with extensive evidence to support their validity and reliability (Ferreira-Valente, Pais-Ribeiro, & P Jensen, 2011; Hawker GA., Mian S, Kendzerska T, & French M, 2011; Price, A. McGrath, Rafii, & Buckingham, 1983). The form instructs participants to indicate their response on the 100 mm line, which is anchored at both ends with word descriptors. A score out of 100 is taken as a measurement from left (0) to the point where the patient has marked on the line.

7.2.4 Quality of Life EUROQOL (EQ-5D-5L)

The EQ-5D-5L is a generic health-related quality of life instrument completed by the patient. The instrument contains 5 multiple choice questions in the domains of mobility, personal care, usual activities, pain/discomfort and anxiety/depression. Each domain is categorised in three degrees of increasing severity or difficulty. The EQ-5D-5L has a supplementary multi-attribute score, reported on a continuous vertical VAS, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This secondary outcome measure will be utilised to examine potential impacts on quality of life throughout study participation.

7.2.5 Grip and Pinch Strength

Maximal isometric grip strength will be assessed using a calibrated hydraulic Jamar™ dynamometer. Three measurements for both the hands will be recorded and an average of the three measurements will be used in the data analysis (Mathiowetz, 1990). The measurements will be performed from a seated position, alternating between left and right hands to avoid fatigue. Maximal lateral and two-point (index and thumb) pinch strength will be measured using a calibrated hydraulic Saehan™ pinch gauge. These assessments are frequently and reliably used as a measure of hand function (Mathiowetz, Weber, Volland, & Kashman, 1984) and is routinely performed as part of a patient's standard care.

7.2.6 Adverse Events

Any adverse events occurring during the trial will be closely monitored and followed up until the complete resolution of symptoms. This will include all reactions listed for the cortisone injection and any reactions to the thermoplastic splint. These will be checked at each assessment stage and recorded on the adverse events / complication forms. Adverse events may include:

1. Any adverse reaction from the intra-articular corticosteroid injection, including but not limited to those provided in the product information brochure;
2. Any adverse reaction to use of the thermoplastic wrist splint
3. Wrist instability
4. Reinjury of affected wrist
5. Other (including Chronic Regional Pain Syndrome, or hypersensitivity)

Other changes in symptoms and function noted by participants will be noted at each interval in the event that the change noted progresses to an adverse event or complication.

8 STUDY PROCEDURES

8.1 PARTICIPANT RECRUITMENT, ENROLMENT AND RETENTION

8.1.1 Screening and Recruitment

The study population will primarily be recruited from the private consulting practices of orthopaedic surgeons at the Brisbane Hand and Upper Limb Clinic at the Brisbane Private Hospital. In addition, local general practitioners will be invited to refer patients to be assessed by an orthopaedic upper limb specialist, to be considered for potential research participation.

8.1.1.1 Orthopaedic Surgeon Referral

Surgeons involved in the study will identify eligible study participants at the time of presentation to clinical appointments, based on the inclusion and exclusion criteria *(Eligibility Criteria, 6.1).* Patients with injuries deemed suitable for randomised conservative management by the treating surgeon, will be informed of the study. If the participant is interested in participation or would like more information, they will be referred to the Brisbane Hand & Upper Limb Research Institute. At the time of referral to the Brisbane Hand & Upper Limb Research Institute, the surgeon will complete a research referral indicating the participant's eligibility for study participation (Appendix 14.1). A research assistant will explain in detail the procedures, risks and benefits associated with the study and provide the Participant Information and Consent Form (PICF) for the participant to consider.

8.1.1.2 General Practitioner Referral

General Practitioners (GPs) are often the first point of contact for patients with acute or recalcitrant, ulnar sided wrist pain. GPs who frequently refer patients to surgeons at the Brisbane

Hand & Upper Limb Clinic will be notified of the study and provided with information regarding participant eligibility and study procedures. If a GP identifies a potentially eligible patient who is interested in research participation, they will provide the patient with contact details for the Brisbane Hand & Upper Limb Research Institute (BHULRI) for more information. If, after speaking to a research member, the participant decides they would like to be considered for trial participation, their GP will write a referral for an appointment with a participating orthopaedic surgeon at the Brisbane Hand & Upper Limb Clinic.

If deemed suitable for randomised conservative management and eligible for study participation, the patient will be referred to research as described above *(Orthopaedic Surgeon Referral, 8.1.1.1).*

8.1.2 Consent and Enrolment

Patients will be screened for eligibility and suitability by the referring surgeon. Consent procedures will be carried out by research assistants in line with the NHMRC National Statement on Ethical Conduct in Human Research (2007). After review of the Participant Information Consent Form (PICF) and acknowledging that they have understood the proposed research and the implications of participation, patients who voluntarily elect to participate will be asked to sign the consent form (Appendix 14.2). Once a participant has consented and completed their pre-treatment assessment, they will be randomised and allocated to an intervention group.

8.1.3 Participant Withdrawal and Attrition

8.1.3.1 Withdrawal Prior to Treatment

Individuals who express reluctance to receiving any of the study treatments prior to consent will be discouraged to volunteer for study participation. If a patient has consented to study participation but does not wish to follow through with their randomised treatment allocation, they will be given the option to withdraw from the study. Participants who, after receiving cortisone, splinting or therapy treatment, have not benefitted from the randomly allocated intervention may wish discuss alternatives with their treating health provider. Any additional treatment received will conclude research participation. See Section 4.8.3 for more information on participant attrition.

8.1.3.2 Elective Withdrawal After Treatment

Any participant who wishes to withdraw during the study of his/her own accord and for whatever reason is entitled to do so without obligation and prejudice. In the event of this occurring, the participant will be asked to sign a study withdrawal form.

Participants who, after receiving cortisone, splinting or therapy treatment, have not benefitted from the course of conservative treatment may wish to discuss alternatives with their treating

health provider. If the participant chooses to undergo additional interventions, remedies or treatment external to the study within the initial 12-week primary or 24-month secondary study end point, their active research participation will be ceased. The participant will be invited to complete a final assessment prior to receiving further treatment if possible, at which point the type of treatment planned (e.g. surgical TFCC repair) will be recorded. If the participant is agreeable, the research team will follow up (via phone or email) with inactive participants 6 months after their active research participation has concluded, to confirm details of injury resolution. Attrition rate and wrist outcomes of participants who have received treatment outside of the study protocol will be reported in the final publication.

8.1.3.3 Participant Loss to Follow-Up

Participants that do not return for scheduled appointments without notice may be deemed lost-to follow-up (LTFU). Up to three attempts will be made to contact enrolled participants who miss a follow-up interval on phone and/or email, at each interval missed. Participants will be recorded as LTFU if they are absent and uncontactable for two consecutive assessments. Singular attempts to contact LTFU participants at long-term assessment intervals may still be attempted. If a participant previously marked as LTFU makes contact or returns for clinical review, they will be asked if they would like to withdraw from or continue active participation in research.

8.2 RANDOMISATION

Block randomisation will be performed to achieve balance in the allocation of participants to the different treatment arms throughout the course of the recruitment period. Fifteen blocks will be generated, with three multiples of each treatment arm per block. As a result, for every 12 randomly assigned treatment allocations, each intervention arm will have a comparable number of participants.

The randomisation sequence will be concealed in sequentially numbered sealed, opaque envelopes. The randomisation procedure will be administered by a research assistant who will not be blind to allocation for the duration of the study. They will open an envelope and reveal the allocation to the patient. As all treatment groups involve a hand therapy session, all participants will be provided with a referral for hand therapy by their referring surgeon when enrolled in the study. A dual randomisation procedure will be implemented, with one envelope opened at baseline and the other at the 6 week interval. At the baseline appointment, the assessor will open an envelope to reveal whether the participant will be receiving a splint.

A second randomisation will occur at 6 weeks to reveal whether the participant is to have a cortisone injection. Each envelope will contain a sheet of paper with the intervention group, as listed below.

Group A Hand Therapy (HT)	Group B HT + Splint	Group C HT + Cortisone	Group D HT + Splint + Cortisone

If randomly allocated into Group C or Group D, the participant's study surgeon will issue a referral for a cortisone injection to be administered at Brisbane Private Imaging, 6 weeks after the baseline appointment. The treating surgeon will not be blind to allocation to maintain standard medical care.

8.3 PARTICIPANT DATA COLLECTION

We will collect data using digital questionnaires to record patient-reported outcome measures in addition to physiological strength measure. Data collection forms will be used at baseline (pre-intervention) and at all post-intervention intervals.

8.3.1 Clinical Notes

The assessing surgeon will perform a clinical assessment of the patient as part of the routine standard of care. Patients suffering from localised, ulnar-sided wrist pain often experience tenderness, crepitus and DRUJ instability of the affected wrist (Haugstvedt & Søreide, 2017). A clinical exam is routinely performed to determine the site of TFC tenderness; crepitus noted with rotation or deviation; evidence of DRUJ laxity in pronation or supination; "Lift Off" in pronation or supination; and response to carpal grind tests. Notes from clinical examinations are recorded and stored in the patient's medical chart, whether or not the patient is to be involved in any research trial (Appendix 14.3). If the patient consents to study participation, clinical notes recorded by the surgeon at the time of initial assessment will be collected and deidentified to be used in data analysis, to investigate possible relationships between physiological factors and outcome measures.

8.3.2 Demographic Information

Basic demographic information will be obtained from the participant after consent, but prior to random allocation of an intervention. This will include:

1. Age and gender;
2. Hand dominance;
3. Primary occupation type;
4. Sports or recreational activities;
5. Compensation status/insurance;
6. Medical history including smoking status and concomitant medical conditions;
7. Details of current and previous trauma to the affected wrist;
8. Current pain medications;
9. Surgical history of both wrists;
10. History of any interventions or therapies used by patients in an attempt to treat the affected wrist

8.3.3 Patient-Reported Questionnaires

Participants will complete a digital questionnaire at assessment intervals with the help of a research assistant, to record changes to wrist pain and function (Appendix 14.4). The patient-reported surveys comprise the primary and secondary outcome measures specified in section 7, *Study Outcomes.* These questionnaires will be completed by participants at baseline prior to randomisation and at 6 weeks, 12 weeks, and long-term follow-up intervals.

8.3.4 Range of Motion and Strength

Participants will have their active wrist range of motion recorded by a research assistant at all intervals to record any change to wrist movement throughout the study. A manual goniometer will be used to measure wrist flexion, extension, supination, pronation, radial deviation and ulnar deviation. The research assistant will use hydraulic dynamometers/strength gauge to record the participant's average grip and pinch strength. All measures will also be taken on the contralateral wrist.

8.4 TREATMENT INTERVENTIONS

Following the completion of all research data collection and randomisation allocation at the baseline appointment, the participant will have treatment appointments made with the hand therapist and radiologist if necessary.

8.4.1 Hand Therapy

It was deemed unethical to the investigators to have a control group where participants did not receive any treatment at all, as all participants will be patients referred to the surgeons seeking relief of their symptoms.

For this reason, all participants irrespective of the group they are allocated to, will receive hand therapy. The active control group (Group A) will receive only the hand therapy. Hand therapy with a qualified hand therapist will be provided by Extend Rehabilitation (www.extendrehab.com.au) or EKCO Hand Therapy (www.ekco.com.au) at Brisbane Private Hospital. The baseline treatment appointment and the follow-up sessions for all participants at 2- and 6-weeks post intervention will be provided at a subsidised cost of $180 for the three sessions. The normal cost for patients outside of the research would be $360 for these three sessions (Appendix 14.5).

Participants will receive a standardised exercise program and advice on pain management including joint protection and activity modification. This therapy protocol will be reinforced with the provision of a participant exercise booklet, vinyl dumbbells and a compliance log (Appendix

14.6). Therapists will undergo a regular in-service training program to ensure that all participants receive standardised treatment.

Routine follow-up appointments will be provided at 2, 6- and 12-weeks post-intervention. Participants having any concerns or queries between clinical visits will have the contact details for the research institute as first point of contact. The research team will advise their consulting surgeon's practice or treating hand therapist clinic so that appropriate advice can be provided. Any deviation from the prescribed treatment protocol will be recorded at follow up research assessments.

8.4.2 Thermoplastic Wrist Splint

All participants in Group B and Group D will be fitted with a standardised design, thermoplastic, volar wrist splint. This will be custom fitted by a qualified Hand Therapist at Extend Rehabilitation or EKCO Hand Therapy, following the baseline hand therapy session. All hand therapists making splints for study participants will be instructed to follow a standardised design protocol to ensure consistency amongst therapists and practices. The splint will be worn for 6 weeks full time (with the exception of washing and when performing prescribed exercises). After 6 weeks, participants may cease splint wear and use as required for symptomatic relief only.

Minor adjustments may be made to alleviate discomfort caused by the splint. Any deviation from the prescribed orthosis design or non-compliance with orthosis use will be recorded at follow up research assessments.

8.4.3 Corticosteroid Injection

A single dose of ultrasound guided intra-articular corticosteroid injection will be provided by radiologists at Brisbane Private Imaging (Brisbane Private Hospital, Brisbane) at the 6 week interval. The steroid (Celestone Chronodose™) and local anaesthetic (Marcain™) combination to be administered, is the current hydrocortisone & local anaesthetic (HCLA) medication routinely used at Brisbane Private Imaging. A standard procedure will be followed:

1. Participant will be asked to lie in a supine position on the examination table with the affected wrist resting comfortably palm side down on the table or across their abdomen.
2. Antiseptic solution will be applied to the skin.
3. A 25 gauge, 38mm needle will be inserted into the dorsal aspect of the TFCC using ultrasound guidance.
4. A mixture of 1 mL of Celestone Chronodose and 1 mL of 0.5% Marcain will be injected into the TFCC.

The injections will be provided by radiologists at Brisbane Private Imaging, at the Brisbane Private Hospital. The treatment will be bulk billed for the participants (Appendix 14.7)

Celestone Chronodose™ (Merck Sharp & Dohme Pty Ltd, Australia) contains 1ml of betamethasone 5.7mg. It has full TGA approval (Appendix 14.8).

Marcain™ (AstraZeneca PTY Ltd, Australia) contains the active ingredient bupivacaine hydrochloride monohydrate. It has full TGA approval (14.9).

8.4.4 Treatment Compliance

A hand therapy compliance log will be provided to all participants to record the frequency of exercises performed over the 12 week treatment period. Participants will be instructed to record on the log each time the set of prescribed exercises are performed. At post-intervention assessment intervals, participants will be asked to answer survey questions about their compliance to the prescribed therapy and splint wear if applicable. Data on participant compliance will be analysed to investigate possible correlation to response to treatment.

8.5 STUDY COMPLETION

Patients outside of research studies are routinely assessed by specialist clinicians at the Upper Limb Clinic at 12 weeks following prescribed conservative management. The assessment intervals for the primary end-point of this study are aligned with the routine clinical follow up schedule for patients having conservative TFCC treatment at this clinic. The secondary end point invites research participants to be reviewed at intervals at 6, 12 and 24 months. These longer-term intervals are often part of routine clinical follow up, dependant on the status of the injury.

8.5.1 Primary End-point

Participants will be assessed by their referring surgeon and have outcomes measured by a research assistant at 12 weeks to assess effectiveness of the randomised conservative treatment for treating the injury. Patients who demonstrate no benefit from conservative management, or an aggravation in symptoms may be considered for further conservative treatment or surgical intervention at the surgeon's discretion. Any further treatment received will result in the conclusion of the participant's ongoing study involvement. Assessments will be made at 2 and 6 weeks to monitor compliance to the treatment allocated, complications/adverse events and an interim assessment of treatment outcomes (6 weeks only).

Data Collection Interval	Range	Review Method
Pre-intervention/baseline	≤ 12 months post initial injury	In person at the clinic Surgeon + Researcher + Hand Therapist
2 weeks Compliance & complications	2 weeks +/- 5 days	In person at the clinic Researcher + Hand Therapist
6 weeks Interim Assessment	6 weeks +/- 10 days	In person at the clinic Researcher + Hand Therapist + Surgeon

12 weeks Primary End-Point	2 – 4 months	In person at the clinic Surgeon + Researcher

8.5.2 Secondary End-point

Participants will be invited to be assessed by the referring surgeon and research assistant at 6 months, 12 months and 24-month intervals to determine long-term outcomes and ascertain rates of re-injury. If possible, these assessments will be conducted at the Brisbane Hand & Upper Limb Clinic to allow for completion of patient-reported questionnaires as well as strength measurements to be recorded. If the participant is unable to present in person, they will be invited to complete a partial assessment, comprised of only the patient-reported outcome questionnaires, via completion of the digital survey.

Data Collection Interval	Range	Review Method
6 months	5 – 7 months	In person (Surgeon + Researcher) or digital survey via email
12 months	10 – 14 months	In person (Surgeon + Researcher) or digital survey via email
24 months	22 – 26 months	In person (Surgeon + Researcher) or digital survey via email

9 DATA MANAGEMENT AND ANALYSIS

9.1 SAMPLE SIZE

180 participants will be recruited in the study, with 45 in each of the four groups. Sample size calculations were performed to detect an effect size suitable for the primary outcomes of pain and function, using the Patient Rated Wrist and Hand Evaluation (PRWHE).

The minimal clinically important difference (MCID) for pain and function in patients with wrist injury using the PRWHE is 14 points with a standard deviation of (Sorensen, Howard, Tan, Ketchersid, & Calfee, 2013). Using a global rating of change as an anchor, a minimum change of 5 points out of 15 is required for patients to reliably detect a notable improvement in symptoms and function at 3 months post intervention. To ascertain a clinically significant change in pain and function perceivable by the patient, the project has been designed to detect a relatively large effect size. It is not necessary to detect small effects in patient outcome scores, as clinically this small change is not perceivable by patients. Effect size (f) was set at 0.29, to allow detection of a medium-large effect.

The statistical test used to analyse outcomes data will be a factorial ANOVA, to analyse fixed effects, special, main effects and interactions. This will allow a comparison of treatment groups

compared to the control (Group A) and also examine the interactions between combination interventions (Group D).

- Effect size (f) = 0.29
- Type-I error (α) rate = 0.05
- Power (1-β err prob) = 80% (0.8)
- Number of groups (n) = 4
- Numerator df (n - 1) = 3

The above parameters are entered into sample size calculation software *G*Power* (Version 3.1.9.4), with the result that the study must recruit a minimum of 134 participants to achieve 80% power.

F tests - ANOVA: Fixed effects, special, main effects and interactions

Analysis:	A priori: Compute required sample size		
Input:	Effect size f	=	0.29
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	Numerator df	=	3
	Number of groups	=	4
Output:	Noncentrality parameter λ	=	11.2694000
	Critical F	=	2.6742856
	Denominator df	=	130
	Total sample size	=	134
	Actual power	=	0.8013103

Using historical participant retention at the Brisbane Hand and Upper Limb Clinic as a model, an attrition rate of 25% is anticipated. If 134 is the smallest remaining cohort after attrition (75% retention) required to achieve 80% power, the minimum recruitment sample required would be 179. Due to the balanced study design necessitating even group numbers, the target recruitment sample size is 180 participants, with 45 participants allocated to each group.

9.2 DATA STORAGE, MANAGEMENT AND CONFIDENTIALITY

Information about study subjects will be kept confidential and managed accordingly to the requirement of Human Research as determined by the NHMRC Guidelines, and the local ethics review board, the Metro South Human Research Ethics Committee.

The master subject list will be kept strictly confidential on a protected server, only accessible by essential members of the investigative team on a password protected computer. The master list will not be removed from the study site and will record the full name and contact details of all of the participants. This list will only be used to contact participants as required for research follow

up. All electronic data forms will be kept in re-identifiable format using a study-specific numerical identifier. All data will be reported in a non-identifiable format.

9.3 DATA ANALYSIS

Baseline demographic and clinical data will be reported using descriptive statistics and will be tabulated. Between groups differences in baseline data will be examined using unpaired conventional tests of hypothesis depending on the nature of the data. Between group and within group differences in outcome measures over time will be examined using a priori unpaired and paired conventional tests of hypothesis depending on the nature of the data. Linear mixed effects models will be used to examine the within and between group variability of the four groups. Bonferroni adjustments for multiple comparisons will be made where appropriate to mitigate risk of type-1 error.

The complication rates will be reported in terms of frequency. The frequencies of complications will be compared using statistical analysis such as the Pearson chi-square statistic.

10 DISSEMINATION OF FINDINGS

Findings from this investigation will be disseminated locally through existing state- and nation-wide clinical networks and in-service education amongst relevant clinical teams (e.g. multi-disciplinary upper limb teams in hospital facilities).

Findings from this research will be disseminated widely through peer reviewed publications (e.g. The Journal of Bone and Joint Surgery) as well as through local, national and/or international conferences (E.g. Australian Hand Surgery Society, International Federation of Societies for Surgery of the Hand). The proposed wide dissemination of these findings is likely guide models of healthcare both nationally and internationally.

11 BUDGET AND FUNDING

11.1 STUDY RELATED COSTS

Item	Source	Details	Study Costs
Staff time	BHULRI	Protocol development, ethics, randomisation, study assessments, participant follow-up, data entry, analysis, writing paper for publication, submission.	In Kind (BHULRI) Research assistant time as part of MPhil degree
Corticosteroid Injection	Brisbane Private Imaging	Ultrasound guided Injection Participants to be bulk billed	Nil

		See agreement letter	
Hand Therapy	Extend Rehabilitation + EKCO Hand Therapy	Participants to pay at a subsidised cost of $180 to the therapy clinic. This reduced rate is 50% of the normal fees charged.	Nil
Thermoplastic Splint	Extend Rehabilitation + EKCO Hand Therapy	$70 per splint (90 participants)	$6300
Vinyl dumbbells	Wholesaler	$8 per 2kg weight, $4 per 500g	$700

11.2 FUNDING

The Brisbane Hand & Upper Limb Research Institute was awarded a $7000 grant from the Queensland Hand Surgery Society for this project. These funds will be used to cover splinting costs for the 90 participants randomised to treatment Groups B and D. The remainder will be used to purchase vinyl dumbbells for participants to loan during the 12-week treatment period of study participation.

12 GLOSSARY OF ABBREVIATIONS

ADL	Activities of daily living
BHULRI	Brisbane Hand & Upper Limb Research Institute
DRUJ	Distal radioulnar joint
ECU	Extensor carpi ulnaris
GP	General practitioner
GRC	Global Rating of Change
HCLA	Hydrocortisone and local anaesthetic
ICC	Intraclass correlation coefficient
MCID	Minimal clinically important difference
PICF	Participant information consent form
PRWHE	Patient Rated Wrist Hand Evaluation
QuickDASH	Disabilities of the Arm, Shoulder and Hand Score short form
TFCC	Triangular fibrocartilage complex
UCL	Ulnar collateral ligament
VAS	Visual Analogue Scale

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14 APPENDICES

14.1 PATIENT REFERRAL FORM

14.2 PARTICIPANT INFORMATION CONSENT FORM

14.3 CLINICAL EXAM FORM

14.4 PARTICIPANT ASSESSMENT QUESTIONNAIRE

14.5 HAND THERAPY AGREEMENT LETTERS

14.6 HAND THERAPY PROTOCOL

14.7 BRISBANE PRIVATE IMAGING AGREEMENT LETTER

14.8 TGA CELESTONE CHRONODOSE

14.9 TGA MARCAIN