Optimising the Investigation of Interventional Treatments in Lateral Elbow Tendinopathy

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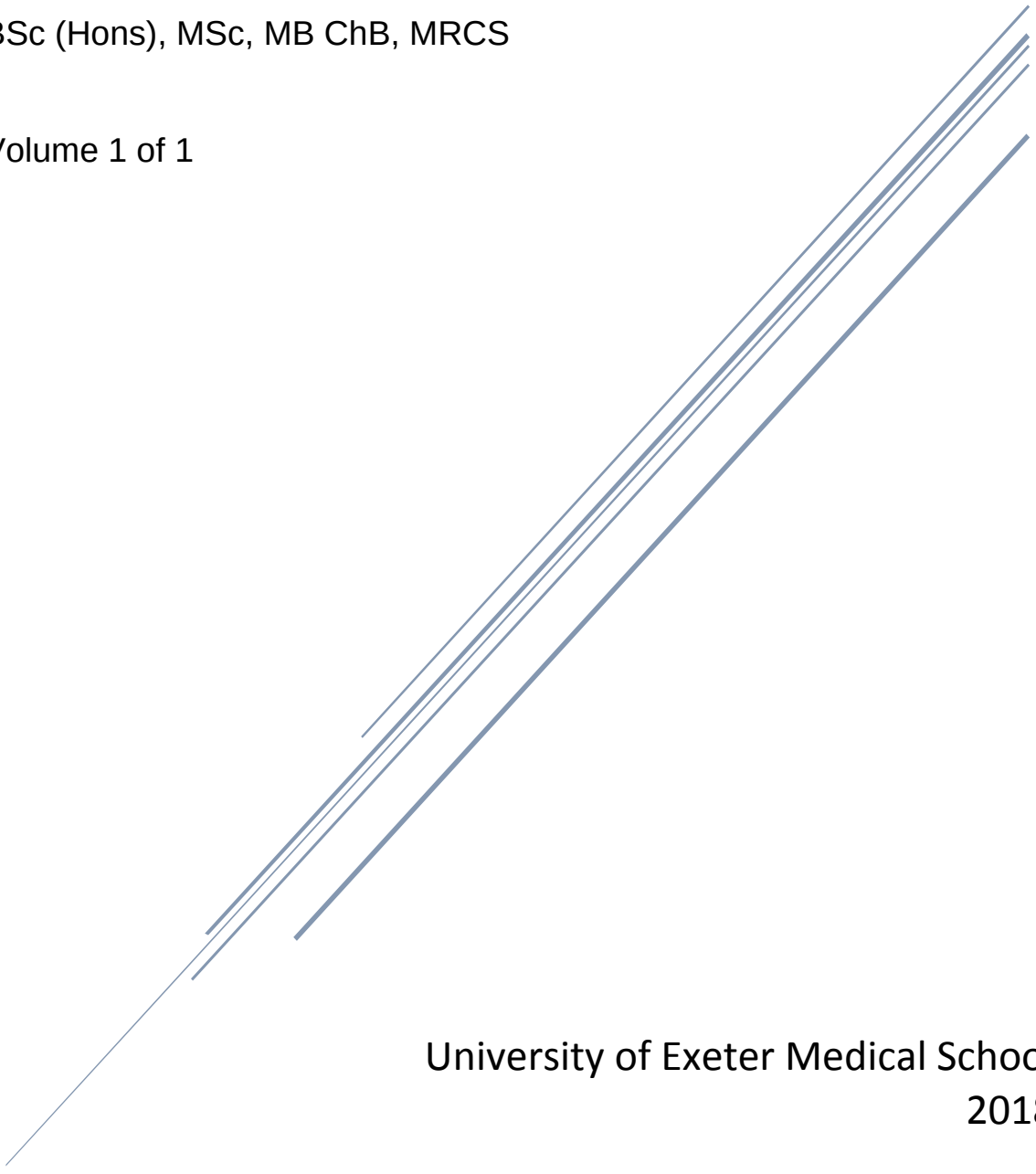
Volume 1 of 1



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Optimising the Investigation of Interventional Treatments in Lateral Elbow Tendinopathy

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I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

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Abstract

Background and Aim

Lateral Elbow Tendinopathy (LET) is a common, painful condition, predominantly affecting working age people. Although numerous studies have been conducted assessing a multitude of therapeutic interventions, fundamental information regarding outcome measure choice, treatment delivery techniques, and trial feasibility have not been explored. This thesis aims to optimise the investigation of interventional therapies in lateral elbow tendinopathy by furthering the foundational knowledge from which future researchers can inform their study design.

Methods

A portfolio of studies was undertaken to explore three main themes: the choice of patient-centred outcome measure, the rationale for injection therapy technique and the feasibility and acceptability of a randomised controlled study methodology in Platelet-Rich Plasma (PRP) injection therapy. Seven studies addressing these themes were undertaken: a three-phase systematic review and standardised evaluation of patient-centred clinical rating systems in elbow pathology, a validation study of outcome measures in a UK population of lateral elbow tendinopathy patients, a cadaveric assessment of elbow injection distribution, a Delphi consensus study of PRP injection use and a feasibility randomised controlled trial of PRP versus surgery for chronic LET.

Results

The systematic review identified 72 clinical rating systems used in elbow pathology, 15 of which had a history of validation in lateral elbow tendinopathy patients. Standardised comparative assessment found that only four reached the minimum threshold for recommendation (QDASH, DASH, OES and PRTEE). The correlation between the frequency of clinical rating systems use and their performance was r = 0.35. Cross-culturally specific validity of these rating systems in a UK population was limited to 20 patients embedded in mixed pathology cohorts. Evaluation of the psychometric properties of the highest performing clinical rating systems was performed in 50 tendinopathy patients recruited across general practice, physiotherapy and secondary care settings, with all instruments achieving adequate internal consistency (Cronbach's alpha >0.87), reliability

(intraclass correlation coefficient >0.85) and responsiveness (effect sizes >0.46). The cadaveric evaluation found no statistical difference between the intratendinous distribution of lateral elbow injections between 1ml and 3ml or between single shot or fenestrated injection techniques. The Delphi consensus study on the application of platelet-rich plasma injections found poor levels of agreement amongst experts on the technical preparation and application of this treatment. The feasibility randomised control trial found that a randomised controlled trial is technically feasible (86% recruitment rate, 8% drop-out and 8% cross-over). Qualitative interviews with these patients identified very high levels of procedural injection pain.

Conclusion

This research improves upon the knowledge base from which future evaluations of interventional treatment in lateral elbow tendinopathy can be constructed. It is the first one to identify the wide choice and disparate utility of patient-centred outcome measures in elbow pathology. It can recommend the QDASH, DASH, OES or PRTEE for use in the English language and provides evidence of the validity and reliability of these instruments in the UK. Injection methodology should be rationalised to low volume single-shot injections, and research priorities should be allied to areas identified as lacking expert consensus. Though feasible and acceptable, future parallel group studies should quantify and report procedural pain.

Thesis components at a glance

Study	Question	Methods	Results	Conclusion
I	What clinical rating systems are used to assess patient-focused outcomes in elbow pathology?	A systematic review identifying all rating systems used in elbow disorders, categorised by pathology, time period of use and geographical distribution.	980 studies were identified that used 72 separate rating systems. 41% of studies used two or more separate measures. Overall 54% of studies used the Mayo Elbow Performance Score (MEPS).	A vast number of instruments exist, although recently developed PROMs are increasingly used, historic instruments continue to be reported. The use of multiple rating systems is common, increasing participant burden. Lack of conformity is likely to hinder evidence synthesis.
II	In Lateral Elbow Tendinopathy (LET), what is the evidence that the available clinical rating systems meet acceptable psychometric standards?	Systematic review and standardised evaluation of all rating systems with a history of development, metric property assessment or use in LET.	229 articles report the development and/or application of 15 separate rating systems. Standardised evaluation using the EMPRO tool identified the QDASH, DASH, OES and PRTEE as meeting minimum criteria for recommendation.	Though numerous rating systems exist, only four meet minimum criteria for recommendation in LET.
III	Are LET rating systems used in the UK cross-culturally valid and is it possible to conform to outcome measure reporting guidelines?	Focused review of data on the use and validity of rating systems in the UK. Assessment of accordance with cross-cultural & COSMIN-PRO guidelines.	16 articles reporting the use of seven rating systems. No RCT complied with COSMIN-PRO guidelines. Comprehensive assessment of metric properties of the seven rating systems has only been undertaken on 20 individual UK participants.	No rating systems have been adequately cross-culturally validated in UK individuals. Consequently, COSMIN-PRO guidelines cannot be adhered to.
IV	Are Patient-Reported Outcome Measures (PROM) valid, reliable and responsive for LET patients in the UK?	Comparison of the three best performing PROMs identified from study II and new PROMIS short forms. Assessment of validity, reliability and responsiveness in LET participants.	738 invitations yielded 81 recruits and 50 participants who completed all questionnaires. Internal consistency, reliability, construct validity were all found to be adequate. Effect sizes were found to be greatest in pain sub-scales.	This study expands the evidence base for PROM validity in UK populations, allowing future authors to adhere to COSMIN-PRO guidelines. Poor recruitment and retention hinders this study from making clearer recommendations on specific PROM superiority.
V	When an intratendinous injection is undertaken for LET, where does the injectate distribute and is there an optimal technique?	Cadaveric assessment of Common Extensor Tendon (CET) injection volumes and techniques. Distribution assessed through arthroscopy, dissection and cross-sectional image analysis of microtome sections.	No statistical difference between 1 and 3ml injection distribution or single shot or fenestrated injection protocols. Distribution fraction of over 97% of the cross-sectional area of the tendon. Joint contamination occurred in all cases.	Commonly used injection volumes and techniques distribute injectate widely through the CET with no evidence of superiority in higher volumes or fenestration. Joint contamination may be inevitable.
VI	Can an expert consensus be reached to guide patient selection, delivery and follow-up of Platelet-Rich Plasma (PRP) in LET.	Assessment of consensus between international group of PRP users and researchers using the Delphi consensus methodology.	28 individuals completed three rounds of consensus statement scoring. Overall agreement was reached for 17/40 statements. Only 2/6 statements on PRP formulation reached consensus.	Amongst an international group of expert researchers and users, only limited consensus on the application of PRP can be achieved. The area identified as not reaching consensus should be utilised as research priorities.
VII	Is it feasible to undertake a randomised controlled trial of PRP vs surgery in chronic LET?	Feasibility assessment of 12 participants recruited to receive PRP injection or surgery. Recruitment, retention and adherence to study design and qualitative assessment of the patient experience.	The target sample was achieved in 10 months. Recruitment rate was 86%. One participant dropped out and one crossed-over from PRP to surgery. Qualitative interviews revealed very high levels of patient discomfort on injection delivery.	It is technically feasible to undertake a study assessing PRP to surgery. Reporting guideline adherence was achieved, and qualitative assessment deemed the methodology acceptable. Future studies must assess and report procedural pain.

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List of abbreviations

A&C	Andrews and Carson
AB	Autologous Blood
ACD-A	Anticoagulant Citrate Dextrose-A
ASES-E	American Shoulder and Elbow Surgeons - Elbow
CET	Common Extensor Tendon
CI	Confidence Interval
CINHAL	Cumulative Index to Nursing and Allied Health Literature
CLAHRC	Collaboration for Leadership in Applied Health Research and Care
COMET	Core Outcome Measures in Effectiveness Trials
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments.
COSMIN-PRO	COnsensus-based Standards for the selection of health Measurement INstruments - Patient Reported Outcomes
COX	Cyclooxygenase
CV	Coefficient of Variation
CVD	Coefficient of Variation Difference
DASH	Disabilities of the Arm Shoulder and Hand
ECRB	Extensor Carpi Radialis Brevis
ECU	Extensor Carpi Ulnaris
EDC	Extensor Digitorum Communis
EDM	Extensor Digiti Mimini
EMPRO	Evaluating Measures of Patient-Reported Outcomes

EQ5D – 3L	Euroqol Five Dimension questionnaire – three Level
EQ5D – 5L	Euroqol Five Dimension questionnaire – five Level
EQ5D-VAS	Euroqol Five Dimension - Visual Analogue Scale
ES	Effect Size
ESWT	Extracorporeal Shock Wave Therapy
FDA	Food and Drug Administration
GP	General Practitioner
GROC	Global Rating Of Change
HSS	Hospital for Special Surgery
ICC	Intraclass Correlation Coefficient
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICF	International Classification of Functioning, Disability and Health
ICHOM	International Consortium for Health Outcomes Measurement
IQR	Inter Quartile Range
IRT	Item Response Theory
ISOQOL	International Society for Quality of Life Research
KJOC	Kerlan-Jobe Orthopaedic Clinic overhead athlete score
LES	Liverpool Elbow Score
LET	Lateral Elbow Tendinopathy
MCID	Minimally Clinically Important Difference
MEPS	Mayo Elbow Performance Score
MIBO	Minimum Information for Studies Evaluating Biologics in Orthopaedics
MMP	Matrix Metalloproteinases

MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NIHR	National Institute for Health Research
NPS	Numeric Pain Scale
OES	Oxford Elbow Score
OES ΨS	Oxford Elbow Score Psychosocial sub-scale
OR	Odds Ratio
PIN	Posterior Interosseous Nerve
PPI	Patient and Public Involvement
PRFE	Patient-Rated Forearm Evaluation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Patient Reported Outcome Measure
PROMIS	Patient-Reported Outcomes Measurement Information System
PROMIS UE	Patient Reported Outcome Measurement System Upper Extremity
PROSPERO	International prospective register of systematic reviews
PRP	Platelet-Rich Plasma
PRTEE	Patient-Rated Tennis Elbow Evaluation
QALY	Quality-Adjusted life year
QDASH	quick Disabilities of the Arm Shoulder and Hand
R&M	Roles and Maudsley score
RCT	Randomised Controlled Trial

REC	Research Ethics Committee
SANE	Single Assessment Numerical Evaluation
SD	Standard Deviation
SDC	Smallest Detectable Change
SEM	Standard Error of Measurement
SPADI	Shoulder Pain and Disability Index
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TEFS	Tennis Elbow Functional Score
THIN	The Health Improvement Network
UCLA	University of California, Los Angeles
ULFI	Upper Limb Functional Index
USS	Ultrasound Scan
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organisation

Publications and presentations to date

Publications

Evans, JP., Smith, CD., Porter, I., Gangannagaripalli, J., Bramwell, C., Davey, A., Fine, N., Goodwin, V., Valderas, J. **Clinical rating systems in elbow research—a systematic review exploring trends and distributions of use**. Journal of Shoulder and Elbow Surgery. 2018 Feb 12. pii: S1058-2746(18)30014-4. doi: 10.1016/j.jse.2017.12.027.

Evans, JP., Smith, CD., Porter, I., Gangannagaripalli, J., Goodwin, VA., Valderas, JM. (2018) **Patient-Centred Outcomes in Lateral Elbow Tendinopathy: a systematic review of available evidence in UK populations.** Shoulder and Elbow. Accepted for publication July 2018.

Evans, JP., Metz, J., Anaspure, R., Thomas, W., King, A., Goodwin, V., Smith, CD. (2018) **The Spread of Injectate after Ultrasound-Guided Lateral Elbow Injection - A Cadaveric Study**. Journal of Experimental Orthopaedics. Accepted for publication July 2018.

Presentations

Evans, JP., Smith, CD., Porter, I., Gangannagaripalli, J., Bramwell, C., Davey, A., Fine, N., Goodwin, V., Valderas, J. **Clinical Rating Systems in Interventional Elbow Research: Exploring trends and distributions of use**

- Podium Presentation – British Elbow and Shoulder Society (BESS) annual Conference, Coventry, 23rd June 2017
- Poster presentation – British Orthopaedic Association (BOA) annual Congress 19th, Liverpool, September 2017

Evans, JP., Smith, CD., Porter, I., Gangannagaripalli, J., Bramwell, C., Davey, A., Fine, N., Goodwin, V., Valderas, J. **Assessing Condition-Specific Patient-Reported Outcomes in Lateral Elbow Tendinopathy: A systematic and standardised comparison of available instruments**

- Podium Presentation – International Society for Quality Of Life Research (ISOQOL) annual conference, Philidelphia, 20th October 2017.
- Poster presentation – Advances in Patient Reported Outcomes Research annual conference, Oxford, 7th June 2017.
- Poster presentation – British Elbow and Shoulder (BESS) Society annual conference, Coventry, 23rd June 2017.
- Poster presentation - Société Européenne pour la Chirurgie de l'Epaule et du Coude (SECEC) annual conference, Berlin, 13th September 2017.

Evans, JP., Metz, J., Thomas, W., King, A., Anaspure, R., Smith, CD. **Cadaveric Evaluation of the Spread of Injectate After Ultrasound-Guided Lateral Elbow Injection**

- Podium presentation – British Elbow and Shoulder Society (BESS) annual conference, 23rd June 2017

Evans, JP., Smith, CD., Thomas, WJ., Guyver, P., Ramesh, R., Porter, I., Gangannagaripalli, J., Goodwin, V., Valderas, J. **A comparative assessment of patient reported outcome measures for lateral elbow tendinopathy in a UK population**

- Podium presentation - British Elbow and Shoulder Society (BESS) annual conference, 22nd June 2018

Evans, JP., Smith, CD., Maffulli, N., Watts, A., Valderas, J., Goodwin, V. **Platelet-rich-plasma injection in lateral elbow tendinopathy: exploring international expert consensus with the Delphi method**

- Podium presentation - British Elbow and Shoulder Society (BESS) annual conference, 22nd June 2018

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Most importantly, none of this would be possible without the support of my wife Tanya, who met all of my doubts and anxieties with boundless encouragement and a wry smile.

Authors' declaration

I, Jonathan Peter Evans, declare that this thesis was composed by myself, that the work contained herein is my own except where explicitly stated otherwise in the text, and that this work has not been submitted for any other degree or processional qualification.

1 Introduction

1.1 Overview

“There is probably nothing which brings the surgical profession into greater discredit at the present time than the inability to cure “tennis elbow”. The condition is extremely common, and so helpless have we been in treatment that most sufferers now never consider consulting a medical man at all”.

(G.Percival Mills, 1928)

“Tennis elbow does not threaten quantity of life, but is a major impediment to quality of life.”

(R. Nirschl 2015)

Lateral Elbow Tendinopathy (LET) is a condition characterised by pain on the outside of the elbow. The pain is associated with gripping and manipulation of the hand. The level of discomfort can range from mild and self-limiting, to severe and debilitating. In some cases, the pain, and consequent functional impairment cause the patient significant daily intrusion and disruption to general health and wellbeing.

In this thesis, the approach to investigating treatments for LET will be explored. This will proceed with a review of the aetiology, burden and impact of the disease, and will be followed by an appraisal of the current levels of evidence supporting the most popular interventions. These elements will then be aligned with an evaluation of the methods currently applied to assess the therapeutic effect of interventional treatment. A summary of knowledge gaps, justification and scope of the thesis will precede the presentation of seven studies which aim to identify, inform and assist in the optimisation of future research into LET. An overarching

synthesis of this evidence, the potential impact of its findings and the author's perspective on the future of LET research will then conclude this thesis.

1.2 History

The first description of Lateral Elbow Tendinopathy (LET) is regularly attributed to the German physician Dr F. Runge [1], who in 1873 published his paper entitled "On the causes and management of writer's cramp". The little known Dr Runge is also believed to have been a pioneer of sclerosing therapy, whereby he cauterised the skin at the outer aspect of the elbow, under the belief that the resultant scarring provided sustained pain relief and return to function, with good results reported at a year following the procedure [2]. The condition's most colloquial term of reference is "Tennis Elbow", a derivation from the description reported by esteemed surgeon Sir Henry Morris who introduced the term "Lawn tennis arm". Sir Henry surmised that the use of a frequent backstroke with forceful pronation led to a sprain of the pronator teres muscle. This original description, therefore, contains some confusion, being that Sir Henry may have been describing what we now term "Golfer's elbow", a condition that presents with pain on the inside of the elbow.

Following Sir Henry's publication, a multitude of correspondence from interested parties ensued in the British Medical Journal. In a review of the early history of Tennis Elbow, Thurston [3] describes the impassioned communication whereby Dr H.P. Major, speaking of his own affliction, felt the condition emanated from the annular ligament, Dr Winkworth felt an entrapment of the posterior interosseous nerve was far more likely, and Dr O'Sullivan who felt the radial nerve was implicated and a treatment of "continuous current of electricity" would be beneficial. Therein we see the beginning of aetiological and therapeutic arguments

that continue to this day. At the turn of the century the volume of literature was disproportionately high, particularly for a condition many believed too trivial to merit discussion, and though the condition was recognised in numerous recreations and occupations, for some reason, the term “Tennis Elbow” persisted. This was much to the disdain of the German literature who tended to call it “Sogenannten Tennisellenbogen” (“so-called tennis elbow”) [3].

Lack of consensus surrounding an exact term of reference for LET continued through the 19th century. In fact, the persistence of the colloquialism “Tennis Elbow” may be related to the medical community’s reticence to commit to common terminology. Cyriax (1936) [4] in his correspondence to the British Medical Journal, cautions on a change of name to that proposed by Mr McKee, “traumatic periostitis at the origin of the extensor carpi radialis brevis” as it is “premature to label tennis elbow with a name that precludes a difference of opinion on pathology”. In his communication he collates the succession of terms applied in the literature including Remak (1894) and Bernhardt (1896) who apply the term “periosteal tear of the extensor muscles”, Couderc (1896) “ruptured epicondylar tendon”, Fere (1897) epicondylalgia and Franke (1910) epicondylitis. Though Cyriax concedes that “tennis elbow” will have to remain, this “does not imply the acceptance of any particular theory or pathology”.

Though 80 years have passed from Cyriax’s perceptive commentary, numerous authors have continued in earnest to define the terms of reference. Most recently, veracious commentary provided by two authors within a year of one another proposed very different terms, Waugh (2005) [5] championed the term “epicondylalgia” and Stasinopoulos (2006) [6] “lateral elbow tendinopathy”. Interestingly both cite the lack of consensus on pathophysiology as reasons behind the adoption of their respective generic term. It is without surprise that

varied terminology continues, which beyond those already mentioned includes “lateral humeral epicondylitis” [7], “peritendinitis of the elbow” [8] and “enthesopathy of the extensor carpi radialis brevis” [9].

It, therefore, becomes a challenge for an author to choose a term that is acceptable to a collective readership. Though nearly all studies qualify their chosen term with the statement “also known as tennis elbow”, it seems rather improper to include a term for which many authors postscript their term with versions of the statement “a condition that is far from exclusively experienced by tennis players”. Indeed this colloquialism upsets many sufferers, and in many respects is felt to trivialise a painful and functionally limiting condition. Therefore, the term “lateral elbow tendinopathy” seems appropriate at this juncture, where simple reference to the anatomical site, the tissue of reference and the suffix derived from the Greek “pathos” denoting “suffering”, without allusion to the pathology of a condition that is still a source of debate.

1.3 Epidemiology

Historically, estimations on the prevalence of LET were nominally reported as between 1-3%; these figures were based on the assessment of small cohorts of patients [10, 11] and are felt to be ungeneralisable [12]. Of the larger epidemiological studies, Walker-Bone et al [13] estimated the point prevalence to be 0.8% in males and 0.7% in females in a cross-sectional assessment of 6038 participants from two UK general practices. Shiri et al [14] performed a cluster analysis of Finnish population-based survey respondents, of 4,783 individuals who were interviewed. They reported a prevalence of LET of 1.3% (95% CI 1.0-1.7). Roquelaure et al [15] in an analysis of 3,710 French workers participating in a surveillance programme of musculoskeletal disorders, where the disorders were diagnosed by occupational

physicians, reported a prevalence of LET of 2.7% (95% CI 1.8-3.1) in men and 2.7% (95% CI 1.9-3.5) in women. Salaffi et al [16] as part of a large study assessing the prevalence of musculoskeletal conditions in an Italian population of 3,664 individuals estimated the prevalence of LET at 0.74% (95% CI 0.47-1.33).

The incidence of LET has been reported in three large epidemiological studies, Titchener et al [12], deriving data from the UK health improvement network database (THIN) whose records are estimated to cover the primary care health records of 5.7% of the UK population, assessed general practitioner-reported cases of LET over the period 1987-2006. They reported an overall incidence of 2.45 (95% CI 2.43-2.46) per 1000 person-years, significantly higher in males at 2.63 (95% CI 2.60-2.65) than females 2.55 (95% CI 2.53-2.58) (P<0.001). Sanders et al [17], reported on the population-based incidence of LET in a sample of 144,260 residents of Olmsted County, Minnesota. They reported an overall incidence of 3.4 (95% CI 3.3-3.5) per 1000 person-years, lower in males at 3.3 (95% CI 3.2-3.5) than females 3.5 (95% CI 3.4-3.7). Bot et al [18] in their analysis of the second Dutch national survey of general practice assessed over 1.5 million primary care contacts over a 12 month period. They reported an incidence of 5.1 (95%CI 4.8-5.3) per 1000 person-years with no difference between male and females.

Studies conducted in specific populations demonstrate wide variations in the epidemiology of LET, dependent predominantly on occupational exposure. Hopkins et al [19] in their systematic review reported an average prevalence of 8.9% in those with occupational exposure, with a notably high prevalence reported in spinal surgeons [20] (18%) and coal miners [21] (41%). Limited data are available on those in sedentary work, but the findings of Kryger et al [22] are notable for

reporting a prevalence of 5.8% in a population of 1369 computer-based workers presenting with neck and/or arm pain.

A common aspect reported in almost all of the epidemiological studies on LET is the age-dependent spread of LET. The condition has been reported as uncommon in those under 18 years, with a rise in incidence which peaks between 40-55 years to as high as 10.2 per 1000 person-years [17], followed by a decrease towards the eighth decade when it becomes very rare [12, 14, 17, 23]. Of note, this age-related distribution of LET parallels that of cumulative incidence of neck and upper extremity musculoskeletal disorders [18]. Both the patient age of highest prevalence of LET being at a time of occupational activity, and many analogous descriptors from occupation-specific prevalence studies, correspond to occupational exposure as a potential risk-factor for LET. Walker-bone et al [23] report LET to be associated with manual work (Odds ratio (OR) = 4.0, 95% CI 1.9-8.4) and both Walker-Bone et al [23] and Shiri et al [14] report an association between repetitive and forceful movements of the arm resulting in repeated bending/straightening at the elbow and wrist to be an independent risk factor (OR = 2.5, 95% CI 1.2-5.5 and OR 5.6, 95% CI 1.9-16.5 respectively). One may surmise that these findings correspond with an association with hand dominance. Although studies do report a higher prevalence of LET symptoms in the right side, 63% right vs 25% left reported by Sanders et al [17], few have studied or recorded hand dominance. Shiri et al [24] in their Finnish population study of 6,254 adults do however report that LET was significantly more prevalent in the dominant elbow (p=0.03 in men and p=0.05 in women). Interestingly, LET was more common in left dominant individuals (2.5% prevalence) than right dominant individuals (0.7%); however, this only reached statistical significance in men (p=0.001). This tallies with studies such as Sanders et al [17] who report a higher than the expected proportion of left-handed patients

when the population distribution is approximately 10% [25]. These hand dominance findings are, however, not repeated in the study by Walker-Bone [23] of 6,038 participants.

Epidemiological analysis of LET has identified that it represents a disease of middle age. Though the population prevalence is often quoted as between 1-3%, larger epidemiological studies would suggest this may be an overestimation. What is more relevant, however, is the risk of development of the disease in the fourth decade of life and in the context of occupational exposure.

1.4 Anatomy

The site of the lesion in LET is most commonly ascribed to the proximal extensor radialis brevis (ECRB) tendon (Figure 1.1) [26-29]. The ECRB is a component of a conjoint tendon, which also includes the tendons of the extensor digitorum communis (EDC) and extensor carpi ulnaris (ECU) that have their origin at the anterior aspect of the lateral epicondyle and lateral supracondylar ridge [30]. This is also the site of attachment for the extensor digiti minimi (EDM) and supinator which merge with the ECRB, EDC and ECU to form the common extensor tendon (CET). The ECRB is a wrist extensor that inserts at the base of the 3rd metacarpal, it is innervated by the deep branch of the radial nerve and has an arterial supply from branches of the radial artery. Its mode of action on muscle contraction is to extend and abduct the hand at the wrist joint [31]. In the action of grasping and pinching at the hand, a flexion moment is caused at the wrist joint, to counteract this moment an equilibrium of moments is initiated by the

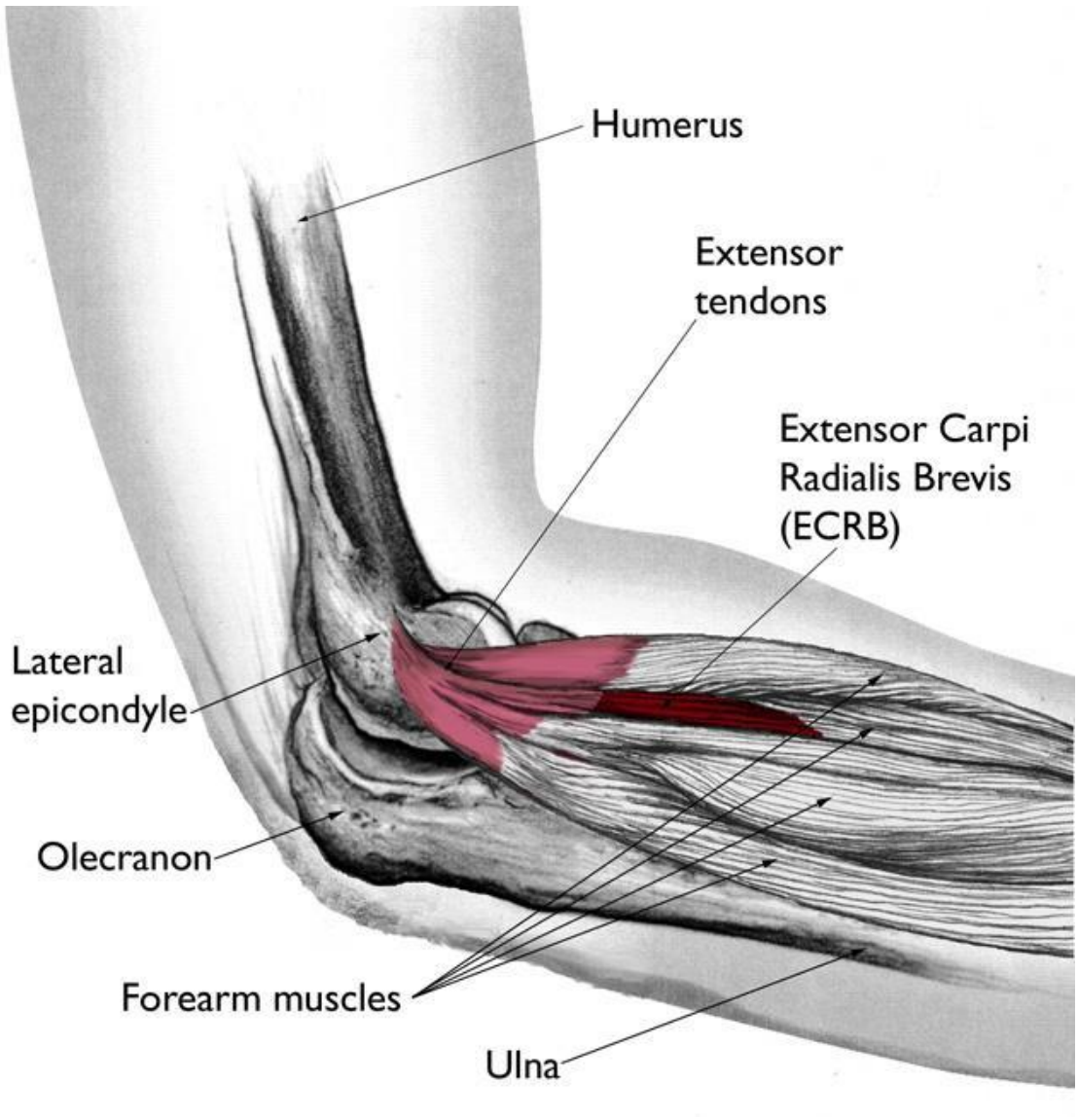


Figure 1.1: Anatomical drawing of the lateral aspect of the elbow. Position of ECRB highlighted in red. Reproduced and modified from The Body Almanac. © American Academy of Orthopaedic Surgeons, 2003.

contraction of the extensor musculature [32]. The bony origin of the ECRB can be reliably identified beneath the distal-most aspect of the supracondylar ridge, with a mean dimension of 13 ± 2mm in length by 7 ± 2mm in width [33]. This origin is particularly small in comparison to the surrounding tendons of the CET [34]. This origin is also purely tendinous, in contrast to the EDC, EDM and ECU which originate as a mixture of tendon and muscle, it has been postulated this may correspond to a reduction in vascularity in comparison to the surrounding extensor

origins [35]. The undersurface of the ECRB has a close relationship with the joint capsule that varies across the origin, on the anterior side it appears delicate and thin, posteriorlodistally there is a stronger, thicker origin attachment as the ECRB merges with the supinator [35]. This anterior edge has been proposed as a factor causing the initiation of the pathology of LET [35], this is particularly pertinent when combined with dynamic assessments of the tendon position, whereas when the elbow is extended the undersurface of the ECRB has been shown to rub against the lateral edge of the capitellum, whilst overlying ECRL compresses brevis against underlying bone [36].

It is worth noting that although there is an anatomical basis for ECRB being the predominant site of LET, some authors have questioned whether one can ascribe this so specifically. Greenbaum et al [37] report that the relative difficulty in isolating the origin of the ECRB from the surrounding tendons of the CET and state that the pathology would appear to be coming from the whole common extensor. In a pathological study of the common extensor tendons, it has also been noted that one-third of patients have involvement of the EDC [38, 39].

1.5 Pathology, aetiology and pathogenesis

Lateral elbow tendinopathy is considered to be an overload injury [40], where minimal cumulative trauma to the elbow extensor muscles initiates a cascade of pathological changes to the tendon, where the resultant effect is the symptomatology already discussed. Though this aetiological mechanism is relatively well accepted, consensus on the associated pathological alterations to the tendon itself has not been reached. This is in keeping with the overarching theories on the pathophysiology of tendinopathy that have been described by Millar et al [41] as varied, probably not mutually exclusive and largely unproven.

In keeping with the nomenclature of LET, prior to the 1990s the pain associated with LET was referred to as a ‘tendinitis’ and the associated pathology was thought to be inflammatory in origin, consequently treatments were directed at resolving this, relying predominantly on non-steroidal anti-inflammatory medications [42]. Though the view of an inflammatory component was deeply ingrained in the medical literature [43], the work of Nirschl [44] and Regan [38] began to cast doubt on this assertion. Microscopic and histological analysis of pathological tendons identified four key changes, collectively termed “angiofibroblastic hyperplasia”: 1) increased cell numbers and ground substance, 2) vascular hyperplasia or neovascularisation, 3) increased concentration of neurochemicals and 4) disorganised and mature collagen [38, 44]. However, it was the consistent absence of inflammatory cells which led to the development of the term “degenerative” tendinopathy [38, 44]. This finding, analogous with tendinopathies at other sites led to a move away from the term “tendinitis”, this was summed up in an editorial in the British Medical Journal by Khan et al [43] urging their readership to “accept the irrefutable evidence that the term tendinitis must be abandoned”.

The non-inflammatory or degenerative theories of tendinopathy were the principal thinking of the first decade of the 21st century, leading Rees et al [42] to term this period “Degeneration without inflammation: the paradigm of the 2000s”. This led to the development of models of thinking as to why tendons fail and why they are unable to repair themselves. Furthermore, models that integrate the interrelated components of: 1) local tendon pathology, 2) changes in pain systems and 3) motor system impairments, have been particularly popular in the pursuit of targeted or individualised treatments in LET [45]. Pathophysiologically guided treatment algorithms have maintained momentum, even in the scenario of

underdeveloped understanding of true tissue changes, Bhabra et al [46] have proposed a four-stage treatment algorithm based on four histologically defined grades of tendon tendinopathy: 1) collagen fibre pattern becomes increasingly wavy. Although cellular and vascular changes are minimal, there is an increase in the proportion of type 3 collagen, 2) tendinosis and angiofibroblastic hyperplasia as described by Nirschl [44], 3) programmed cell death leading to the depletion of functional tendon cells and breakdown of collagen and extracellular matrix and 4) gross structural and mechanical failure. They propose a spectrum of therapeutic interventions targeted at each stage of the disease, from conservative measures to surgery for stage 4 disease. However, this is clearly limited by the need to gain a tissue biopsy for grading and the current lack of evidence base for many treatments in LET. Miller et al [41] also note that the absence of pain and functional limitation make the diagnosis of early tendinopathy difficult, consequently one of the major limitations of human studies on tendinopathy is that tendon biopsy samples are usually only obtained when patients are sufficiently symptomatic. Therefore the tissue is likely to represent chronic rather than early stage disease.

The various models proposed to explain the pathological process of tendinopathy have suggested a primarily degenerative process, with some clearly stating that the process of tendon overuse is non-inflammatory in nature [42]. However, the limitations of this view have begun to be highlighted with a particular focus on the role of, thus far, underappreciated inflammation and neuronal regulation. Though not yet specific to the pathology of LET, systematic analysis of studies assessing inflammation using modern techniques have identified a plethora of inflammatory mediators [47, 48]. Indeed, a proportion of the more historic studies refuting the role of inflammation had only attempted to identify neutrophils [48]. Modern research tools have confirmed the presence of inflammatory cells including macrophages

and lymphocytes in chronic tendinopathy [41, 42]. Also, inflammatory mediators including numerous inflammatory cytokines, substance P, MMPs, VEGF and COX have all been identified and associated with a role in chronic inflammation [41]. The neuronal component has become a source of interest for two key reasons, firstly that there is often a mismatch between the tendons' histological appearance and the patients' level of pain, and secondly that there is growing recognition that there is an increased expression of glutaminergic pathways at tendinopathic sites. Patients with histologically matched tendinopathy but differences in pain symptomatology have been found to differ in their levels of glutamate receptor expression [49] in the rotator cuff. Though these findings are yet to be translated to LET, there remains a level of equipoise over the pathology of tendinopathy that is likely to hamper or confuse directed treatments until these issues are resolved. Even at its simplest terms, as recognised by Rees et al [42], even if inflammation is not seen at a particular point in time, this does not in itself imply that inflammation has not played a role in the initiation of tendinopathic change.

With a condition whose basic pathoaetiology remains a source of significant scientific exploration, and an expert consensus that has shifted almost 180 degrees on at least two occasions, it is unsurprising that the choice of pathologically linked treatments has taken a parallel course. It is vital however, that the treating clinician also heeds the fact that the patient presenting with LET may have pathological changes that reside on a spectrum. Whereby the above discussed tissue alterations may not be exclusively right or wrong, but rather occur a different stages of the disease. Analogous to many musculoskeletal disease, this continuum of pathology is likely influence the efficacy of interventions directed toward the treatment of a particular pathological element. This aspect of the disease is particularly relevant in the conduct of trials of interventions, whereby the

selection of participants with the same overarching diagnosis may be in different stages of the disease and thereby respond in differing ways, introducing and unappreciated bias. As yet no pathology specific trial guided treatments has been conducted in LET, which in many ways mirror the overarching infancy of tendinopathic pathology.

This is of no conciliation to the vast number of people suffering from LET and their clinicians who strive to provide evidence-based treatment. Fundamentally, a better understanding of the pathogenesis of the condition is necessary to develop long-term treatment strategies but this, in turn, must then be allied to valid clinical outcome recording methods, a thorough understanding of treatment delivery methods and the exploration and development of consensus amongst clinicians.

1.6 Clinical features

As with many other tendinopathies, LET characteristically presents with gradual activity-related pain, decreased function and sometimes localised swelling [41]. It has been commented that the combination of pain on the outer aspect of the elbow that is exacerbated by lifting objects is almost invariably related to LET [9] and that the clinical presentation is reasonably straightforward [50], yet the same authors also caution that there is distinct heterogeneity in the intensity and frequency of these symptoms, both between individuals and over the time course of the disorder [9, 50].

The pain is most commonly localised to the lateral epicondyle but has also been reported to spread up and down the upper limb [51]. Nirschl and Sobel [52] have described a “phases of pain” classification for LET; this seven phase system describes the levels of patient affliction from mild pain to an unremitting discomfort affecting times of activity and rest:

- Phase 0: No pain or soreness
- Phase 1: Stiffness or mild soreness after exercise activity. Pain is usually gone in 24 hours.
- Phase 2: Mild stiffness and soreness before activity which disappears with warm up. No pain during activity, but mild soreness after activity that disappears within 24 hours.
- Phase 3: Same as above with mild pain during activity which does not alter activity, disappearing in 24-48 hours.
- Phase 4: Mild to moderate pain before, during, and after exercise which alters the exercise or activity. ADLs are affected. Phase 4 is indicative of some level of tendon damage.
- Phase 5: Moderate or greater pain before, during, and after exercise or activity, forcing the patient to discontinue the exercise. Pain is experienced with ADLs. Usually reflects permanent tendon damage
- Phase 6: Phase 5 pain that persists with complete rest. Pain disrupts ADLs, many activities have to be eliminated.
- Phase 7: Phase 6 pain with disruption of sleep on a consistent basis. Pain is aching in nature and intensifies with activity.

It is highly relevant to note that in the context of a chronic pain state, patients with LET experience changes in both the peripheral and central nervous system, Coombes et al [50] has termed this complex issue as “pain system changes”. Patients with LET have demonstrated states of hyperalgesia with reductions in pain pressure thresholds by 45-54% compared to the contralateral side [53-56] and control participants [57]. Selective improvement in cold hyperalgesia in chronic LET patients who had undergone guanethidine regional block (a principle often employed in those afflicted with chronic regional pain syndrome), point to a

potential sympathetic driver to the chronic pain. It is clear that the complex pain picture associated with LET should not be underestimated; once this hyperalgesic state ensues, correlations to catastrophic thinking, kinesiophobia or low self-esteem have been reported within the secondary analysis of a randomised trial of steroid vs placebo injection [58].

Although there is interplay between pain and function, specific motor impairments have been noted in LET. Pain-free grip force is reduced by an average of 43-64% when compared to the contralateral side in LET patients [54, 55, 59-61]. Though the cut-off in this regard relates to the onset of pain, rather than a true limitation in functional strength, the onset of pain can be seen as limiting functional ability, particularly in the context of occupational demand. Testing of maximal strength has revealed varied results, be it unilateral weakness [57], bilateral weakness [62] or no deficit [59], the confounder of pain clearly makes collection of these data challenging, particularly in reference to the interplay with hyperalesic symptomatology.

Reduced activity of the ECRB has been demonstrated in LET patients during isometric extension exercise [63] and gripping tasks [64] which may imply an endurance deficit [50]. Optimal wrist position for maximal grip strength is in slight extension [65, 66] and LET patients have been shown to demonstrate a more flexed position (11° less extension) [59], in accordance with the length-tension relationship model [67]; this may also account for a component of grip strength deficit noted by LET patients [50]. Furthermore, LET patients also demonstrate reduced forearm reaction time and speed of movement with reaching tasks [59, 68]. A synthesis of this information, in light of the occupation associations highlighted above, underlines the potential impact of this condition on the ability to work if manual tasks are required, or if the wrist position is in an extended position such as it is

when typing at a keyboard. This has been explored by Haahr and Andersen [69]; in 267 new cases of LET in Denmark against a population reference, they reported increased odds of LET in non-neutral posture of the hands (OR 7.4 95% CI 2.9 – 18.7), or high physical strain index established on posture, repetition and force (OR 4.4 95% CI 1.6 – 4.6).

1.7 Diagnosis

Diagnosis of LET is typically made on clinical grounds [70], where a suggestive history of pain around the lateral humeral condyle is supplemented with confirmatory examination findings. As an adjunct to the supposed 'classical history' and diagnosis, which is reliant on the clinical acumen of the attending clinician, attempts have been made to supplement the identification of LET with specific diagnostic criteria, clinical tests and imaging studies.

The first set of diagnostic criteria for LET emerged as a set of consensus definitions for the surveillance of work-related upper limb pathologies using an iterative Delphi methodology [71]. The resultant criteria for LET were;

- Lateral epicondylar pain
  AND
- Lateral epicondylar tenderness on palpation
  AND
- Pain on resisted extension of the wrist with the elbow extended.

It was subsequently reported that the relaxing of these criteria to include one of the two clinical examination signs led to a sensitivity of 73% and a specificity of 97%. The one further attempt to produce diagnostic criteria was produced by Sluiter et al [72], again for occupational health research, who derived a set of symptom and sign criteria through literature review.

Symptom criteria:

1. At least intermittent, activity-dependent pain directly located around the lateral epicondyle
   AND
2. Symptoms present now or on at least 4 days during the last 7 days
   OR
3. Symptoms present on at least 4 days during at least 1 week in the last 12 months

Symptom and sign criteria:

4. Symptoms present now or on at least 4 days during the last 7 days
   AND
5. At least intermittent, activity-dependent pain directly located around the lateral epicondyle
   AND
6. Local pain on resisted wrist extension

The authors also suggest the application of the International Statistical Classification of Diseases and Related Health Problems (10th Revision) (ICD-10) code M77.0.

A plethora of examination 'special tests' have been proposed to assist in the diagnosis of LET. These include active examination where pain is provoked at the lateral epicondyle by Cozen's test [73], where wrist extension is resisted, the holding a book test [74], the 'chair test' [75] elicits pain when the patient lifts a chair with a pronated hand, the Maudsley's test where dorsal extension of the middle finger is tested against resistance and the Mill's test which is performed by passively bringing the elbow from a flexed to extended position whilst the wrist is fully pronated and flexed [76]. None of these tests has had their diagnostic accuracy assessed [76]. Only the grip strength reduction test has been formally assessed [77], where a 5% deficit in power has an 83% Sensitivity and 80% Specificity, 8% deficit

has an 80% Sensitivity and 85% Specificity, and 10% deficit has a 78% Sensitivity and 90% Specificity.

Imaging modalities have been employed in the investigation of LET. Plain radiographs are not felt to be additive in the assessment of LET, other than when an alternative diagnosis is a possibility or the patient also presents with symptoms of crepitus, restricted motion or loose body symptoms that may be suggestive of arthritis [9]. There has been far more interest in the role of ultrasound and magnetic resonance imagery (MRI). Ultrasound scanning of symptomatic patients has reported common findings of hypoechogenecity, calcifications and tendon tears [78-81], similarly MRI has demonstrated deficits in the enthesis and high signal in the tendon substance [82, 83]. However, it is unclear how these findings relate to the prognosis [9] and high levels of abnormalities have also been identified in asymptomatic individuals [84, 85]. A single study has positively correlated the pathological grade of LET to a validated outcome measure, Qi et al [86] reported a positive correlation ($r= 0.920$ $p<0.01$) between their modified three-stage grading system based on tendon signal change and the Patient-Rated Tennis Elbow Evaluation (PRTEE) in 96 LET patients. There has been greater interest in the assessment of neovascularity in the common extensor tendons, the absence of which is highly predictive of LET not being the diagnosis [80], however, no correlation with symptoms has been identified.

The prevalence of LET is such that in patients between 35-65 years with suggestive symptoms, LET is almost certainly the diagnosis [9], however two possble differential diagnoses are worth mentioning; arthritis in those with restrictions of range of motion, and radial tunnel syndrome, a compressive neuropathy of the Posterior Interosseous Nerve (PIN) at the radial tunnel in those

not responding to LET treatments. The latter being very difficult to prove owing to the fact that MRI and electrodiagnostic studies are often inconclusive [87].

1.8 Patient-level and societal impact of lateral elbow tendinopathy

Lateral Elbow Tendinopathy is often referred to as a self-limiting condition [26]. One supposes that this terminology implies that, without specific treatment, LET resolves. However, it is vital that the patient and societal impact of this "self–limiting" condition are quantified and appreciated, therein to what duration do we denote boundaries of self-limitation, and to what level of personal symptoms or societal burden is deemed acceptable to offer "watchful waiting" as a treatment choice. Information on the natural history of LET is extremely limited, however, the best available evidence would suggest that of the population of LET sufferers who have had symptoms for at least four weeks, between 80 - 90% report improvement at 1 year [88-90], of note the authors classify resolution as a self-report of "completely resolved" and "much improved", beyond this time point the data are even more uncertain, Hudak et al [91] report evidence from a systematic review of moderate quality studies reporting symptoms beyond two years but the proportional representation within this cohort is not provided. Bot et al [18] in their analysis of elbow complaints, of which LET was the most common, in contrast, report very low rates of improvement within the first 12 months, with only 34% of patients reporting a full recovery. Recurrence rates within two years of initial onset have been reported as 8.5%, a figure that remained constant between 2000 and 2012 [17]. It has been estimated that between 5-10% of patients with symptoms longer than six months will eventually undergo surgical intervention [92].

Though it has been estimated that 25% of LET sufferers report difficulty dressing, carrying objects [62], driving and sleeping and that up to 5% of LET patients have

claimed sickness absence with a median duration of 29 days per year [23]. No estimation of personal burden, be it economic costs associated with work absence or treatments has been made. Furthermore, though it is recognised that LET sufferers experience significant levels of depression and anxiety [62], societal costs associated with caregiving, societal integration or individual well-being have also not been quantified.

Though it may be surprising that for a condition so prevalent in the general population, information on the individual natural history and burden of the condition, on which a clinician can base their advice to patients, remains limited. It may be more surprising that information on the global socio-economic impact of LET, a disease of the working age, is even more restricted. Hopkins et al [19] in a global assessment of the burden of tendinopathy, performed the only estimate of socio-economic burden utilising figures on work absenteeism derived from the work of Walker-Bone et al [23] and applying 2012 population statistics and a United Kingdom derived median wage, that LET in the UK alone is estimated to cost £27 million. Due to a paucity of data this evaluation was limited to the UK only.

The relative paucity of data may be one of the reasons that upper limb tendinopathy draws a relatively low profile compared to its relative high prevalence. The available data are in stark contrast to other musculoskeletal ailments of the working age population, with the prime example being back pain [93-96]. As a foundational aspect it has been proposed that the difficulty gaining this information may be related to the coding structures and documentation of this condition. Though it has been mentioned that the nomenclature has changed on numerous occasions, it is notable that the International Classification of Diseases (ICD-10) [97] continues to apply the term ‘lateral epicondylitis’, and does not recognise the terms ‘tendinopathy’ or ‘tendinopathy at the elbow’. Furthermore, the

International Classification of Functioning, Disability and Health (ICF) [98] that aims to classify health and health-related domains does not recognise tendon as a body structure, unlike muscle and ligament which are registered. Without this recognition within such well-utilised coding structures, adequate epidemiological study will remain limited.

1.9 Treatments

There are no UK guidelines for the optimal management of LET [99] and though there is a wealth of interventional study data, there is also a perceived lack of expert consensus [9]. Treatment options discussed and recommended to a patient population who often desperately seek a cure, tend to be based on clinician level experience and expertise, availability and acceptability. Broadly, the armamentarium of treatments available fall into the categories of non-interventional (conservative) and interventional (injections or surgery). It is also important to recognise that there are numerous “over the counter” or alternative remedies that fall outside of the empirically represented treatments. The utilisation and effectiveness of these treatments are unknown, however as a proxy, the ubiquitousness of products in chemists and websites purporting a new miracle cure should be considered.

The place that most patients will start their treatment is the self-administration of analgesia. Bisset et al [45] are the only authors to synthesise the available evidence on oral and topical analgesia. They report very low-quality evidence from two RCTs that oral NSAIDs may be more effective at improving pain than placebo in the short term but no assessment of global or functional improvement can be made. For topical NSAIDs, they report moderate quality evidence from three RCTs that they seem more effective at improving pain than a placebo. However, they

may be no more effective than placebo at improving function. The effect of other simple analgesics or compound analgesia has not been assessed in a systematic review.

Beyond simple analgesia, many patients use counter-force braces. These braces, when correctly applied have been found to alter forearm muscle activity and angular joint acceleration in tennis players [100]. However, there have never been studies against a sham orthosis or no treatment. Low-quality evidence from four RCTs found counter-force bracing to be less effective at reducing pain than physiotherapy alone and corticosteroid injection [45].

The most extensive review of conservative therapies was conducted by Long et al [101]. Their overview of 29 systematic reviews and 36 randomised controlled trials reported the clinical and cost-effectiveness of therapies in LET. Of the therapies assessed, it was concluded that there was insufficient evidence to demonstrate either benefit or lack of effect of extracorporeal shockwave therapy (ESWT), laser therapy and exercise therapy. They report moderate quality and consistency of results for pain relief using therapeutic ultrasound in the short and medium term. Their cost-effectiveness assessment was based on the assessment of only two studies and reported that physiotherapy might be more cost-effective than glucocorticoid injection in the longer term, however, estimates of effectiveness relied on the accompanying trials which were deemed to be too small to overcome uncertainty about the size of the effect. This evidence has been more recently expanded following the work of Coombes et al [99] who in an assessment of randomised control data on 165 LET patients report a superiority and improved cost-effectiveness of physiotherapy over glucocorticoid injection, where the probability of being more cost-effective than placebo at values above the quality-adjusted life year (QALY) threshold of £28,000 was 81% for physiotherapy and

53% for corticosteroid injection. Phsyiotherapy as an intervention does, of course, include a great variety of modalities and therapies. Most commonly patients will undertake a structured exercise programme to primarily address motor impairments. Coombes et al [102], in the above study utilise three main exercise groups: 1) sensoy retaining of grip and and forearm movements, 2) progressive resistance exercise utilising both concentric and eccentric execises and 3) exercises directed at general arm strengthening. This intensive protocol was delivereed during eight 30minute specialist physiotherapy sessions delivered over eight weeks. Although commonalities exist within exercises for LET, the level of supervision varies within each healthcare structure and hence generalisability of the findings of such protocols should be contrasted with the intended delivery system.

The review conducted by Long et al [101] concludes that for all of the non-interventional studies, the analysis is significantly limited by the lack of well-conducted randomised controlled trials, of adequate follow-up and inclusion of validated outcome measurement. Their report is particularly concerning regarding our most commonly deployed intervention of physiotherapy and exercise, where synthesis of results has been particularly hampered by poor quality methodology, use of unvalidated outcome measures and short follow-up periods. Of particular interest throughout this review are the 28 randomised controlled trials that are excluded for outcome measure or study design reasons, rendering their potential contribution to the evidence base minimal at best.

The use of injection therapy in LET has become a common second-line treatment following the failure of conservative treatments [103]. Corticosteroid injections have been a mainstay of treatment over the last 60 years [104] but numerous other injectates have been applied, these include blood product injections such as

Platelet Rich Plasma (PRP), sodium hyaluronate, sclerosant solutions, glycosaminoglycan polysulphate and botulinum toxin. Of the less common injection therapies, Long et al [101] report low-level evidence for short, medium and long-term pain relief from sodium hyaluronate injection, a finding supported by two further, more recent, network meta-analyses [105, 106]. There is moderate level evidence showing no benefit from sclerosant therapy or glycosaminoglycan. Botulinum toxin has demonstrated large benefits in short-term pain relief. However, this should be assessed in the context of a high complication rate of temporary paresis of finger extension [105]. The use of prolotherapy, an injection of dextrose +/- a local anaesthetic is supported by low-level evidence of a large reduction in pain, but this assessment is hampered by a limited number of studies [101, 106].

One of the most interesting conclusions of the recent reviews on LET treatment is their consensus on the use of corticosteroid injections. These injections, administered commonly in primary care [107], secondary care and physiotherapy clinics [103, 108] have been shown to have a short-term pain relieving effect, with no benefit for the intermediate and long-term [45, 101]. Though repeat systematic review may be required [101], recent RCT evidence also suggests that long-term outcomes may be worse with corticosteroid injection [109] and that the use of a corticosteroid is associated with inferior outcomes from surgery in refractory cases [110]. Kachooei et al [111] identify that of the 13 RCTs conducted since 1954, that have compared corticosteroids with placebo, it was deemed to have favourable outcomes in three of the five early studies, but in these studies they did not blind their patients or clinicians; among the eight double-blind studies, two found an early benefit (one with a later detriment) and six found no benefit.

The use of Platelet-Rich Plasma (PRP) injection as a treatment for LET has received particular focus in systematic reviews of injection therapies. PRP is a term used to describe a concentrate of platelets prepared using autologous blood [112]. The principle of its application is the potential to enhance tendon healing and tissue regeneration by delivering various growth factors and cytokines, thereby affecting cell proliferation, chemotaxis, cell differentiation and angiogenesis [113]. The theory is that by injecting PRP intratendinously, repair mechanisms will be upregulated and tissue healing will be promoted.

As an autologous formulation, PRP production, dosing and safety has not been scrutinised as a medication. In the UK the medical device must hold a CE mark, whereby it meets the European Union's safety, health and environmental requirements, but the blood product itself is not assessed, and no statement or application of clinical evidence is required. The modest regulatory barriers and the patients' desire for new treatments have, unsurprisingly, been accompanied by a rise in the use of this treatment [114]. The PRP international market has been valued at $160 million in 2015, and over 40 different PRP systems are available on the market [115]. However, the evidence for its use is not commensurate with this rapid adoption. The discussed review by Long et al [101] does not comment specifically on the clinical effectiveness of PRP and evidence for its cost-effectiveness is derived from a single abstract and therefore not recommended for interpretation, however they do call for further systematic review as no high-quality and limited RCT evidence was available. Pooled analysis of PRP use in tendinopathy of all pathologies (e.g. LET, Achilles tendinopathy, rotator cuff tendinopathy) [79, 116, 117] have been conducted but the disease specificity of these findings is challenging to elucidate. For reviews on LET specifically, the findings are incredibly challenging to untangle. Four key reviews, with a focus on PRP in

LET have been published. Ahmad et al [118] found eight studies that met inclusion criteria, de Vos et al [119], using a more rigorous inclusion criteria based on the Physiotherapy Evidence Database score (PEDro), identified six studies, Dong et al [106] selected five and Arirachakaran et al [120] selected seven. There is significant crossover between the studies selected with the exception of Arirachakaran et al [120] who included three more recent studies. Interestingly their headline conclusions are somewhat different. Ahmad et al [118] cautiously state that their assessment adds strength to the case for clinical benefit of PRP, as does Arirachakaran et al [120], yet de Vos et al [119] conclude that their review provides strong evidence against PRP for LET and Dong et al cautiously state that PRP may be a treatment candidate but current evidence is inconclusive. It is worth noting the de Vos et al and Ahmad et al reviews have received a critical response [121] both for their identification criteria and data synthesis, however beneath their primary conclusions, all four reviews clearly state what may be the key issue: that the quality of evidence within the literature is not yet strong enough to provide a clear insight into PRP's efficacy. The key methodological limitations within the present literature include the lack of a proper control group, the variation in PRP preparations and outcome scoring methods.

The concerns regarding the interpretation of PRP research has been elegantly highlighted by Murray et al [122]. Utilising an iterative Delphi methodology they have proposed a study checklist named the Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO). The authors are very clear that the current confusion regarding the efficacy of PRP can only be resolved following the clear reporting of the study methodology and outcomes. However, no level of consensus on study methodology standards or outcome measure choice is currently available.

Surgery is deemed to be reserved for patients who have failed conservative and injection therapy. Surgery can be conducted using an open, arthroscopic or percutaneous technique [123]. The predominant technique was described by Nirschl and Pettrone in 1979 [27], whereby the diseased tendon is excised. However,13 other techniques have been defined with over 300 modifications reported [123]. The outcome of surgery is often quoted as yielding good to excellent long-term results with improvement rates of up to 97% at 10 years [124] with no difference in outcomes reported between differing techniques [123]. However, systematic review evidence of the available RCTs have been less favourable. Buchbinder et al [40] and Bisset et al [45] both state that due to a small number of studies, large heterogeneity of interventions, small sample sizes and poor outcome reporting, there is insufficient evidence to support or refute surgery as a treatment. Buchbinder et al [40] performed the largest review of four RCTs comparing surgical techniques and one comparing surgery to a therapy (extracorporal shock wave therapy), they were unable to find any studies comparing surgery versus no treatment, or surgery versus the more commonly applied treatments (e.g. corticosteroid, physiotherapy or PRP). Recent reports of pilot trial evidence of a placebo-controlled trial of surgery did not demonstrate any evidence of superiority over surgery [125], but this requires further corroboration in larger studies. A randomised, double-blind sham-controlled trial of arthroscopic release is currently being conducted [126].

It is of interest to compare the trends in use of the common treatments to the evidence presented. The use of corticosteroids as a treatment of LET by 1000 Australian general practitioners was assessed over a 15 year period (2000-2015) [107]. Despite the growing body of evidence questioning its long-term efficacy, the authors report that the rate of corticosteroid injection did not change over this

period. In a population cohort study of approximately 144,000 people, assessed between 2000 and 2012, the proportion of surgically treated cases of LET tripled over time, despite a lack of compelling level one evidence of its effectiveness [92]. The apparent mismatch between the evidence base and treatments offered to patients is in many respects unsurprising. The lack of compelling evidence for any particular treatment method will, of course, prompt the clinician to offer the suffering patient what their experience leads them to believe will work. In a 2017 UK survey of 142 physiotherapists and 123 surgeons, physiotherapy or exercise-based treatments were the first-line treatment for 81% of respondents and corticosteroid injection was the most popular second-line treatment, recommended by 27%. Surgery and PRP injection were both recommended as a preferred second-line treatment, both by 9.82%. Of the surgeons, 59% would consider surgery only following symptoms of at least 12 months' duration. There is no doubt that treatments are being prescribed, which carry an associated healthcare cost, complication rate and in some cases inferior outcome. Drake et al [9] state that those "*who endorse the current best evidence acknowledge that no treatments have been proven to alter the natural history of LET… because patients often feel vulnerable and seek a cure, conveying this expert advice whilst maintaining this is a delicate endeavour*". This dour summation of current best evidence is a stark representation of our current time, and as interesting as it is to reflect on our progress from 1928 when Percival Mills said "*…and so helpless have we been in treatment…"* , it is not to say that research into the condition should be halted and we should be resigned to failure, rather that it is a call to arms to ensure that future research is undertaken with great attention to methodological and reporting details, that inferior treatments are not employed by the practising clinician and

that treatments which offer hope are tirelessly evaluated and translated into clinical practice according to best practice guidelines.

1.10 Outcome evaluation

"Each patient who entered the operating room was provided with a 5-inch by 8-inch card on which the operating surgeon filled out the details of the case before and after surgery. This card was brought up 1 year later, the patient was examined, and the previous year's treatment was then evaluated based on the patient's condition. This system enabled the hospital and the public to evaluate the results of treatments and to provide comparisons among individual surgeons and different hospitals."

(Ernest Codman 1910) [127]

"The biggest problem in health care isn't with insurance or politics. It's that we're measuring the wrong things the wrong way."

(Robert S. Kaplan and Michael E. Porter 2011) [128]

It is over 100 years ago that the orthopaedic surgeon Ernest Amory Codman, MD, established the principle of "end results based care", whereby the patients' outcome of surgery is systematically assessed and placed at the centre of the healthcare system. This principle, and his further promotion that this information should be within the public domain, was surprisingly dissident at the time and had the unfortunate result of him being professionally segregated. His forethought is now considered as pioneering, and his actions regarded as paving the way for

outcome measurement. One would surmise, therefore, that even within a system known to be slow to adapt to change, a healthcare focus on patient outcomes would now be established. It is hence surprising that a shift from focusing on the volume of services delivered to an emphasis on "value" created for patients [129], is conceptually rather modern. In musculoskeletal health, where an exemplary model of a common burdensome condition is LET, patient improvement is the purpose of all intervention, ergo the realisation of any effective interventional treatment in LET is dependent upon the measurement of its impact on patients. "Value" in healthcare has been defined with simplistic elegance as $Value = \frac{Outcomes}{Costs}$ [130]. The calculation of 'cost' may be dependent upon the system structure, but as a financial summation of resources it is broadly simple to derive. The calculation of 'outcome' is far more challenging to quantify as it is a less tangible construct. In interventional treatments, historically it was the easily defined binary outcomes such as: 30 day readmission, infection or death. However, these factors do not quantify the patient experience of a treatment. In the scenario of low-risk, high-volume intervention, such as injection for LET, these binary outcomes may be so infrequent and therefore of little relevance to patients as to not provide any indicator of "value". For these reasons musculoskeletal conditions, amongst many other chronic conditions, where the outcome is inherently condition-specific and multidimensional [130], have seen a shift to try and quantify Health Related Quality of Life (HRQoL). This is achieved by focusing assessments on domains such as pain and physical function and psychosocial health. Though instruments aiming to place a score on these dimensions were traditionally reported by clinicians, there has also been a move to collect Patient Reported Outcomes (PROs) utilising instruments collectively known as Patient Reported Outcome Measures (PROMs). These instruments are standardised and are designed to measure specific

phenomena or constructs of the health status in defined patient populations [131]. They can be generic quality of life measures, or specific to particular diseases, organs, body regions or body functions [132]. This fundamental shift in focus has seen the use of PROMs in interventional trials being much more common, furthermore they are now either recommended, or seen as a mandatory requirement, by national regulatory bodies and research funders [131, 133].

The ability to measure something, be it blood pressure, range of motion or patient-reported pain, is first dependent upon the availability of an instrument that is designed to undertake this task. Whereas a sphygmomanometer or goniometer have been commonplace in the physician's office over the last century, the use of questionnaires that report patient outcomes has only emerged since the late 1970s [134]. Though the field of clinical and educational psychology applied standards for the assessment of subjective variables decades ago [135], these principles have only recently crossed over to questionnaire validation in clinical medicine. The reason for the relatively slow uptake of PROMs may, therefore, be that there were no instruments available, or that the instruments were not of an appropriate standard, or due to a deeper reticence to embrace this form of measurement by paternalistic clinicians [136], or simply a combination of all of these factors. Of course, we may never know the true reasons behind the relatively recent emergence of PROMs in healthcare and its exponential rise in utilisation. More pertinent is the fact that they are now accepted as part of our outcome assessment, are supported and recommended by high-level organisations, and crucially, can now be designed with and critiqued against an agreed set of psychometric standards.

Psychometrics is the field of mathematics concerned with the statistical description of instrumental data and the relationships between variables [137]. A mature field in

psychology, its principles are now commonly applied to the design and assessment of PROMs in healthcare. Commensurate with an instrument that aims to quantify something of such importance as quality of life, each instrument should comply with a set of methodological standards to ensure sufficient accuracy, while also being feasible regarding cost and complexity [138]. Therefore, a PROM is far more than a mechanism for gathering an opinion, it should be designed to measure and quantify a specific concept in a standardised way; to that end there is a great deal of science involved in producing good quality PROMs and the process requires careful consideration of several key issues [139]. The construct is the aspect the PROM is designed to assess, the content of the PROM itself should be a reasonable representation of a patient's experience (content validity), and it should measure what it purports to measure (construct validity), the level of measurement error should be acceptable (reliability), it should not change when no change has occurred (repeatable) and should be sensitive to measure real change in the construct (responsive), the resultant score, and the change related to it after an intervention should mean something to the clinician researcher and patient (interpretability) [135]. Each of these metric properties should be evidenced through the use of statistical tests or qualitative assessment. Each instrument should finally be rigorously tested in the population of interest [135, 140].

In the absence of gold standard treatments, lateral elbow tendinopathy research continues to assess the effectiveness of novel interventions. In this endeavour, it is clear that the researcher should aspire to include PROMs if the assessment of patient impact is to be understood. The researcher and clinician bear the responsibility for selecting an instrument and ensuring that it meets the previously discussed standards. The choice of a poor PROM can have significant implications on the quality of the study, resulting in potentially biased or unreliable

effect estimates, which can mislead decision makers as well as harm patients and waste resources [141]. To be able to inform the choice of outcome measure, it is essential that four key pieces of information are explored and understood:

1. What patient-centred outcome instruments are available?
2. Of these instruments, how frequently are they being used?
3. For the specific condition of interest, which instrument/s perform best?
4. In the particular population of interest, have the best-performing instruments been used and validated?

Though points three and four are commonly cited as key aspects in the process of choosing a PROM, essentially as a confirmation of validity [140, 142-144], much of the criticism of outcome measure choice is related to the lack of conformity within the research literature. Multiple systematic reviews in LET have discussed the heterogeneity of outcome measure choice as the major stumbling block in the comparison of study results, rendering attempts at meta-analysis or meta-synthesis impossible [40, 45, 101, 118]. Therefore for any progress to be made, it is essential that points one and two are explored, to assess not least the levels of choice facing the researcher, but also any level of disparity between the validity and the proportional application. Only then can any barriers to conformity be explored, for example, is it that some of the best designed and validated PROMs are burdensome on both patient and researcher, and therefore not chosen [140], are some of the heritage outcome measures reported due to a ‘follow the leader’ approach to PROM choice [141], and do some researchers simply apply an unjustified battery of PROMs [143], often exploring the same constructs, in an effort to optimise the impact of their work.

1.11 Context of the presented research

It is the author's opinion that this exploration of background research in LET highlights why there is an absence of clear treatment pathways. The inability for clinicians to practise evidenced-based medicine, for a condition so prevalent is somewhat surprising. It is also apparent that the only way in which patients will realise the benefit of new treatments for LET, will be through diligent dedication to methodologically robust research. The author believes that for LET this can only be achieved with new foundational study, which uses a critical eye to question the basis of the contemporary research approach. As has been explored, thus far interventional treatments for LET have failed to show a significant benefit beyond placebo. There are two possible explanations, firstly that no treatment ever tested is superior to the body's healing mechanisms, or secondly, that the methodologies applied have failed to reveal the true efficacy of treatment. However, owing to the consistent criticisms directed at the intervention techniques, outcome choices and parallel comparator groups, it remains almost impossible to elucidate which of these explanations is true.

Short of giving up in the pursuit of interventions for a condition which clearly imparts significant levels of morbidity, it is the research community's responsibility to ensure that the investigational approach for LET is optimised, all previous methodologies and outcomes approaches should rightly be questioned, and a robust strategy is required to justify future research protocols. This approach is in accordance with guidance on the early stages of intervention development by the Medical Research Councils [145], whereby the development-evaluation-implementation axis should lie as the check rein for the production of a trial methodology, with all elements being important, and caution given to neglecting

the adequate feasibility work or practical consideration of implementation issues, lest it result in weaker conclusions.

This background evidence review has revealed three significant themes related to future LET research. Firstly, that the outcome evaluation of interventional research is becoming dominated by efforts ensuring that the instruments used are patient-centred, however, there is no guidance available on instrument choice in LET. Secondly, there is a particular emergence of injection-based therapies for LET, with PRP being the most popular. However, there is a paucity of basic research into injection techniques and limited discussion on both the technical aspects and patient experience associated with injection treatments. Finally, the feasibility of performing randomised trials aiming to investigate Platelet-Rich Plasma in LET should be assessed with a particular focus on compliance with outcome measure reporting standards, injection technique reporting and qualitative assessment of acceptability to patients. This work will therefore endeavour to: inform the selection of valid outcome measures, rationalise the methodology behind the delivery of injection-based interventions, and assess the feasibility of a trial directed at an intervention in clinical equipoise in LET.

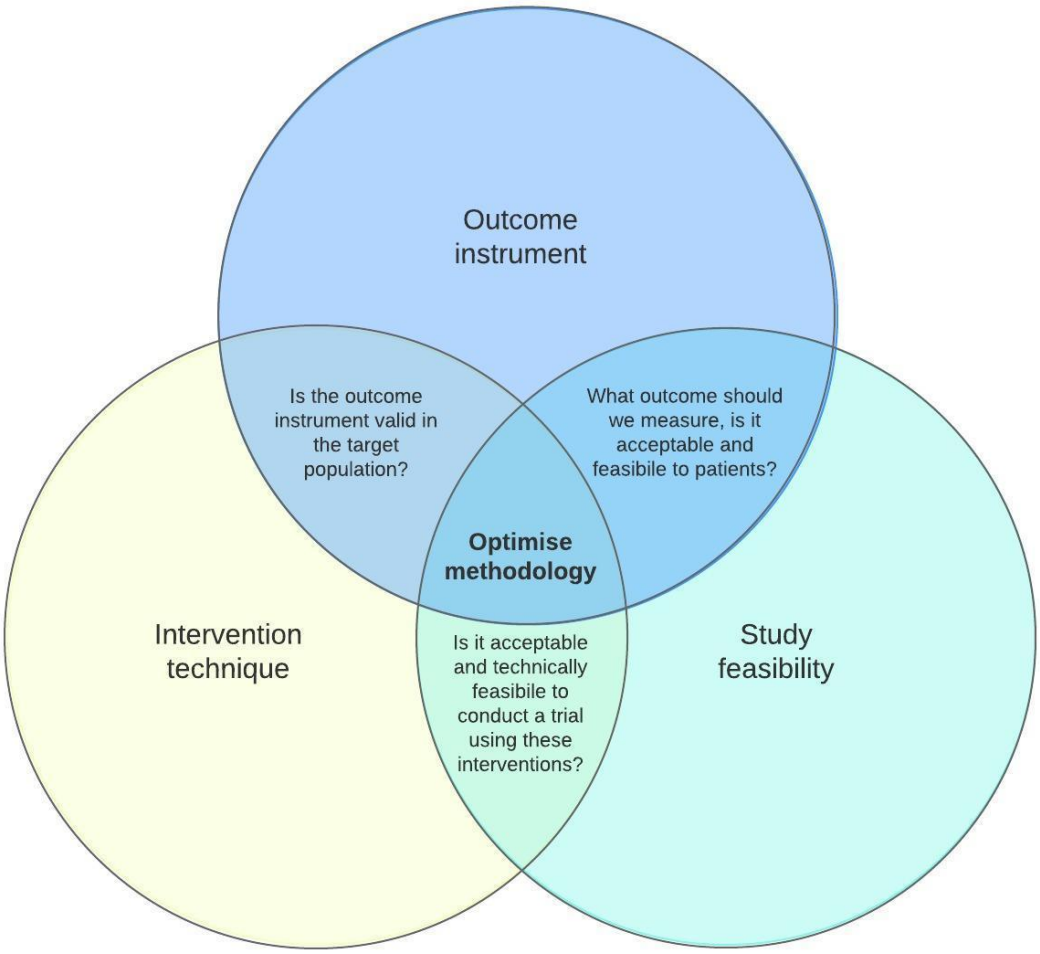


Figure 1.2: Venn diagram outlining the three main research themes and their association with the primary aim of optimising the research methodology

1.12 Aim, research themes and objectives

This thesis will use multiple methodologies in an effort to realise this aim:

<u>To optimise the investigation of interventional treatments in lateral elbow tendinopathy</u>

The overarching aim is informed by investigation of three strategic themes (Figure 1.2), which are in turn informed through the individual studies. Each study is designed to collate information relating to these themes by addressing specific questions (Figure 1.3).

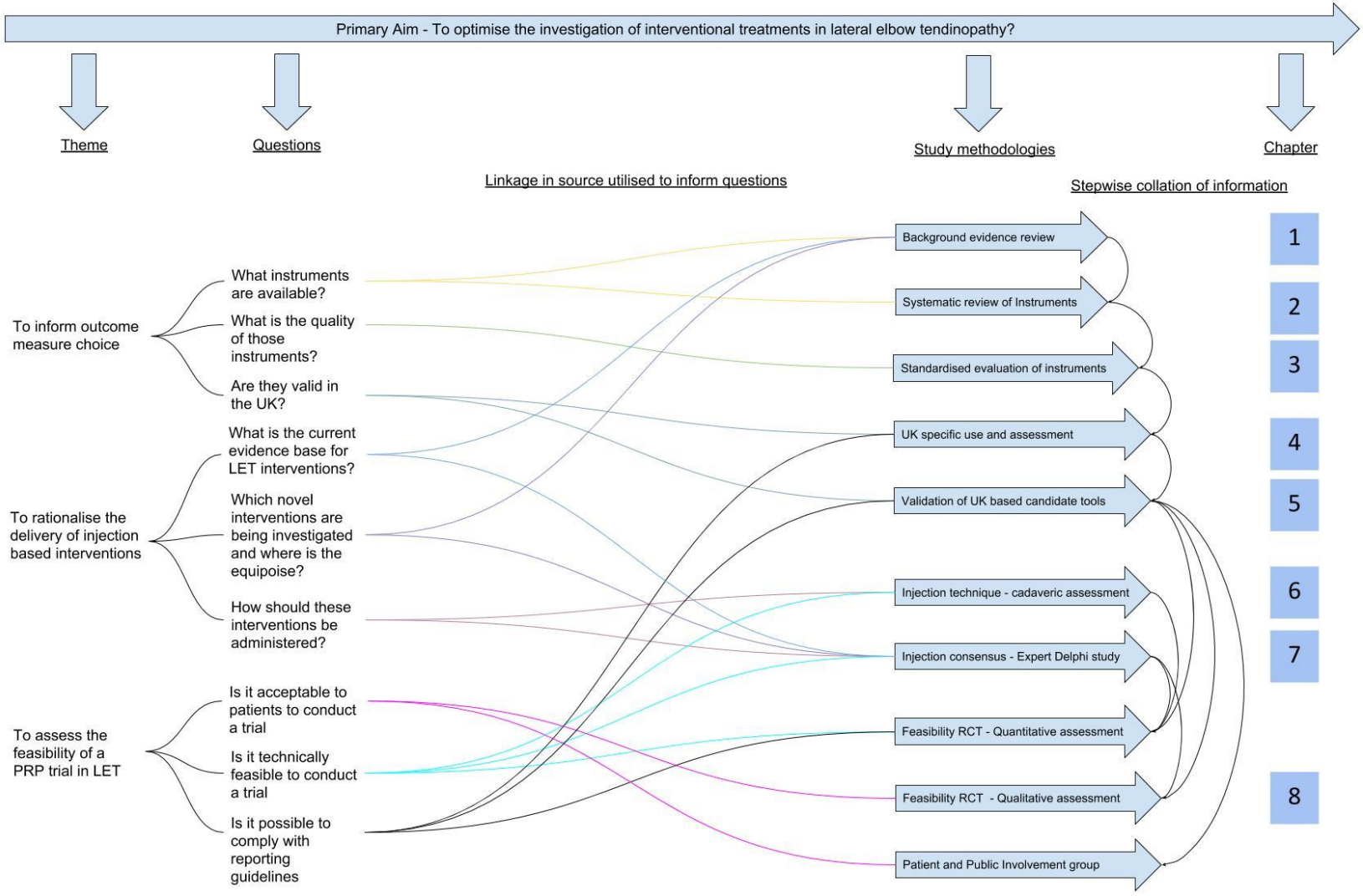


Figure 1.3: Visual representation of the linking information from individual chapters to inform the three main themes of the thesis

Themes and Objectives

1. To inform outcome measure choice
    - To explore and uncover the breadth of patient-centred outcomes available for elbow pathology and specifically elbow tendinopathy.
    - To assess for particular trends in outcome use over time and geographic location
    - To systematically assess the evidence for LET outcome measures using a standardised methodology
    - To assess whether the best performing outcome measures are the ones in use in interventional trials
    - To assess the UK-based validity of outcome measures in LET
    - If required, to undertake validation of the best performing LET outcome measures in a UK population
    - To assess the feasibility of using the outcome measures in an interventional trial
    - To gain patient and public involvement feedback on the delivery and use of outcome measures in LET
2. To rationalise the delivery of injection-based interventions
    - To evaluate the accuracy and distribution of commonly applied volumes and techniques of injectate using a cadaveric model
    - To develop levels of expert consensus in the use and application of injections in LET using Platelet-Rich Plasma as the model novel intervention
3. To assess the feasibility of PRP trials in LET

- To undertake a feasibility trial of a novel intervention (PRP) against an established UK-based gold standard therapy for chronic LET
- To collect and compare quantitative and qualitative feedback from patients to assess trial feasibility
- To compare qualitative feedback of PRP in LET with literature reports of safety and adverse events

1.13 Research methods and clarification of the researchers' role

To achieve the research aims the multiple methodologies were undertaken. The methods employed to undertake the PROMs systematic review were undertaken in a stepwise manner. The methods employed to inform injection technique and trial feasibility occurred in parallel.

An initial systematic review was conducted assessing patient-centred outcomes in elbow pathology. This was then followed by a focused systematic review and standardised evaluation of outcome instruments in LET. This highlighted the requirement for an in-depth assessment of outcome instruments in UK studies which was undertaken through a further iteration of the systematic review. The collation of information from these reviews informed the requirement for a UK-based validation study of outcome instruments in LET patients.

- The systematic review search strategy was constructed by the thesis author with assistance from Professor J Valderas and Dr J Gangannagaripalli (Health Services and Policy Research Group, University of Exeter).

- The manuscript screening was conducted by the thesis author with co-review at all stages by Dr I Porter and Dr J Gangannagaripalli (Health Services

and Policy Research Group, University of Exeter), Mr C Smith and Miss N Fine (Department of Orthopaedics, Royal Devon and Exeter Hospital)

- The standardised evaluation (EMPRO) was conducted by the thesis author with co-review of all instruments by Dr I Porter, Dr J Gangannagaripalli, Dr C Bramwell and Mrs A Davey (Health Services and Policy Research Group, University of Exeter), all of whom received training from Professor J Valderas.

- The validation study was devised by the thesis author under guidance from Professor J Valderas. Ethical approval was sought by the lead author and granted following proportionate review by the NHS East of Scotland Research Ethics Service (REC reference 17/ES/0017). Assistance in the administration of the study was provided by the NIHR CRN South West Peninsula (following NIHR portfolio adoption ID 33853). Statistical analysis was undertaken by the lead author following in-house training in psychometrics and completion of the International Society for Quality of Life Research (ISOQOL) quality of life and patient reported outcomes theory, measurement and application research course. The study was funded following successful application by the lead author and independent scientific review by the British Elbow and Shoulder Society (funding reference Ltr014PPG) and Royal Devon and Exeter Research and Development Directorate (funding reference JV/11/11/16).

    - Assessment of the delivery of injection-based interventions was conducted through two parallel studies; a cadaveric study and Delphi study.

- The cadaveric study was devised by the thesis author with assistance from Mr C Smith. Proportional NHS ethical approval was sought by the thesis author and granted by the NHS North West Preston Research Ethics Service

(REC reference 17/NW/0065). The study was funded following successful application by the thesis author and independent scientific review by the British Elbow and Shoulder Society (funding reference Ltr014PPG) and industry sponsorship from Stryker UK.

- The cadaveric study was undertaken by the thesis author with the assistance of Dr Rahul Anaspure (Consultant musculoskeletal radiologist, Royal Devon and Exeter Hospital) who administered the injections and Mr C Smith and Mr W Thomas (Consultant orthopaedic shoulder and elbow surgeons) who dissected the specimens following injection delivery.

- The cadaveric study's image processing methodology was devised and conducted by the thesis author with assistance and processing by Dr J Metz (Head of imaging analysis, Wellcome Trust Biomedical Informatics Hub).

- The cadaveric study's statistical analysis was conducted by the thesis author with assistance from Dr Fiona Warren (Senior Lecturer in Medical Statistics, University of Exeter Medical School).

- The Delphi study was conceived by Professor R Taylor (Health Services Research, University of Exeter) and Professor Valderas (Health Services Policy Research Group, University of Exeter) and devised by the thesis author with assistance from Associate Professor V Goodwin (Associate Professor of Ageing and Rehabilitation, National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) South West Peninsula). Institutional ethical approval was sought by the thesis author and granted following review approval by the University of Exeter Medical School Research Ethics Committee (Nov16/B/105).

- The Delphi study was run by the thesis author with overview from a committee of Southwest England orthopaedic consultants: Professor A Watts (Consultant hand and upper limb surgeon, Wrightington, Wigan and Leigh NHS Foundation Trust) and Professor N Maffulli (Consultant orthopaedic surgeon and director of the centre for sport and exercise medicine, Barts and the London school of medicine and dentistry).
    - The feasibility randomised controlled study was conducted in parallel to the above studies.
- The feasibility study was devised by the thesis author with assistance from Mr C Smith. Ethical approval was sought by the thesis author and granted following review by the NHS Devon and Torbay Research Ethics Committee (REC) (16/SW/0007). The study was funded following successful application by the lead author and independent scientific review by the Royal Devon and Exeter Research and Development Directorate (funding reference 1510155).
- The trial was run by the thesis author with assistance from Mrs Sian Gallacher (Upper limb research nurse, Royal Devon and Exeter Hospital) and Dr Rahul Anaspure (Consultant musculoskeletal radiologist, Royal Devon and Exeter Hospital) who delivered the injections.
- The qualitative data collection and analysis was conducted by the thesis author with assistance in the semi-structured interview design and thematic analysis from Mrs Antoinette Davey and Dr Ian Porter (Health Services and Policy Research Group, University of Exeter).
- Patient and public involvement group meetings were designed and run by the thesis author with assistance from Dr Emma Cockcroft and Mrs Kate Boddy (Patient and Public Involvement Team, National Institute for Health

Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) South West Peninsula).

2 Chapter 2 – Clinical Rating Systems in Elbow Research – A Systematic Review Exploring Trends and Distributions of Use

2.1 Abstract

Background

Clinical rating systems are used as outcome measures in clinical trials and attempt to gauge the patient's views of their own health. The choice of clinical rating system should be supported by its performance against established quality standards.

Methods

A search strategy was developed to identify all studies reporting the use of clinical rating systems in the elbow literature. The strategy was run from inception in Medline Embase and CINHAL. Data extraction identified the date of publication, country of data collection, pathology assessed and outcome measure used.

Results

980 studies were identified that reported clinical rating system use. 72 separate rating systems were identified. 41% of studies used two or more separate measures. Overall 54% of studies used the Mayo Elbow Performance Score (MEPS). For Arthroplasty 82% used MEPS, 17% used Disabilities of Arm, Shoulder and Hand (DASH), 7% used quickDASH. For Trauma 66.7% used MEPS, 32% used DASH, 23% used the Morrey Score. For Tendinopathy, 31% used DASH, 23% used Patient-Rated Tennis Elbow Evaluation (PRTEE), 13%

used MEPS. Over time there is increased proportional use of the MEPS, DASH, QDASH, PRTEE and Oxford Elbow Score (OES).

Conclusions

This study has identified the wide choice and usage of clinical rating systems in the elbow literature. Numerous studies report measures without a history of either pathology-specific or cross-cultural validation. Interpretability and comparison of outcomes is dependent on the unification of outcome measure choice. This is not currently demonstrated.

2.2 Overview

The previous chapter has identified the paucity of information on clinical rating systems in elbow pathology.

The following three chapters document a three-stage systematic review that ultimately aims to provide a comprehensive assessment of clinical rating system validity in LET. Specific methodologies are utilised in order collate and refine information, starting from a broad international perspective and honing down on to UK-specific application, a conceptualisation for this decision making process is shown in Figure 2.1.

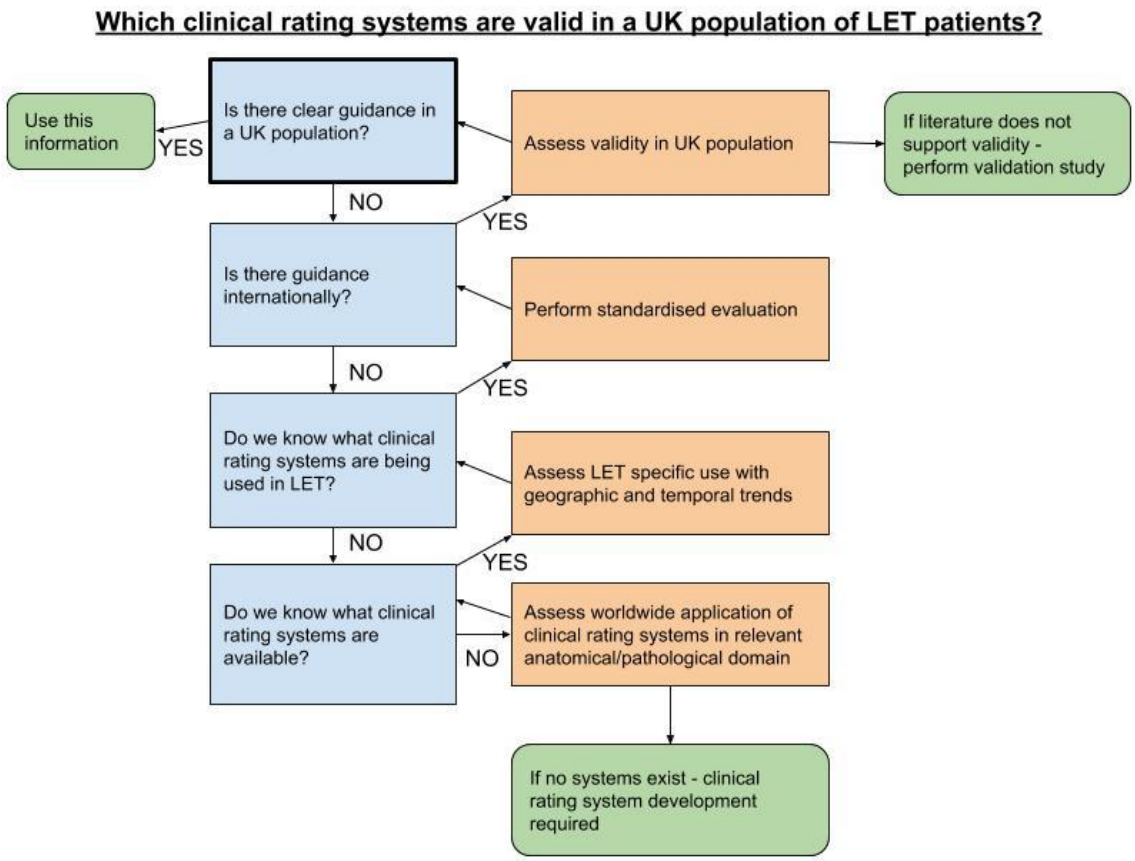


Figure 2.1: Systematic review decision chart utilised in the following chapters.

Though the application of instruments that aim to quantify patient-centred impact in interventional trials is believed to be becoming more frequent, the level and patterns of use has not been assessed. This chapter attempts to address this gap in the knowledge by quantifying the number of instruments available and assessing patterns in their use.

2.3 Background

The ultimate measure of success in healthcare is whether it helps patients as they see it [146]. In an effort to capture the effect of health interventions on patients, there has been a considerable investment of resources by academics and clinicians to develop systematic, robust and valid ways of collecting health data from patients [147]. It is now an agreed standard that treatment evaluations include clinical rating systems as an outcome metric [133].

Currently, clinical rating systems in elbow research utilise both physician and patient completed measures. They aggregate various attributes of interest such as elbow pain, range of motion and ability to perform specific tasks [148]. Though there was a historical focus on physician-administered tools, recent emphasis has been on the patient-rated outcome measurement (PROM), whereby information is gathered pertaining to the patients' perception of their elbow function [149].

The rise in the use of clinical rating systems has accompanied a fundamental shift in how we measure health. Traditional measurements of treatment effect, such as length of hospital stay, radiographic markers or range of motion, are increasingly accompanied by, or indeed replaced by rating systems, with a particular emphasis on PROMs [147]. In the United States, the Food and Drug Administration (FDA) recommends the use of PROMs in clinical trials [150].

Within the UK, the National Institute for Health and Care Excellence (NICE) advocates the necessity of PROMs in assessing the effectiveness and cost-effectiveness of healthcare technologies [133].

The increasing popularity of patient-focused outcome measurement has accompanied a consequent rise in the production of numerous rating systems, though the number in use is unknown. When choosing the appropriate rating system for clinical or research purposes, it is necessary to identify existing instruments that measure the outcome of interest in the target population [151]. An appropriate measure should be supported by published evidence demonstrating that it is acceptable to patients, reliable, valid and responsive (sensitive to change) [152]. Furthermore, these properties should have been tested on similar reference groups of patients to those being studied, thereby ensuring the validity of a tool from a language and cultural perspective [153]. Within the domain of musculoskeletal health, particular emphasis has been placed on the use of clinical rating systems for particular anatomical locations (predominantly joints) rather than generic health measures. More recently this has evolved to concentrate on condition specific tools, where, in certain groups or in certain conditions, generic or region specific tools miss important aspects of health status [147]. For the appropriate interpretation, it is, therefore, vital that the clinical rating system selected is validated for use in the population of interest and for the specific condition being investigated.

Systematic reviews assessing elbow-specific clinical rating systems have concluded that a paucity of quality measures exist [149, 154-156]. The most recent review by The et al [149] included the assessment of 12 rating systems using the Consensus-Based Standards for the Selection of health Measurement Instruments (COSMIN) checklist, although pathology specific assessment was

not undertaken, the authors conclude that the Oxford Elbow Score (OES) is the only system that has been developed using high-quality methodology. What is not known from this, and other elbow specific outcome measure reviews, is whether these reviews are assessing all of the outcome instruments that are being reported within the contemporary literature. It is interesting to note that the extensive review of shoulder outcome measures conducted by Smidt et al [157] do not include scores identified by Booker et al [158] as commonly used in shoulder research.

The use of elbow-specific rating systems across different elbow pathologies is not known. Riedel et al [148] reviewed 65 articles, which used elbow specific aggregate scores specifically in elbow arthroplasty published between 2004 - 2011. They report the predominant use of the Mayo Elbow Performance score in 75% of the literature they identified. They criticise the use of this physician-administered score that was not developed with a formal methodology and is frequently inconsistently applied.

It is therefore recognised that evaluation of outcome measures in elbow pathology is very limited, this study forms the starting point for the assessment of the use of clinical rating systems in elbow-related, and specifically LET-related interventional studies. It is this primary exploration that will assess the appropriation of rating systems to specific elbow pathologies and their use across populations and any change in trends of use over time. Only when armed with the knowledge of either the conformity or heterogeneity of rating systems, can compelling arguments be made for the need for standardisation. Furthermore, once it is extrapolated which instruments are favoured and used in LET research, can a full and comprehensive standardised evaluation be conducted. This study will provide a rounded assessment of ratings system use

that can then be used to inform pathology-specific assessment in lateral elbow tendinopathy.

2.4 Method

A comprehensive systematic review of elbow-specific clinical rating systems in the elbow literature was conducted. This review aimed to identify all articles reporting the use of both physician and patient-reported rating systems. Both rating systems designed specifically for use in elbow pathology and generic upper limb rating systems with a history of validation and in elbow pathology were included. The report has been written following PRISMA guidelines [159] (appendix 1).

A search strategy was constructed using MeSH and free text terms (appendix 2). The strategy was modeled to each database through the modification of thesaurus terms, wildcards, and truncation. The search was run on 10th April and subsequently updated on 1st May 2017 in Medline (Ovid MEDLINE, 1948 to 2016 & Ovid MEDLINE In-Process & Non-indexed Citations) accessed through OVIDSP, Embase (Embase 1974 to 2017) accessed through OVIDSP and CINHAL (CINHAL 1981 to 2017) accessed through EBSCO host.

The search strategy development was guided by previously published search strategies for systematic reviews published within the Cochrane library. The first focused on interventions in elbow pathology [40] and the second on the identification of outcome measures[160] The construction of the two strategies had undergone rigorous methodological evaluation in line with the expectation of Cochrane reviews. The identification of outcome measures has previously posed significant challenges owing the wide spectrum of technical language and evolving terminology. This has resulted in an extensive search strategy

including 57 stems including extensive psychometric text word searching to produce a highly sensitive filter. Along with these terms, known outcome measures were included in order to capture relevant instruments published in previous systematic reviews of elbow-specific rating scales [149, 154-156] and search of the online library of Patient-Reported Outcomes and Quality of Life Database (PROQOLID) [161] was conducted to identify outcomes not previously explored as part of previous reviews. The final composite search strategy was assessed independently by the University of Exeter's evidence synthesis team for structure, redundancy and optimisation of its structure. The final strategy extended to 57 stems including 663 items of 303 were included in a block assesses psychometric mesh and text word items. The resultant strategy was made publically available (http://medicine.exeter.ac.uk/research/healthresearch/healthservicesandpolicy/projects/proms/optimisinginterventionaltreatmentoftenniselbow/medlinesearchstrategyforelbowoutcomemeasures/#d.en.504281).

Following the extraction of the search strategy outputs, the review was conducted in a step-wise manner, through title, abstract and full text screening prior to data extraction. At each stage, dual review was employed with the lead author and a further co-reviewer. In cases of disagreement between reviewers, the article proceeded to the next stage of review to ensure maximum sensitivity. The review process was used to exclude duplicates, non-elbow-based studies, case-reports, case-studies, surgical technique papers and conference abstracts. Abstract and full text screening utilised the above criteria and also excluded studies in a paediatric population, known non-elbow or non-upper limb rating systems, systematic reviews and papers reporting exclusively on development and or validation of a rating system. The resultant dataset

included all extracted articles reporting the use of clinical rating systems to assess patient outcome in elbow research.

Data extraction was conducted by JE and NF. Publication date, geographical location of lead author or publishing institution, elbow pathology investigated and specific clinical rating systems reported were extracted.

The elbow-specific pathology or intervention of interest was grouped into the following categories for ease of interpretation: arthritis interventions (non-arthroplasty), arthroplasty (trauma and elective), arthroscopy, distal biceps intervention, neuropathy intervention, sports-specific population, tendinopathy (non-sports specific population) and trauma interventions (non-arthroplasty). Data are presented as proportional percentage of use of designated outcome measure within the predefined pathology, time period or geographic location of study.

References were retrieved and imported into reference management software (Endnote X7, © 2017 Clarivate Analytics, PA, USA). Database management was conducted in Excel (Microsoft® Excel® 2013, Redmond, WA, USA).

2.5 Results

The review identified 980 articles reporting the use of elbow-specific clinical rating systems (Figure 2.2). Articles from 52 countries were included; 72 separate instruments were identified (appendix 3).

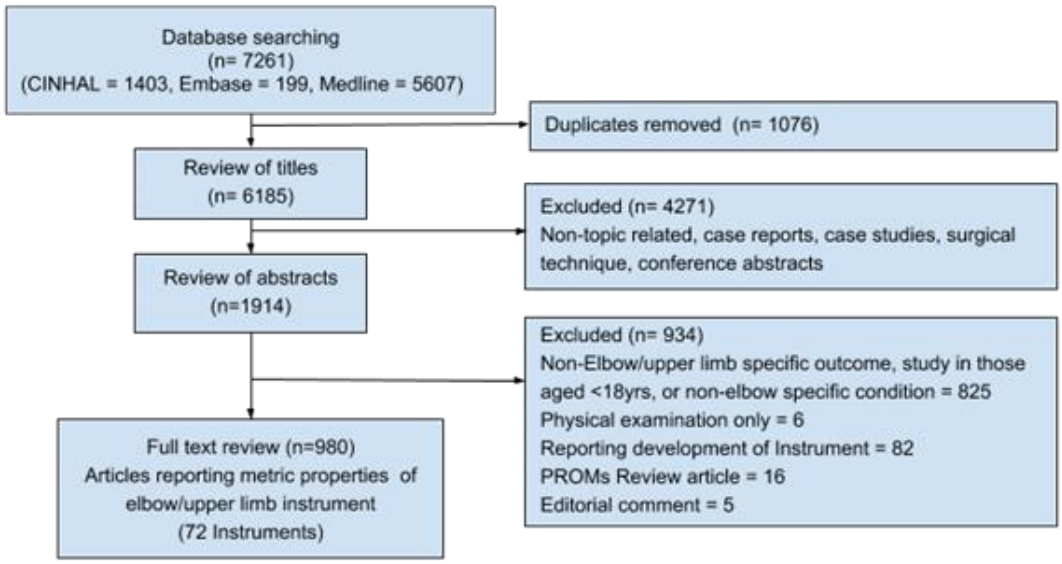


Figure 2.2: PRISMA flowchart

The 980 articles reported 1,383 separate outcomes; 322 (32%) of articles reported the use of two separate elbow-specific clinical rating systems, 77 (8%) reported the use of three, four (0.4%) reported the use of four separate elbow-specific clinical rating systems.

The number of articles reporting elbow-specific rating systems has increased over time (Figure 2.3) reaching 106 published articles in 2016.

Overall, from database inception, the Mayo Elbow Performance (MEP) score was reported in 54% of articles, the Disabilities of Arm Shoulder and Hand (DASH) in 29%, the Morrey Score 12%, the abbreviated DASH (quickDASH) in 8%, the Patient-Rated Tennis Elbow Evaluation (PRTEE) in 5%, the American Shoulder and Elbow Society-Elbow score (ASES-e) in 4%, the Oxford Elbow Score (OES) in 4%. All other scores were reported in less than 2% of articles.

Since 2000 and 2010 respectively, the proportionate use within the literature for the above rating systems are: MEPS 55% & 61%, DASH 30% & 34%, Morrey 12% & 9%, quickDASH 9% & 13%, PRTEE 5% & 7%, ASES-e 4% & 3%, and OES 4% & 6% (Figure 2.4).

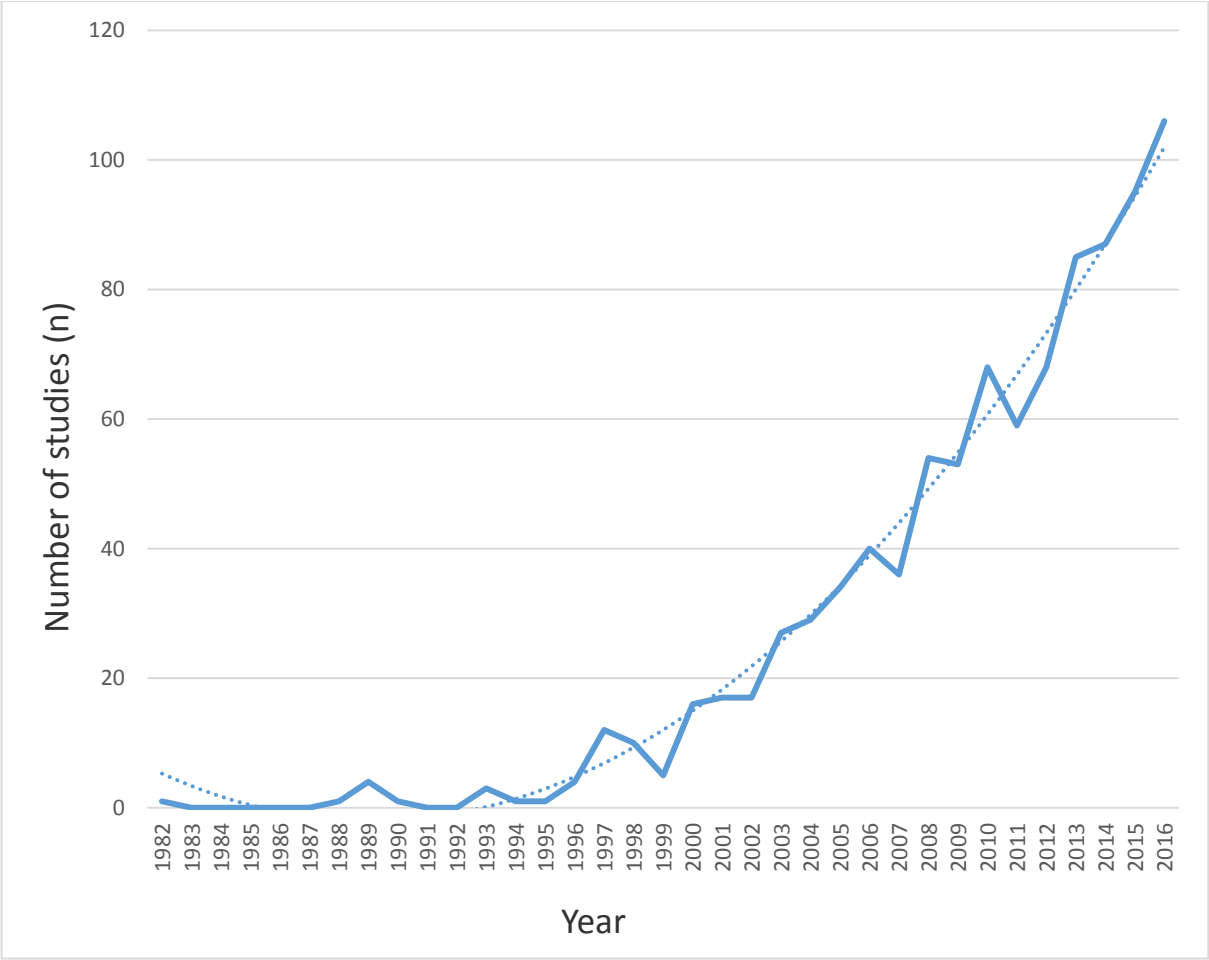


Figure 2.3: Number of studies published per year that report use of elbow/region-specific clinical rating systems.

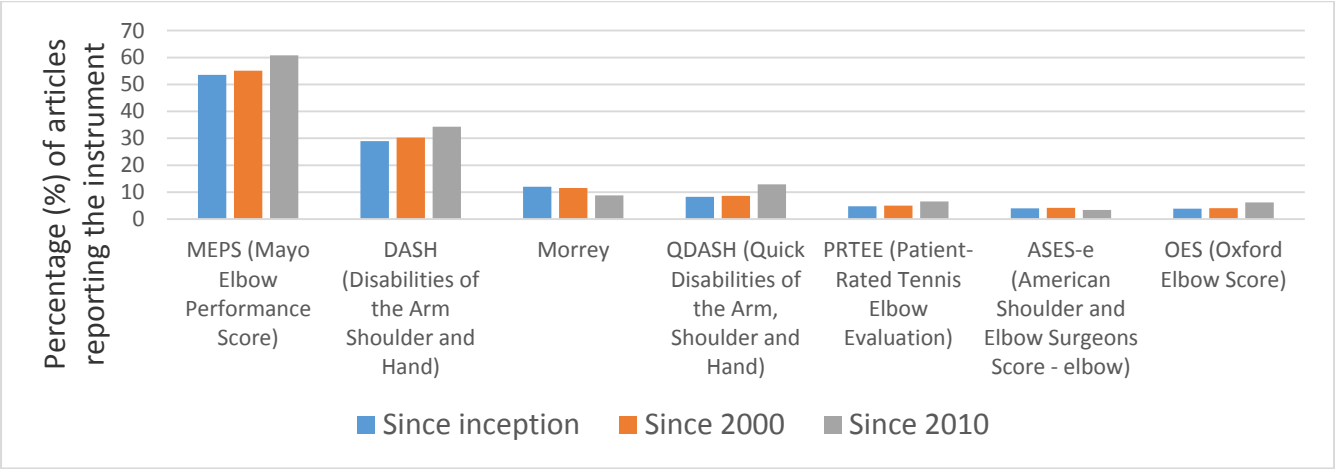


Figure 2.4: Proportional prevalence of the most common rating systems in articles since database inception, 2000 and 2010.

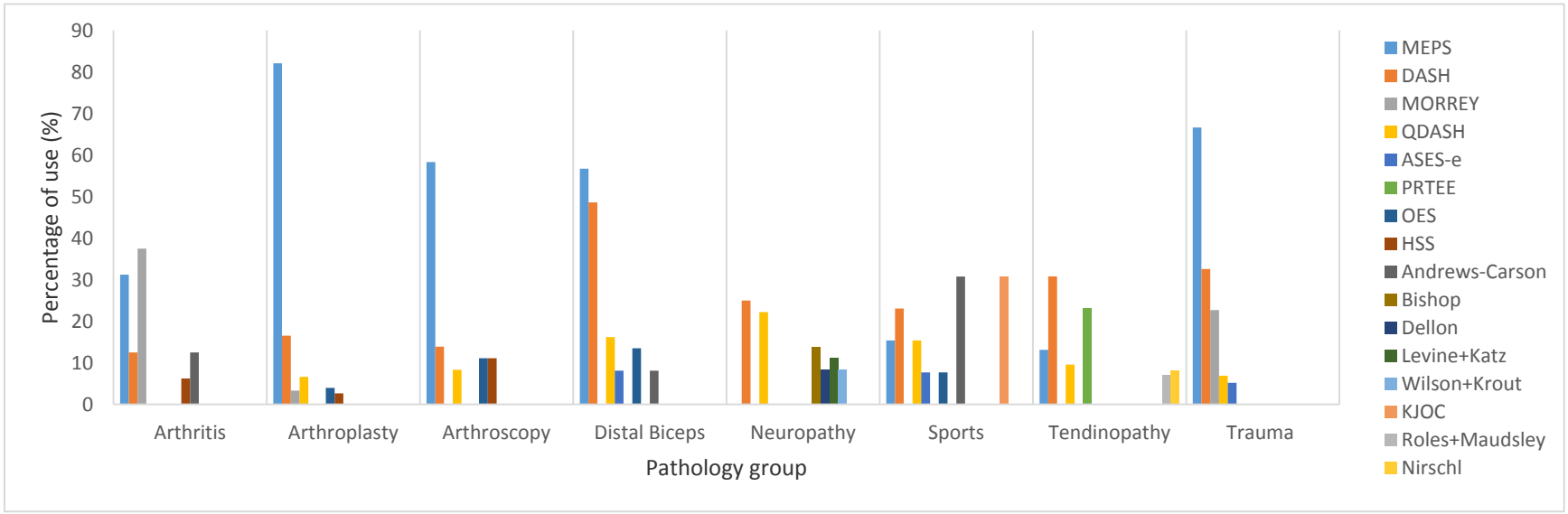


Figure 2.5: Top five clinical rating systems in each pathology group.

The top five clinical rating systems for the individual pathology or intervention group are outlined in Figure 2.5.

For the three largest groups: arthroplasty, tendinopathy, and trauma, the most popular clinical rating systems are further grouped by time periods; database inception, since 2000 and since 2010 (Table 2-1)

Geographic distribution is shown in Table 2-2, with data grouped into three broad localities; North America, Europe, and Rest of the World.

Table 2-1: Change in use of clinical rating systems over time in the three largest indication subcategories

	Arthroplasty						**Tendinopathy**						**Trauma**					
	Database Inception		Since 2000		Since 2010		Database Inception		Since 2000		Since 2010		Database Inception		Since 2000		Since 2010	
Articles (n)	151	%	133	%	74	%	198	%	190	%	128	%	405	%	365	%	128	%
Total Outcomes (n)	199		180		109		244		235		162		621		580		162	
MEPS	124	82.1	116	87.2	66	89.2	26	13.1	25	13.2	22	17.2	270	66.7	270	74.0	200	74.6
DASH	25	16.6	24	18.0	17	23.0	61	30.8	61	32.1	46	35.9	132	32.6	132	36.2	100	37.3
MORREY	5	3.3	3	2.3	1	1.4							92	22.7	85	23.3	46	17.2
QDASH	10	6.6	10	7.5	9	12.2	19	9.6	19	10.0	19	14.8	28	6.9	28	7.7	27	10.1
ASES-e													21	5.2	21	5.8	12	4.5
PRTEE							46	23.2	46	24.2	39	30.5						
OES	6	4.0	6	4.5	6	8.1												
Roles+Maudsley							14	7.1	13	6.8	2	1.6						
Nirschl							17	8.6	16	8.4	10	7.8						

Table 2-2:Geographical use of clinical rating systems grouped by locality and major indication subcategories

	North America								Europe								Rest of the World							
	Total		Arthroplasty		Tendinopathy		Trauma		Total		Arthroplasty		Tendinopathy		Trauma		Total		Arthroplasty		Tendinopathy		Trauma	
Articles (n)	264	%	50	%	47	%	86	%	370	%	76	%	66	%	151	%	319	%	26	%	77	%	155	%
Total No. of Outcomes	370		58		57		140		558		109		78		254		411		32		98		204	
MEPS	117	44.3	37	74.0	8	17.0	47	54.7	198	53.5	63	82.9	6	9.1	101	66.9	195	61.1	25	96.2	13	16.9	114	73.5
DASH	97	36.7	6	12.0	16	34.0	43	50.0	109	29.5	15	19.7	19	28.8	50	33.1	73	22.9	3	11.5	24	31.2	35	22.6
MORREY	20	7.6	1	2.0			16	18.6	59	15.9	3	3.9			42	27.8	35	11.0	1	3.8			31	20.0
QDASH	15	5.7			2	4.3	4	4.7	22	5.9	11	14.5	5	7.6	15	9.9	18	5.6	1	3.8	9	11.7	5	3.2
ASES-e	23	8.7	2	4.0			12	14.0	10	2.7							5	1.6					5	3.2
PRTEE	9	3.4			9	19.1			10	2.7			9	13.6			26	8.2			21	27.3		
OES	4	1.5							29	7.8	6	7.9			15	9.9	3	0.9						
HSS	2	0.8	1	2.0					6	1.6							6	1.9						
Roles+ Maudsley	1	0.4							11	3.0			10	15.2			3	0.9						
Nirschl	5	1.9			6	12.8			3	0.8			3	4.5			8	2.5			8	10.4		

2.6 Discussion

The elbow has long been thought of as the forgotten joint, with pathologies that are difficult to treat and surgical procedures that carry higher complication rates than any other major joint [162]. However, modern diagnostic and treatment practices have shown great promise, and clinical effectiveness research has sought to accurately quantify the benefits patients are experiencing. In keeping with modern research reporting practice, the ultimate goal has been to demonstrate the ability of an intervention to restore or preserve functioning and well-being related to health [163]. This study has demonstrated that the use of elbow-related clinical rating systems that aim, in some form, to demonstrate patient-related benefit following an intervention has rapidly expanded year on year. Though previously published reviews have highlighted the deficits in many of the available instruments [73, 149, 154, 164], this study has failed to show large shifts in choice towards clinical rating systems produced with high quality methodology.

Global data across pathologies and interventions of 980 articles identified the Mayo Elbow Performance Score (MEPS) as the predominant rating system. The MEPS was developed by Morrey and Adams in 1992 [165], for outcome assessment in total elbow arthroplasty. It consists of a physician assessment of pain, arc of motion and stability, with a patient rating of daily function. It has a history of validation in elective elbow surgery patients with mixed pathology [166, 167], arthroplasty [165], trauma [168] and rheumatoid arthritis [156]. Assessment under the COSMIN checklist rated all its development and validation domains as fair to poor [149]. The Disabilities of Arm Shoulder and Hand (DASH) is also commonly employed. This patient-reported outcome measure (PROM) was introduced in 1996 [169]. It consists of a 31 core item questionnaire with eight

additional questions for sport and work assessment. It was designed to evaluate the entire upper limb but has a history of validation in elbow-specific pathology including: arthrolysis [170], arthroplasty [171, 172], lateral epicondylar tendinopathy [173-180], rheumatoid arthritis [181], neuropathy [182, 183], elective elbow surgery [166, 167, 184, 185], biceps tendon repair and radial head surgery [186]. Interestingly, it has not been included in reviews that perform systematic evaluation and head-to-head comparison with other elbow-specific rating systems using recognised techniques such as COSMIN [144] or EMPRO [187]. Of the other scores, large heterogenicity of application was demonstrated, astoundingly 72 separate instruments were identified across the literature, since 2010, 45 of these separate instruments are continuing to be used.

Assessment of the use of rating systems in the predefined criteria groups showed some element of preference for specially designed scales. Neuropathy, sports-specific population, and tendinopathy groups showed the utilisation of scores specifically designed for population or pathology use. Examples include the Dellon score [188] in neuropathy, Andrews-Carson score [189] in sports population and the Patient-Rated Tennis Elbow Evaluation (PRTEE)[175] in the tendinopathy group. Of note, within all the above-mentioned groups and distal biceps group, the DASH score remains the first or second score of preference. The three largest condition subgroups were assessed for a change in use of rating scale over time. The recent emergence and promotion of patient-rated over physician-rated evaluation would lead most to the hypothesis of increased proportional representation within these groups over time. Within all groups, the use of DASH and quickDASH is rising, the tendinopathy group also demonstrated a particular emergence of the PRTEE. Yet, whilst the Morrey and

HSS are declining in use, of interest is the progressive rise of the MEPS across all groups.

Trends in rating systems in differing geographical areas since 2010 was also assessed. Though the sub-division of areas is rather crude it yields groups of a size substantial enough to interpret broad distribution trends. The MEPS, though developed in the USA, has a higher total proportion of use in Europe and Rest of the World groups. The MEPS has only been formally assessed for cross-cultural validity in Turkish [190, 191], UK English [166, 167] and Dutch [192]. The DASH score is proportionally more popular in North America, though it has been cross-culturally adapted to multiple languages. Interestingly, the abbreviated quickDASH is twice as commonly employed in Europe when compared to the USA. Again the quickDASH is available in multiple languages, but it is important to note that in terms of elbow-specific cross-cultural adaptation and validation, this has only been conducted in Turkish, Italian and Dutch [174, 185, 193].

The shift in focus from physician to patient-reported outcomes is well documented, with support both within the literature and from a governmental/health service level [194]. Within elbow-specific literature Dawson et al [166] stated that patient-reported results are more likely than clinically assessed outcome measures to reflect patient satisfaction with elbow surgery and that condition-specific measures are more likely than generic measures to be closely aligned with patient satisfaction. Yet, we have shown that within the literature there remains a persistent reticence to embrace PROMs more fully. As Snyder et al [195] comment, though PROMs have the potential to improve the quality of patient-centred medical care, there is a great deal of research to be done before they are fully embraced by all stakeholders. Within elbow-specific

literature, it may be the consensus that the literature is, as yet, uncompelling and lacking clear recommendations. Recent review evidence, that systematically assesses the development and psychometric properties of elbow-specific rating systems, has only emerged since 2013 [148, 149] and it may be that the trickle-down effect may simply not have been felt. Currently, no pathology-specific reviews utilising recognised outcome measure evaluations (COSMIN [144] and EMPRO [187]) exist. This information is clearly of great importance to assist practitioners in their choice of outcome measure. Furthermore, if rating systems do not possess clear validation information, it is the duty of the researcher to undertake this process prior to instigating clinical studies.

It is vitally important to recognise that inappropriate rating system choice can have a great impact on the interpretation of results, particularly where they are used as the primary endpoint in clinical studies [149]. The choice of a rating system should be optimally aligned with a conceptual framework that defines the health condition and will meet the performance requirements of the clinical context and measurement needs [164]. Therein, a score developed for the elbow may not be valid across all populations and all pathologies. Quantification of health-related quality of life in an elderly rheumatoid arthritis patient undergoing total elbow arthroplasty may require an evaluation of very different domains to a middle-aged manual labourer with tennis elbow. This must also be the case for the geographical population of interest, where the cross-cultural validation of an outcome measure is a vital component in ensuring its interpretability [135]. Consequently, for example, an American-developed measure in the English language, does not have automatic validity in other English speaking

populations. This study has identified that currently pathological or geographical application of ratings system is not well aligned with their known validity.

Though previous reviews have highlighted the psychometric aspects of clinical rating systems, this is the first comprehensive assessment of their use within the literature and underlines the need for standardisation, or at least general consensus, of outcome evaluation in the clinical and scientific community. Only then will we be able to compare results between different groups, hospitals, and protagonists [196]. As we look forward, initiatives to combat this include the Core Outcome Measures in Effectiveness Trials (COMET) and the International Consortium for Health Outcomes Measurement (ICHOM), who utilise expert panels to devise agreed 'outcome sets' that include validated PROMs and objective measures of function in an attempt to represent what really matters to patients. By producing these sets, they hope to unlock the potential of value-based healthcare, where patients ask their doctors about meaningful outcomes, and doctors can respond with clear, validated, data-driven answers. As yet there are no published outcome sets for elbow pathology. National societies can also hold great influence in the ongoing selection of outcomes, the American Shoulder and Elbow Surgeons (ASES) Value Committee has recently produced a consensus document recommending a package of patient-centred outcomes that includes the QDASH, VR-12 generic quality-of-life score and the Single Assessment Numeric Evaluation (SANE); for research purposes they also recommend the MEPS, though they recognise the ongoing need for pathology specific-validation studies [197]. The U.S. National Institutes of Health (NIH) Patient Reported Outcomes Measurement Information System (PROMIS®) aim to bring standardisation to PROM selection using instruments that employ Item Response Theory (IRT) techniques. These instruments, that focus on health

domains rather than disease-attributed scales, produce universally relevant scores that can be compared across populations and pathologies, furthermore the IRT approach also allows ‘cross-walking’ between other PROMs to produce equivalent scores. This review has not identified any studies that have utilised this system for elbow pathology. Only by adopting common standards and metrics will clinical researchers be able to directly compare patients’ evaluations; once achieved this will have a huge impact on the ability to undertake international syntheses of evidence, such as meta-analyses [153]. Furthermore, the use of registries may force some level of conformity in data collection. In the UK the National PROMs programme has collected Oxford hip and knee scores since 2009. With the inclusion of elbow arthroplasty into the National Joint Registry in 2012, it remains likely that an outcome measure will be added to this dataset. The New Zealand joint registry started collecting the Oxford Elbow Score for all elbow arthroplasties in 2015.

Limitations

As with all systematic reviews, this study is limited by the search strategy used, however, considerable care was taken to produce a strategy that was as sensitive as possible. The subclassifications of data into pathology and population groups were derived to give the best impression possible of rating scale use. The use of arthroplasty, for example, was kept as a single group, though a case can be made that rheumatoid and trauma patients may respond differently and require different rating systems, under the recommendations outlined above. Equally, the trauma group could easily be further sub-classified. However, we feel that the strength of the data is the representation of the three large sub-classification groups.

2.7 Conclusion

This study is the first to identify the true magnitude of choice of clinical rating systems for the elbow. From 980 manuscripts we identified 72 individual clinical rating systems. Although we are seeing a small advance in the use of validated condition-specific PROMs, such as the PRTEE, the overwhelming key players in outcome measurements remain the historic or generic measures, such as the MEPS and DASH score. The co-administration of multiple scores may be seen as a panacea, but there is little justification for ever increasing the patient burden. Though the rapid progression of outcomes research may provide computational models of comparison between measurements, in the immediate term, it is clear that a systematic evaluation of condition-specific elbow-related rating systems, using well-recognised methods such as the COSMIN checklist [144] or EMPRO tool [187] is needed. Only then can clinicians and researchers make informed decisions on the appropriate tool for the elbow pathology and population of interest. In chapter 3, having defined this need and the clinical rating systems that are used, a systematic and standardised evaluation in lateral elbow tendinopathy (LET) will be undertaken.

3 Chapter 3 - Assessing patient-centred outcomes in lateral elbow tendinopathy: a systematic review and standardised comparison of clinical rating systems

3.1 Abstract

Background

Lateral Elbow Tendinopathy (LET) is a common condition affecting adults. A lack of treatment consensus has resulted in numerous effectiveness studies, which commonly aim to quantify patient outcome. Our aim was to undertake a standardised evaluation of the available clinical rating systems that report patient-centred outcomes in LET.

Methods

A systematic review of studies reporting the development, assessment of metric properties, and/or use of instruments aiming to quantify LET-specific patient-centred outcome measures was conducted in MEDLINE, Embase and CINAHL (inception-2017) adhering to PRISMA guidance. The evidence for each instrument was independently assessed by two reviewers using the standardised EMPRO method evaluating overall and attribute-specific instrument performance (metric properties and usability). EMPRO scores >50/100 were considered indicative of high performance.

Results

Out of 7,261 references, we identified 105 articles reporting on 15 instruments for EMPRO analysis. Median performance score was 41.6 (range: 21.6-72.5), with four instruments meeting high-performance criteria: QDASH (72.5), DASH (66.9), OES

(66.6) and PRTEE (57.0). 179 articles reported instrument use internationally with DASH the most frequent (29.7% articles) followed by PRTEE (25.6%), MEPS (15.1%) and QDASH (8.1%). The correlation between frequency of use and performance was r=0.35.

Conclusions

This is the first study to provide standardised guidance on the choice of measures for LET. A large number of clinical rating systems are both available and being used for patients with LETs. Robust evidence is available for just a few of such measures, with QDASH obtaining the highest scores. The use of instruments in the literature is only in part explained by instrument performance.

3.2 Overview

The previous review identified the great variety of clinical rating systems available and makes the case for unification of outcome measure choice. Though it identifies the measures in existence and quantifies their application, this information, in and of itself, does not provide information on the psychometric superiority of one measure over another. This chapter attempts to progress the information available to researchers and clinicians by focusing on the pathology-specific application of clinical rating systems in LET. It applies a standardised evaluation to all the available evidence that imparts information on their development and metric properties.

3.3 Background

The 2013 review by The et al [149] represents the only previous attempt at a standardised assessment of elbow-specific measures. They included 12 outcome measures using the Consensus-Based Standards for the Selection of health Measurement Instruments (COSMIN) checklist which concluded that the Oxford Elbow Score (OES) was developed using highest quality methodology. However, for certainty of use, the performance of clinical rating systems needs to be assessed specifically for the condition of interest. As The et al [149] comment, it is essential to be aware that established validity characteristics might not be applicable when using the rating system in a different population. Therein, a rating system originally designed for the assessment of elbow joint arthroplasty, may not be appropriate for use in LET, unless evidence of performance has been explicitly presented. Furthermore, a narrow focus on elbow-specific instruments neglects the possibility that region-specific (i.e. upper limb) instruments may have been robustly assessed for certain pathologies. Finally, reviews of measures with a region/anatomical

location perspective disregard the very different characteristic clinical presentations of different conditions, though they may advise on the use of measures that work best across conditions, but not necessarily the best option for any given condition.

To our knowledge, no systematic review has previously identified the clinical rating systems for patients with LET and assessed both their use in the scientific literature and their performance against validated standards, both to establish what instruments offer the best performance and whether these are indeed the ones most widely used. This study aims to apply a standardised system to evaluate evidence available on the metric properties, development process and utility of clinical rating systems assessing patient-centred outcomes in LET.

3.4 Methods

Systematic Review

The search strategy (appendix 1) and resultant systematic review database applied in chapter 2 was re-analysed from the title screening level down, to isolate published studies on the development and/or use of clinical rating systems in patients with LET. This systematic review was registered with the PROSPERO International prospective register of systematic reviews (PROSPERO 2016:CRD42016037317) (appendix 4) and the report has been written following PRISMA guidelines [159] (appendix 5).

All articles reporting the development, psychometric evaluation, or use of clinical rating systems in Lateral Elbow Tendinopathy in English-speaking adults (>18yrs), were included. In instances where the study included multiple elbow pathologies, it had to specify that this comprised, at least in part, a population of LET patients.

Multi-item upper limb or elbow-specific instruments that were either clinician or patient-led were included.

Study selection utilised a step-wise approach. Screening was conducted by two reviewers at all stages. To ensure highest levels of sensitivity, in cases of disagreement, the study proceeded to the next step for more in-depth assessment. Reviewer comprehension of the research aims was assessed using a 20-manuscript pilot, achieving an Inter-rater agreement (Kappa) of 0.85. Titles and abstracts were disseminated to reviewers using electronic sifting software (Rayyan) [198]. Full text assessment was undertaken using hard copy manuscripts. Studies were excluded if reporting case studies, case reports, surgical technique papers, conference abstracts and manuscripts not in the English language. Forward and backward searches were undertaken on full-text manuscripts using Scopus® (Elsevier B.V.). Instrument manuals or complementary support material, were available, where sourced via the instruments' associated website or in direct contact with the developer.

Due to the principles of cross-cultural adaptation, the metric properties of an instrument are not directly comparable across different versions. Hence, only full-texts of instruments developed or tested in the English speaking populations were included in the standardised assessment [187]. By convention, the instruments were identified by their name and acronym, when one had been given, or by the name of the first author in the seminal paper, and the clinical rating systems were classified as either Patient Reported Outcome Measures (PROMs), Clinician Reported Outcome Measures (CROMs) (where the clinician makes a judgement on the health status of the patient [199]) or mixed PROMs/CROMs.

Evaluating Measures of Patient-Reported Outcomes (EMPRO)

The EMPRO tool [187] was developed to measure the performance of patient-centred outcomes for informing the identification of the best candidates among measures competing for the same purpose. Originally designed for PROMs, the content, structure and methodology are apt for the evaluation of all clinical rating systems. It has been utilised in a number of areas, including assessment of shoulder outcome instruments [157] and it has been found to be valid and reliable [187]. Its particular strength includes the synthesis of the whole body of evidence surrounding an outcome instrument, and its ability to facilitate the selection of the most appropriate outcome instrument [187]. Unlike the COSMIN checklist, it does not evaluate the quality and design of the evaluation of the psychometric properties, but rather the performance of the instrument.

EMPRO consists of eight scales measuring the following attributes each: Conceptual and measurement model (7 items); Reliability (8); Validity (6); Responsiveness (3); Interpretability (3); Administrative burden (7); Alternative modes of administration (2) and Cross-cultural adaptations into chosen reference language (3). Each item consists of a short statement, together with suggested aspects to be considered. Reviewers then express their agreement on an ordinal Likert-type response scale of 1-4. Where appropriate, ‘not applicable’ and ‘no information available’ response categories are available. At the end of the tool, reviewers are requested to provide an overall recommendation in reference to the relevant research question [187] (Table 3-1).

Each instrument was evaluated independently by two researchers using the EMPRO tool and based on the following information:

- The instrument to be assessed
- The instrument's user manual (where available)
- Full-texts of all publications which provide information concerning the development process, the metric properties or administration of the instrument including a sample which, at least in part, contains participants with LET.

The researchers were experts in outcomes research, they received additional training in the use of the EMPRO, and none of them had been involved in the development of the reviewed measures. EMPRO scores were consolidated and tabulated. Where discrepancy in scores exists, the two reviewers initially discussed the case to resolve through consensus, where necessary a third reviewer opinion was sought.

Attribute	Definition	No. of items	Higher scores represent…
Conceptual and measurement model	The rationale for and description of the concept and the populations that a measure is intended to assess and the relationship between these concepts	7	The concept to be measured is clearly stated. The empirical basis and methods for obtaining the item and for combining them are more appropriate
Reliability	The degree to which an instrument is free from random error	8	More clearly described and superior methods to collect internal consistency data. Better values of Cronbach's alpha and/or KR-20 coefficients
Validity	The degree to which the instrument measures what it purports to measure	6	More evidence regarding content-related validity of the instrument for its intended use
Responsiveness	An instrument's ability to detect change over time	3	More clearly described and more appropriate methods to assess sensitivity to change. The estimated magnitude of change is more clearly described, and the results are better
Interpretability	Possibility of assigning meaning to quantitative scores	3	The strategies to facilitate interpretation are more clearly described and appropriate
Burden	The time, effort, and other demands placed on those to whom the instrument is	7	The skills and time to complete the instrument are more clearly described and acceptable

	administered (respondent burden) or on those who administer the instrument (administrative burden)		
Alternatives modes of administration	Alternative modes of administration used for the administration of the instrument	2	The metric characteristics and use of each alternative mode of administration are specifically described and are adequate.

Table 3-1: EMPRO attributes definition, number of items, and scoring description (adapted from (Maratia et al., 2016 [200]) & (Garin et al., 2014 [201])).

Analytic Strategy

Attribute-specific scores were calculated as the response mean of the applicable items. Items for which the response was 'no information' were assigned a score of 1 (lowest possible). This raw mean was linearly transformed into a range of scores from 0 (worst possible) to 100 (best possible).

From the attribute scores, an overall attribute mean score was calculated. The scores of the five attributes that relay the psychometric-related information (conceptual and measurement model, reliability, validity, sensitivity to change, and interpretability) were included. The overall attribute score was only calculated when at least three of the five attributes have a score. EMPRO overall attribute scores for each outcome instrument are considered adequate if they reach at least 50 out of the maximum score of 100 [187].

Agreement between reviewers was assessed using a weighted Cohen's Kappa Coefficient. All analysis was undertaken in STATA (2015. Release 14. College Station, TX: StataCorp LP). Databases of instruments' distribution were managed in MS Excel (2013, Redmond, WA: Microsoft®). Kappa scores and resource numbers are displayed as (median) (Interquartile range (IQR) (Range). Spearmans correlation coefficiant was used to assess the relationship between EMPRO score and proportional use of the instrument within the literature.

3.5 Results

The primary review search strategy identified 7,261 articles (Figure 3.1). Following duplicate removal 6,185 articles were reviewed at the title level. After evaluation of references screened as full-texts, 15 clinical rating scales were identified (Table 3-2).

Assessment of the instruments' reported use in LET studies found four instruments to be reported much more frequently than the remaining 11 (Figure 3.2). The Disabilities of the Arm Shoulder and Hand (DASH) score was the most frequently reported (29.7% of articles), followed by the Patient-Rated Tennis Elbow Evaluation (PRTEE) (25.6%), Mayo Elbow Performance Score (15.1%) and Quick Disabilities of Arm Shoulder and Hand (QDASH) (8.1%). Over time this trend has shifted with the reporting of these scores increasing over time. Of note, of the 179 articles in the international literature, 40 (22.3%) reported two using two or more clinical rating systems to assess patient-centred outcomes.

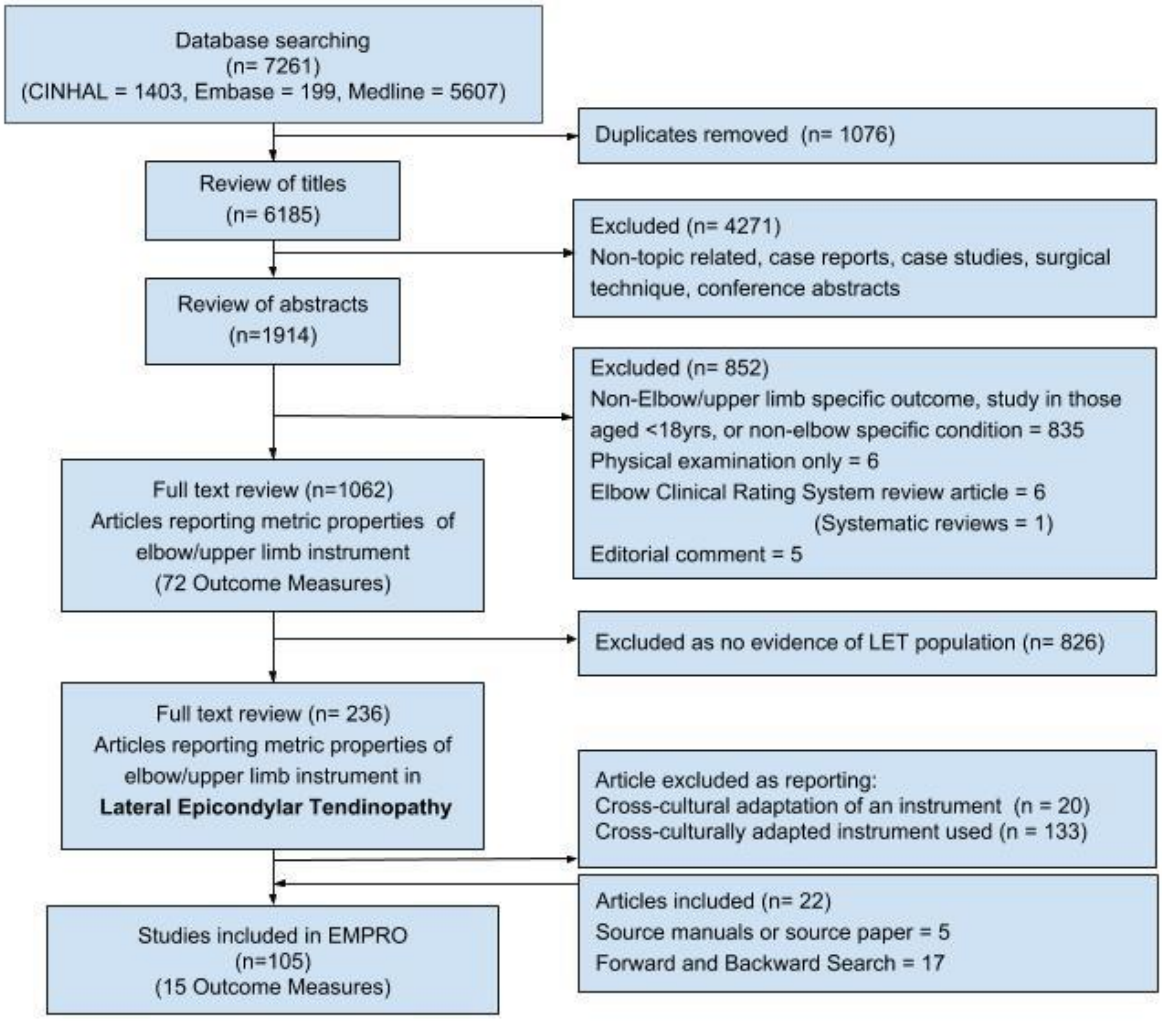


Figure 3.1: PRISMA flowchart of systematic literature review. Review of articles reporting development/metric properties or use of outcome instruments presented as separate streams.

Instrument	Author (year)	Development purpose	Assessor	Dimensions (No. items)	Scales	No. documents reporting development and metric properties (appendix 6)	No. documents reporting instrument use internationally (English speaking) (appendix 6)
A&C (Andrews and Carson)	Andrews et al [189] (1985)	To evaluate subjective and objective results of elbow arthroscopy	Clinician	Symptoms (3) Activities (1) Function (3)	4 point Likert scale Scored out of 200 then interpreted as one of four groups (poor – excellent)	1	2 (2)
ASES-e (American Shoulder and Elbow Score-e)	King et al [202] (1999)	Elbow functional assessment	Patient and Clinician	Pain (5) Function (12) Satisfaction (1) + Clinical assessment	Mixture of visual analogue scale and four point Likert scales.	3	5 (5)
DASH (Disabilities of the Arm, Shoulder and Hand)	Hudak et al [169] (1996)	Region (arm) specific measure of disability and symptoms with any or multiple musculoskeletal disorders of the upper limb.	Patient	Physical function (21) Symptoms (5) Psychosocial (4) (Optional work and sport/music module)	5 point Likert scale Raw score converted to 0-100 scale	18	60 (23)
HSS (Hospital for Special Surgery)	Inglis and Pellicci [203] (1980)	Pre and post op assessment of elbow arthroplasty	Clinician	Pain (2) Function (2) + Clinical assessment	Categorical scoring of pain at rest (5 options) and in bending (4). Function split into A (4) and B (5) + Clinical assessment Scored 0-100	3	1 (1)
LES (Liverpool Elbow Score)	Sathyamoorthy et al [204] (2004)	Elbow specific measure of function and clinical state	Patient and Clinician	Physical Function (8) Pain (1) + Clinical assessment	5 point Likert scale Raw score converted to 0-10 scale	1	1 (0)

MEPS (Mayo Elbow Performance Score)	Morrey and Adams [165] (1992)	For the assessment of total elbow arthroplasty	Clinician	Pain (5) Function (15) + Clinical assessment	10 point Likert scale Scored out of 100 then interpreted as one of four groups (poor – excellent)	6	24 (9)
Morrey	Broberg and Morrey [205] (1986)	For the assessment of radial head fractures excision	Clinician	Pain (1) + Clinical assessment	Categorical scoring of pain (4 options) Scored out of 100 then interpreted as one of four groups (poor – excellent)	2	4 (0)
Nirschl	Nirschl [27] (1979)	Assessment of LET based on phases of pain	Patient and Clinician	Pain (1) + addition of VAS and surgical findings	Categorical scoring of pain (7 options)	2	16 (7)
OES (Oxford Elbow Score)	Dawson et al [142] (2004)	For the assessment of the outcome of elbow surgery	Patient	Pain (4) Function (4) Limitation to work and leisure activities (2) Psychosocial (2)	Categorical scoring options Converted to numerical value (0-4) Domains scored individually	5	5 (2)
PRTEE (Patient-Rated Tennis Elbow Evaluation) (formally PRFE)	Overend et al [206] (1999)	For measurement of forearm pain and disability in patients with LET	Patient	Pain (5) Function • Specific (6) • Usual (4)	10 point Likert Scale Raw score converted to 0-100 scale	9	53 (21)
QDASH (quick Disabilities of the Arm Shoulder and Hand)	Beaton et al [207] (2005)	Abbreviated DASH score	Patient	Physical Function (6) Pain (2) Psychosocial (3)	5 point Likert scale Raw score converted to 0-100 scale	8	18 (5)
R&M (Roles and Maudsley)	Roles and Maudsley [208] (1972)	To classify the outcome of surgery in Radial Tunnel Syndrome	Clinician	Pain Movement Activity	Placed in 1 of 4 groups (poor – excellent) dependent on composite of dimension finding	2	16 (2)

TEFS (Tennis Elbow Functional Score)	Lowe [209] (1999)	For the assessment of disability in patients with LET	Patient	Pain (10)	5 point Likert scale Scores of 10 items added together	1	3 (0)
ULFI (Upper Limb Functional Index)	Pransky et al [210] (1997)	For the assessment of upper limb function	Patient	Function (8)	10 point Likert scale Scores of 8 items added together	1	6 (3)
Verhaar	Verhaar et al [211] (1993)	For the assessment of the outcome of surgery in LET	Clinician	Pain Satisfaction Movement Strength	Placed in 1 of 4 groups (poor – excellent) dependent on composite of dimension finding	1	6 (1)

Table 3-2: Summarised characteristics of the 15 identified outcome instruments.

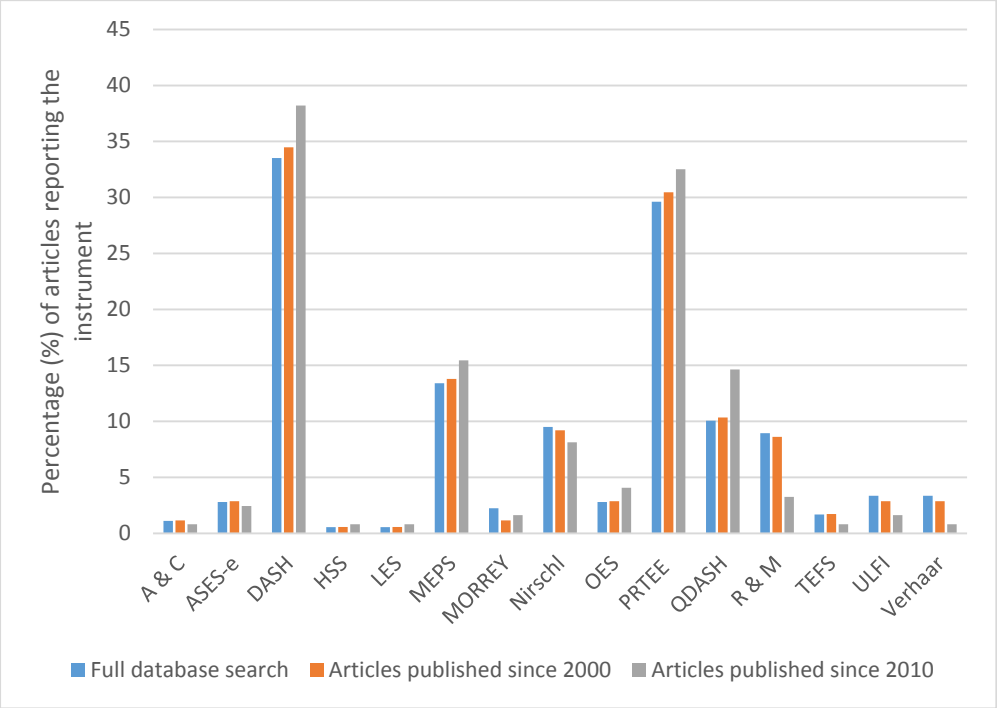


Figure 3.2: The change in the percentage of use of outcome instruments over time.

Clinical rating systems

Of the 15 outcome clinical rating systems, six were Patient Reported Outcome Measures (PROMs), six were clinician-reported outcome measures (CROMs), and the remaining three included both clinician and patient-reported information (Table 3-2).

The instruments had been developed between 1979 and 2008. Four instruments had been designed specifically for the assessment of LET: Patient-Rated Tennis Elbow Evaluation (PRTEE), Nirschl score, Tennis Elbow Functional Scale (TEFS) and Verhaar score. Three more instruments had been designed as elbow-specific across different pathologies: American Society of Shoulder and Elbow Surgeons-Elbow (ASES-e), Liverpool Elbow Score (LES) and Oxford Elbow Score (OES). Three other instruments (DASH, QDASH, and ULFI) are region-specific (upper limb), and the

remaining five Instruments had been designed for the assessment of other pathologies (eg arthroplasty, radial head fracture), but have been used in the assessment of LET outcomes.

Psychometric evaluation

All instruments were assessed using the EMPRO methodology (appendix 7). The volume of resources informing each EMPRO assessment averaged four articles (IQR 8.5) (Range 1-41) (Table 3-2).

Concordance between individual EMPRO evaluations was moderate to substantial in all cases, Kappa Median 0.72 (IQR 0.36) (range 0.47 – 0.94) [212]. Resolution of score differences was achieved by consensus in all cases. The overall summary scores ranged from 72.5 (QDASH) to 21.6 (ASES-e). Only four instruments met the threshold score of 50/100: one LET specific (PRTEE), one elbow specific (OES) and two upper-limb specific (QDASH, and DASH). It was not possible to calculate overall scores for the Morrey, Andrews and Carson, Roles and Maudsley, HSS, Nirschl and Verhaar instruments, because of lack of available evidence (Figure 3.3).

Whereas no reviewer ‘strongly recommended’ any of the outcome instruments, QDASH, DASH, OES and PTREE were all ‘recommended (with provisos or alterations)’. Of those instruments, recommendations of use extended only to group comparison of a general adult population rather than individual monitoring, owing to lack of clear responsiveness data in LET patients.

The Spearman correlation coefficient between overall performance and frequency of use in the literature was r = 0.35 (95%CI: -0.11; 0.83).

1

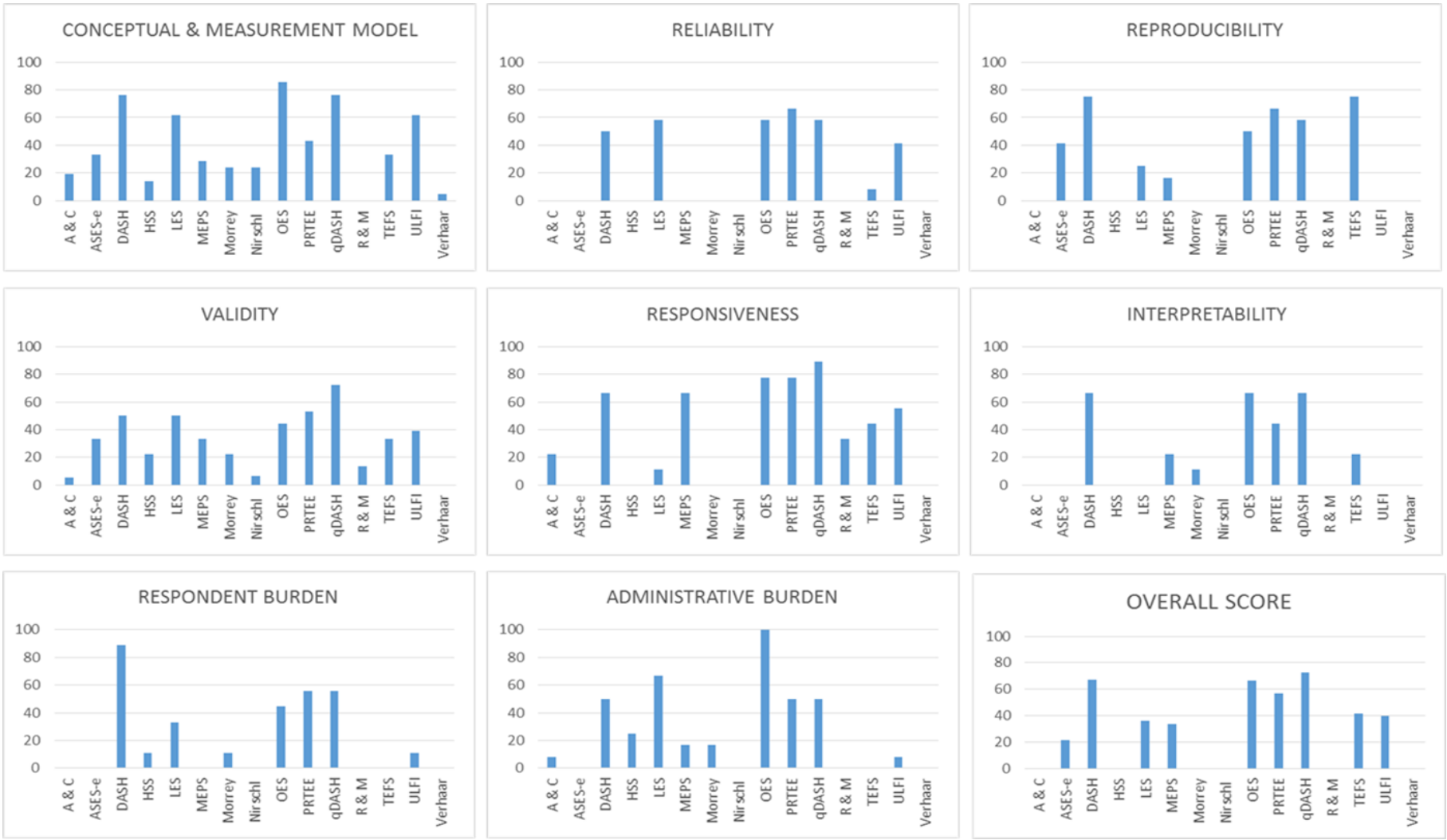


Figure 3.3: Attribute specific and Overall EMPRO scores. 0 (worst) - 100 (best).

3.6 Discussion

This study identified 15 clinical rating systems that, to varying degrees, attempt to assess patient outcomes in individuals suffering from Lateral Elbow Tendinopathy (LET). All 15 clinical rating systems were systematically evaluated in view of their development, metric properties and history of use within the LET literature. Of those instruments, only four met both the overall attribute benchmark score of 50 and overall recommendation of the reviewers, to suggest that their use can be justified in the evaluation of LET. This study has gone a step further than previous elbow-specific outcome instrument evaluations [149, 154, 213-215] in attempting to systematically compare the instruments in a condition-specific context, furthermore it is the first to attempt to quantify both the properties of the instruments, and the instruments' distribution of use within the literature, which both feature significantly in the researcher's or clinician's mind when choosing a tool. From this assessment, we would recommend authors of future studies of LET participants, where English language instruments will be used, consider the QDASH, DASH, OES or PRTEE. Furthermore, summary tables from the EMPRO evaluation can be used to guide instrument choice when the quantification of a particular attribute is desirable, for example, responsiveness in longitudinal studies or the inclusion of specific dimensions such as psychosocial effect. This presentation of condition-specific quality may also reduce the 22% of studies that utilise two or more clinical rating systems, with its consequent burden on the study participants.

To the author's knowledge, this is the first upper-limb specific study that has quantified the condition-specific quality of the instrument, and formally identified the instruments' distribution of use. Previous EMPRO evaluations have found concordance between the quality of the instruments and their history of use [201].

Though there is some agreement between quality and use of instruments in LET, instruments are being widely used although the evidence for their metric properties are significantly limited compared to alternatives. While the results of our standardised evaluation would support the common use of the DASH and PRTEE, the MEPS, which did not meet our minimum benchmark is used twice as often as the QDASH and seven times more often than the OES. Furthermore, this trend has not changed significantly over time. The QDASH is the abbreviated version of the DASH, scored more highly than the full version owing to a more compelling record of validation in LET populations. Its use is becoming increasingly popular, yet between 2010 - 2017 it was only utilised in a minority (14.6%) of LET studies.

High performing instruments

The QDASH, DASH, OES and PTREE exceeded the minimum criteria for recommendation. Of note, both the QDASH and DASH scored >50 on every attribute-specific score. Of these four measures, particular strengths (identified as a particular metric attribute specific score >80/100), were the conceptual development of the OES and responsiveness of the QDASH. The OES developed its items with patient groups and expert panels, using a high-quality methodology, however, it is worth noting that due to the unidimensional nature of the three discrete constructs of pain, function and psychosocial impact, the resulting instrument should be presented as a profile of scores rather than a single composite score, a fact ignored in many subsequent studies using the instrument. The assessment of dimensionality assesses the fit of items in an instrument around a construct (e.g. pain or function). A unidimensional instrument can provide a single score once it can be proved that the items used measure similar things (that there is a level of interrelatedness between the items of the questionnaire). However, if it is revealed that the instrument is

multidimensional (assesses multiple discrete constructs), then the instrument should be divided into subscales. Further analysis of each subscale is then required to ensure that the items for each construct are in themselves unidimensional. The resultant score should be presented as multiple subscale scores. The responsiveness of the QDASH has been complemented by studies containing considerable proportions of LET patients [216, 217], however, it is worth noting that the DASH, OES and PRTEE all scored well in this attribute. The condition-specific PRTEE, though reliable, valid and responsive, was developed without clear patient involvement. Factor analysis has not been reported and the justification of visual numeric scales is not clear.

Areas where further data could enhance these scores include: assessment of metric properties in isolated LET groups for the QDASH, DASH and particularly the further assessment of condition-specific construct validity of the OES. Furthermore, future studies focusing on the interpretability through minimal change scores would strengthen this specific attribute considerably.

Other instruments

The TEFS, ULFI, LES, MEPS and ASES-e scored below the minimum criteria for recommendation. Though the TEFS is a condition-specific score, the reporting of its metric properties has only occurred in a University Masters thesis published in 1999 [209]. However, it has a history of use in peer-reviewed publications as recently as 2012. Though scoring well for reproducibility, the weight of evidence for the remaining metric properties currently precludes its recommendation. The ULFI is a generic upper limb score with a history of use in LET and although conceptually well designed and responsive, lack of information on its metric properties within a

condition-specific context preclude its recommendation. The LES is a robustly designed instrument that has been employed in LET studies, however, a significant lack of data on the instrument's responsiveness and interpretability hugely hamper the instrument's utility to the researcher. The MEPS is a commonly used instrument; within the LET literature it is reported in 15% of studies. However, this tool was never designed for application in LET and consequently, its domain structure may not reflect the experience of LET patients. Lack of data across all metric aspects highlight that this is likely to be an unsuitable instrument, yet its use appears to be increasing over time. The particular lack of data on the instrument's interpretability in the context of LET exemplifies that though this is historically popular, researchers may struggle to justify its use. A similar scenario is present for the ASES-e score, which again lacks metric details in LET populations.

The remaining instruments scored below the required three out of five attribute scores for calculation of a composite score. They were all developed prior to 1986 and are clinician rated. The lack of data on all of their metric properties implies that their use does not stand up to modern reporting requirements of outcome instruments [135, 218]. This is prescient information due to the continued reporting of these instruments in contemporary literature.

Limitations

This study should be interpreted with reference to limitations inherent to its methodology. Firstly, our results are dependent on the information retrieved from the search strategy. It is important to note that the strategy was developed with reference to extensive protocols, and the largest health science databases (MEDLINE, Embase and CINHAL), were utilised and complemented with the

addition of thesis searching and hand searching in recognised repositories. Furthermore, authors of the identified instruments were contacted and asked to confirm whether the list of manuscripts identified were as comprehensive as possible. Nevertheless, inherent in all search strategies is the possibility of missed or omitted evidence.

Secondly, the choice of the EMPRO tool itself should be scrutinised. Multiple attempts have been made to quantify the strength of evidence surrounding a set of instruments. The EMPRO tool was used owing to its emphasis on assessing the whole body of evidence relating to an instrument. We feel the validated output of a 'score' and recommendation is very beneficial to the clinician and researcher. The authors recognise that this may be complemented with the addition of the commonly cited COSMIN (Consensus-based standards for the selection of health measurement instruments), which would scrutinise the methodological quality of the studies assessing the metric properties, rather than the instrument itself. This approach may be complementary, but to our knowledge this method has not yet been reported.

Thirdly, it is recognised that our use of English language tools only, limits the generalisability of our findings. However, we feel that the use of both non-English language instruments and data derived from cross-culturally adapted instruments imparts variables that the EMPRO tool was not conceived to deal with. Where the EMPRO provides comparative scores across instruments, the addition of information derived from a different cultural context is unhelpful for the researcher/clinician. Where adaptation of a tool is undertaken, certain aspects of its metric properties cannot be compared and should not be collated to complement the body of evidence [219] [135]. Strictly speaking, though all English language in origin and application, the use of data from different English-speaking countries could be questioned. The

presented data should therefore be followed with the exploration of culturally-specific metric properties, that would allow a detailed country-specific analysis.

Fourthly, beyond the assessment of LET-specific studies, this assessment derived some information from studies that contained a component of non-LET participants. Therefore, contamination of our findings is possible as, in many instances, it is not possible to quantitatively extract the LET information and assess it in isolation from other pathologies. Here a pragmatic and more subjective assessment was required to assess what are perceived as strengths and weaknesses of the tool in this specific cohort. The authors feel that at present, though pathology-specific advice is highly sought after, it is a significant challenge in musculoskeletal health owing to the traditional use of region or joint-specific instruments. We advise our methods as a best possible route, but would recommend that the reporting of pathology-specific details in all future development or assessment of musculoskeletal PROMs instruments, will greatly enhance this process.

Future research

We hope that the presentation of information on both quality and distribution of use will compel researchers to carefully consider their instrument choice. Though this study reports the current strengths and weaknesses of LET instruments, it is important to comment on the changing landscape of outcome measure assessment in upper limb pathology. New novel instruments have been developed that integrate both patient-reported PROMs assessment and patient-reported objective function, including the German language Elbow Self-Assessment Score (ESAS)[220]. There is also an emergence of computer-based systems that use predictive algorithms to administer streamlined PROMs, easing data collection, analysis and decreasing

participant burden. These systems offer great potential but are in the early stages of use in upper limb pathology [221]. Of note, the NIH PROMIS system, the largest computer adaptive testing system, has not yet reported specific properties for the elbow region or specific elbow pathologies [221].

3.7 Conclusion

This study is the first to provide a systematic evaluation of LET-specific PROMS instruments. The available evidence would currently support the use of the QDASH, DASH, PRTEE or OES instruments. Though the QDASH scored highest, the choice of instrument should also depend upon the study's particular requirements. The evidence presented for each metric attribute will facilitate in the selection process. Future instrument development and validation, particularly for those not meeting the recommended standards, can also be optimised using the presented evidence. It is now clearly recognised that the choice of outcome instrument must be justified from both a validity and burden standpoint. The information presented should therefore be used in conjunction with a culturally specific analysis, which should be used in combination with this EMPRO assessment to select a high performing instrument.

4 Chapter 4 - Patient-Centred Outcomes in Lateral Elbow Tendinopathy: A Systematic Review of Available Evidence in UK Populations

4.1 Abstract

Aim

To systematically review the evidence for clinical rating systems in the assessment of outcomes of UK patients with Lateral Elbow Tendinopathy (LET).

Methods

A systematic search was performed in Ovid MEDLINE, Embase and CINAHL. Studies were included if they reported the administration of PROMs in UK populations with LET. PROMs characteristics and the populations in which they had been used were assessed using a structured classification system. PROMs reporting in randomised controlled trials was assessed against CONSORT standards (PRO extension).

Results

A total of 16 articles were included based on eligibility criteria. Out of seven different PROMs, there was evidence of partial validation for five of them. The assessment of validity, reliability and responsiveness of all PROMs in LET UK populations extended to just 20 individual patients. No articles conformed to the CONSORT PRO extension standards.

Conclusion

There exists a huge paucity of data on the psychometrics and usability of PROMs in UK LET populations. Without these data, trial design and interpretation of health technology assessment are significantly hindered. The high prevalence of this condition allied with the significant volume of studies being conducted into novel treatments, highlight the need for this knowledge gap to be resolved.

4.2 Overview

The standardised EMPRO evaluation, presented in the preceding chapter, has identified the English language PROMs that can be recommended for use in LET. Though this pathology related validity is of utility to the researcher, it is also vitally important that they are confident that the instrument is appropriate, valid and interpretable in the chosen population. In this chapter, the level of evidence available for clinical rating systems in UK populations is explored through systematic review. The evaluation of EMPRO evidence and this cross-cultural assessment can then be used to inform the need for further culturally specific validation.

4.3 Background

Appropriate outcome measures must demonstrate that they are acceptable to patients, reliable, valid and responsive (sensitive to change) [152]. When the outcome measure has been developed in a different clinical or geographical population, there needs to be evidence of equivalence both in a disease-specific and cross-cultural context [153, 222]. The validation of a PROMs in a new language is accepted as integral to its interpretability, what may be less appreciated is the requirement for cultural adaptation, for a PROM delivered in its original language but in a different geographical location and in a different population [219]. Though not previously investigated in elbow pathology, it is notable that a recent evaluation of population norms of English language shoulder outcome measures, the Association of Shoulder and Elbow Surgeons (ASES) shoulder score, University of California, Los Angeles (UCLA) shoulder rating scale and Shoulder Pain And Disability Index (SPADI), administered to

Canadian and Australian population samples reported statistically significant variability in the scores between the two countries [223]

A structured assessment of outcome measurement in LET in UK populations has not been undertaken. This study aimed to address this gap by systematically assessing the outcome measures used for measuring PROMs in Lateral Elbow Tendinopathy in a UK population, and to assess the reporting of randomised controlled trials using PROMs in LET. Only when valid outcomes have been identified, can recommendations on choice of outcome measures for future research be made.

4.4 Methods

PRISMA guidelines on the reporting of systematic reviews were followed [159] (appendix 8). All articles reporting the development, psychometric evaluation, or use, of clinical rating systems in LET in UK adults (≥18yrs) were included. Any measures of symptoms and functioning in LET that involved a patient-centred outcome measurement (regardless of whether this also contained a physician-reported outcome component) were included. Studies in paediatric populations, case-reports, case-studies and conference abstracts were excluded.

The search strategy and resultant systematic review database applied in chapter 2 was re-analysed. The specific inclusion/exclusion criteria above were applied to full-text articles identified from the chapter 3 EMPRO evaluation. Dual screening was utilised.

At the full-text level, articles were also sub-categorised in two groups to: articles reporting primary research on the development and/or psychometric evaluation

of PROMs in LET in UK populations (development); and articles reporting the use of outcome measures in clinical studies in UK populations (use).

Data synthesis

Development articles were classified according to three guiding concepts, using the structured classification system proposed by Valderas and Alonso [143]: construct (the measurement object), population (based on age, gender, condition and culture) and measurement model (dimensionality, metric and adaptability) [143].

The assessment of construct denotes, for the purpose of this study, the range of characteristics measured by the outcome measure, which are affected by LET. The construct analysis has, at its foundation, the conceptual strengths of the Wilson and Cleary model [224] in which psychological variables, symptom status, functional health, general health perceptions, and overall quality of life are considered in an attempt to unify biomedical and social science paradigms and build and overarching conceptual model of Health Related Quality of Life (HRQoL) [225]. The Valderas and Alonso integrate the Wilson and Cleary model with the similar theoretical model that underpins the International Classification of Functioning, Disability and Health (ICF), this classification system proposed by the World Health Organisation is based on the sociological perspective of health and considers disability along the whole functioning continuum [143]. The integration of these models thereby produces a descriptive classification system for PROMs based around valid conceptual models of health. A strength of the model that is particularly pertinent in the assessment of LET outcome measures, is the systematic consideration of intended population of use. Within

the axis of population, consideration of culture is also made, where there is information pertaining to the dyad of language and country for which the outcome measures have been devised.

It should be noted that this system is only descriptive and does not provide any fundamental evaluation of measurement properties [143]. But in this stage of outcome measure assessment, where the adequacy of information to conduct a full culturally specific standardised assessment (e.g. EMPRO of COSMIN), this approach provides the clearest method of identifying the candidate pool of measures.

Articles reporting the use of clinical rating systems were all peer-reviewed, published articles with outcome measure evaluation in a population of LET patients. Date of publication, outcome measure(s) chosen and population of use were extracted. For randomised control trials, the CONSORT Patient-Reported Outcome (PRO) extension [218] was used to systematically assess the reporting of outcome measure choice and justification. The original CONSORT statement aims to encourage transparent and complete reporting of clinical trials and is associated with improved reporting practice [226].

An *a priori* hypothesis was formulated with regard to informed choice of outcome measures in UK populations. We hypothesised that articles reporting the use of PROMs would more frequently use PROMs for which there would be evidence from studies of validation of such measures in specific UK populations.

4.5 Results

From the original 7,261 records derived in chapter 2,236 articles reporting metric properties of elbow/upper limb instruments in LET derived in chapter 3 were re-analysed, yielded 16 articles that met the UK specific inclusion criteria. This comprised five articles reporting the development and/or psychometric evaluation of outcome measures in LET-specific patients and 11 articles reporting their use in a UK population (Figure 4.1) (appendix 9).

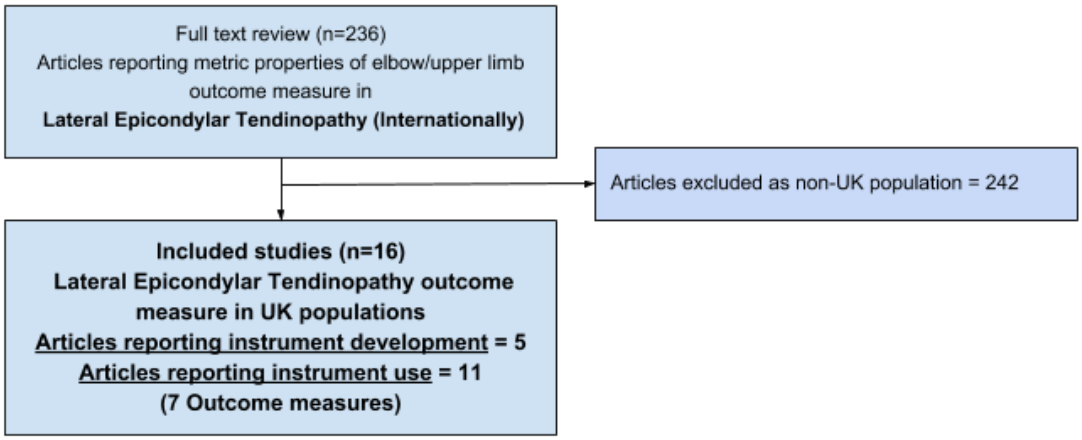


Figure 4.1: PRISMA Flowchart of the UK specific elements of the systematic literature review.

Measures

Five outcome measures were identified that were developed, or had undergone psychometric evaluation, on UK populations that at least, in part, contain patients with LET (Table 4-1). They were all fully standardised measures that had all been developed for measuring symptoms (mainly pain) and functioning in English speaking UK adults of either gender. However, only one of them, the Patient-Rated Tennis Elbow Evaluation (PRTEE) was LET-specific, the remaining instruments were developed as elbow-specific tools designed for

varying pathologies, but including in their validation a sub-sample of LET patients. Two outcome measures were originally developed for UK populations: the Oxford Elbow Score (OES) and the Liverpool Elbow Score (LES). The remaining three outcome measures were developed in the English language outside of the UK (US, Canada and Australia), but had undergone some level of psychometric evaluation in UK populations. Of note, no modification was deemed necessary in the wording or description of the symptoms or activities measured for any of those instruments.

Only the PRTEE has been assessed in a UK cohort that was exclusively diagnosed with LET in an assessment of its interpritability. This was conducted on 57 patients to quantify the Minimally Important Difference (MID) of the PRTEE. This study formed part of a larger prospective trial assessing microcurrent therapy in LET and analysed data from 57 individuals with clinically and sonographically diagnosed LET who all underwent microcurrent therapy. They report a weak correlation between the PRTEE and global change scale, but no assessment of construct validity or any other metric assessment was undertaken and hence, it cannot be used as formal evidence of cross-cultural validity. For the four remaining outcome measures, the proportion of patients included within their study cohorts who were diagnosed with LET ranged from 11% to 12.7% (Table 4-1). None were evaluated in more than 12 patients, and as multiple measures were reported on the same patient cohorts, when all individual patients from these studies were tallied, it reveals that this equates to 20 UK LET patients in total.

Eleven additional articles reported using PROMs to evaluate disease impact in UK populations with LET. These studies were published between 2003 and 2014 (Table 4-2). Out of the five outcome measures for which there had been a previous psychometric evaluation, only three were subsequently applied to evaluate LET outcomes (DASH, OES and PRTEE). The outcome measures that were not utilised were the LES and the Mayo Elbow Performance Score (MEPS). Perhaps more surprisingly, two additional measures were used, the Nirschl score and the Patient-Rated Wrist Evaluation (PRWE), although no evidence on the psychometric properties or even their cross-cultural equivalence was available. Overall, the PRTEE (and precursor PRFEQ) was reported six times, the DASH four times, the Nirschl score twice, the OES once and the PRWE once. Seven of the 11 studies stated that the outcome measure was their study's primary outcome.

Outcome measure	Country of origin	Exclusively Patient Reported (no. items)	Construct (no. items)	Population*	Measurement model $	UK LET assessment
Oxford Elbow Score (OES) [142]	United Kingdom	Yes (12)	A1. Symptoms Pain (4) A2. Function Elbow function (4) Psychosocial (4)	Assessment of outcome of surgery of the elbow [142]	C1. Profile C2. Psychometric C3. Completely Standardised	Surgically treated LET patients make up 11.2% (n= 12/107) of the total development and validation cohort [142, 167, 227]
Liverpool Elbow Score (LES)[204]	United Kingdom	No, physician administered (15)	A1. Symptoms Pain (1) A2. Function Range of motion (4) Strength (1) Ulnar nerve function (1) Activity (8)	B1. Adults B2. All genders B3. Assessment of elbow pathology in tertiary care setting [204] B4. UK English	C1. Index C2. Psychometric C3. Completely Standardised	Tertiary care patients with LET make up 12.7% (n=8/63) of the total development and validation cohort [204]
Patient-rated Tennis Elbow Evaluation (PRTEE)[206]	Canada	Yes (15)	A1. Symptoms Pain (5) A2. Function Activity (10)	B1. Adults B2. All genders B3. Lateral Epicondylar Tendinopathy patients [206] B4. UK English	C1. Index C2. Psychometric C3. Completely Standardised	57 LET patients (100% of cohort) [228] (MCID only) (PRTEE delivered in a modified form but not formally cross-culturally validated)
Disabilities of the Arm Shoulder and Hand (DASH)[169] **2x Optional modules Work Sporting/performing arts**	US, Canada, Australia	Yes (30)	A1. Symptoms Pain (5) A2. Function Physical function (21) Psychosocial (4)	B1. Adults B2. All genders B3. Applied to multiple elbow pathologies [229] B4. UK English	C1. Index C2. Psychometric C3. Completely Standardised	Surgically treated LET patients make up 11.2% (n= 12/107) of the total development and validation cohort [142, 167, 227]. Tertiary care patients with LET make up 12.7% (n=8/63) of the total development and validation cohort [204]

						(DASH delivered in original form, without any modifications) (UK English DASH translation available from 2015 [230])
Mayo Elbow Performance Score (MEPS)[165] **Physician administered** **8 Items:** **1x pain** **1x Range of motion** **1x Instability** **5x Function**	United States	No, physician administered (15)o	A1. Symptoms A2. Function	B1. Adults B2. All genders B3. Applied to multiple elbow pathologies [231] B4. UK English	C1. Index C2. Clinometric C3. Completely standardised	Surgically treated LET patients make up 11.2% (n= 12/107) of the total development and validation cohort [142, 167, 227] (MEPS delivered in original form, without any modifications)
*** All measures were developed for English-speaking adults of either gender. $ All measures were fully standardised.**						

Table 4-1: Outcome measures for the assessment in Lateral Elbow Tendinopathy (LET) with psychometric evaluation in UK population

Author	Year	Title	Study Type and Population	Outcome measure (* Primary outcome)
Melikyan, E. Y., et al.	2003	Extracorporeal shock-wave treatment for tennis elbow: a randomised double-blind study	RCT LET patients who failed conservative treatment	DASH
Dunkow, P. D., et al.	2004	A comparison of open and percutaneous techniques in the surgical treatment of tennis elbow	RCT LET patients who failed conservative treatment	DASH*
Connell, D. A., et al.	2006	Ultrasound-guided autologous blood injection for tennis elbow	Prospective Cohort LET patients who failed conservative treatment	Nirschl*
Alizadehkhaiyat, O., et al.	2007	Pain, functional disability, and psychologic status in tennis elbow	Cross-sectional LET with symptoms lasting >3 months	DASH PRWE PRFEQ
Connell, D., et al.	2009	Treatment of lateral epicondylitis using skin-derived tenocyte-like cells	Prospective Pilot Study (Not Randomised) LET patients who failed conservative treatment	PRTEE*
Clarke, A. W., et al.	2010	Lateral elbow tendinopathy: correlation of ultrasound findings with pain and functional disability	Prospective Cohort of LET who had not undergone invasive treatment	PRTEE*
Creaney, L., et al.	2011	Growth factor-based therapies provide additional benefit beyond physical therapy in resistant elbow tendinopathy: a prospective, single-blind, randomised trial of autologous blood injections versus platelet-rich plasma injections	RCT LET patients who failed conservative treatment	PRTEE*
Nazar, M., et al.	2012	Percutaneous Tennis Elbow Release Under Local Anaesthesia	Prospective Cohort LET patients who failed conservative treatment	DASH* OES
Stenhouse, G., et al.	2013	Do blood growth factors offer additional benefit in refractory lateral epicondylitis? A prospective randomized pilot trial of dry needling as a stand-alone procedure versus dry needling and autologous conditioned plasma	Prospective Pilot Study (Randomised) LET patients who failed conservative treatment	Nirschl
Maffulli, G., et al.	2014	Assessment of the Effectiveness of Extracorporeal Shock Wave Therapy (ESWT) For Soft Tissue Injuries (ASSERT): An Online Database Protocol	Online Database Protocol of Clinically or Radiologically confirmed LET	PRTEE*
Tonks, J. H., et al.	2007	Steroid injection therapy is the best conservative treatment for lateral epicondylitis: a prospective randomised controlled trial.	RCT LET patients who had not had treatment for the preceding 6 months.	PRTEE

Table 4-2: Studies reporting the use of PROMs in patients with Lateral Elbow Tendinopathy.

Reporting guideline adherence

Four of these 11 studies were randomised controlled trials (RCTs). The level of adherence to CONSORT-PRO standards for reporting PROMs in RCTs for the four trials suggested substantial room for improvement (Table 4-3). No information was available for three CONSORT-PRO standards for any RCT and only partial information was available for the other two standards in a minority of studies.

CONSORT 2010 statement	PRO Extension	Studies meeting the requirements
Structured summary of trial design, methods, results, and conclusions	The PRO should be identified in the abstract as a primary or secondary outcome	1/4
Specific objectives or hypotheses	The PRO hypothesis should be stated and relevant domains identified, if applicable	0/4
Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Evidence of PRO Instrument validity and reliability should be provided or cited if available, including the person completing the PRO and methods of data collection (paper, telephone, electronic, other)	0/4 (validity of PROM in UK population) vs 2/4 (validity of PROM in another LET population) 1/4 (data collection method)
Statistical methods used to compare groups for primary and secondary outcomes	Statistical approaches for dealing with missing data are explicitly stated	0/4
Trial limitations addressing sources of potential bias, imprecision, and, if relevant multiplicity of analyses	PRO-specific limitations and implications for generalisability and clinical practice should be discussed	0/4

Table 4-3: Adherence to CONSORT reporting standards (PRO extension) of UK-based lateral elbow tendinopathy randomised controlled trials.

4.6 Discussion

This study has identified a lack of evidence with which to inform outcome measure choice in Lateral Elbow Tendinopathy in the UK. Future validation of outcome measures in UK populations is required in order to be able to ground any recommendations on a firm evidence base. Furthermore, some outcome measures are currently being used as primary outcomes in UK-based studies in the absence of any evidence for their cross-cultural appropriateness and psychometric properties.

We were able to retrieve at least some evidence of the evaluation of the psychometric properties of five outcome measures. The PRTEE is the only measure specifically designed for the evaluation of a LET population. All measures attempt to measure the domains of function and symptoms in adults. All but the DASH have been designed to assess these domains in reference to the elbow exclusively.

The total reporting of validity, reliability or reproducibility of outcome measures in UK LET patients is limited to 20 patients [142, 204]. All of these patients have been embedded in larger cohorts containing a heterogeneous group of elbow pathology. Due to the limited size of this LET sample, it has been unfeasible to conduct a culturally specific standardised psychometric assessment of the outcome measures using methods such as COSMIN or EMPRO.

The largest assessment outcome measure utility in UK LET patients was published by Poltawski et al [228] and included 57 patients. Although this is by far the largest sample of LET patients of any of the studies included here, outcome interpretability through derivation of MCID score was undertaken with no

evaluation of other relevant psychometric characteristics. The PRTEE was not originally designed for a UK population and no evidence of the assessment of cross-cultural appropriateness is presented. This would always be necessary when applying a new instrument to a different population, as the use of language across continents, though English in origin, confers both linguistic and cultural differences. Even more interesting is that in this case, the need was additionally increased by the fact that items in the PRTEE were altered by the authors prior to administration (the words coffee and milk were removed from the item “Lift a full coffee cup or glass of milk to your mouth’, “pants” were replaced by “trousers” and “washcloth or wet towel” by “wet cloth”). The authors acknowledge that the altering of the outcome measure wording may have altered its measurement properties [228].

In many circumstances it will be completely appropriate and even highly advisable to alter the wording of outcome measures if this has been suggested as needed by patients. When required, it should be undertaken under the principles of cross-cultural adaptation [219, 222]. It is widely recognised that if a measure is to be used across cultures, the items must be both linguistically translated and culturally adapted to maintain the content validity of the outcome measure at a conceptual level [219]. Guillemin et al [232] have proposed scenarios that should alert authors to situations where translation or adaptation should be undertaken. In the situation of an outcome measure being used in another country, but in the same language, cultural adaptation is required. For LET in UK populations, this would be the case for the DASH, MEPS, PRTEE and Nirschl outcome measures. Of note, the DASH and quickDASH score have

been culturally adapted to UK English since 2015 [230]. To the best of our knowledge, this particular score was not used in any of the identified studies.

This study has identified that the reporting of outcome measures in UK LET randomised controlled trials does not conform to the CONSORT-PRO guidance. Though two of the studies were published prior to the guidance publication in 2010, the stark paucity of reporting of outcome measure detail is concerning. This lack of reporting is in line with the deficits in outcome measure validity highlighted through the Valderas [143] classification system. Though we hypothesised that there would be a preference for outcome measures with published validity in the target population, we have identified that with the current level of evidence this is not possible. Long et al (2015) [101] reported in their National Institute of Health Research Health Technology Assessment review of systematic reviews of conservative treatments in LET, that a lack of standardised application of outcome measures hindered interpretation and synthesis of results. They recommend that the inclusion of a valid patient-reported measure of upper extremity function in interventional trials would ease results synthesis. However, though we have identified candidate English language PROMs valid for use in LET, we have identified the lack of a clear choice for specific UK populations.

Limitations

The inherent limitations of this study should be discussed. The search strategy may have failed to identify all outcome measures used, and the identification of the study populations' nationality in interventional trials can be prone to error. However, attempts were made to ensure that the strategy was as robust as

possible. Outcomes in LET can be measured in numerous ways, including grip strength, pain provocation tests and visual analogue scales to mention a few, and this may be a highly legitimate method in UK populations, but was not assessed as part of this study. Although it should be noted that a background literature review (chapter 1) did find that validation studies on these methods had not been undertaken in UK populations. The authors feel that the approach to concentrate on patient-centred outcomes is justified owing to the recommendation by the NIHR in the UK that they are included in clinical effectiveness trials [133, 147]. Furthermore, the use of condition-specific PROMs is increasingly common in musculoskeletal medicine and are collected as part of the English NHS PROMs programme [233]. With the increasing use of PROMs used as primary outcomes in clinical trials, it is therefore highly relevant that their use is rigorously assessed.

4.7 Conclusion

This study has identified that, with current levels of evidence, it is not appropriate to recommend any PROMs for LET studies in UK populations. Though the OES, PRTEE and DASH show potential as patient-reported measures, with domains likely to be appropriate in LET, further assessment is required in UK populations to quantify their validity, reliability, responsiveness and patient acceptability.

5 Chapter 5 - A Comparative Assessment of Patient Reported Outcome Measures for Lateral Elbow Tendinopathy in a UK Population

5.1 Abstract

Background

There is currently no guidance on the validity of Patient Reported Outcome Measures (PROMs) for the assessment of Lateral Elbow Tendinopathy (LET) in a UK population. This study aimed to evaluate the psychometric properties of four candidate instruments, identified as the best performing PROMs in a standardised evaluation of available measures.

Methods

A prospective validation study was conducted assessing the four candidate PROMs. Recruitment was conducted in primary care, secondary care and physiotherapy clinics. Repeat administration at baseline, 1 and 8 weeks allowed assessment of the psychometric properties (reliability, validity, responsiveness and interpretability) of the Oxford Elbow Score (OES), quick Disabilities of the Arm Shoulder and Hand (QDASH), Patient-Rated Tennis Elbow Evaluation (PRTEE) and Patient Reported Outcome Measures Information System (PROMIS). The EQ-5D-5L, Numeric Pain Scale and Global Change Criteria were also collected.

Results

Invitations to 738 yielded 81 recruits, of which 50 completed all questionnaires. Psychometric evaluation suggested adequate internal consistency for all instruments (Cronbach's alpha >0.87), adequate reliability (Intraclass Correlation Coefficient >0.85), construct validity was supported by agreement with hypothesised correlation strengths in all cases, effect sizes were found to be greatest in pain sub-scales (0.56-0.63).

Conclusions

This study's low recruitment and retention constrains it from making clear recommendations on PROMs choice for a UK population of LET patients. The OES, QDASH, PRTEE and PROMIS all performed adequately in the assessment of LET. Generic upper limb measures (QDASH and PROMIS) were not found to be inferior to region-specific (OES) or condition-specific (PRTEE) measures. Measures that allow sub-scale assessment of pain (OES, PRTEE and PROMIS) demonstrated superior responsiveness to change. These findings support the use of the candidate PROMs in future LET research.

5.2 Overview

The previous chapters have highlighted the need for standardisation of outcome measurement in elbow pathology and looked in detail at the English language clinical rating systems available for use in LET. An assessment of these instruments in UK populations has highlighted that use of the candidate PROMs identified in the EMPRO evaluation cannot be fully justified without their psychometric properties being tested in this target population. Therefore, the following study aims to undertake a validation study in a UK-based population of LET patients.

5.3 Background

The extensive systematic review conducted in chapter 3 was the first to assess the psychometric properties and trends in utilisation of patient-centred outcome measures in LET. The evidence for each instrument was independently assessed by two reviewers using the Evaluating Measures of Patient-Reported Outcomes (EMPRO) method evaluating overall and attribute-specific instrument performance [187]. EMPRO scores >50/100 were considered indicative of high performance. Of 7,261 references, 105 articles reporting on 15 instruments developed and/or validated in the English language were identified for EMPRO analysis. Median performance score was 41.6 (range: 21.6-72.5), with four instruments meeting high-performance criteria: the quick Disabilities of the Arm Shoulder and Hand (QDASH) (overall score 72.5/100), Disabilities of the Arm Shoulder and Hand (DASH) (66.9), Oxford Elbow Score (OES) (66.6) and Patient-Rated Tennis Elbow Evaluation (PRTEE) (57.0).

A total of 179 articles reported instrument use of these scores in research studies, with DASH the most frequently reported (29.7% articles) followed by PRTEE (25.6%), Mayo Elbow Performance Score (MEPS) (15.1%) and QDASH (8.1%). Of these popular scores, the MEPS has no history of validation in LET, the DASH is a generic arm score, though robustly designed, its condition-specific LET based validity is limited [173], and it has never been explored in a UK population, the PRTEE, though condition-specific and extensively used, has never been fully validated in a UK population. Within specific UK populations, there is also the use of the Oxford Elbow Score (OES), the only elbow-specific PROM designed and validated in a UK population. However, all validation work of the OES has been conducted on a heterogeneous population of patients with differing elbow-related diagnoses [142].

Internationally, the most rapid increase in utilisation over the last five years has been with the abbreviated DASH score (QDASH). This score was developed with validated item-reduction approaches [207], and since 2010 is reported in 13% of elbow tendinopathy publications, and performed the best in the EMPRO evaluation. It is familiar to clinicians and has a similar number of items to the OES and PRTEE. However, much like the DASH score, it has not been validated in a UK LET population. Owing to these outlined factors, the three PROMs most likely to demonstrate adequate development, validation and appropriate burden in a UK-based population are the PRTEE, OES, and QDASH.

In addition to the above review, it is also important to realise that the PROMs landscape is changing rapidly. Though traditional PROMs of the type stated

above, where a standardised and fixed set of questions are administered, continue to be the predominant type, the use of large question banks and adaptive testing techniques are emerging. There are concerns that fixed length scales may not be adequately assessing the individual, therefore large question banks that utilise adaptive testing based on Item-Response Theory (IRT) modelling, using probability-based computer algorithms select only the minimum number of informative questions, will be more valid on an individual level whilst also reducing respondent burden [234].

The Patient-Reported Outcomes Measurement Information System (PROMIS) developed by the National Institutes of Health (USA) is attempting to address the deficiencies in traditional fixed-length PROMs. Evaluation of several PROMIS computer-based adaptive tests (CATs) in a variety of orthopaedic patients has revealed high correlation with traditional PROMs but with reduced floor and ceiling effects, increased reliability and greatly reduced test length [234, 235]. One of the main drawbacks of CAT testing in PROMs is the requirement for computer-based completion. Therefore there is a significant resource cost in computer infrastructure. To address this issue, PROMIS has also issued fixed-length short forms. Though they are fixed in length and can be administered on paper, the score metric remains fixed to the principles of IRT. This family of statistical models links individual questions to a presumed underlying trait or concept of physical function or pain, represented by all items in the item bank. In upper limb pathology, PROMIS recommend the use of the Upper Extremity Item Bank (46 Items) or short form (7 Items) and Pain Interference Item Bank (40 Items) or short form (6 Items). As yet, these tools have not been assessed in a UK population with elbow pathology.

Currently, evidence on the validity of PROMs in UK populations of LET is lacking to the extent that it is impossible to conform to contemporary PROM reporting standards. The creation of a new measure is not justified in the presence of PROMs that have been identified as processing adequate psychometric properties in their country of original development. This study is aiming to assess the culturally-specific and pathology-specific validity of the best performing candidate PROMS, the QDASH, PRTEE, OES and PROMIS instruments, in a UK population of LET patients.

5.4 Methods

This study was conducted as a cross-sectional validation of elbow-specific Patient Reported Outcome Measures (PROMs) in UK participants with LET. The properties of three PROMs, selected from the EMPRO evaluation identifying them as the best performing candidate instruments, plus one selected as an emerging instrument with a strong psychometric pedigree, were assessed in a UK population. The PROMs were assessed on their ability to perform as health status instruments by being internally consistent, valid, reproducible and interpretable.

Sample size and recruitment strategy

There is no unified method power calculation for validation of PROMs, rather consensus methodologies. The recommended minimum sample size for validation studies (based on optimal numbers for correlations) ranges from 50 to 100 [236-238].

The recruitment strategy targeted participants via three sources. These sources were set to assess a spectrum of tennis elbow symptoms. Participants were sourced in primary and secondary care and through physiotherapy clinics. Recruitment targets for these three sources were set at primary care (n=50), secondary care (n=20), physiotherapy (n=30). The recruitment target split was chosen to be representative of UK treatment practice and give a broad representation of the spectrum of symptoms, however, data assessing the true division of treatment practice in the UK have not been published.

Inclusion and exclusion criteria

Participants were eligible for inclusion if they were adults (>18yrs) with active LET symptoms within the month before the completion of the first questionnaire. To enhance the diagnostic categorisation of the participants, only those with LET diagnosed by a consultant orthopaedic surgeon, general practitioner or physiotherapist were included. No active exclusion criteria will be set owing to the remit of including adult patients with a full spectrum of tennis elbow symptoms.

Recruitment sources

Primary care participants were identified through Read-code analysis at GP practices. Recruitment of practices was facilitated through collaboration with the National Institute of Health Research (NIHR) Clinical Research Network South West Peninsula. Following pilot testing, the Read codes ‘Tennis Elbow’ (N213211), "Lateral epicondylitis" (N2132), ‘Lateral epicondylitis of the elbow’ (N213200) and "Enthesopathy of elbow" (N313) were searched. Following identification, postal communication was used to request participation in the

study. On return of a signed consent form, questionnaires were sent out, completion used pre-paid envelopes for return. Using the NIHR Primary Care Resource Requirement Template, for a sample size of 100, we were recommended to invite 278 patients (50% response rate, 20% screen failure, 10% dropout rate). Estimating a 1.5% prevalence [12] a patient population of 18,519 was estimated to be required to yield 278 invitations. UK average general practice list size is 7,000, therefore initially three local practices were asked to participate.

Secondary care participants were identified at upper limb specialty orthopaedic clinics at three hospital sites (Royal Devon and Exeter NHS Foundation Trust, Plymouth Hospitals NHS Trust, and Torbay and South Devon NHS Foundation Trust). Four orthopaedic consultants (CS, WT, RR and PG) who run weekly upper limb clinics recruited participants and provided questionnaires for participants to complete onsite initially, then postal returns of the one-week and eight-week repeat administrations.

Physiotherapy clinics recruited participants at multiple sites. Recruitment and administration was led by musculoskeletal physiotherapists at each site. Patient information, consent, and questionnaire packs were provided to participants with pre-paid postal returns of the consent form and three questionnaires.

Following the initial return of the consent form, email reminders were sent to all participants who provided addresses to remind them to complete the questionnaires at the three time-points.

Recruitment centres are documented in appendix 12. During the second round of recruitment, a £10 shopping voucher was provided to each participant who completed the 8 week questionnaire process.

Instruments

The Oxford Elbow Score (OES) is a 12-item patient-reported questionnaire. It was developed for the outcome assessment of surgery on the elbow [142]. It has three subscales: elbow pain, elbow function and socio-psychological effects [142]. Each item is scored from 0 (worst) to 4 (best). Scores for each domain are calculated as the sum of each individual item score within that domain. This gives a score range of 0–16 for each domain. Dimensionality analysis isolated three separate domains, with each domain being unidimensional. Therefore composite 'total' scores are not recommended by the instrument developers [142]. Individual domain scores are scaled by converting to a metric score of 0–100 (lower scores representing greater severity) [239].

The Quick Disabilities of the Arm Shoulder and Hand (QDASH) is an 11-item patient-reported questionnaire. It has been designed as a region-specific measure of disability and symptoms in people with any or multiple musculoskeletal disorders of the upper limb [185], and is an abbreviated version of the DASH score. It has three subscales: function, symptoms, and psychosocial impact. Each item is scored from 1 ('no difficulty', 'no symptoms', 'no impact') to 5 ('unable to do', 'very severe', 'high impact'). The composite score has been deemed unidimensional and therefore the items are summed to form a raw score and then converted to a 0 to 100 scale where a higher score reflects greater disability [185].

The Patient-Rated Tennis Elbow Evaluation (PRTEE) is a 15-item patient-reported questionnaire used to measure perceived pain and disability in people with tennis elbow [206]. It has three subscales: pain, usual activities, and specific activities covering two dimensions, pain, and function. Each item is scored on a scale of 0 ('no pain', 'no difficulty') to 10 ('worst ever', 'unable to do'). To calculate the total score, the items of the pain score are totalled out of 50, and the usual activities subscale and the specific activities subscale scores are added [240]. The total score ranges from 0 to 100, where high scores indicate greater pain and disability.

The PROMIS Upper Extremity Short Form 7a is a seven-item patient-reported questionnaire. It has been designed using Item Response Theory to identify an underlying trait represented by a larger item bank of questions. Each item is scored on a scale of 5 ('without any difficulty') to 1 ('unable to do'). It is recommended to administer this alongside the Pain Interference Short Form 6a. This has been produced using the same methodology. The items are scored from 1 ('not at all') to 5 ('very much'). All PROMIS short forms are scored using item-level calibrations. Items are scored through the PROMIS Assessment Centre that looks at the responses to each item for each participant. This is referred to as 'response pattern scoring'. The resultant score is termed the 'T-score', this is a metric on a scale of 0-100, in which 50 is the mean of a reference population, which in this case is a USA-based general population sample (the UK population norms are yet to be assessed).

Co-administration of EQ-5D-5L, numeric pain scale (NPS), and symptom Global Rating of Change (GROC) was undertaken. The EQ-5D-5L is a standardised

patient-reported questionnaire for the measurement of generic health status. It is one of the most commonly used generic health measures and can be converted to UK-specific value index scores using the EUROQOL Index value Calculator [241]. The numeric pain scale is commonly employed in the assessment of pain and measures the participant's attitude to pain characteristics across a continuum of values, a scale from 0 to 10 was utilised [242]. Symptom Global Rating of Change (GROC), also known as transition questions, assess perceived alterations in a condition from baseline and have a history of use in musculoskeletal validation studies [236]. Eleven response options were utilised on a scale from minus five (very much worse) through zero (unchanged) to plus five (completely recovered). Key demographic information was also recorded, including age, weight, side of the affected arm, dominant hand, and profession. To facilitate thorough psychometric assessment, questionnaire responses were collected three times: day one, one week and eight weeks. Repeat administration allowed assessment of validity (baseline and 8 week administration), reliability (one week), responsiveness and interpretability (8 weeks). Present infrastructure does not allow widespread use of electronic PROM collection within NHS hospitals. The validity of the QDASH, OES and PRTEE have, thus far, only been confirmed using paper format [142, 175, 243]. Therefore paper versions of these three PROMs and the short-form versions of the PROMIS PROMs were utilised for the formal analysis and a voluntary parallel electronic administration was offered to the participants.

Examples of the PROMs and patient information pack can be found in appendices 10 and 11.

Funding, ethical approval and portfolio adoption

This study attained a favourable ethical opinion from the East of Scotland Research Ethics Service (REC reference 17/ES/0017) and Health Research Authority (HRA) approval (appendix 13). As this study was conducted at multiple sites, individual site-specific approval was gained from the local NHS trust research and development teams. The study was adopted as part of the NIHR Clinical Research Network portfolio (CPMS ID 33853). The study was funded by grants from the British Elbow and Shoulder Society and Royal Devon and Exeter Hospital Foundation Trust following external scientific review.

Statistical Methods

Data were analysed in STATA (STATACorp, Texas, USA). Statistical significance was set at $p<0.05$. The following measurement properties of the PROMS were examined:

- **Reliability**

Reliability assesses the extent to which scores for objects of measurement that have not changed are the same for repeated measurement under several conditions: for example, using different sets of items from the same PROM (internal consistency) and over time (test-retest) [244]. The essence is the stability and consistency of the measure.

Internal consistency was assessed using Cronbach's Alpha. This measure can be defined as an estimate of the ratio of true variance (variance due to the underlying construct), to total variance (true variance plus error) for a measure [244]. When items are inter-correlated, the collection of items is assumed to

reflect the intended latent construct [244]. An alpha value of between 0.7 and 0.9 is recommended [245]. Values above 0.95 can represent redundancy of items. Importantly, the Cronbach's Alpha should be assessed only within the dimension of interest. For example, when assessing internal consistency of the OES, Cronbach's Alpha should be calculated for each subscale of pain, function and psychosocial [149].

Intraclass correlation coefficient (ICC) was used to assess the test-retest stability of PROMs scores over one-week repeat administrations where symptom scores were felt unlikely to have changed. It can be conceptualised as the ratio of between-group (i.e. repeated administration) variance to total variance [244]. Minimum ICC values of 0.7 are considered acceptable [245] however higher values are required if a score is being used on an individual level [236]. Scores from the baseline and one-week questionnaires, where the participant has graded their GROC as minus one , zero or plus one were utilised to calculate the ICC. Participants who demonstrated change greater than this were excluded from the reliability analysis as this was felt to represent real change beyond error and therefore not true stability of the PROM.

- **Validity**

Validity assesses the relative lack of systematic error, or rather, whether a measure actually measures what it is supposed to [244]. Where no gold-standard or 'criterion' exists, as is the case with LET measurement, quantification of construct validity can be employed. This assesses whether the scores of a measure are consistent with a hypothesis, based on the assumption that the

measure validly quantifies the construct of interest. The *a priori* hypotheses for the above measures were:

- At least moderate correlations (Spearman's rho in all cases) should exist between the PROMs and the generic health measure EQ-5D-5L index score (negative correlations for PRTEE, QDASH and PROMIS pain interference and positive correlations for OES and PROMIS upper extremity).
- At least moderate correlations should exist between Numeric Pain Scale (NPS) and the PROMs pain subscales (positive correlations for PRTEE pain subscale and QDASH, PROMIS pain interference and negative correlations for OES pain subscale), and between the pain subscales themselves. At least moderate correlations should also exist between the functional subscales of the PROMs.
- At least moderate correlations should exist between the PROMs used, as they purport to measure the similar constructs.

Correlation (r) strength was classified as r=0.0-0.29 (none/weak), r=0.3-0.69 (moderate) and r=>0.7 (strong).

Floor and ceiling effects, where the score is the absolute maximum or minimum were evaluated. Assessment of floor effect (worst possible symptoms) was assessed at baseline. Assessment of ceiling effect (complete resolution of symptoms/no pain/normal function) was assessed at eight-week completion. Floor and ceiling effects are felt to be present for a health measure if more than 15% of the study population score the minimum or maximum on any questionnaire (sub)scale [246].

- **Responsiveness**

The ability of the PROMs to detect symptomatic change was assessed using two methods: assessment of correlation between PROM change scores (baseline measurement minus eight week measurement) and Global Rating of Change/generic health measure, and quantification of effect size (mean change score / standard deviation of baseline score) as a method of calculating the extent of change measured by the instrument in a standardised way [247]. Clinical change in LET is known to occur over time as this is often a self-limiting condition. However, change can also occur following an intervention, be it conservative or surgical in nature. The eight-week interval in measurement was implemented to assess conservative change and, where interventions were utilised, improvement post-intervention.

Responsiveness of the PROMs to change will be assessed using *a priori* hypotheses regarding correlation strength:

- The change in PROM score should at least moderately correlate with EQ-5D change scores.
- The change in PROM should at least moderately correlate with the relevant pain or function GROC score change or NPS scores.
- Change scores should at least moderately correlate between PROMs. Again these should be stronger between the PRTEE and OES than between these PROMs and the QDASH and PROMIS scores.

A paired t-test was performed between baseline and 8-week scores with significance set at $p<0.05$. Strength of effect size, in reference to Cohens

criteria [248] (0.2 = small, 0.5 = moderate, 0.8 = large) was compared between PROMs with the *a priori* hypothesis of greater effect size in the PRTEE and OES as elbow specific scores.

- **Interpretability**

This can be defined as the degree to which one can assign quantitative meaning to a quantitative score [144]. The assessment of interpretability was undertaken using both a distribution-based method and anchor-based method.

The distribution-based method was used to define the Smallest Detectable Change (SDC). This represents the smallest intra-personal change score that denotes a difference above measurement error [249]. Initially, the standard error of the measurement (SEM) was calculated using the equation: $SD(baseline)\sqrt{(1 \times (test - retest\ reliability))}$. The test-retest score utilised was already quantified as the Intraclass Correlation Coefficient (ICC). As we were taking multiple measures, this was then multiplied by the $\sqrt{2}$ and then confidence intervals (CI) applied using a chosen Z value, for rigour the 95% CI using the Z value 1.96 was applied using the method proposed by Terwee et al [236, 250].

Interpretability was also considered using the anchor-based approach, whereby the relationship between the PROM and the patient-reported Global Rating of Change (GROC) was assessed to achieve a Minimal Clinically Important Difference (MCID) score. This score is defined as the smallest measurable change that is perceived as significant by patients [251] which differentiates it from the statistical approach of the distribution-based method. This process

assesses the change scores in the group of patients deemed to have experienced ‘minimal change’. For this cohort, we selected the patients who scored plus two (+2) to plus three (+3) on the GROC for pain or function. Thereby selecting patients likely to have changed beyond error (+1) but less that those experience a more than minimal difference (>+3). The MCID is defined as the mean change score of the PROM for this subgroup of participants. This MCID was related to the specific pain or function domain, dependent upon whether it was derived from the pain or function GROC. In composite scores (qDASH and PRTEE total) an average of the GROC for pain and function was taken.

5.5 Results

Between 12/4/2017 and 1/12/2017 invitations to participate were sent to 738 primary care and physiotherapy patients. In secondary care, 30 potential participants were identified and invited to participate in the outpatient clinic. Of the 738 invitations, 81 individuals agreed to participate (10%) (n=23 primary care, n=34 physiotherapy care, and n=24 secondary care). Of the 81 recruited participants, 50 (62% of recruited, 7% of invited) completed the eight-week questionnaire process (n=13 primary care (26% target), n=19 physiotherapy care (63% target), and n=18 secondary care (90% target). The average age of the participant was 54 yrs (range 31-78yrs), 34 were female and 16 male. The LET affected the dominant hand in 37 (74%). The average duration of symptoms was 2.43 years (mean), 1.5 years (median) (Range 1 month – 14 years). Seven (14%) of participants were manual workers. Mean baseline

scores subcategorised by sex, recruitment source and symptom duration is seen in Table 5-1.

	No.	*OES pain*	*OES function*	*OES ΨS*	*QDASH*	*PRTEE total*	*PROMIS UE*	*PROMIS Pain*
Male	16	50.55	63.60	50.74	43.34	56.34	34.17	59.90
Female	34	53.52	68.75	56.64	37.94	43.38	35.69	59.23
Primary care	13	49.04	57.21	46.63	48.04	62.77	31.78	63.03
Physiotherapy	19	56.91	74.67	64.14	31.76	47.19	36.85	57.74
Secondary care	18	47.57	61.11	44.79	47.36	49.44	34.42	59.33
Duration <6 months	11	52.27	69.89	55.68	37.27	39.55	35.33	58.95
Duration >6months	39	51.28	63.94	51.76	42.83	55.74	34.47	59.89

Table 5-1: Subcategories of mean baseline PROMS scores.

N.B., OES ΨS denotes OES psychosocial subscale score.

Results are presented for paper completion only as voluntary electronic data collection was not completed by any study participant.

Reliability

Cronbach's alpha was assessed for the three subscales of the OES, the QDASH, PRTEE, PROMIS Upper extremity and PROMIS pain, with all exceeding the threshold value of 0.9 with the exception of OES pain (Table 5-2).

	OES pain	*OES function*	*OES ΨS*	*QDASH*	*PRTEE*	*PROMIS UE*	*PROMIS Pain*
Cronbach's alpha	0.87	0.91	0.93	0.93	0.97	0.94	0.94

Table 5-2: Cronbach's alpha values for all scales.

There were 27 participants whose symptoms did not change between repeat administrations (GROC = -1 to +1). The results from these participants were used for test-retest reliability (ICC) (Table 5-3).

	OES pain	*OES function*	*OES ΨS*	*QDASH*	*PRTEE*	*PROMIS UE*	*PROMIS Pain*
ICC	0.93	0.97	0.97	0.96	0.93	0.96	0.85
(95%CI)	(0.83 to 0.97)	(0.93 to 0.98)	(0.92 to 0.99)	(0.90 to 0.98)	(0.85 to 0.97)	(0.92 to 0..98)	(0.70 to 0.93)

Table 5-3: Intraclass Correlation Coefficient (ICC) (95%CI) in participants with stable scores between collection points 1 and 2.

Ceiling and floor effects, whereby absolute maximal (i.e. no pain or functional limitation) or minimal (worst possible pain or function) values as demonstrated by the PROMs was assessed. Floor effects were assessed at baseline, percentage of respondents demonstrating lowest possible scores; OES pain 0%, OES function 0%, OES psychosocial 7.1%, QDASH 0%, PRTEE pain 0%, PRTEE function 0%, PRTEE total 0%, PROMIS UE 0%, PROMIS pain 0%. Ceiling effects were assessed at eight-week completion; OES pain 14.8%, OES function 18.5%, OES psychosocial 7.4%, QDASH 3.8%, PRTEE pain 3.7%, PRTEE function 7.4%, PRTEE total 3.7%, PROMIS UE 3.7%, PROMIS pain 18.5%.

Validity

Correlation between instruments was found to be broadly consistent with *a priori* hypotheses of direction and strength. Spearman's rho between baseline PROMs scores and generic health PROM EQ-5D-5L index scores are seen in Table 5-4 and are classified as strong correlations in all cases.

	OES pain	*OES function*	*OES ΨS*	*QDASH*	*PRTEE*	*PROMIS UE*	*PROMIS Pain*
EQ5D-5L	0.78	0.76	0.83	-0.79	-0.74	0.75	-0.80

Table 5-4: Correlation between PROMs baseline scores and the EQ-5D-5L as a generic health measure

Correlations for the pain dimension were assessed between the relevant PROM or subscale and the Numeric Pain Scale (NPS). All correlations were graded as moderate both between the PROM and NPS and strong between the PROMs themselves (Table 5-5).

	OES pain	*QDASH*	*PRTEE pain*	*PROMIS pain*	*NPS*
OES pain	1.00				
QDASH	-0.84	1.00			
PRTEE pain	-0.80	0.92	1.00		
PROMIS pain	-0.79	0.86	0.80	1.00	
NPS	0.43	-0.45	-0.43	-0.45	1.00

Table 5-5: Correlation matrix between PROMs baseline pain scores

Functional correlations were assessed between PROMs subscales and again, were uniformly strong (Table 5-6).

	OES function	*QDASH*	*PRTEE function*	*PROMIS UE*
OES function	1.00			
QDASH	-0.92	1.00		
PRTEE function	-0.82	0.79	1.00	
PROMIS UE	0.92	-0.90	-0.86	1.00

Table 5-6: Correlation matrix between PROMs baseline function scores

Responsiveness

Change score correlations were assessed initially between the PROMs and the EQ-5D-5L index score (Table 5-7). These were found to be directionally as expected from the *a priori* hypothesis but moderate rather than strong.

	OES pain Change	*OES function Change*	*OES ΨS Change*	*QDASH Change*	*PRTEE total Change*	*PROMIS UE Change*	*PROMIS Pain Change*
EQ5D-5L Change	0.69	0.63	0.66	-0.75	-0.72	0.64	-0.81

Table 5-7: Correlation between PROMs change score and EQ-5D-5L change

This pattern was reflected in the correlations between the subscale responses and corresponding pain or functional Global Rating of Change (GROC) score or Numeric Pain Scale change score (Table 5-8). Of note is the only just moderate correlation between the change scores for OES function and Global Change Score (GCS) for function.

	OES pain Change	*QDASH Change*	*PRTEE pain Change*	*PROMIS Pain Change*
NPS Change	-0.64	0.51	0.62	0.61
GROC Pain	0.51	-0.55	-0.54	-0.69

	OES function Change	*QDASH Change*	*PRTEE function Change*	*PROMIS UE Change*
GROC Function	0.44	-0.62	-0.60	0.56

Table 5-8: Subscale correlations of PROMs change scores and NPS change or GROC score anchors

The correlations between the PROMs change scores themselves were stronger than against the GCS anchor, with all at least moderate. Of note is no discernable pattern of the superiority of the elbow specific outcomes (OES and PRTEE) and the generic upper arm scores (QDASH and PROMIS) (Table 5-9).

	OES pain	*OES function*	*OES ΨS*	*QDASH*	*PRTEE total*	*PROMIS UE*	*PROMIS Pain*
OES pain	1.00						
OES function	0.78	1.00					
OES Psychosocial	0.75	0.69	1.00				
QDASH	-0.83	-0.85	-0.71	1.00			
PRTEE total	-0.71	-0.65	-0.72	0.79	1.00		
PROMIS UE	0.62	0.53	0.65	-0.67	-0.65	1.00	
PROMIS Pain	-0.70	-0.59	-0.60	0.75	0.76	-0.57	1.00

Table 5-9: Correlations between PROMs change scores

The effect size of the change calculated by the individual instruments was quantified between baseline and 8 week scores. The majority of instruments changed significantly ($p<0.05$) between baseline and eight-week measurements with the exceptions being the OES function and psychosocial, the PROMIS UE and the EQ5D-VAS. The effect size as a comparator between instruments reaches a moderate level (≥0.5) for the pain scores (OES pain, PRTEE pain, and PROMIS pain) and the QDASH (Table 5-10).

	Baseline	SD	8 Weeks	SD	Change	SD	p-value	Effect size
OES pain	52.92	21.96	66.81	25.52	13.89	17.97	0.00	0.63
OES function	66.53	22.42	74.58	24.87	8.06	20.32	0.01	0.36
OES ΨS	54.03	24.86	63.12	28.89	9.09	23.67	0.01	0.37
QDASH	40.20	21.73	29.80	25.88	-11.06	18.56	0.00	-0.51
PRTEE pain	23.96	12.08	17.24	12.94	-6.72	10.25	0.00	-0.56
PRTEE function	27.53	19.62	19.17	19.42	-7.76	17.40	0.00	-0.40
PRTEE total	51.22	29.91	36.41	30.97	-13.67	27.68	0.00	-0.46
PROMIS UE	35.09	7.18	37.98	8.60	2.89	6.20	0.00	0.40
PROMIS Pain	59.39	7.45	54.89	9.51	-4.50	8.12	0.00	-0.60
EQ5D-5L Index	0.65	0.19	0.70	0.22	0.05	0.16	0.02	0.28
EQ5D-VAS	75.67	14.32	75.43	20.81	-1.91	21.56	0.90	-0.13
NPS	4.14	2.91	3.12	2.79	-1.02	2.62	0.03	-0.35

Table 5-10: Mean and standard deviation PROM baseline, 8 week and change score. Paired t-test significance value (p-value) and effect size

Interpretability

The Smallest Detectable Change with 95% confidence intervals (SDC 95) was calculated for the PROMs using the baseline standard deviation and previously described ICC values (Table 5-11).

	OES pain	*OES function*	*OES ΨS*	*QDASH*	*PRTEE pain*	*PRTEE function*	*PRTEE total*	*PROMIS UE*	*PROMIS Pain*
SEM	5.90	3.89	4.38	4.41	2.42	6.63	7.97	1.48	3.25
SDC 95	16.35	10.80	12.14	12.23	6.71	18.36	22.09	4.11	9.00
MCID Pain	12.83				8.85				4.25
MCID Function		10.71				8.14		3.91	
MCID Composite				8.85			17.82		

Table 5-11: PROMs standard error of measurement (SEM), smallest detectable change (SDC) and subscale minimal clinically important change (MCID)

The Minimally Clinically Important Change (MCID) was derived from participants reporting a Global Rating of Change (GROC) between the baseline and eight-week outcome measurements of +2 to +3 on the 11 point scale. This was separately assessed for the pain GROC (n= 19/50) and the function GROC (n= 14/50). The mean change scores for the individual PROMs for these groups are reported as the MCID for the relevant pain or functional subscale, or composite total score (Table 5-11). The MCID for the OES psychosocial (OES ΨS) could not be calculated owing to the GROC not being anchored to this domain. Of note is the SDC being higher than the MCID for all scores except PRTEE pain, against the *a priori* hypothesis.

5.6 Discussion

This study has aimed to address the gap in the assessment of psychometric properties in a UK population of Lateral Elbow Tendinopathy (LET) patients. Though this remains the largest study to date for the target population, more than doubling the currently available evidence base, it is unfortunate that due to very poor recruitment and retention of participants, we are only able to report preliminary results confirming the validity of the OES, PRTEE, QDASH and PROMIS instruments.

The overall participant retention rate for this study was 7%. Throughout the course of the study, efforts were made to optimise the recruitment and retention, this included substantial ethical and protocol amendments to make the patient information documents as concise and clear as possible, instituting financial incentives (£10 shopping voucher) and telephone follow-up to discuss and encourage participation. Despite these measures, the recruitment rate

remained low. There may be multiple reasons behind this but they are likely to be broadly associated with two key factors, participant burden and the natural history of the LET. It is appreciated that the burden of completing multiple questionnaires, over an eight-week period, in a group where patients are not all being actively managed in a healthcare setting, is very challenging. The individual questionnaires used were intentionally short, but the total number still amounted to a seven-page booklet. Importantly, the questionnaires were not piloted in a patient or lay group prior to the study commencing which may have influenced an amendment in the structure of the data collection. The participants did not see the questionnaires until they were recruited and although 62% of those recruited did complete the questionnaires, this could have been imporved it the questionnaires were reduced. Though email reminders were sent, remembering to complete the questionnaires in a timely manner and then post the prepaid envelopes back to the research team may not be appropriate or feasible for the majority of people. Though the quantity of data required was significant, it is worth noting that it was the minimal amount required to attain the level of detail needed to meet the requirements of the psychometric calculations. A potential route to improving this situation, particularly in this study's working age demographic, is the utilisation of remote electronic data collection via a web interface or mobile application. There are distinct challenges for this to be achieved, firstly a cross-validation of equivalence of the questionnaires in electronic format would be required. Following this, it is still the case that the creation of such an interface can be very costly, greatly exceeding that of paper communication. An electronic system for completion of a Computer Adaptive Test (PROMIS) was offered in

this study, though additional to the paper questionnaires and optional, it is relevant to note that no participants completed it. Though electronic data capture in the UK has been very successful in some instances [252, 253], it is interesting that within the UK the national PROMs programme continue to only offer paper-based completion of PROMs after hip and knee arthroplasty procedures [233], and that paper collection of PROMs in clinical scenarios remains the status quo.

The natural history of this condition may have inhibited the ability to collect substantial data. As a largely self-limiting condition, many of the invited participants' symptoms may have resolved. It is, therefore, noteworthy that the recruitment for primary care, who were sourced through recent Read code categorisation in GP records, was particularly poor, and that previous attempts at validating PROMs in LET have focused exclusively on surgical or secondary care participants who complete their questionnaires in a clinical setting [142, 206, 217, 228]. This recruitment bias alters the generalisability of the results owing to the fact that the large majority of LET sufferers are treated with simple community care. It is also interesting that this is likely to be a difficulty that is common to the validation of PROMs in a variety of self-limiting musculoskeletal conditions. Finally, it is vital to note that the acquired population within this study may not be representative of a "normal" LET population. The average age of the participants (54yrs) is relatively high when compared to epidemiological studies of LET in populations which point to the greatest prevalence between 40 - 55 yrs (sanders}. Furthermore, 68% of the study population were female, and only 14% were manual workers which is in contrast to the large epidemiological studies that report broadly equal variance between sexes [12, 17, 18] and

occupational exposure [19]. This limitation in the data may relate to a sampling bias, whereby younger manual workers have been less likely to participate which may relate to the significant burden of questionnaire completion.

The psychometric evaluation of the study should be interpreted in view of the low numbers. Though the recommended number of participants (50) for assessment of associations (correlations) [250] was reached, estimates of reliability and interpretability cannot be confirmed with the numbers presented, although true sample requirements for psychometric assessments of these aspects has not been defined. Though the presented figures should be viewed with caution, as a marker of potential accuracy the psychometric findings can also be compared against the best available standards of comparable patient groups.

Initially, the reliability of the instruments was assessed, starting with their internal consistency. This measurement quantifies the interrelatedness of the items of a single domain [236]. The findings from this study are comparable to non-pathology specific studies for the OES [142, 193, 254] and the QDASH [255] with alpha values over 0.9. The pathology-specific PRTEE results were comparable to the non-UK population [175, 180]. The PROMIS scores have not been assessed specifically in elbow disorders, but this study would suggest that they are internally consistent.

Test-retest reliability results were also strikingly similar between this study and previous non-UK studies of the PRTEE [175, 176, 206, 256] and a UK-based OES assessment of elbow surgery patients [142]. Test-retest for the QDASH has only been reported once in LET patients in a USA-based population [217]. In this

retrospective review of QDASH scores taken over an entire treatment period (Mean 39 days), using GROC of -2 to +2 (15 point scale) to denote stability between start and end visit, the authors report an ICC of 0.69, worse than that found in this study with GROC scores of -1 to +1 (11 point scale). The retrospective nature of this study, extended time between test-retest, and the addition of treatment during this period, is likely to have had an effect on the robustness of their findings and comparability to the findings presented in this study. The PROMIS scores have not been assessed in isolated elbow pathologies. Results from this study suggest that the OES, QDASH, PRTEE, and PROMIS scores are internally consistent at an item domain level, and reliable on repeat administration, however assessment in a larger sample would be recommended.

There is no literature on the LET specific construct validity of OES or PROMIS scores, a single study has assessed the validity of an English language QDASH score, in an American LET population, against a GROC score and using a Pearson's correlation (r=0.39)[217]. The Turkish version of the QDASH has been assessed against the Turkish PRTEE, where r=0.59 [174]. The construct validity of the PRTEE has been assessed against the non-abbreviated DASH score on numerous occasions, and in multiple languages (results ranging from r=0.67 [174] to r=0.88 [180]), but not in UK populations. None of the PROMs have been assessed against the standardised EQ-5D-5L in LET. Results from this study support convergent construct validity between the EQ-5D-5L UK index and all of the included PROMs (r>0.71 in all cases) and between the PROMs themselves both for total scores and subscales. The concordance in the validity of the PROMs in a homogeneous population of LET, when measuring similar

constructs, would be expected to be strong, however, the hypothesis that the region-specific OES and PRTEE would demonstrate superior concordant validity was not met, demonstrating that the QDASH and PROMIS instruments may possess similar levels of construct validity.

The responsiveness of the PROMs was initially explored through assessment of the correlation of change scores with the EQ-5D-5L change score. Moderate to strong change scores correlations were seen for all PROMs implying LET has a significant impact on general health and quality of life. This was further explored through correlations between subscale correlations and NPS or GROC pain or function change scores, moderate correlations were found for all PROMs. In the only assessment of PROMs change scores in LET, Smith-Forbes et al [217] report a comparable correlation strength between the QDASH and GROC scores of r=0.39.

Responsiveness was also judged through an assessment of statistical change between the baseline and eight-week completion, all PROMs were found to have changed ($p<0.05$). Effect size was calculated to allow comparison between scores. According to Cohen's criteria [248], all of the effect strengths can be categorised in the mild to moderate range. Higher effect sizes have been calculated for the OES [227] and PRTEE [176] but these stand as reflections of the patients within the study, that were part of interventional trials or undergoing surgical treatment. As a group of LET sufferers primarily undergoing conservative therapy, the effect size in this study is likely to be muted and stand better as a comparison between the PROMs themselves. Of note, are the stronger effect sizes seen in the pain subscales (OES pain 0.63, PRTEE pain

0.56 and PROMIS pain 0.60), in comparison with the functional scores (OES function 0.36, PRTEE function 0.40 and PROMIS UE 0.40), highlighting that for the patient, LET is a pain predominant condition, and both treatments and outcome assessments should be directed at this. This may suggest that the isolated use of composite scoring of the QDASH (Effect size 0.51) and PRTEE total (0.46), where pain and functional domains are combined, in interventional trials may risk the underestimation of treatment effect.

Finally, the interpretability of the scores should be discussed. Minimally important change scores are increasingly applied in the analysis of outcome measure results, under the knowledge that simple statistical differences mask difference that may be due to measurement error, or not clinically discernible at a patient level. Numerous methods have been ascribed to undertake this assessment, in this study two methods were employed, the assessment of Smallest Detectable Change (SDC) and application of the anchor-based methods to derive a Minimally Important Clinical Difference (MCID) using the mean change method. There are particular nuances to the use of these scores that need to be regarded. These values (SDC and MCID) are population and condition specific, and should not be applied to studies outside of this context [250, 257], and comparison of an MCID can only be justified if similar GROC and decision limits are applied [258]. Furthermore, the results should only be applied on an individual level, where the MCID can be used to dichotomise a group into those responding or not responding to an intervention [257] (as long as the individuals score is above the SDC that assesses measurement error). However, some ascribe to the raw SDC score being scaled to the particular study by being multiplied by the square root of the sample size being used [250].

The scores derived in this sample remain broadly equivalent to those published for the OES [227] (pain SDC_{90} 8.25, MCID 12.5, function SDC_{90} 18.73, MCID 5.0, psychosocial SDC_{90} 9.3) in elbow surgery patients, but are lower than those published for LET patients with the QDASH in American populations [217] SDC_{90} 22.49, MCID 15.3. In an Italian population of mixed upper limb patients (including LET) the findings of QDASH SDC_{90} 12.85 are more in line with this study's SDC findings, though we have reported the narrower confidence intervals of SDC_{95}. The MCID of the PRTEE was assessed in a UK population, but using a modified questionnaire without confirmation of validation, limited GROC, and no subscale analysis, the MCID was 7 for the PTREE total [228], these findings are substantially lower than the MCID calculated in the current study. Values for PROMIS have not been published, and it is relevant that as their norm values are based on an American population, they would be difficult to interpret. Overall, it must be stated that the MCID values reported should not be applied without further assessment owing to the small number of participants used in this analysis.

This study held the *a priori* hypothesis that the SDC (measurement error) should be lower than the MCID (patient relevant change). This hypothesis was violated for all instruments. Though this is a finding in PROMS interpretation that is not particularly uncommon [64] and has previously been demonstrated for the OES function [227], it can limit the PROMs utility as you cannot distinguish relevant change from measurement error. As with the other psychometric calculations, the inadequate sample size is of major relevance, however, the broad equivalence of the combined interpretability data with other populations,

namely the only other UK population with the OES [227], suggest that the instruments do have utility and justifies their continued exploration.

Limitations

This study's assessment of the psychometric properties of the included PROMs is overwhelmingly limited by its small sample size. The reasons behind the low recruitment and retention numbers have been discussed. Working with the current recruitment rate, to reach a sample size of 100, one would have to invite 2,635 individuals with a recent diagnosis of LET. This would require considerable resources and may not be feasible. However, the author would like to point out that the assessment of PROMs psychometrics in community populations of self-limiting conditions is very rarely undertaken, this study highlights the challenges in undertaking such research and therein such work may require different, or at least more flexible, methodologies. A discussion on such aspects is vital as these conditions are commonly researched and there is a rapidly increasing utilisation of PROMs as a study outcome, of which many may not be appropriately validated.

Unfortunately, the routine collection of PROMs in primary or secondary care does not occur within the NHS for musculoskeletal conditions, therefore secondary data analysis is unlikely to be feasible. The analysis of psychometric properties of outcomes within clinical trials is also challenging as the data collection schedule does not often correspond to the optimal schedule for psychometrics and the use of GROC anchors is not often employed. The authors were unable to identify data from UK-based studies that could have supplemented this study.

Though preliminary results from this study suggest potentially adequate psychometric properties, there are two notable aspects that would need to be addressed even in the context of an adequate sample size. Though the convergent construct validity may be confirmed, as the OES, QDASH and PROMIS scores were not originally designed for use in LET, it would be necessary to assess the content validity in this context with supplemental qualitative interview data from patient groups [135, 259]. The minimal change data (SDC and MCID) should also be carefully regarded. Firstly, the MCID scores, though derived in this cohort require assessment in larger cohorts prior to any application in clinical study. Furthermore, owing to limited numbers, overall SDC and MCID scores were derived; however, the value of these scores is dependent upon the patient's baseline status and their demographic details. Therefore secondary care patients, physiotherapy patients, and primary care patients may all derive different scores and sex, age, occupational status etc may also have a bearing that should be assessed. The methodological caveat to this being that even greater cohorts of patients are required.

5.7 Conclusion

This study aimed to evaluate the psychometric properties of four candidate PROMs, the OES, QDASH, PTREE, and PROMIS in the assessment of Lateral Elbow Tendinopathy. Poor recruitment and retention inhibit the recommendation of any particular PROM, or position on the superiority of particular instruments, but the results of this study suggest that all four instruments may possess adequate reliability, validity, responsiveness and interpretability for use in UK-based LET patients. This study highlights the difficulty in collection of data in

musculoskeletal conditions of a self-limiting nature. Future studies may optimise data collection through the use of electronic PROMs or analysis of routinely collected data, if available within their healthcare system.

6 Chapter 6 - The Spread of Injectate after Ultrasound-Guided Lateral Elbow Injection – A Cadaveric Study

6.1 Abstract

Background

Injections into the tendinous portion of the common extensor origin are a common intervention in the treatment of Lateral Elbow Tendinopathy (LET). Clinical trials report a heterogeneous selection of injectate volumes and delivery techniques, with systematic reviews finding no clear consensus. The aim of this study is to assess the intratendinous distribution and surrounding tissue contamination of ultrasound-guided injections into the Common Extensor Tendon (CET) of the elbow.

Methods

20 cadaveric elbows were injected by a Consultant Radiologist under Ultrasound guidance. Elbows were randomised to equal groups of 1 or 3mls of methylene blue injection, delivered using single shot or fenestrated techniques. Following injection, each cadaver underwent a dry arthroscopy and dissection of superficial tissues. The CET was excised, set and divided into 1mm sections using microtome. Each slice was photographed and analysed to assess spread and pixel density of injectate in four colour graduations. The cross-sectional area of distribution was calculated and compared between groups.

Results

In all 20 cadaveric samples, contamination of the joint was noted on arthroscopy and dissection. Injectate spread through over 97% of the cross-

sectional area. No differences were found in intratendinous spread of injectate between differing volumes or techniques.

Conclusion

This study found that commonly used injection volumes and techniques distribute widely throughout cadaveric CETs. There was no improvement when the volume was increased from 1 to 3mls or between single shot of fenestrated injection techniques. It should be noted that joint contamination using these techniques and volumes may be inevitable.

6.2 Overview

The background literature review presented in chapter 1 reveals that though injection therapy remains a popular and heavily researched intervention in LET, the evaluation of the fundamental aspect of injection distribution has not been adequately addressed. This cadaveric study attempts to further our understanding of injection delivery mechanics and aims to assist in the future rationalisation of injection technique.

6.3 Background

Injection therapy for chronic lateral elbow tendinopathy (LET) remains a popular treatment choice [260]. Though corticosteroids were historically the most common preparation, recent evidence of its negative long-term sequelae [45] may see its usage decline. However, the emergence of novel therapies such as platelet-rich plasma (PRP), autologous blood (AB), botulinum toxin, glycosaminoglycan polysulphate, sodium hyaluronic or prolotherapy continue to promote interest in injection treatment. Systematic reviews of these therapeutic options remain inconclusive, with a recurring criticism of the heterogeneity of injection dosing and technique between studies [101, 106, 117-119].

Pathological change in LET occurs within the proximal tendons of the common wrist extensor muscles, with particular reference to the extensor carpi radialis brevis (ECRB). Hence this is the intended site of injection therapy in LET. The ECRB tendon originates from the lateral epicondyle, lying deep to the remaining common extensor tendons and superficial to the thin articular capsule of the elbow [35]. Injection volumes delivered to this area commonly range from 0.5 – 3.5mls [106] and employ either a single shot or fenestrated (pepper pot)

administration techniques [106, 117]. Cadaveric assessment has only been undertaken for anatomically guided injections [261]. The injections were delivered by experienced clinicians using their standard techniques, the study reported poor localisation of injectate, within only 33% (partially) localised to the ECRB tendon and 60% localised intra-articular.

The location of the injectate in lateral elbow injections is of clear importance. Under the premise that many of these substances confer benefit due to their active constituents, it is of vital importance that the retention and distribution of injectate within the tendon is quantified, and furthermore that the commonly employed volumes and techniques are compared. Assessment of the contamination of joint space and surrounding tissues is also warranted owing to the potentially noxious or unwanted effects of botulinum toxin, or the potential chondrolytic effects of corticosteroid [262] and local anaesthetics [263]. This study aims to determine the intratendinous distribution and surrounding contamination of commonly utilised injection volumes and techniques, delivered under ultrasound guidance, in cadaveric specimens. It was hypothesised that ultrasound guidance would ensure accurate delivery to the common extensor tendons and that intratendinous distribution was dose-dependent and improved with fenestrated techniques.

6.4 Methods

In this cadaveric study, 20 fresh-frozen, unembalmed upper-limb specimens from 10 individuals were used. Age of the specimens ranged from 70 to 96yrs, four were female, and six were male. The specimens were sectioned at the upper 3rd of the humerus proximally and radio-carpal joint distally. Specimens

had not undergone previous upper limb surgery. Information regarding any history of tendinopathy or other pathological abnormalities was not known by the authors. Ethical approval (REC 17/NW/0065) was obtained from the NHS North West - Preston Research Ethics Committee.

Injections technique

The specimens were block randomised (block size = four) stratified by side (left or right) to receive either a 1 or 3 millilitre (ml) injection, delivered using a single pass or fenestrated technique, yielding four groups of five specimens. Injection volume was derived from the 25% and 75% percentile of injection volumes from studies reported in a recent comprehensive systematic review [106]. The single pass technique delivered the injection into the mid portion of the anterior Common Extensor Tendon (CET) origin, corresponding to the position of the ECRB [264] and the most commonly injected position, the fenestrated technique used nine passes delivered in a 3x3 square pattern across the anterior CET origin. The injected material was 2.44% methylene blue; all injections were delivered using a 5 ml syringe and 21 gauge needle. Injections were delivered by a Consultant musculoskeletal radiologist, with six years' experience, using a Siemens RS80A ultrasound machine (Seimens, Munich, Germany) using a16 MHz transducer in both transverse and longitudinal planes (Figure 6.1). The prosections were positioned with the elbow flexed to 45-50°. Evidence and size of intrasubstance and footprint tendon tears before and after injection and calcification was quantified using ultrasound.

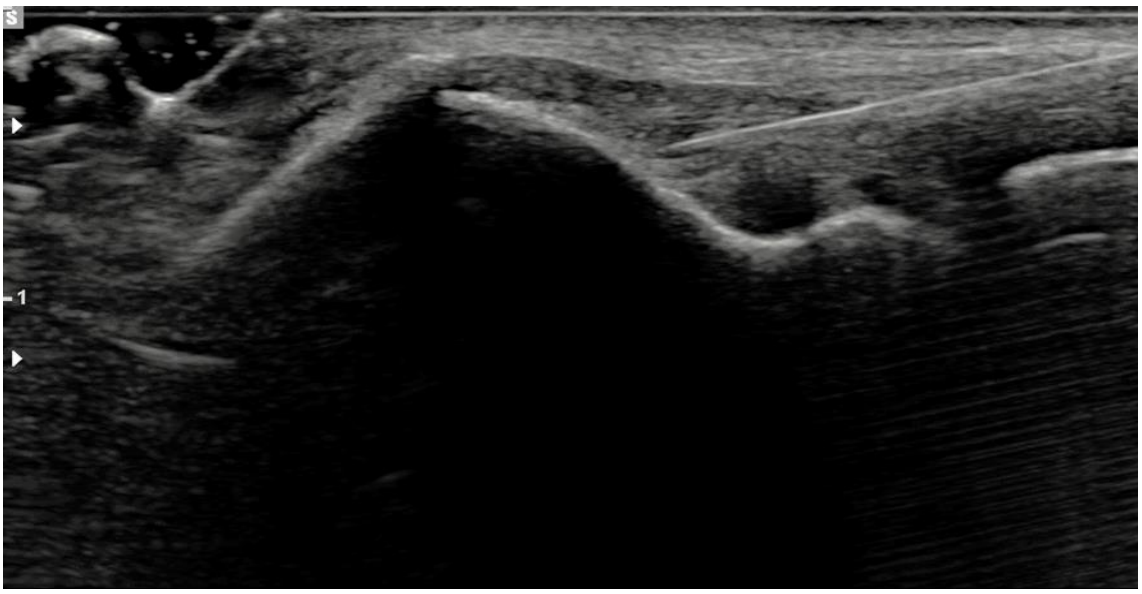


Figure 6.1: Longitudinal ultrasonogram of the Common Extensor Tendon (CET). The hypodermic needle can be seen entering at the right side of the image. This particular specimen underwent a 1ml single shot injection.

Anatomic dissection

Following injection the elbows were positioned with the arm over a bar, mimicking the lateral decubitus position. The specimen was held with a single clamp on the skin overlying the triceps muscle. Dissection was preceded by a dry arthroscopy using a single high proximal anteromedial portal. The presence of joint contamination of injectate was recorded.

Dissection was performed through a posterior midline incision, with subdermal excursion to the lateral side. Soft tissue contamination was recorded. The CET was identified. This was excised proximally subperiosteally to the lateral epicondyle, and distally at least 1cm distal to the musculotendinous interface. The excised CET was transferred to a dissection table where periosteal tissue was removed from the insertion, the musculotendinous junction was identified and tissue distal to it removed, leaving the isolated CET (Figure 6.2). The macroscopic appearance of the CET was digitally photographed and recorded.

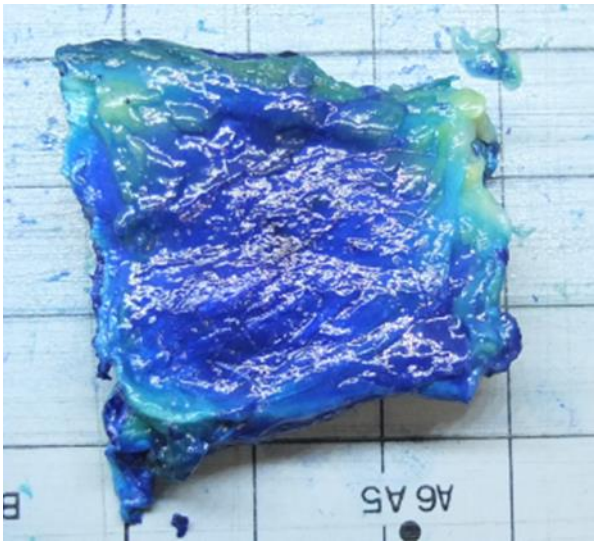


Figure 6.2: Dissected Common Extensor Tendon (CET). Showing non-articular side. Blue colouration from methylene blue dye injection.

Image analysis

The dissected CETs were placed in microtome template and surrounded with low melting point paraffin wax. Specimens were stored in the dissection room cold store at 6°C for 12 hours. The specimens were then mounted in a bench microtome (Brunel Microscopes Ltd, Chippenham, UK) and were sectioned in an axial plane at 1 millimetre intervals. Each section was digitally photographed using a static high-resolution 12-megapixel camera (Fujifilm, Tokyo, Japan).

Each digital photograph underwent a two-stage image analysis process. Semi-automated segmentation of the tendon border from the wax surround was undertaken and lighting normalised between sections using the median intensity of the region outside the tendon/wax specimen. Following this, algorithmic contour lines denoting intensity of the dye (i.e. the retention of the methylene blue from light blue (distributed dye) to dark blue (concentrated dye) in four increments representing quartiles of the blue colour spectrum) were overlaid using the red channel, following light smoothing with a Gaussian filter (Figure

6.3). The second stage quantified the total number of pixels denoting the tendon area, and subsequently, the number of pixels within the four increments of dye intensity was quantified. Pixel number was transformed to fractional area to allow comparison within and between the tendon samples. Finally, the slices were reformatted using the marching cubes algorithm to provide 3-dimensional representations which were visually assessed for patterns of injectate spread and pooling.

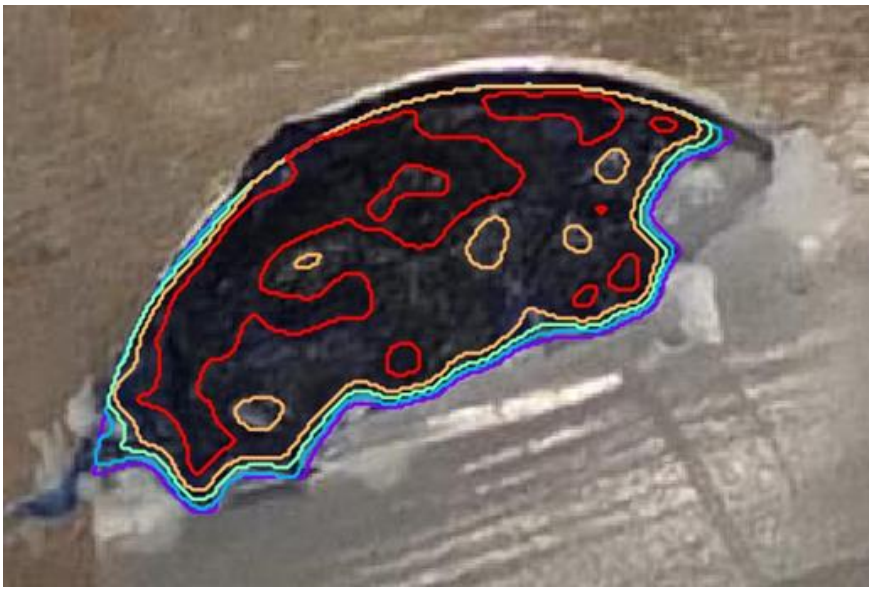


Figure 6.3: Common Extensor Tendon (CET) held in wax surround of bench microtome. The four areas of algorithmically derived colour intensity are seen within each of the four contour lines.

Statistical analysis

The primary outcome, percentage of pixels, is reported descriptively using means and standard deviation. Further analysis was performed using hierarchical linear regression modelling, with a fixed effect on injection technique, injection volume, and dye intensity, and a random effect on the cadaveric specimen, nested within patients. Each specimen was tested under each of the two conditions (technique and volume) with pixel percentage reported in four gradations (density of blue dye). Regression coefficients and

95% Confidence Intervals (CI) are reported and statistically significant differences in pixel percentage between injection technique and volume was defined as a global $p<0.05$ for catagorical variables. All statistical analysis was undertaken using Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

6.5 Results

Pre-injection ultrasound identified that 60% of the 20 cadavers had CET tears, 33% of those tears were located at the footprint and an average size on ultrasound measurement of 5.8mm (Range 6-8mm). Of the eight CETs without a pre-injection tear, the post-injection ultrasound identified a tear in five (62.5%). Intra-tendinous calcification was evident in seven (53.8%) of the CETs. Following injection, elbow joint contamination was evident in all 20 specimens on dry arthroscopy. Macroscopic assessment consequently found contamination in both the lateral and medial joint space and on the articular and non-articular sides of the CET.

The appearance of the external surface of all 20 CETs demonstrated the focus of the dye at the tendon site with widespread surrounding soft tissue contamination that diminished in proportion to the distance from the injection position.

The mean volume (mm^3) of the CET specimens, derived from the total pixel density, was $1040mm^3$ (± 371.91 Range $344.72mm^3$ to $1845.74mm^3$). When separated by group (injectate volume or technique), no statistical differences in tendon volume were found.

The mean percentage of intratendinous pixel density, at the most sensitive dye intensity (lightest blue), was 98.76% (±2.0) for 1 ml and 97.91% (±2.27) for 3 ml, 98.63% (±1.96) for single shot injections and 98.05% (±2.35) for fenestrated injection. Mean percentage of blue dye concentration, in the four colour intensities from lightest blue to darkest blue is shown in Table 6-1 and graphically in Figure 6.4 and Figure 6.5. Statistically significant differences were found between the groups of blue pixel distribution against the baseline of group 1 (group 2 regression coefficient -0.06 (95% CI -0.10 to -0.02), group 3 -0.21 (-0.25 to -0.17) and group 4 -0.60 (-0.61 to -0.54)) with a global p-value of <0.001. However, no statistically significant differences in blue pixel distribution were found between groups for the dependent variables of injection volume (p=0.255, 95% CI -0.10 to 0.03) or injection technique (p=0.514 95% CI -0.04 to 0.08). Potential differential effects of brightness level for different injection types and volumes were investigated by addition of an interaction term between brightness and injection type/volume (only one interaction term was included per model). No differential effects of brightness across injection type/volume were observed.

	Blue pixel distribution group **Lightest blue ←→ Darkest blue**							
	Group 1		Group 2		Group 3		Group 4	
Injection type	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1ml	98.76%	2.00%	94.00%	4.01%	79.55%	7.49%	44.04%	12.54%
3ml	97.91%	2.27%	90.87%	7.92%	74.98%	12.59%	37.83%	15.30%
Single shot	98.63%	1.96%	92.04%	7.26%	74.86%	11.25%	39.21%	10.29%
Fenestrated	98.05%	2.35%	92.82%	5.59%	79.67%	9.32%	42.66%	17.33%

Table 6-1: Mean percentage +/- Standard deviation (SD) of the Blue pixels distributed within the CET tendon from lightest blue to darkest blue in four groups of blue colour graduation (lightest blue = group 1, darkest blue = group 4)

Three-Dimensional (3D) reconstructions of the intratendinous injectate distributions visually confirmed broad tissue penetration centred in the midportion of the tendon with no discernable patterns of longitudinal or cross-sectional spread or pooling, or a particular anatomical localisation (e.g. to the anterior or footprint component of the tendon in the position of the ECRB) (Figure 6.6).

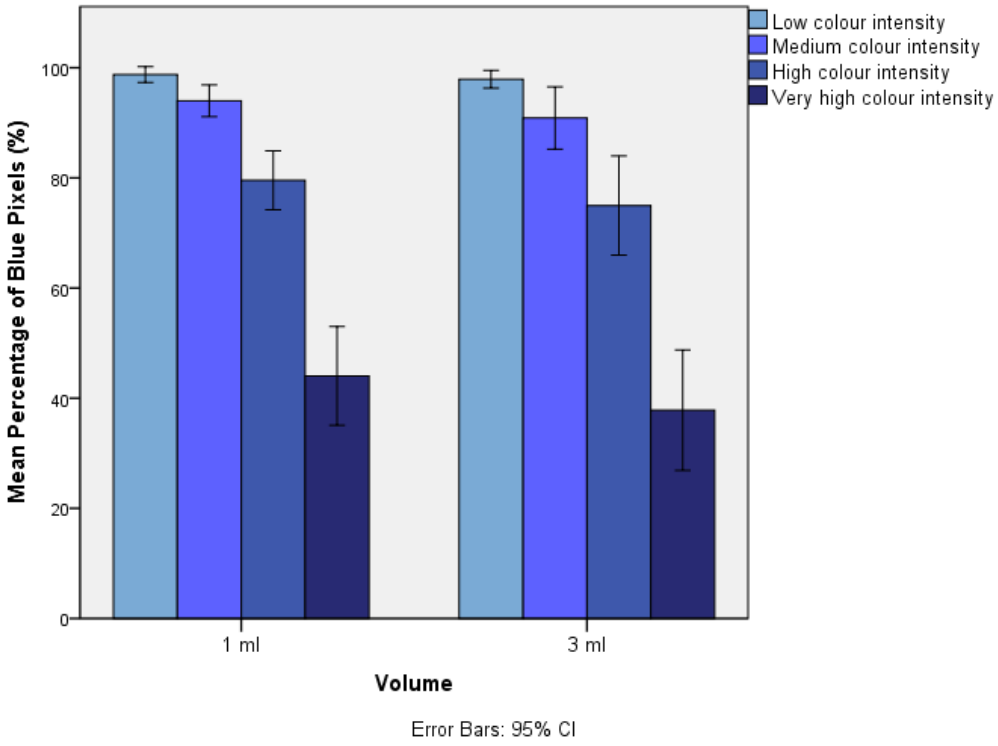


Figure 6.4: Bar chart showing the mean percentage of blue pixels in each of the four colour intensity groups for the 1ml and 3ml volume injections. Error Bars = 95% Confidence Intervals.

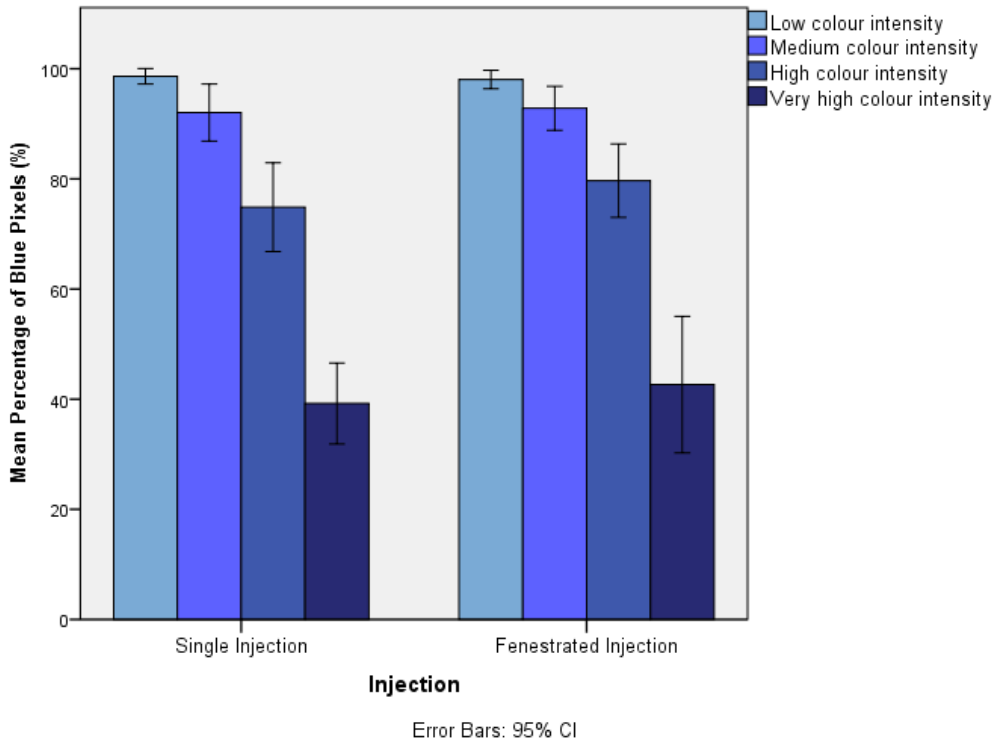


Figure 6.5: Bar chart showing the mean percentage of blue pixels in each of the four colour intensity groups for the single injection and fenestrated injection techniques. Error Bars = 95% Confidence Intervals.

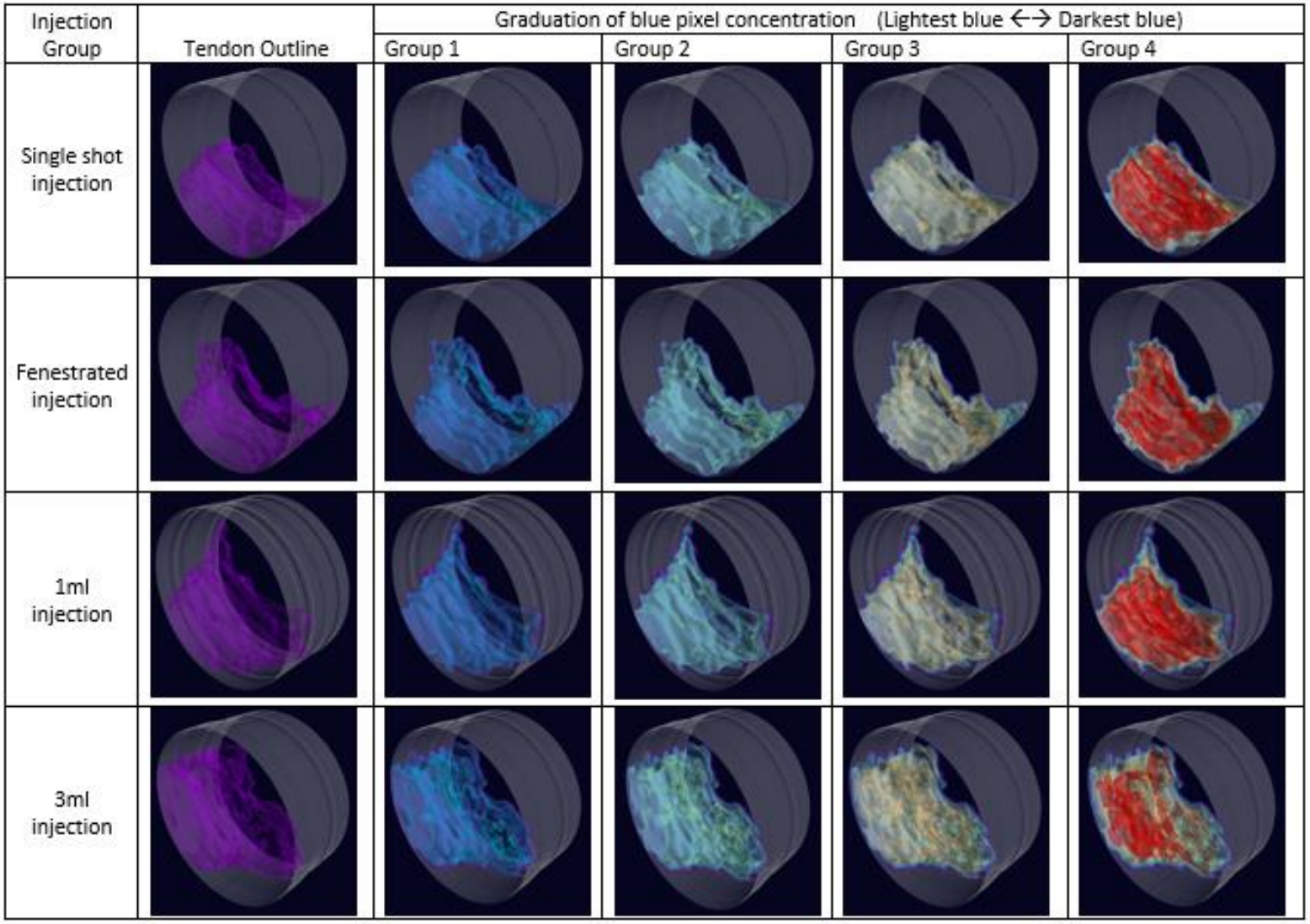


Figure 6.6: Examples of 3D reformats of tendon segments for the four injection techniques. From left – tendon outer border, then working through four colour intensity contours. Note the absence of a pattern of pooling or longitudinal spread.

6.6 Discussion

This study has identified that commonly used elbow injection volumes and techniques, distribute injectate throughout 97% of the common extensor tendon in cadaveric specimens. No differences were found between injection volumes or techniques. Dye contamination of the joint surface was noted in every specimen, and post-injection ultrasound revealed tears to the tendon in over 60% of specimens that were previously uninjured.

This is the first study to assess intratendinous injectate distribution of the elbow extensors in cadaveric tissue, although the use of human tissue has greater utility in its generalisability to a clinical context, the tissue morphology of cadaveric specimens should be taken into consideration in relevance to its generalisability to clinical use. The cadaveric tissue utilised in this study was of subjects with an average age much higher (range 70-96) than the peak age of onset of LET (45-60yrs), and though the specimens had no history of elbow surgery, their detailed medical history was not known. Pre-injection tears were noted in 60% of specimens, and though the tear rate in asymptomatic individuals is felt to be very low [265, 266], the proportion of tears in this study population corresponds to the tear rate seen in tendinopathic individuals, which has been reported as 57% by Walton et al [83] and 58% by van Kollenburg et al [84]. Furthermore, calcification was noted in over half of specimens, and though the appearance of calcification is a common finding, known to increase with age, it may be of poor diagnostic value in LET [267]. Our finding of 53% is equable to asymptomatic 50yr olds and is, in fact, lower than normally reported in those >70yrs [265]. We, therefore, feel that the sample, though limited in

number, is morphologically representative of a LET population. It is currently unknown whether the fresh frozen cadaveric tissue of the elbow behaves as in vivo tissue would under injection. It is therefore prudent to highlight that although morphologically similar, there is an inherent limitation common to all cadaveric studies and some of the conclusions may not be generalizable to human tissue.

Previous authors have commented upon the contamination of the joint and surrounding tissues in lateral elbow injections [261, 268]. However, the current literature has either assessed unguided injections in cadavers, or assessed the distribution on retrospective assessment of ultrasound images, without the known validity of such a method. Ultrasound injection is advocated in lateral elbow injections to improve accuracy and decrease contamination rate [261], but the present study reports that even with the application of ultrasound guidance, the joint contamination rate was 100%. The target site for elbow injection is the ECRB and though very challenging to isolate on USS from the CET, its position is deep and has a delicate and intimately associated connection to joint capsule, particularly at its anterior edge [35]. The presence of tears in this region and the propagation or creation of tears with guided injections may inevitably force the injection into the joint space. In five of the eight samples that did not have evidence of a pre-injection tear, a new tear was noted following injection. This finding, though only demonstrated on a very small sample, may have important clinical relevance. As discussed, joint contamination is an important consideration depending on the injectate substance, but furthermore the creation of a new tear may have an important part to play in and consequential effect of the injectate, be it therapeutic or detrimental.

The CET tapers from the musculotendinous junction to its origin at the lateral epicondyle. Its footprint has been defined as approximately 10mm in anteroposterior width [35], its true tendinous length is approximately 16mm [269], its thickness at the radiocapitelar joint is 4.4mm [270], the average width of the CET at the musculotendinous junction though not previously defined, was 35mm in the current study. Calculating the volume of an oblique wedge [271] ($V = \frac{bh}{6(2a+c)}$), from these figures yields a volume of 938.66 mm^3, which is similar to the mean total volume, derived from the pixel density, found in the current study (1040 mm^3). The volume of 1 and 3ml injections clearly equates to a fluid volume of 1000 and 3000 mm^3. Therefore, with localised injection of common injectate volumes, in an area of densely packed collagen, it is unsurprising that the tendon itself is both damaged and that the injectate is disseminated down a path of least resistance. With the delicate anterior capsular edge presenting as a likely route, joint contamination becomes inevitable. Dependent on the injection substance, this finding may be very relevant, particularly in the otherwise pathology free elbow joint.

Cross-sectional analysis of the CET segments, including 3-dimensional reformatting, found widespread dissemination of the injectate dye regardless of volume or technique, with no apparent pattern or pooling. Previous cadaveric and animal studies have reported a preponderance toward longitudinal spreading of injectate [272-274], in line with collagen fibre orientation. However, these studies have predominantly utilised oval tendons including lamb distal forearm extensor and flexor tendons [272] and horse flexor tendons [274]. CET tendons were included by Loftus et al [273] but as 14% of a cohort of

predominantly hamstrings and patellar tendons, exclusively assessed with ultrasound. This is the first study to report widespread cross-sectional spread in the broad flat tendon morphology of the CET, where tears were either present or induced. Indeed, collagen cross-linking is likely to have been disrupted as part of the injection process, allowing cross-sectional spread. The cross-sectional distribution and high injection induced tear rate within this study demonstrate the notable effect on tendon structure that injections have which, regardless of injectate, should be considered as a potential driver of procedural pain, post procedural discomfort and as a component of any consequential healing response.

The use of needle fenestration has been advocated as a method of distributing injectate more evenly [272], however systematic review of CET injections report conflicting findings of its superiority over single shot injections [106, 117]. This study did not demonstrate any statistical difference in the cross-sectional distribution of injectate between the two techniques using either 1ml or 3ml volumes. Further visual assessment of injectate distribution on 3D reconstruction did not isolate any noticeable difference in distribution patterns. It is important to note that significant escape of active injectate occured regardless of technique with the volumes used in this study, and the presented findings may be different if smaller volumes were employed. It is important to recognise that this study assessed fenestration as a method of distributing small aliquots of injectate around the CET. It is also recognised that fenestration is also utilised as a therapy in LET, where a needle is used to create micropunctures in the affected region and abraide the adjacent periosteum. The goal of this therapy is cause local bleeding promote tendon healing [275].

Currently, no clinical evaluation on the effect of fenestration alone versus, fenestration and delivery of injectate in LET has been conducted.

This study has identified that using commonly utilised injectate volumes and techniques with ultrasound guidance into a cadaveric common extensor tendon can create tendon tears and joint contamination may be inevitable. The structural disruption to the CET seen in this study raises questions about the potentially destructive, or indeed therapeutic, effect a large injection volume may have on the CET. The disruption could be thought of as analogous to a volumetric debridement, therein an injection of 1ml of saline may in itself have a treatment effect, and in this regard may not be an appropriate placebo intervention. Though no clinical evidence of high volume injections efficacy has been presented in LET, a 2017 randomised controlled trial of Achilles tendinopathy treatment reported them as superior to PRP injection and physiotherapy treatment [27]. Further preclinical and subsequent clinical studies of high and low volume injections are therefore warranted and future placebo randomised controlled trials may require a placebo where no fluid is injected.

Limitations

The authors recognise several limitations present within this study. Although the number of cadaveric specimens used in the current study is greater than previously published tendon injection studies [261, 276], the volume and technique groups are of a small number. However, variability in injectate distribution was within acceptable limits, and the statistical methods were appropriate to the small group, repeated measures design. The use of fresh frozen cadaveric material, dry arthroscopy, careful dissection practice and avoidance of freezing

techniques for microtome slicing were all employed to reduce the risk of tissue destruction and degeneration not related to the injection. The choice of methylene blue was made to derive clear visualisation of contamination and to assess graduated tissue penetration. However, the dye used has a lower viscosity than some of the commonly used injectate preparations, with particular reference to PRP. Wilson et al [272] reported that there was no difference in the longitudinal spread of injectate in lamb tendons injected with pure methylene blue or methylene blue mixed with PRP. However, they do report cross-sectional distribution was lower in the combined group, and it, therefore, remains a possibility that cross-sectional distribution observed in the current study may be reduced in higher viscosity injectates. The authors suggest that the volume effect, rather than viscosity, is likely to have a greater effect on collaged cross-link disruption.

6.7 Conclusion

Both 1ml and 3ml injections into cadaveric elbow common extensor tendons distribute injectate equally across 97% of the intratendinous area, with no difference demonstrated between single-shot or fenestrated injection techniques. The injection of these volumes into a small anatomical space may cause damage to the tendon structure, and due to the close association of this tissue to the joint capsule, elbow joint contamination may be inevitable and this should be taken into consideration when selecting the injection substance.

7 Chapter 7 - Platelet-Rich Plasma Injection in Lateral Elbow Tendinopathy: Exploring Expert Consensus with the Delphi Method

7.1 Abstract

Background

Platelet-Rich Plasma (PRP) has become a popular treatment modality for Lateral Elbow Tendinopathy (LET) despite conflicting evidence on its effectiveness. With high levels of user experience, this study aimed to assess the levels of consensus amongst experts on the clinical application of this novel intervention.

Methods

An international Delphi study was conducted. The development of treatment statements and consensus measurement was developed over three rounds. Round one utilised a ten person primary working group who answered open questions on their clinical approach, and their answers were subsequently developed into 40 statements. Clinical users and researchers were invited through national society mailing lists and contact lists derived from a systematic search of PRP literature. In rounds two and three, an international group of PRP researchers and clinical users scored their levels of agreement with these statements on a five point scale. Consensus was defined as an interquartile range of ≤1.

Results

Thirty-eight participants completed round two and 28 (74%) completed round three. Overall, consensus of agreement was reached for 17/40 (42.5%) statements. For statements on PRP formulation, consensus of agreement was reached in 2/6 statements (33%). No differences were observed between high volume (>20 per annum) or low volume (≤20 per annum) users.

Conclusion

Amongst experts, only limited consensus could be reached on the application of PRP in LET. High levels of user experience does not result in a convergence of opinion on the technical components of PRP formulation and delivery, echoing calls for further study and improved trial reporting.

7.2 Overview

The previous chapter assessed injection technique using a cadaveric model, and reported that the perceived thinking on injection delivery may be flawed. The following study develops this theme by focusing on the clinical application of injection therapy. It explores the level of expert consensus on the process of delivering injections in LET with specific attention on Platelet-rich plasma.

7.3 Background

The use of Platelet-rich plasma (PRP) for the treatment of LET has rapidly increased in recent years [119]. Tendinopathy itself is multifaceted condition, with varied highly complex imflamatory system modulation dependent upon the patients,age, position of tendinopathy and chronicity of the condition. Biological therapies are currently being lorded as a potential treatment that seeks to meet these continuum of tendinopathy by boosting healing mechanisms [277]. What this grand claim revolves around is the modulation of inflammatory pathways and the promotion of anabolic and proliferative effects on tendon cells. Initial animal studies emerged in the early 2000s with studies reporting increased TGFβ and PDGR in equine tendon which are involved in increasing the production of Type I collagen (the main collagen component of tendon), and the reduction of matrix metalloproteins (MMPs) involved in breaking down Type III collagen (the main collagen form in early tendon repair) [278, 279]. These findings have been replicated in in vitro human tissue where exposure to PRP has prompted increased concentrations of PDGF, VEGF, TGFβ, growth factors all involved in matrix production [280] and proliferation of human tenocytes [281]. However, clinical studies have been less positive, the latest Cochrane review

suggests no evidence to support the use of PRP for the management of musculoskeletal soft tissue injuries [116]. For Lateral Elbow Tendinopathy specifically, reviews have produced conflicting results on PRP efficacy [118, 119].

Much of the criticism directed towards PRP research relates to the heterogeneity of patient selection, PRP preparation, and administration techniques [105, 116, 118, 119, 277]. Furthermore, inconsistency of protocol reporting, outcome measurement, and adverse events reporting has hindered consistent interpretation of treatment effects or harm [101].

PRP is prepared through concentration of the patient's own blood. However, depending on the equipment, the protocol used and the patient's own blood profile, highly variable concentrations of platelets, erythrocytes, and leukocytes are obtained [283]. Administration variability relates to patient selection, the frequency and interval of administration, the use of adjunct ultrasound guidance and post-operative protocols. Furthermore, the use of local anaesthetic, platelet pre-activation, anticoagulation and pH buffering are not standardised.

The lack of treatment standardisation may, in part, be related to the regulation of biological therapies of this nature. Unlike medicinal products, PRP, as an autologous therapy, has not been subject to the standardised methodology of phased trials. Though the administrative device (e.g. centrifuge system) may have been subject to pre-market approval, the product to be administerd to the patients (i.e. PRP) has not been standardised. Therein the treatment constituents, dose, administration and adverse events have not been investigated according to the standards applied to medications. This has resulted in the evolution of the use of PRP being influenced by the reports of

trial data, which to date have yet to result in clear guidance. Nevertheless, the clinical use of PRP continues to increase.

In 2013, it was estimated that 16% of UK orthopaedic surgeons used PRP [103]. Internationally, its use is more common. A 2015 review from Australia of 112 sports physicians found 38% used PRP in their own practice and a further 49% referred patients for this treatment [108]. The experience from those sports physicians surveyed was that, of all conditions, PRP is most effective as a treatment option for LET. However, the patterns of technique and administration in LET were not explored.

Though a large-scale trial of a methodology in accordance with a phase 2 clinical drug trial may be able to elucidate the optimal PRP constituents, dose, and administration, this would require considerable resources and financial support. With the widespread use of PRP, both within the research and clinical community, an alternative approach may be to explore expert opinions in an attempt to gain consensus using a validated methodology.

The Delphi method uses a series of sequential question sets (or rounds), interspersed with controlled feedback to gain the most reliable consensus of opinion of a group of experts [284]. It is a technique that is particularly useful where individual judgments need to be assessed and combined in order to address a lack of agreement or incomplete state of knowledge [285-287]. In addition to identifying a treatment consensus (or lack thereof), the technique can also inform research priorities where knowledge deficits exist [286]. It has an extensive history of use in healthcare settings, and has recently been employed

in expert consensus exploration of Achilles tendinopathy [288] and shoulder rotator cuff pathology [289].

Originally developed by the Rand Corporation for technological forecasting, the classical Delphi achieves group opinion through multilevel group interaction over multiple rounds supervised by a facilitator [290]. Opinions are provided anonymously, thereby avoiding the problems arising from powerful personalities, group pressure, and status that can manifest in open discussion [291]. Recent iterations of the technique include the use of electronic data collection (e-Delphi) [292]. The iterative process uses controlled feedback and statistical group response that, as the rounds of questionnaires are completed, allow participants to reflect and modify their response [290].

This study aimed to elicit opinion and assess levels of consensus on the use of platelet-rich plasma in lateral elbow tendinopathy. In the absence of phased trial data, exploration of expert consensus is justified. Patterns in treatment practice or indeed, lack thereof, may assist in the future formulation of study protocols and treatment guidelines.

7.4 Methods

Study design

This study used a three-stage Delphi technique and was undertaken between January 2017 and October 2017. This methodology has been chosen to develop criteria that are based on consensus gained from an expert panel, where insufficient quality and grade of evidence exists to develop evidence-based criteria [290].

Participant selection and recruitment

A steering group was recruited to undertake round one through personal communication with the lead author (JE). This group of 10 individuals included UK-based upper-limb orthopaedic surgeons, musculoskeletal radiologists and PRP researchers who were invited directly. The steering group was utilised in round one and was asked to participate in the subsequent rounds.

The subsequent rounds recruited the expert opinion of a larger cohort of participants. To increase the heterogeneity of the expert panel, including the desire to gain national and international opinion, two approaches were used to invite both research-based and clinical-based individuals with experience in PRP application. The research cohort was recruited through a database search of published articles on PRP followed by email communication with the lead author; the clinical cohort was recruited through national society mailing lists.

Database searches were undertaken on 15/2/2017 in Medline, EMBASE and CINHAL databases from inception to the present, using modified British Medical Journal (BMJ) research filters for systematic reviews, randomised control trial, cohort and case-control studies (appendix 14). Following title and abstract review, 57 articles were identified. Where possible, contact email addresses were extracted from corresponding author details and invitations to participate in the Delphi process were distributed.

To capture clinical users of PRP who may not be actively involved in research, the European Society for Surgery of the Shoulder and Elbow (SECEC), British Association of Sports and Exercise Medicine (BASEM) and British Society of

Musculoskeletal Radiologists were invited to participate via a mailout of society contact lists.

Expert panel size

The question of participant numbers is dependent on the minimally sufficient number to constitute a representative pooling of judgments [293]. Wide variations in expert numbers have been reported in Delphi studies [286], though nominally they tend to be within 20-60 [294].

The study aimed to recruit a minimum of 25 experts. The primary group of experts in round one was 10. In round two, a minimum of 20 additional experts was required for study progression. Round three required retention of >60% of respondents. Though it has been reported that the reliability of composite judgments increases with respondent numbers, there is little empirical evidence on the effect of participant numbers on reliability or validity of the consensus process [287] if the panel composition is appropriate.

Procedure

- **Round one**

The initial steering group was contacted through the Bristol Online Survey electronic portal (BOS, University of Bristol, Bristol, UK). This expert panel was presented with open questions based on the domains of PRP reporting identified by Murray et al [122]. These open questions asked for the participants' opinions on the themes of patient selection, PRP preparation and delivery, post-procedural care and outcome assessment (appendix 15). Consolidation of text answers was undertaken through content analysis. The answers were read by

two assessors (JE + CS), and, from the response themes, a list of 40 statements was developed for agreement scoring in round two. In cases of disparity between participants, the predominant theme was utilised. The established statements were distributed amongst the study authors for the assessment of thematic structure and comprehension.

- **Round two**

The statements from round one were developed into an electronic questionnaire with each statement requiring an agreement score using a Likert scale from 1 (Strongly disagree) to 5 (Strongly agree). The questionnaire was distributed to all those who responded to the invitation sent to PRP researchers, national society members and those from round one willing to be involved in subsequent rounds. Simple demographic information on the participant was collected to quantify participant PRP experience (Clinical User/PRP Researcher/Both), user occupation (Researcher/Surgeon/Radiologist/Sports Physician) and total number of PRP injections for LET administered annually. Participants were also able to suggest edits to the statements using a free text option. Statements were modified if suggestions by more than three participants were thematically similar and not in contrast to the predominant group response.

- **Round three**

Participants were sent an individualised feedback report including their round two scores and the groups' scores for each statement, represented using a histogram (appendix 16). Participants were able to reflect on their scores and, if necessary, change their score whilst maintaining anonymity. The same Likert

scale was used for round 3. The benefit of continuing the iterative process was assessed following round 3 completion using standardised stopping criteria.

Ethical considerations

This study was granted ethical approval by the University of Exeter Medical School review panel (Nov16/B/105) (appendix 17). The iterative nature of the Delphi technique meant that the participants remained anonymous to each other, but not to the research team [294].

Data analysis

Quantitative analysis of Likert ratings was undertaken using Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). For measures of central tendency and level of dispersion, median and interquartile range (IQR) are strongly favoured when Likert scales are used [290, 294]. The consensus criterion for this study was an interquartile range (IQR) of one or less. An IQR of less than one means that more than 50% of all opinions fall within one point on the scale [295]. For those with an IQR of ≤1, the median score was taken as the agreement level and statements grouped into one of three categories: consensus of agreement (median score 4 or 5), consensus of disagreement (median score 1 or 2) or consensus of 'neither agree nor disagree' (median score of 3). Percentage agreement (participants answering either four or five on the Likert scale) is also presented. The stopping criteria at round 3 was assessed using the parametric method of Coefficient of Variation Difference (CVD) [296]. This was calculated by subtracting the individual item CV (Standard deviation/Mean) from round three, from the corresponding CV from round two. A value close to zero denotes stability of responses with a cut-off

value of >0.5 deemed a decision limit for a need for further rounds [295]. *Post hoc* analysis of response differences between different groups of PRP user experience (clinical user or clinical researcher/pure researcher), clinical occupation (radiologist/physician or surgeon) and injection number per annum (low volume ≤20 or high volume >20), was undertaken at the statement level using a non-parametric Mann-Whitney U test. Statistical significance was set at $p<0.05$.

7.5 Results

Participants

The primary working group consisted of 10 participants, of whom nine were UK-based Consultant orthopaedic surgeons and one a Consultant radiologist. Half of the group were actively involved in PRP research as well as clinical practice. The multimodal recruitment strategy resulted in a further 28 participants, with a total of 38 participants from 14 different countries, completing the round two questionnaires. Following the return of round two feedback and two email reminders, round three was completed by 28 participants (74% response rate). The group completing round three consisted of three radiologists, seven sports physicians, one researcher who did not undertake a clinical role and 17 orthopaedic surgeons. Of this group, 12 (43%) were actively involved in PRP research. As a marker of research impact demonstrated by the research active participants, their h-index was extracted from the Scopus® (Elsevier B.V.)

database yielding a median h-index of 13 (range 5 – 83). The annual use of PRP injection for LET was grouped into five categories, nine participants (25%) administered <5 injections per annum, two (7%) administered 5-10, eight (26%) administered 10-20, five (18%) administered 20-50 and six (21%) administered >50 per annum.

Consensus development

Between rounds two and three, two statements were modified following free text feedback from multiple participants. Statement 2 was changed from “PRP should only be considered following six-months of conservative therapy” to “PRP should only be considered following at least three months of conservative therapy”, and statement 24 was changed from “A 19g needle is the recommended minimum size used to administer PRP” to “A 19g needle is the recommended MAXIMUM size used to administer PRP”.

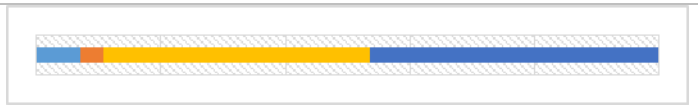
Stability between rounds two and three was assessed and confirmed using the Coefficient of Variation Difference (mean CVD -0.03, SD±0.04, Range -0.11-0.04). Further iterations of the questionnaire were therefore deemed unlikely to result in further change.

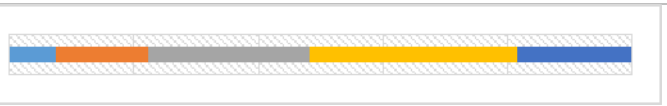
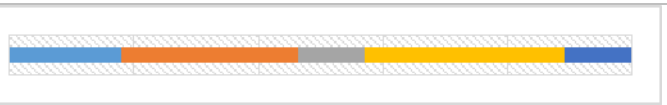
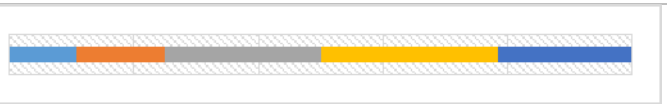
Consensus of agreement (IQR≤1, median score 4 or 5) occurred for 17/40 statements (42.5%) (Table 7-1). Consensus of disagreement (median score 1 or 2) occurred for 2/40 statements (5%). Consensus of ‘neither agree nor disagree’ (median score 3) occurred for 4/40 statements (10%). Consensus was not reached for 16/40 statements (40%) (Table 7-2 and Table 7-3).

Group analysis

Assessment of statistically different median scores between ‘PRP user experience’ groups revealed differences in opinion for statement 2 (“PRP should only be considered in patients who are experiencing considerable intrusion into their activities of daily life”) with clinical users scoring a median of 3 and clinical researchers/pure researchers scoring a median of 4.5 (p=0.007). For occupation type, grouped into two categories of radiologist/physician or surgeon, statistically different median scores were found for statement 3 (“PRP should only be considered in patients who are experiencing considerable intrusion into their activities of daily life”) (3 vs 4 respectively (p=0.04)), statement 25 (“Ultrasound guidance should be utilised in all PRP injections for Lateral Elbow Tendinopathy”) (5 vs 4 (p=0.03)), statement 26 (“Needle fenestration is recommended over a single injection technique”) (4.5 vs 4 (p=0.01)) and statement 30 (“Surgery is recommended for patients in whom PRP treatment is not effective”) (3 vs 4 (p=0.004)). No differences in statement scores were noted between low volume users (0-20 per annum) and high volume users (20->50 per annum).

Table 7-1: Results of round 3. Statements in categories presented with Interquartile Range (IQR), median score and percentage agreement (a score of 4 or 5) and score histogram.

Statement	IQR	Median	% Agreement	Response distribution histogram
1. PRP should only be considered in patients presenting with characteristic tennis elbow pain.	1	4	89.29	
2. PRP should only be considered following at least 3 months of conservative therapy.	2.5	4	64.28	
3. PRP should only be considered in patients who are experiencing considerable intrusion into their activities of daily life.	1	4	64.29	
4. PRP treatment can be considered in patients over the age of 18, with no upper age limit.	1	5	96.43	
5. PRP treatment can be considered in patients with manual or sedentary occupations.	0.5	5	96.43	
6. PRP treatment can be considered in both high demand (e.g. sports people) and low demand (e.g. office worker) patients.	0.5	5	100	
7. PRP is contraindicated in patients with a coagulopathy.	1	2	21.43	
8. PRP is contraindicated in patients with large wrist extensor tendon tears.	2	2	28.57	
9. PRP is contraindicated in patients taking anticoagulant medication.	1	2	21.42	
10. PRP is contraindicated in patients with a dependence on Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).	3	3	42.85	

Statement	IQR	Median	% Agreement	Response distribution histogram
11. PRP is contraindicated in patients with known thrombocytopenia (less than 150,000 platelets per microlitre of whole blood).	1	4	51.85	
12. PRP is contraindicated in patients who have received a steroid injection for LET, within 3 months of the intended PRP treatment date.	2	3	42.85	
13. The minimum recommended platelet concentration of injected PRP is 2x baseline.	1.5	3.5	50	
14. The maximum recommended platelet concentration of injected PRP is 5x baseline.	1	3	39.29	
15. The minimum recommended volume of PRP is 1ml.	1.5	4	71.43	
16. The maximum recommended volume of PRP is 3mls.	1	3	46.43	
17. Leukocyte deplete PRP is the recommended formulation.	1.5	3.5	50	
18. A single spin cycle of 20 minutes or less is recommended.	1	4	64.29	
19. The addition of an anticoagulant to the whole blood sample is recommended prior to PRP preparation.	1	3	21.42	
20. PRP activation, through the addition of additives prior to its administration, is not required.	1	4	82.14	

Statement	IQR	Median	% Agreement	Response distribution histogram
21. Once processed, PRP should be administered within 30mins.	1	4	82.14	
22. Local anaesthetic should be administered to the skin and subcutaneous tissue.	2	4	60.72	
23. Local anaesthesia should not be administered to the tendon.	2.5	4	60.71	
24. A 19g needle is the recommended MAXIMUM size used to administer PRP.	1	3	35.71	
25. Ultrasound guidance should be utilised in all PRP injections for Lateral Epicondylar Tendinopathy.	2	4	67.86	
26. Needle fenestration is recommended over a single injection technique.	0.5	4	82.14	
27. Following the first administration of PRP, the patient should be reassessed to discern the need for repeated administration.	1	5	85.72	
28. A maximum of 3 administrations is recommended for each episode of Lateral Epicondylar Tendinopathy.	2.5	3.5	50	
29. If symptoms recur following a successful course of treatment, PRP injection can be reattempted.	1.5	4	75	
30. Surgery is recommended for patients in whom PRP treatment is not effective.	1	4	71.43	

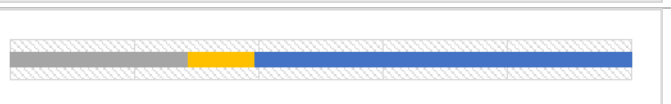
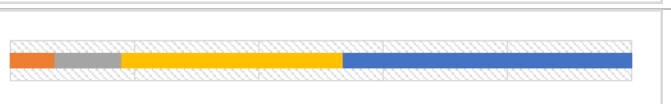
Statement	IQR	Median	% Agreement	Response distribution histogram
31. Immobilisation of the elbow following injection is not necessary.	1	5	89.29	
32. Light loads should be avoided for the first 48 hours following injection.	1	4	85.71	
33. Heavy loads should be avoided for 6 weeks.	2	4	64.28	
34. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should be avoided for 1 week prior to PRP administration.	2	4	67.86	
35. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should be avoided for at least 2 weeks following injection.	2	4	71.43	
36. Acetaminophen (Paracetamol) and weak opioid-based analgesia can be offered as required following PRP administration.	1	5	96.43	
37. Clinical assessment is recommended to assess the outcome of PRP administration.	0.5	5	96.43	
38. A Visual Analogue Pain Score (VAS) should be collected in addition to clinical assessment.	2	5	71.42	
39. A validated Patient-Reported Outcome Measure (PROM)) should be collected in addition to clinical assessment.	1	4	82.14	
40. Resolution of tendinosis on US or MRI can be utilised to assess outcome.	1.5	2	25	

Table 7-2: List of statements categorised by consensus group – Consensus of: agreement and disagreement,

Consensus of agreement (median score = 4 or 5)	Statement Category
PRP should only be considered in patients presenting with characteristic tennis elbow pain (lateral elbow pain exacerbated by wrist extension).	Patient Selection
PRP should only be considered in patients who are experiencing considerable intrusion into their activities of daily life.	Patient Selection
PRP treatment can be considered in patients over the age of 18, with no upper age limit.	Patient Selection
PRP treatment can be considered in patients with manual or sedentary occupations.	Patient Selection
PRP treatment can be considered in both high demand (e.g. sports people) and low demand (e.g. office worker) patients.	Patient Selection
PRP is contraindicated in patients with known thrombocytopenia (less than 150,000 platelets per microlitre of whole blood).	Contraindication
A single spin cycle of 20 minutes or less is recommended.	PRP formulation
PRP activation, through the addition of additives prior to its administration, is not required.	PRP Formulation
Once processed, PRP should be administered within 30mins.	Administration Technique
Needle fenestration is recommended over a single injection technique.	Administration Technique
Following the first administration of PRP, the patient should be reassessed to discern the need for repeated administration.	Administration Strategy
Surgery is recommended for patients in whom PRP treatment is not effective.	Administration Strategy
Immobilisation of the elbow following injection is not necessary.	Post Procedural Care
Light loads should be avoided for the first 48 hours following injection.	Post Procedural Care
Acetaminophen (Paracetamol) and weak opioid-based analgesia can be offered as required following PRP administration.	Post Procedural Care
Clinical assessment is recommended to assess the outcome of PRP administration.	Outcome Assessment
A validated Patient-Reported Outcome Measure (PROM) (e.g. PRTEE, DASH, OES) should be collected in addition to clinical assessment.	Outcome Assessment
Consensus of disagreement (median score = 1 or 2)	**Statement Category**
PRP is contraindicated in patients with a coagulopathy.	Contraindications
PRP is contraindicated in patients taking anticoagulant medication.	Contraindications

Table 7-3: List of statements categorised by consensus group – Consensus of neither agree nor disagree or consensus not reached

Consensus of 'neither agree nor disagree' (median score = 3)	Statement Category
The maximum recommended platelet concentration of injected PRP is 5x baseline.	PRP Formulation
The maximum recommended volume of PRP is 3mls.	PRP Formulation
The addition of an anticoagulant to the whole blood sample is recommended prior to PRP preparation.	PRP Formulation
A 19g needle is the recommended MAXIMUM size used to administer PRP.	Administration Technique
Consensus not reached	**Statement Category**
PRP should only be considered following at least 3 months of conservative therapy	Patient Selection
PRP is contraindicated in patients with large wrist extensor tendon tears.	Contraindication
PRP is contraindicated in patients with a dependence on Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).	Contraindication
PRP is contraindicated in patients who have received a steroid injection for treatment of their Lateral Epicondylar Tendinopathy, within 3 months of the intended PRP treatment date.	Contraindication
The minimum recommended platelet concentration of injected PRP is 2x baseline.	PRP Formulation
The minimum recommended volume of PRP is 1ml.	PRP Formulation
Leukocyte deplete PRP is the recommended formulation.	PRP Formulation
Local anaesthetic should be administered to the skin and subcutaneous tissue.	Administration Technique
Local anaesthesia should not be administered to the tendon.	Administration Technique
Ultrasound guidance should be utilised in all PRP injections for Lateral Epicondylar Tendinopathy.	Administration Technique
A maximum of 3 administrations is recommended for each episode of Lateral Epicondylar Tendinopathy.	Administration Strategy
If symptoms recur following a successful course of treatment, PRP injection can be reattempted.	Administration Strategy
Heavy loads should be avoided for 6 weeks.	Post Procedural Care
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should be avoided for 1 week prior to PRP administration.	Post Procedural Care
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should be avoided for at least 2 weeks following injection.	Post Procedural Care
A Visual Analogue Pain Score (VAS) should be collected in addition to clinical assessment.	Outcome Assessment
Resolution of tendinosis on US or MRI can be utilised to assess outcome.	Outcome Assessment

7.6 Discussion

This study has attempted to assess levels of expert consensus on the use of Platelet-rich plasma (PRP) in patients suffering from Lateral Elbow Tendinopathy (LET). The use of PRP is increasing despite inconclusive evidence of clinical efficacy [297]. It is likely that this expansion in its use arose both from the availability and inherent safety of this technology, and the desire to offer a treatment for a condition which is recognised as challenging to treat, with limited evidence of a gold standard treatment approach [101]. In a situation of lack of data regarding clinical efficacy, but widespread use, it was deemed both legitimate and practical to assess expert consensus. In doing so, an assessment of clinical experience can be made, in the scenario of a commonly administered treatment, one may presume that a convergence of opinion on patient selection, production, technique, and follow-up may be revealed that is not currently demonstrated in clinical trials. The current study has isolated some commonality in patient selection, administration techniques and post-procedural follow-up care, with 57.5% of all statements reaching consensus. However, this study has demonstrated wide variations in expert approach to PRP production and formulation, application of local anaesthesia, use of imaging adjuncts and the interplay with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and corticosteroids.

Statements involving patient selection demonstrated adequate consensus, with agreement that participants can be selected if they have characteristic LET pain, are over the age of 18 yrs and are experiencing considerable intrusion into their lives. Furthermore, there was agreement that occupation or level of

demand on upper limb function should not be a factor in participant selection. The statement within this section which did not reach consensus related to the duration of symptoms, given the wide score dispersion apparent with an IQR of 2.5. Furthermore, this statement was altered between rounds owing to feedback from multiple participants to lower the duration of conservative therapy from six to three months. Though this shifted the median from 3 (round two) to 4 (round three), significant dispersion remained. A significant majority of PRP studies have concentrated on chronic LET (>6 months of symptoms), and this lack of consensus may highlight an area of future research on the effect of PRP on early onset LET.

There is limited evidence available on both the potential contraindications to PRP delivery and the potential post-procedural complications. Miller et al [298], in a recent systematic review, comment that the potential for unreported complications remains a major limitation of the PRP literature. As a consequence of its autologous nature, there may realistically be few safety concerns, but the paucity of explicit information on adverse outcomes leaves the clinical user uninformed and simply guided by clinical experience. Though consensus was reached on PRP being contraindicated in patients with known thrombocytopaenia, consensus could not be reached on whether the presence of large wrist extensor tears, dependence on NSAIDs or a steroid injection within three months are contraindications, with experts providing very varied scores. Interestingly, consensus was reached on the statements regarding known coagulopathy and concurrent anticoagulation medication, with experts deeming that neither is a contraindication to PRP treatment in LET.

There have been recent calls to dramatically improve the reporting of the PRP formulation used in clinical effectiveness trials [122, 299-301]. Without this information, the ability to make decisions upon the plethora of PRP devices remains extremely challenging for the clinician. In this regard, it may not be surprising that limited consensus could be reached for the PRP formulation category. Consensus was gained on the use of a 20 minute or less, single spin cycle, and that the administration of additives for platelet activation was not deemed necessary. For the remaining statements, consensus of uncertainty (a median score of 3) or an inability to reach consensus was observed. Therein, the expert consensus group was unable to provide further information from their collective experience on the optimal volume, platelet concentration, addition of anticoagulant or leucocyte level. It is worth noting that though 71% of respondents did agree with the statement that 1ml of PRP was the minimum volume necessary, the overall score distribution resulted in an IQR above the *a priori* limit of one. The findings of limited consensus on PRP formulation, therefore, support the current call for improved reporting of PRP formulations, and studies undertaking formulation comparisons in an effort to greatly enhance the knowledge base in this area.

Levels of consensus on the administration technique were equally lacking. Consensus could not be reached on the application of local anaesthetic, either to the skin/subcutaneous tissues, or deeper into the tendon itself, whether Ultrasound guidance for administration was preferable or a guide as to the optimal needle size. The needle size statement was altered between rounds two and three following the free text comments by several participants, but this did not reduce the overall dispersion of results. Consensus was reached on the

requirement to deliver the PRP within 30 minutes of preparation, which is in accordance with a recent synthesis of available evidence [297]. Interestingly, there was consensus on the use of a fenestrated needle administration technique over a single shot approach, an aspect that currently remains controversial in the research literature with conflicting results from large systematic reviews [106, 117].

Administration strategy garnered two out of four statements reaching consensus. The participants reached agreement that patients should be followed up following the first administration to discern the need for a second injection. This opposes the studies employing standardised multiple administration methodologies [302, 303], and is in accordance with the only review of multiple administration strategies conducted through retrospective cohort analysis [304]. Currently, no prospective studies have compared PRP administration strategies. Consensus was reached in favour of offering surgery for treatment failures: subgroup analysis found that surgery was favoured by surgeons, but not by the group containing radiologists and sports physicians. Consensus was not reached concerning three injections being the maximum in one clinical episode, further research or expert consensus measurement could be considered to assess injection numbers either side of this value. Although 75% of participants agreed that PRP could be reconsidered if symptoms were to reoccur, the spread of the responses was too great to provide a clear picture and the IQR exceeded one.

Partial consensus of agreement was found for the post-procedural care statements. The participants did not deem immobilisation of the elbow to be

necessary following the procedure, but 48 hours of avoidance of light loads is recommended. However, the statement regarding avoidance of heavy loads for six weeks did not reach consensus and demonstrated a broad range of opinions. Further research would assist clinicians in refining this post-procedural element. Though Acetaminophen (paracetamol) and weak opioid based medications were deemed appropriate post-procedural analgesics, consensus could not be reached on whether NSAIDs should be avoided one week prior or for two weeks following PRP injection. Although the majority of respondents (68% and 71% respectively) agreed that NSAIDs should be avoided for these two periods, there was a considerable spread of results resulting in an IQR of 2 for both statements. Although there are recommendations in the literature to avoid NSAIDs during this period [297], it is possible that limited prospective evidence, once again, appears to affect the ability to derive consensus on this important post-procedural element.

Criticism from systematic reviews of PRP treatment often reference the heterogeneity or lack of validated Patient Reported Outcome Measures (PROMs) recorded as part of follow-up [101, 298]. Consensus was reached in the current study on the necessity to record validated PROMs in addition to the clinical examination. Furthermore, a strong consensus of agreement was recorded for the recommendation to conduct a clinical review of each patient undergoing PRP injection. However, consensus could not be reached on whether a Visual Analogue Scale (VAS) was beneficial, or whether adjunct imaging (MRI or USS) could be utilised as part of the outcome assessment.

Limitations

The authors recognise that there are limitations to the current study. The sample size of 28 respondents represents a very small pool of international users of PRP injections in LET. Although this number would be insufficient for a simple survey, within the iterative methodology of a Delphi study this sample size is commensurate with published guidance on sample size to produce a representative pooling of judgments, particularly when stability between rounds can be demonstrated [290, 294]. Efforts were made to draw a varied international sample of research and clinical communities. However, a potential bias exists with a greater representative sample of surgeons over physicians and radiologists. *Post hoc* testing did not identify a disparity of agreement between these groups' statement scores with the exception of the application of surgery as a second line treatment. This stability of response was also demonstrated between those categorised as high-volume and low-volume users, with no differences in statement scores.

The method of statement production, through a semi-structured questionnaire to a smaller primary round of respondents, is in keeping with previously published Delphi studies [290]. However, the authors recognise that this strategy has the potential to miss certain domains of interest or produce an unrepresentative stance. Nevertheless, efforts were made to represent all domains identified in previous reviews of PRP [122] and at all stages participants were able to provide free text comments if they felt domains were not represented. Furthermore, in subsequent rounds, both agreement and disagreement with these statements were then assessed along with the spread of scores being utilised as the

consensus criterion, as recommended by Heiko (2012) [295]. Although percentage agreement levels are presented, and in some cases discussed above are >70% even though the IQR did not reach the consensus target, the authors feel that when assessing consensus on a novel therapeutic intervention the spread of scores, and therefore overall collective opinion, is the preferred consensus criterion, rather than a simple cut-off percentage.

The use of PRP, regardless of the evidence base, appears to have advanced through the early stages of technology adoption outlined by Wilson (2006) [305]. Studies on the prevalence of use suggest that we have progressed through the innovators and early adopter of novel technology, and are now at a level of early majority adoption (between 18% and 45% using the technology) [103, 108], despite the clear lack of consensus on fundamental aspects of the treatment. Although no clear framework for the development of medical devices exists, if one were to extrapolate from the internationally recognised surgical IDEAL framework [306], levels of consensus from the present study would seem to suggest that PRP remains in the ‘Development’ or ‘Exploration’ phase, where there is a requirement for continued modification of techniques, indications, the reporting of adverse effects and development of parameters of quality. However, the majority of new publications and review articles are focused on Randomised Control Trial (RCT) data more befitting the Assessment stage [307], which should be utilised once stability of procedure, quality standards, and indications have been achieved.

7.7 Conclusion

This study is the first to assess level of consensus in the applied use of Platelet-Rich Plasma in Lateral Elbow Tendinopathy. Although the results should not be confused with evidence of effectiveness, the findings have utility in defining areas in which those with expert experience, acquired through a personal synthesis of published data and experiential practice, agree. In areas of agreement, this information can be used as clinical corroboration with reported evidence, and can guide those with more limited experience of the technique. Of course, what may be more relevant is where lack of consensus exists or where disagreement with manufacturers' guidance is apparent. Though consensus existed on many of the aspects of patient selection, this study has identified a striking lack of consensus on optimal PRP formulation and many aspects of the delivery techniques, reinforcing calls for improved reporting in clinical trials and a more thorough dose-dependent exploration [122, 297]. Although avoidance of PRP treatment in those with coagulopathy, drug-induced or otherwise, was not deemed necessary, the peri-procedural use of NSAIDs, steroid injections, and local anaesthetics are not held with consensus by this expert group and require further study. The findings from this study support the requirement for a more structured approach to the fundamentals of PRP application and future research.

8 Chapter 8 - A Feasibility Randomised, Controlled Trial of Platelet-Rich Plasma injection vs Surgery for Chronic Lateral Elbow Tendinopathy

8.1 Abstract

Background

Lateral Elbow Tendinopathy is a common condition of middle age. Though often self-limiting it can be associated with significant life-impairing disability. In chronic LET, surgery has traditionally been utilised following failed conservative therapy, recently there has also been an emergence of interest in Platelet-Rich Plasma therapy in this patient group. A prospective comparative study of these treatments has not been undertaken.

Methods

The feasibility of conducting a full-scale randomised prospective trial was assessed. Twelve participants were randomised to receive either open surgical release or two injections of leukocyte-rich PRP delivered under ultrasound guidance. Primary outcome was the measurement of recruitment and safety. Secondary outcomes were Patient Reported Outcome Measures (PROMs), qualitative analysis of patient interviews, analysis of a trial team debrief and patient and public involvement group (PPI) and adherence to reporting guidelines.

Results

Target sample was achieved in 10 months. Recruitment rate was 86% (12/14). One participant dropped out of the surgical group prior to intervention and one participant from the PRP group crossed over following failed treatment at three months, there was no loss to follow-up. All PROMs scores improved over a six-month follow-up period. Patient safety concerns were highlighted through qualitative interviews with significant injection-induced discomfort. Adherence with PROMs data collection was excellent and participants and PPI group preference this as a primary outcome.

Conclusion

This study confirmed the feasibility of conducting a full-scale randomised prospective trial comparing open surgical release to PRP with PROM-based primary outcomes. However, qualitative analysis, which has not previously been applied to PRP research, highlight significant injection pain that should be recognised as part of any future protocol and appropriately managed. Intervention-related pain assessment is also recommended.

8.2 Overview

The following chapter assesses the feasibility of conducting an interventional trial in LET. It aims to discover whether it is possible to adhere to a best available evidence-based study protocol, whilst observing recognised trial reporting guidelines. In doing so it evaluates the feasibility of a patient-centred approach to LET research, with attention paid to adverse event evaluation and the ability and burden of using PROMs by applying both quantitative and qualitative data collection techniques

8.3 Background

Although LET is managed at a rate that is equivalent to hip and knee osteoarthritis in primary care [107], there is no consensus or standardised guidance on the optimal management of LET [99]. A vast quantity of options exist ranging from rest and analgesia to surgery, yet large systematic evaluations of treatments only reveal uncertainty as to their relative effectiveness [101, 118, 119].

Though non-operative management is successful in more than 90% of cases [308], for those patients with symptoms persisting for over six months, surgery may be offered. Debridement of the common extensor tendons has been reported to yield good to excellent results [70], with clinical remission of symptoms of up to 97% at 10 years [124]. However, it has also been reported that 24% of post-surgical patients remain in pain at one year [211] and the surgical procedure carries the associated risks of infection, haematoma, and nerve injury [308]. It is also prohibitive in terms of both healthcare costs and economic impact to the patient owing to a protracted recovery period and avoidance of exacerbating activity for up to three months [118] . In view of these

concerns, there has been a recent interest in alternative injection therapies, with the particular emergence of Platelet-rich Plasma.

Platelet-rich Plasma (PRP) relies on the concept of delivery of humoral mediators that promote normal tendon healing [309]. PRP contains a concentrate of platelets, isolated from the patients' whole blood using cell-separating systems [310]. Though clear guidance is not yet available, PRP is purported to be most effective in chronic cases where symptoms have been present for longer than three months [118, 119], of the preparations of PRP, the leukocyte-rich variant has been recommended [117], ultrasound-guided injections have also been recommended over anatomically-guided techniques [261] and patient-reported outcome measures (PROMs) have been recommended as the primary outcome measure [101]. On the question of control groups, corticosteroid injection, though commonly applied, are felt to be an inferior comparator due to the negative long-term effects [96], local anaesthetics have been shown to have a detrimental effect on the tendon itself [311, 312] and also interfere with platelet functionality by decreasing aggregation [313]. The use of saline injections as a placebo has also been questioned, where a high volume injection may in itself induce a healing response [117, 314]. The question of injection number has also been raised, with calls for trials to assess the therapeutic effect of two injections in previously treatment-resistant cases where the efficacy of a single injection remains in question [119, 277].

The clinical equipoise between surgery and PRP for LET has been recently reported in two retrospective cohort studies [315, 316]. Owing to this equipoise, the comparison of the current gold standard (open tennis elbow surgery), to the

novel intervention (PRP) of which the formulation and administration is guided by the best available evidence whilst also attempting to assess knowledge gaps, would seem both ethically acceptable to patients and clinically relevant.

No full-scale randomised trial has been undertaken to compare these two interventions. Therefore the aim of this feasibility trial was to establish the projected patient eligibility, recruitment rate and adherence to interventions and outcome assessments to inform a future study design. It was also vital to ensure that the study was able to adhere to the reporting principles outlined in the CONSORT statement for reporting randomised trials [317] and recently published Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO) guidelines [122]. Furthermore, no previous assessment of patient acceptability, of both the trial design and PRP intervention, has previously been undertaken. Though PRP use is increasing [103, 108] and is deemed safe and acceptable in principle, the paucity of any qualitative data on patient acceptability is surprising. Previous trial reporting of adverse events has also been criticised [105], the single attempt at data extracted from injection trials in LET has highlighted pain as being the most commonly reported side-effect [105], but no elaboration on the details of this has been made.

8.4 Methods

Study design overview

This trial was a parallel group, randomised, prospective feasibility trial. The trial protocol, conforming to SPIRIT guidelines [318], was registered with clinicaltrials.gov (NCT02755727). It was approved by the National Research Ethics Service (NRES) Devon and Torbay Research Ethics Committee (REC)

and South West REC (appendix 18). The study was funded through the attainment of a Royal Devon and Exeter Hospital Small Grant Award. No external industry sponsorship was gained. All study participants provided written informed consent. Reporting of the feasibility trial is in concordance with CONSORT guidance for parallel group pilot and feasibility randomised trials [319], and Patient-Reported Outcome use [320].

Setting and participants

This study was undertaken at the Royal Devon and Exeter NHS hospital, Exeter, UK. Recruitment was undertaken in the hospital orthopaedic outpatient department. All attendances were secondary care referrals from primary care physicians. Participants were screened by two Consultant upper limb surgeons (CS and WT) and provided with patient information sheets (appendix 19). Interventions were performed in the same hospital with surgery performed at the Princess Elizabeth Orthopaedic Centre and injections performed in the hospital's radiology department. Twelve participants were selected for this study. This number was selected as an achievable target within a 12-month single institution model, which would produce adequate qualitative and quantitative data for feasibility assessment and make the best use of a pump-priming research grant. All participants were provided with an information leaflet outlining the study aims, the two interventions, and follow-up process.

Inclusion and exclusion criteria

Patients diagnosed clinically as experiencing LET with a symptom duration of more than six months were eligible for inclusion. Patients were also required to have failed conservative treatment (physiotherapy, oral analgesia, and activity

modification) and have a baseline elbow pain score of >3/10 on a visual analogue scale (VAS). All had undergone plain anteroposterior and lateral radiographs to exclude other sources of lateral elbow pain.

Patients were excluded from inclusion if they were unfit for surgical intervention, had undergone previous elbow surgery, had previously undergone PRP injection, suffered from systemic autoimmune rheumatological disease, received immunosuppressive treatment, had undergone local steroid injection within three months of potential recruitment (at any site) or were unable to comply with follow-up or previously been treated with biological therapy for their LET.

Randomisation and interventions

Potential participants, once identified by the consulting surgeon, were referred to one of two project co-ordinators (JE and SG). Participants were screened on site and once eligibility was confirmed, were invited to participate through both a verbal discussion and after reading a patient information sheet. Consent and baseline outcome assessments were undertaken within the same appointment.

Randomisation was undertaken using a 1:1 allocation to open surgery or PRP injection using sealed envelopes. Envelope randomisation and storage was undertaken by a third party not associated with the study. Owing to the difference in treatments, blinding of the patient or treating physicians was not deemed pragmatic within the context of a feasibility trial.

Surgery

A standardised Nirschl surgical technique [124] was used. This involved the patient undergoing a general anesthetic. An incision centred over the lateral

epicondyle was made and the plane opened between ECRL (Extensor Carpi Radialis Longus) and EDC (Extensor Digitorum Communis) to expose the damaged ECRB (Extensor Carpi Radialis Brevis) tendon. The amount of abnormal tendon was documented. All abnormal tissue was excised. EDC was also inspected and any abnormal tissue documented then excised. The footprint of the excised ECRB +/- EDC was cleared of soft tissue and the bone scored with an osteotome to promote bleeding. The interval was sutured closed and the skin wound closed with an absorbable subcuticular suture.

Injection

Participants received two injections spaced two weeks apart. They were asked to refrain from using any Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for two weeks prior to the injection. A leucocyte-rich PRP preparation was produced and the procedure was undertaken by a musculoskeletal radiologist using ultrasound control.

For trial validity, the advanced Arthrex Angel™ system was chosen (Arthrex, Naples, Florida). This allows an automated, closed system, platelet capture that produced a leucocyte-rich PRP formulation in liquid form.

In the outpatient setting a 40ml sample of venous whole blood was taken from the patient's anticubital fossa using standard phlebotomy techniques. This was mixed with 6mls of Anticoagulant Citrate Dextrose-A (ACD-A) (7:1 ratio of whole blood to anticoagulant). Addition of an activating agent was not undertaken. The 2% haematocrit double spin protocol was utilised as per the manufacturer's recommendation for tendinopathy applications (Spin 1 @ 3500 rpm for 2 minutes, Spin 2 @ 3000rpm for 9 minutes). Constituent separation was

automated using proprietary technology within the Angel system. Utilising the manufacturer's dilution tables, a 40ml sample of whole blood will produce a platelet concentration of 6.58x baseline in a 2ml yield and 4.54x baseline in a 3ml yield. White blood cell concentrations are 0.97x baseline in a 2ml yield and 0.67x baseline in a 3ml yield.

PRP was injected within five minutes of preparation. The sample temperature was not modified. Prior to injection, the skin was cleaned with 2% chlorhexidine spray. No local anaesthetic was administered. Injection was delivered under ultrasound control using a 5ml syringe and 23g needle. A fenestrated (pepper pot) technique was used. The tendon was fenestrated nine times and the PRP delivered in small aliquots during each fenestration. All injections were delivered by a single fellowship trained Consultant musculoskeletal radiologist with six years of consultant experience using a Siemens-Acuson Antares (SIEMENS medical solution, Mountain View, California, USA) with a 13 MHz linear array probe.

Post-operative and post-injection protocol

Following operative intervention, the participants were placed in a wool and crepe bandage and a broad arm sling. The bulky bandage was removed at 48 hours and full active range of motion was initiated as pain allowed. A graduated resistance programme was undertaken at home from two weeks following advice from a physiotherapist, this included a graduated resistance programme starting with eccentric strengthening and progressing to concentric loading. Return to work for manual jobs or sport was advised at six weeks. Heavy

activities or heavy work before six weeks was to be avoided. Oral analgesia as per the patients' preference was advised for pain control.

Injection participants were placed in a broad arm sling which was advised for the first 48 hours. Full active range of movement was encouraged as soon as patient comfort allowed. The participants followed the same resistance programme but were not restricted in load at any point. Symptom-led progression to full loading was requested. Return to work for manual jobs or sport was advised at three weeks but was participant directed. Participants were asked to restrain from taking Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for the first six weeks. Following feedback from the first two participants, ice packs were suggested for the first 48 hours following injection if required for symptomatic pain relief.

Outcomes and follow-up

Primary outcome measure: feasibility of a full-scale randomised trial.

Number of eligible participants, number recruited, adherence to intervention and loss to follow-up was recorded. The strengths and weaknesses of the research process and design were determined through a debriefing process with research team members and qualitative interviews with participants.

Secondary outcome measures

Participants were asked to attend follow-up appointments at six weeks, three months and six months following the intervention.

Patients completed the quick Disabilities of Arm Shoulder and Hand (QDASH)[207], Oxford Elbow Score (OES)[142] and Patient-Rated Tennis Elbow

Evaluation (PRTEE)[206] at baseline and at all follow-up appointments. These three Patient Reported Outcome Measures (PROMs) meet minimum criteria for recommendation in LET in the previously documented EMPRO systematic review. The generic health measure EQ-5D-3L [321] was also recorded and participants were also provided with a pain diary for completion of a Visual Analogue Scale (VAS) at the time points, day one, two, seven, week two, six and three months and six months.

Qualitative participant assessment

To address the lack of reporting on PRP injection acceptability, adverse events and patient experience during this feasibility trial, we undertook qualitative interviews of those participants who received the PRP intervention. Semi-structured telephone interviews were conducted by a member of the research team (JE) using a topic guide designed to address the patient-focused aspects of feasibility trials suggested by O'Cathain et al (2015) [322] (appendix 20). Interviews were conducted at varied stages in the patient rehabilitation schedule. The interviews were transcribed verbatim (example in appendix 21) and analysed using stepwise thematic analysis. Thematic analysis is an approach based around the principle of grounded theory, whereby the interpretation of the data is 'grounded' in the perceptions and concerns of the participants, that is, that the hypothesis is developed from the data, rather data collection being used to test a predefined hypothesis. Applying this principle, thematic analysis is a method of identifying, analysing, organising, describing and reporting themes found within a dataset [323]. Analysis was undertaken by three researchers (JE)(AD)(IP) who have all received qualitative research

training. A six-phase thematic coding approach was used [323], whereby the researchers independently familiarised themselves with the data, then individually produced initial codes (recognising important moments within the data),individual thematic coding (whereby notable themes and patterns emerge from the document and are recognised as implicit or explicit common ideas within the data), team review of trends in codes, amalgamation of codes and derivation of consensus within the codes (resulting in a coding matrix (appendix 22) to summarise the thematic structure) and report production through synthesis of data. The qualitative data were interpreted in reference to the questions:

1. What was the participant experience of the intervention (PRP)?

2. What was the participant experience of the trial?

3. Is PRP an acceptable and appropriate intervention for further study?

Qualitative analysis was undertaken in NVivo qualitative data analysis software (QSR International Pty Ltd. Version 11, 2017)

Patient and Public Involvement

To inform the outcome measure assessment within this feasibility randomised trial, a patient and public involvement (PPI) group was set up to discuss the application of patient-reported outcome measures (PROMs) within LET research, with a focus on discussion of their utility and collection methods. Adverts were placed in local newspapers for participants previously diagnosed with LET to attend an open meeting. Open discussion, following introduction to paper-based and electronic PROMs collection methods was undertaken.

Discussion themes were recorded and discussed between three PPI co-ordinators to reach a consensus on overall group opinions and themes.

8.5 Results

Recruitment

The Consort flow diagram outlining recruitment, assignment and interventions is seen in Figure 8.1. The recruitment period ran from June 2016 to April 2017 in a single, two surgeon, orthopaedic outpatient clinic. All LET patients were approached during this period, which equated to 14 individuals. Baseline patient demographics can be seen in Table 8-1. No participants were taking antiplatelet medication, were diabetic or had known inflammatory conditions. Prior to delivery of the intervention, one patient withdrew from the study from the surgical arm. This patient had polio, and though eligible through our inclusion/exclusion criteria, stated that as it was their 'good' arm that was affected, she would have had the PRP intervention had she been randomised to it, but was not prepared to undertake the proportionally longer period of immobilisation related to the surgery. Within the PRP group, one patient crossed over to surgery following no clinical improvement at the three-month follow-up. This left five patients in each group who were followed up to the six-month primary end-point. There was no loss to follow-up. The feasibility study was stopped at this point to complete qualitative interviews and research team debriefing.

	Age	*Gender*	*Hand dominance*	*Occupation*	*Symptom duration*
PRP group	46.2	4 female	3 non-dominant	1 manual	13.5 months

	(38-51)	2 male	3 dominant	5 sedentary	(6-24)
Surgery group	56	4 female	2 non-dominant	2 manual	19 months
	(43-63)	2 male	4 dominant	4 sedentary	(12-24)
Total	51	8 female	5 non-dominant	3 manual	16.3 months
	(38-63)	4 male	7 dominant	9 sedentary	(6-24)

Table 8-1: Participant demographic information - mean (range)

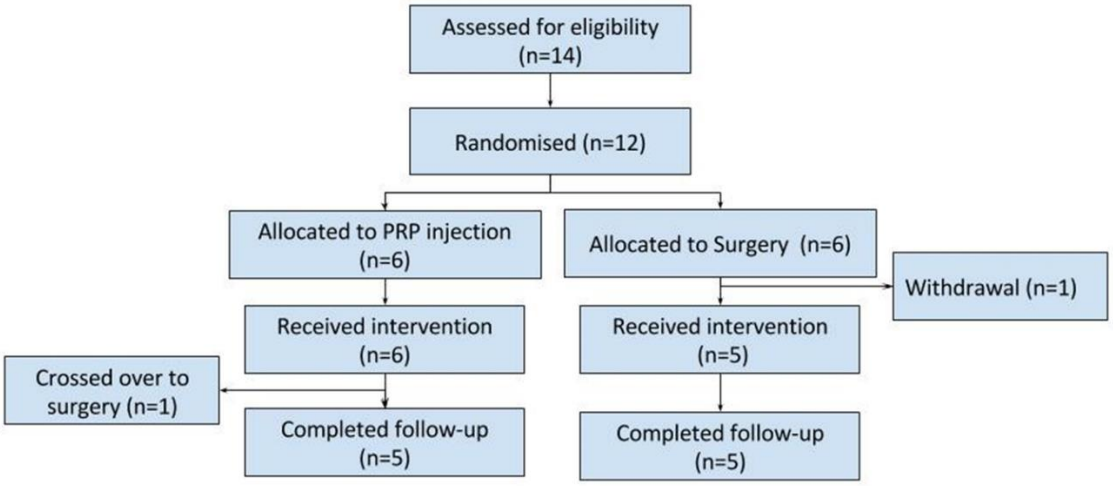


Figure 8.1: CONSORT flow diagram

Interventions

All participants were treated within the National Health Service, consequently following recruitment they were placed on standard waiting lists for surgical intervention (surgical group) or interventional radiology (PRP group). The median delay between recruitment and intervention for surgery was 54 days (range 47-71) and for PRP 64 days (range 34-76). No adverse events were reported in the surgical group, in the PRP group all patients reported significant but temporary procedural pain, this is discussed in detail as part of the qualitative analysis. Post-operative protocols were followed by all patients.

The median volume of PRP injectate gained following processing was 1.55mls (Range 1ml – 4mls). Processing of the 40-47ml whole blood sample yielded a red blood cell concentrated fraction of 19mls (17 – 28mls) and a plasma fraction of 20mls (19-23mls). All injections were delivered within five minutes of processing. Pre-injection ultrasound evaluation within the PRP group of the common extensor origin revealed hyperaemia in all cases, three patients with central footprint tears of >5mm, two patients with small spurs <3mm in size, one patient with a 3mm central calcification lesion within the tendon. Of the surgical group, interoperative assessment reported a degenerative injected appearance of the ECRB in all cases, the presence of osterophytes at the ECRB insertion in one patient, a full thickness tear requiring suture anchor fixation in one patient, and a partial tear with a small plica and Grade IV rim arthritis to the radial head in one patient.

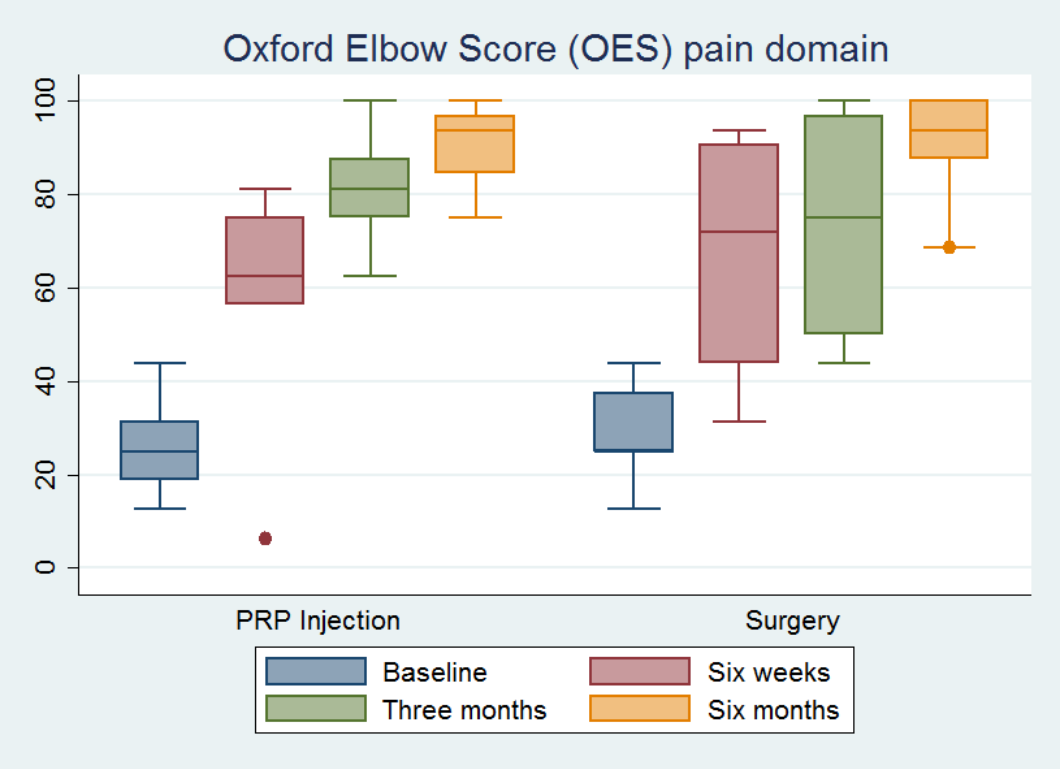
Outcomes

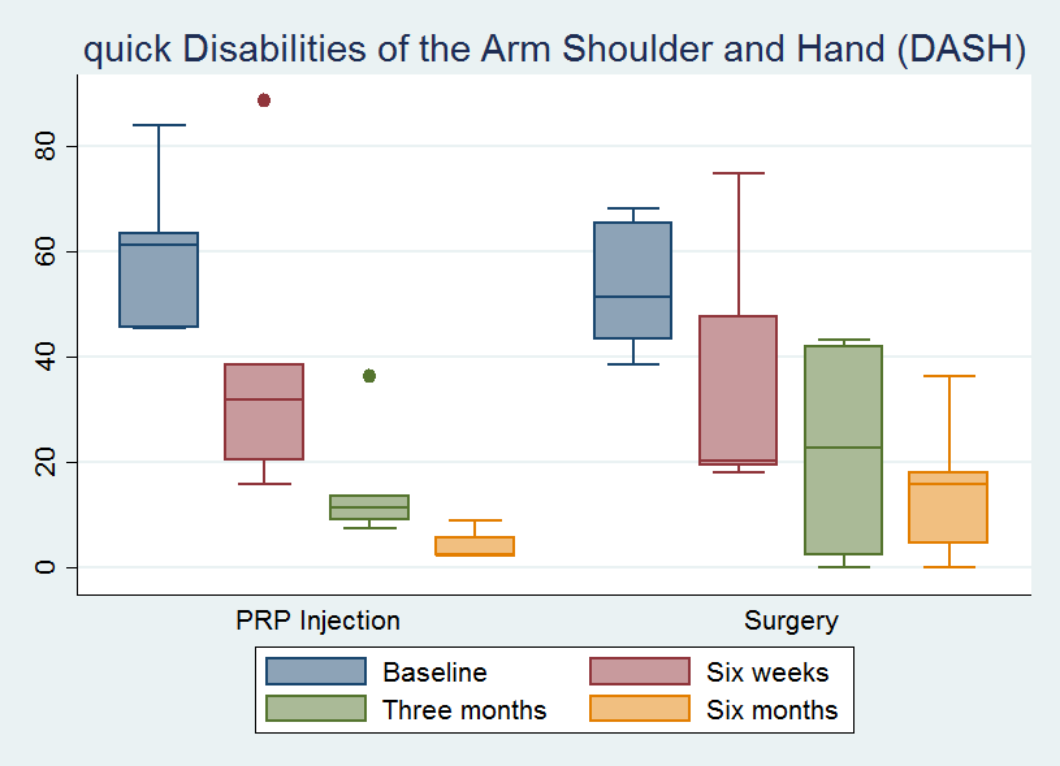
As a component of the feasibility trial participants completed three elbow specific outcome measures and a generic health assessment (Table 8-2 and

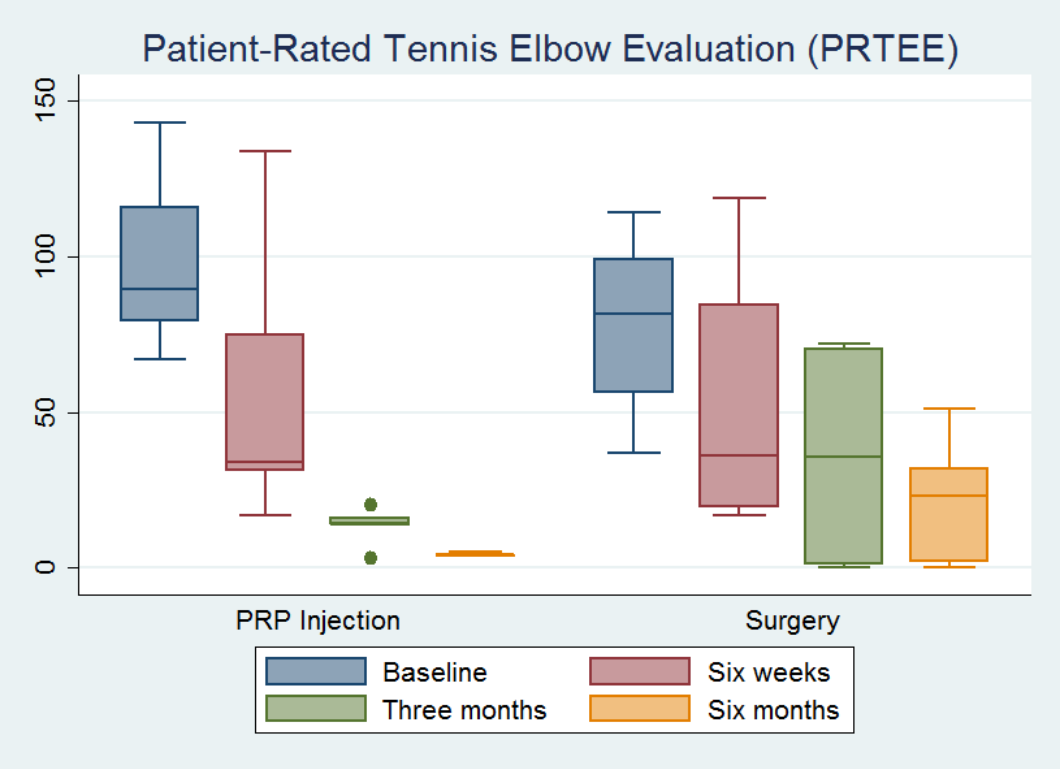
Figure 8.2). Within completed questionnaires, there were no missing item data. Compliance with the pain diary was 50%, all of whom were PRP trial arm participants. Although statistical analysis was not applied to the outcome measures, owing to the small sample size, trend data show improvement over time in both groups and throughout all outcomes. It is notable that from similar baseline scores (PRTEE worse in PRP group and QDASH worse in surgical group), the six-month outcome of the PRTEE and QDASH for the PRP group implies a return to pain-free function, however, the surgical group average is 15%- 20% of total score. As an estimate of the magnitude of the difference between the groups, it is notable that the effect size in favour of PRP for the QDASH and PRTEE is 0.8 for both outcomes signifying a large effect in comparison to surgery [324]. These differences between PRP and Surgery are not reflected in the OES. The EQ-5D-3L, represented as UK index scores (using the Time Trade-Off (TTO) and Visual Analogue Scale (VAS) validation techniques) and EQ5D VAS again show a gradual trend to an improvement over the study period. Large differences in all outcomes between the three and six-month collections, with continued improvement and lack of a clear plateau in any outcome, shows the need to extend the outcome to at least the six-month point.

Table 8-2: Showing mean (SD)(Range) of Patient Reported Outcome Measures (PROM) separated by treatment group.

		Baseline	6 weeks	3 months	6 months
PRP	OES Pain	26 (10.8)(12.5-43.75)	56.3 (29.6)(6.3-81.3)	81.3 (14.0)(62.5-100)	90.6 (10.8)(75.0-100)
	OES function	46.9 (18.9)(12.5-68.8)	67.5 (27.7)(18.8-87.5)	92.5 (6.8)(87.5-100)	98.4 (3.1)(93.8-100)
	OES Psychosocial	12.7 (12.9)(0-31.3)	48.8 (27.7)(9.9-68.8)	86.3 (10.3)(68.8-93.8)	93.8 (5.1)(87.5-100)
	PRTEE	97.3 (28.1)(67.0-143.0)	58.2 (47.6)(17.0-134.0)	13.4 (6.3)(3.0-20.0)	4.3 (0.5)(4.0-5.0)
	QDASH	60.0 (16.0)(45.5-84.1)	39.1 (29.1)(15.9-88.6)	15.6 (11.8)(7.5-36.4)	4.0 (3.4)(2.3-9.1)
	EQ-5D-3L Index (TTO)	0.64 (0.28)(0.07-0.76)	0.67 (0.23)(0.26-0.80)	0.88 (0.16)(0.69-1.00)	0.94 (0.12)(0.77-1.00)
	EQ-5D-3L Index (VAS)	0.66 (0.18)(0.29-0.73)	0.66 (0.20)(0.31-0.76)	0.87 (0.18)(0.67-1.00)	0.94 (0.12)(0.76-1.00)
	EQ-5D-3L VAS	69.2 (19.6)(50.0-95.0)	82.0 (9.1)(70.0-95.0)	92.8 (2.6)(90.0-95.0)	92.3 (8.3)(80.0-98.0)
Surgery					
	OES Pain	28.1 (11.0)(12.5-43.8)	67.2 (29.0)(31.3-93.8)	72.4 (27.7)(43.8-100.0)	90.0 (13.0)(68.8-100.0)
	OES function	58.3 (10.2)(43.8-68.8)	71.9 (31.3)(25.0-87.5)	82.8 (20.0)(62.5-100.0)	91.3 (13.0)(68.8-100.0)
	OES Psychosocial	24.0 (15.5)(6.3-50)	60.9 (20.7)(37.5-81.3)	71.9 (31.7)(31.3-100.0)	81.3 (19.8)(50.0-100.0)
	PRTEE	78.2 (29.1)(37.0-114.0)	52.0 (47.0)(17.0-119.0)	35.8 (40.2)(0.0-72.0)	21.6 (21.4)(0.0-51.0)
	QDASH	53.1 (12.4)(38.6-68.2)	33.5 (27.7)(18.2-75.0)	22.2 (23.1)(0.0-43.2)	15.0 (14.2)(0.0-36.4)
	EQ-5D-3L Index (TTO)	0.44 (0.36)(0.05-0.80)	0.69 (0.17)(0.43-0.80)	0.82 (0.12)(0.76-1.00)	0.85 (0.21)(0.56-1.00)
	EQ-5D-3L Index (VAS)	0.53 (0.23)(0.27-0.76)	0.67 (0.14)(0.73-1.00)	0.80 (0.14)(0.73-1.00)	0.84 (0.22)(0.55-1.00)
	EQ-5D VAS	60.0 (13.2)(40.0-75.0)	72.5 (20.2)(45.0-90.0)	86.3 (9.5)(80.0-100.0)	77.0 (9.7)(65.0-90.0)


Oxford Elbow Score (OES) pain domain
0
20
40
60
80
100
PRP Injection
Surgery
Baseline
Six weeks
Three months
Six months


quick Disabilities of the Arm Shoulder and Hand (DASH)
0
20
40
60
80
PRP Injection
Surgery
Baseline
Six weeks
Three months
Six months



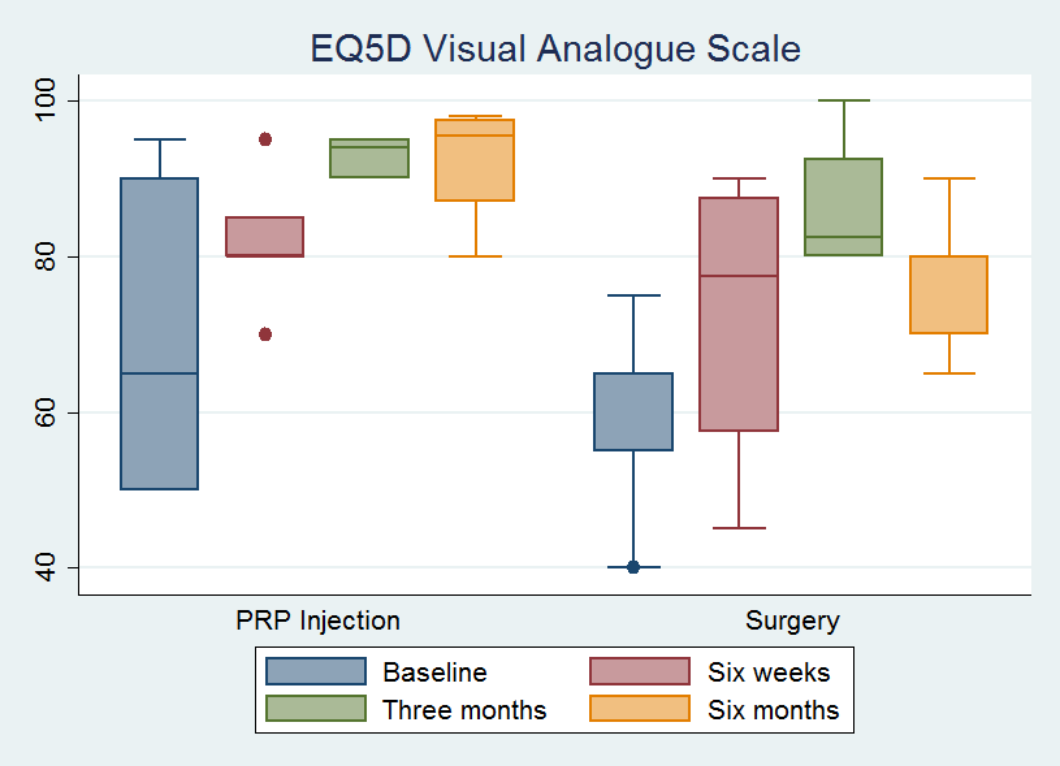


Figure 8.2: Box plots showing Patient Reported Outcome Measure (PROMs) median score (Box = IQR) (Whiskers = Interquartile Range) (Dots = Outlier values).

A power calculation was conducted using data derived from the PROM outcome collection. PROM-based primary outcomes are increasingly employed and encouraged by funding bodies and publishers alike [133, 147, 197]. The previous systematic review has outlined that the QDASH demonstrates the greatest evidence for validity in this LET cohorts and hence it is utilised in this case as the potential primary outcome. The trial would be powered for non-inferiority, under the premise of significant cost saving and amelioration of operative risk in the PRP group. The smallest detectable change in the QDASH is utilised as the equivalence limit, as a measure of the error of the instrument and the smallest change that is detectable between two scores that is beyond error. This can be calculated from the standard deviation (SD) of the feasibility studies baseline sample (14.3), using a technique advocated by Terwee et al [250]. Initially, the standard error of the measurement (SEM) is calculated as $SD_{(baseline)} \times \sqrt{1 - ICC}$, where the Infraclass Correlation Coefficient (ICC) is a measure of test-retest reliability. This has been derived in upper limb musculoskeletal disorders as 0.94 [216, 325]. To account for the repeated measures of the outcome and a 5% probability of Type 1 error, the smallest detectable change (SDC) is calculated as $1.96 \times \sqrt{2} \times SEM$.

Therefore:

SEM = $14.3 \times \sqrt{1 - 0.94}$ = 3.5

SDC = $1.96 \times \sqrt{2} \times 8.0$ = 9.7

Using this figure of 9.7 and the baseline QDASH SD of 14.3 and powering for non-inferiority [326], using the equation $n = f(\alpha, \beta/2) \times 2 \times \sigma^2 / d^2$, (where σ = SD,

d = the equivalence limit (SDC) and $f(\alpha, \beta) = [\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2$, where Φ^{-1} is the cumulative distribution function of a standardised normal deviate [327], then 76 patients (38 per group) are required to be 90% sure that the lower limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will be above the non-inferiority limit of -9.7. Alternatively, were the PRTEE used in this calculation, with the ICC of 0.89 [206] and baseline SD of 29.1, 42 patients (21 per group) are required to be 90% sure that the lower limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will be above the non-inferiority limit of -26.75 (SDC).

Qualitative assessment

Interviews were conducted at a median of 19 weeks post-injection (Range 8.8 – 27.7 weeks). The key themes identified by all the three qualitative researchers were mapped to the study questions (appendix 23). The themes were discussed among researchers and assessed for the level of saturation within this small cohort. Illustrative quotes were grouped to the research questions (Table 8-3).

The most prominent finding relating to the participants' experience of undergoing the PRP intervention related to the level of pain. The consensus among participants was that the pain was very significant and worse on the second injection. Strikingly it was commented by all participants that it was one of the most painful experiences of their entire lives. Though the injection pain was temporary and distinct from the latterly experienced post-procedural pain, it remained very significant to participants who were very clear about their experiences many weeks after their injection. Though the injection was very

painful, the overall process of the injection was felt to be safe and conducted in an appropriate and supportive environment. The post-procedural pain was experienced by participants for some weeks, many developed personal coping strategies not initially part of the post-injection protocol, including intermittent use of a sling and avoidance of the use of the arm for any lifting tasks for some weeks post procedure. It was also commented that though the injection was painful, the interference in their life was acceptable, and in reference to the post-surgery protocol, was deemed to be preferable.

Participants were happy to be part of the trial and did not appear to perceive the extra appointments and outcome assessment a burden. Of interest, it was also identified that none of the participants were aware that a trial was being done, and that the expectations of intervention following a secondary care referral were very low. Only one participant was aware that surgical intervention might be offered. When the study was introduced with randomisation to PRP or surgery, all participants were happy that it was the PRP that was offered. Participants volunteered an opinion on potential improvements to the post-procedural care, with all suggesting that a short period of immobilisation was helpful. At the time of injection, three of the five participants volunteered that anaesthetic or sedation would be preferable, though equally, they deemed the short outpatient style of intervention highly preferable compared to the longer day-case surgical procedure.

Research Question and Themes	Participant quotes
What was the participant experience of the intervention (PRP)? **Themes** • Procedural ○ **Procedural pain** ○ **Experience of health professionals** ○ **Safety** • Post Procedural ○ **Post-procedural pain** ○ **Post-procedural treatments** ○ **Post-procedure interference with quality of life**	• Oh, God. Um… It was excruciating. • I just - I don't think you can prepare anybody for quite how painful it's gonna be. • It was just that thinking, well, I thought my arm was gonna explode. • It was uncomfortable when it was done the first place time cuz it was certainly far worse the second time.. • Ooh-hoo. Um, I- Well, as you know, it was the most- one of the most painful things I've ever, ever done, I think. • I mean the surroundings and the people and everything was brilliant. I mean, [the nurse] was absolutely wonderful. She was just holding my hand and you know, um, and being really good and everything, so from that point of view, but I do- I do th- definitely think that some, if it's possible to give some sort of local anesthetic or something, because it- it was awful. • You know, um… Yeah. I mean, I- At no point did I ever feel unsafe or anything like that. I mean, it was all done, you know, it- in-in good, clean conditions an-and what have you and everythi- every step was explained to me • Um, the recovery was a good couple of hours post-injection. It was still incredibly painful — really, really sore — um, and I— I—I don't think I'm a wimp, but it was really painful. • Um, with the second one, I would say probably about four—about a month or so • It was quite traumatic, and then coming home afterwards, um, you think about, you know, you sort of, um, at- You sort of sit and think about the pain that you were in, and it was quite- quite upsetting for a few days afterwards, actually. • It was, you know, by the time I'd sort of got back into the car and everything, um, it was, you know, th-the pain was sort of virtually, you know, gone from the- the extreme pain • So. Yeah. Yeah. I, um, I used the sling. I used the sling, um, fully for about two days. Um, and [10:00] I just took a paracetamol , um, and that seemed to just sort of help with any residual pain • Um, yeah. I definitely, definitely needed someone with me. Um, and I can't remember if I'd actually to- I don't think I'd taken any pain killers before I came that first time.
What was the participant experience of the trial? **Themes** ○ **Knowledge of trial** ○ **Reflection on being in a trial** ○ **Burden of being in a trial**	• Oh, it's been absolutely brilliant, 'cause it's just sort of like, you know, if- You feel like you're part of something that if you can then help a process along, which then helps, you know, other people [13:47] to then, uh, avoid surgery or to, um, get back to, like, living life normally, 'cause I mean this is something I've not been able to do for a long time is to sort of live life normally, but if it's something that can help people to get back to work or to get back to living life normally, brilliant. I'm- I've been- I've been really pleased to be able to say I've been part of that. • Um, quite frankly, I was prepared to do anything to avoid that surgery. Um, yeah—no, I was—I was more than happy—ecstatic, in fact, to be, um, even considered for it. • No, not really, um, I appreciate that, if you don't do the—the—the pain scoring stuff um… that wasn't, you know, very bad.

○ **Reflection on possibly being randomised to surgery** ○ **Improvements**	• No, not at all. No, not at all, because it worked. • No, it was all right. No, it was fine, actually • Well, I imagine it probably would have been more painful for a longer length of time, cuz any sort of surgery tends to be cuz you've got ripped tissues to repair. • You know, so I'd kind of gone in that. I really didn't want to have the operation and be .. out of action for six weeks. • [If I'd had surgery] the six-week recovery period, which, to me, is an awful long time not be able to do normal duties at work. • So it just felt- It just felt to me like it was, um, an easier optio- uh, an easier version of the surgery, if that makes sense • It's like you're either losing it for six weeks cuz of surgery healing, or I have three days where y—where you're—I'm one-handed for three days • Um, a shorter time span, and the only other thing I found was w-with- with it not being post-surgery, if you didn't have to worry about, um, you know, b- getting it wet or worry about stitches or things like that. • It wasn't, you know, um, uh, yeah. Maybe, I dunno, a little bit of pain relief might have been nice, um, even if it was just, you know, like, all pain relief. • Maybe, um, I think there's, like, mild sedation, like, when you go to the dentist and have stuff like that. • I do- I do th- definitely think that some, if it's possible to give some sort of local anesthetic or something, because it- it was awful.
Is PRP an acceptable and appropriate intervention for further study? **Themes** ○ **Procedural pain** ○ **Safety** ○ **Repeat treatment** ○ **Recommendation or not of treatment**	• Procedural pain and safety quotes as above • I would- wouldn't hesitate to… To say to people, "Oh, yes. You know, do it • Yeah, absolutely, uh, 100 percent I would recommend it, and all I would say to people if they were to go to through with it is, uh, get a that arm in a sling and take time off work, I think—I think you should really push for that. I—I think I could have done—I could have done more for myself on the first injection. • Yeah. Yeah. Yeah, I wouldn't hesitate to, to be honest. • And, um, no, yeah, I, I would do it again. I would prefer this sort of thing to surgery, and I was, as I've said to that before, then if you get tennis elbow then, if you have to opportunity to try that, then I would try it. • But if it was offered to me again on something else, which I had only just started having a problem with, then I would say, "Yep. Fine. Go for it," and even if it was as painful as it- as it was, um, I would say, "Yes. Do it." • And actually, if, you know, I know that I would go for it again, so if it helped me, it can help other people

Table 8-3: Qualitative data – Research Question with identified themes and key illustrative quotes.

Though all participants commented that the procedure was very painful, it is of great interest that when asked whether they would have PRP again or recommend the treatment to friends or family, without exception they all commented very positively. The overall impression of the process and procedure was that it was safe and appropriate. One of the participants had crossed over to surgical intervention due to treatment failure at three months, even with the treatment failure and pain experienced as part of the intervention, this participant would have the PRP intervention again and would recommend it.

Study team debrief

The study process was discussed between the study chief investigator, lead research nurse, lead surgeon (undertaking the surgical intervention) and the radiologist undertaking the PRP injection. The recruitment through the outpatient department was deemed feasible, however, baseline data collection was initially missed on two participants due to unavailability of the research packs. One post-surgical patient was placed in the physiotherapy-led discharge route rather than the designated research clinic, resulting in loss of three-month outcome data. The process of data collection and PRP injection delivery was refined through the study, where the resultant strategy of participants attending 20 minutes early, allowing blood sample collection, then data collection of PROMs, ready for their designated appointment with the radiologist, resulting in a total outpatient time of one hour per participant.

All members of the research team commented on the pain experienced by participants at the time of injection. The lack of local anaesthetic, in line with treatment recommendations, without substitute with pre-intervention analgesia was

deemed inappropriate. The use of conscious sedation techniques in the theatre setting was promoted as a potential approach whilst recognising the resource and cost increase associated with this strategy.

Patient and Public Involvement

A public meeting was held on the 18/4/2017. Nine participants, who suffer with, or have previously suffered from LET attended. One member of the group was a participant in the study. Reflections on the open discussion with the PPI group regarding outcome measurements and data collection methods were recorded and synthesised between two attending PPI co-ordinators and the study Principal Investigator. There was a positive response on the use of elbow specific questionnaires for the assessment of the impact of interventions in a trial. The participants assessed the OES, QDASH, and PRTEE and although all were deemed appropriate, the 10-point scale and particular questions on the PRTEE was liked the most. The general heath questionnaires (EQ-5D-3L and HowRU score were assessed) were not deemed relevant and an annoyance to complete. Overall there was a preference for paper-based questionnaire completion over online. There was also a desire to include a free text option to allow elaboration on the pain triggers and character. There was a split in the group regarding the utility of knowing one's own score or tracking the improvement individually. Some felt this would be useful to individuals within an interventional trial, others felt that they would not use this information at all. What they particularly liked about all the scoring methods, was the objectivity it imparted to the clinician about how significant this problem can be to their lives, in this regard it was deemed highly appropriate to have this as the primary outcome in a clinical trial.

Reporting standards

This feasibility study has been reported in accordance with the CONSORT guidance for pilot or feasibility trials. The ability of a larger trial to comply with the reporting standards of the CONSORT PRO extension guidelines was also assessed. From details within this feasibility trial, we feel that 100% compliance with these guidelines is achievable. For intervention reporting, compliance with the Template for Intervention Description and Replication (TIDieR) and Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO) was assessed. Full compliance with the TIDieR checklist was achieved, for the MIBO checklist, laboratory analysis of whole blood prior to processing for PRP production, and laboratory analysis of the PRP samples themselves was not undertaken within the feasibility study. This aspect will need to be addressed within a full scale randomised trial. Completed checklists can be found in appendix 24.

8.6 Discussion

This study has assessed the feasibility of running a full-scale randomised trial comparing Platelet-Rich Plasma (PRP) injections to Surgery for chronic Lateral Elbow Tendinopathy (LET). Current best available evidence has been used to design a standardised PRP production and delivery protocol that published laboratory-based and comparative studies suggested as the most therapeutic. Recruitment rates and retention were acceptable and the feasibility trial has informed and highlighted the utility and importance of Patient-Reported Outcome Measurement (PROMs) in a study of this nature. This is also the first PRP study to confirm the ability to conform to the reporting standards of the CONSORT, CONSORT PRO, TIDieR and MIBO checklists in PRP research. However, qualitative analysis, which

has not previously been utilised in PRP research, has identified a significant source of patient morbidity not traditionally recorded or reported on the pain associated with injection delivery.

The recruitment for this feasibility showed that, within a National Health Service District General Hospital serving 460,000 people, the secondary care referral rate for LET is low. The recruitment of 12 participants took 10 months. Therefore the recruitment for a full-scale randomised trial, in reference to the above power calculation, would take over five years. Therefore a multicentre approach is likely to be required to complete a trial of this nature within a reasonable period of time. The retention of patients in this feasibility study was 100%, however, it should be noted that there was one withdrawal from the surgical group and one cross-over from PRP to surgery. This 17% non-treatment allocation finding should be taken into account in the implementation of a full trial. In reference to the withdrawal, as the patient subsequently volunteered that they would have only continued in the trial had they been randomised to PRP, it is of vital importance that potential recruits are counselled correctly at the recruitment stage. Findings from this trial would suggest that a follow-up period for the primary end-point would need to be at least six months as gradual improvement was seen up to this point. Of note Merolla et al [328] who followed up PRP patients for nearly two years, demonstrated good treatment response within the first year, that then worsened when compared to patients treated with arthroscopic debridement of their LET, however Gaspar et al [329] reported sustained improvements up to three years. Though evidence is limited, it may be prudent, therefore, to consider longer follow-up periods.

Some of the most informative and compelling information within this feasibility study was gained from the qualitative data. Although pain has previously been reported as

a potential adverse event [105], the level of pain experienced by the participants was striking. Local anaesthetic was not given prior to the administration of the PRP, in line with recommendations from laboratory studies [311, 312]. The use of local anaesthetic infiltration is advocated by 60% of experts questioned as part of the Delphi consensus study into PRP use in LET (chapter 7) which may be due to a practice that is informed through personal experience, or lack of knowledge of the background science. However, this leaves 40% of PRP users whose patients may be experiencing significant pain. To our knowledge, pain at the time of injection using a validated technique such as a Visual Analogue Pain Scale, has never been reported and is not commented on in any systematic review. At the very least, we believe the collection of these data should be mandated and compared to different techniques. Information on the clinical outcome of PRP, administered with or without local anaesthetic infiltration, is also required to compare to the laboratory-based findings.

Although participants reported very significant pain at the time of injection, it is pertinent to note that when asked to reflect on the experience, all responded that they would have the treatment again, would recommend it to friends and family and would still prefer it as a treatment option over surgery. This poses an ethical challenge to the researcher and clinician, in that the principle of “Primum non nocere” is juxtaposed with a patient desire for treatment, regardless of the discomfort. Researchers of lateral elbow injections should be very mindful of this quandary and ensure that everything is done to ensure that analgesia is optimised. Though sedation was suggested by two participants, three participants felt strongly that the anaesthetic component of surgery was a principle reason for them preferencing injection treatment. It may, therefore, be necessary, within a trial to

openly discuss the level of expected pain prior to treatment and offer sedation where requested. Future reporting of PRP trials in LET must include injection induced pain and this should be reported in line with the CONSORT extension for reporting harms [330]. It is also apposite to consider the potential effect of placebo in the design of future trials of interventions in LET. Although beyond the aims of this current feasibility study, the effect of placebo cannot be explored in a standardised two arm interventional study such as this and it remains highly relevant that both injection and surgery may have significant placebo effects. Limited placebo injection and placebo surgery trials have been undertaken in LET [125]. Future investigators should explore placebo designs with patient involvement and carefully construct placebo protocols.

The collection of Patient-Reported Outcomes as part of the follow-up process was logistically feasible and not seen as a burden by participants. Patient and public group involvement ratified the belief that the outcome measures collected data that was deemed important by LET sufferers. In line with the PPI recommendations, paper-based data collection should continue, this also is in line with the validity of the OES, QDASH, and PRTEE, which are yet to be validated for electronic collection [142, 175, 243]. The previous systematic review (chapter 3) has identified the QDASH as demonstrating the highest levels of psychometric validity in LET populations and can be recommended within PRP vs Surgery trials. Of note is the PPI groups' particular liking of the pathology-specific PRTEE from both a question item and scoring scale point of view. However, cross-cultural validity in a UK population and interpretability data (population norms and minimal clinically important difference data) though attempted, contain methodological flaws [228] that currently hinder its recommendation.

Limitations

This feasibility trial is limited to the findings drawn from a small cohort of participants. However, the strength lies in the multimodal approach to assessing the feasibility of a larger trial, wherein the combination of secondary outcomes including PROMs, qualitative assessment, and PPI have provided valuable and unique insights. This feasibility study is attempting to address equipoise in the treatment of chronic LET in patients that have failed physiotherapy and conservative treatment approaches, consequently, the addition of a physiotherapy group as a control, though allowing better quantification of treatment effect, may not be justifiable in this patient group. Placebo injection or sham surgery, though highly relevant in the wider context of LET treatment, do not assist in the answering of the research question that a full-scale randomised trial based on this feasibility studies methodology is trying to answer. The current study did not blind the clinician and blinding of the participant is not possible, though this should be regarded as a limitation, the use of PROMs as the objective primary outcome reduces the potential assessor bias of more clinician-focused outcomes.

8.7 Conclusion

This study has confirmed the feasibility of a randomised trial comparing PRP injection to open surgery in lateral elbow tendinopathy. Were it to be conducted in a similar healthcare setting, a full-scale trial is likely to require a multicentre approach. Patient-reported outcome measures are an appropriate and feasible primary outcome measure and dependent on population validity, the QDASH and PRTEE can be recommended. To enhance study validity it has also been demonstrated that within a stringent methodology, it is possible to conform to all necessary reporting guidelines. This is the first study to explore the patient experience of PRP injection with qualitative analysis and has identified significant pain at the time of injection as

a highly relevant factor that should be reflected on in the protocol design and reporting in all future PRP research.

9 Chapter 9 – Concluding discussion

9.1 Overview

The overarching aim of this research was to optimise the investigation of lateral elbow tendinopathy. Specifically, it applied a multiple methodology approach intending to address three key themes: to inform outcome instrument choice, to rationalise the delivery of injection-based interventions, and to assess if it is feasible and appropriate to apply these outcomes and interventional findings into a PRP trial? The body of this thesis is comprised of seven studies, the findings of which have been discussed within their relevant chapters. Each study addresses certain, or indeed multiple objectives related to the main themes; this chapter, therefore, attempts to synthesise the findings from these studies, discuss the study limitations, implications and the potential clinical and research applications.

9.2 Summary of findings

The work presented in this thesis contributes towards the evidence base for the investigation of interventional treatments in Lateral Elbow Tendinopathy by:

- Identifying the patient-centred outcomes currently available in research on elbow tendinopathy and categorising their proportional use over time, within pathology types and geographical areas. (chapter 2)
- Conducting a standardised evaluation of patient-centred outcomes in LET, the output of which provides evidence on the choice of outcome instrument for future research and clinical application (chapter 3)
- Identifying psychometric attributes of patient-centred outcomes in LET that require further research evaluation to enhance their validity and utility in research and clinical applications (chapter 3)

- Assessing the ability of UK-based LET trials to conform to CONSORT-PRO guidance on the choice and reporting of patient-centred outcomes in LET and reporting that previously published research was not able to adhere to this modern standard (chapter 4)
- Providing the best available evidence on the psychometric properties of patient-centred outcomes in a LET population within the UK (chapter 5)
- Providing quantitative, qualitative and patient and public involvement evidence on the appropriateness and feasibility of using patient-centred outcomes in LET clinical effectiveness research (chapters 5 and 8)
- Evaluating the anatomical basis for ultrasound guided lateral elbow injections using a cadaveric model and providing evidence that assists in rationalising injection volume and delivery techniques (chapter 6)
- Assessing the level of expert user consensus in the patient selection, production, delivery and rehabilitation of LET patients undergoing PRP injection using an international sample and a validated iterative questionnaire methodology (chapter 7)
- Identifying areas of clinical equipoise in the use and techniques of PRP injection that require further targeted research (chapter 7)
- Evaluating the feasibility of conducting a randomised controlled trial of PRP injection versus current standard treatment that is in accordance with reporting guidelines (CONSORT, TiDIER and MIBO) (chapter 8)
- Providing qualitative evidence on the impact and acceptability of PRP injection in the treatment of LET (chapter 8)

9.3 Outcome measure choice

The synthesis of this theme was informed by the literature review (chapter 1), the review of instruments (chapter 2), the standardised evaluation of instruments (chapter 3), the UK specific PROMs assessment (chapter 4), the PROMs validation study (chapter 5) and the feasibility RCT (chapter 8).

The decision to concentrate on the utility and application of Patient Reported Outcome Measures (PROMs) was initially informed by the literature review. Though numerous approaches have been applied to quantify outcomes in LET, from biomechanical evaluation [77] and clinical tests [331], the current attention paid to PROMs is profound and has increased exponentially. The literature review highlighted the poor validity of clinical tests [76] and the consensus of opinion that outcomes should be patient-focused [147, 197], the review of instruments corroborated this by highlighting the increased application of PROMs as primary or secondary outcome measures, the qualitative interviews and patient and public involvement within the feasibility study supported this approach, with all parties commenting that these measures were appropriate and best supported their own perceptions. Although only a small aspect of the study, it is also worth noting that within the Delphi study, a statement that reached strong consensus was that validated PROMs should be collected as part of the treatment evaluation.

The systematic review of instruments was the first to reveal the truly startling number of instruments available aiming to quantify patient-centred outcomes in elbow pathology. Even though many of the 72 instruments have only been applied a small number of times, the difficulties the research community may have in the interpretation and synthesis of information relating to this vast array of instruments was beginning to become apparent. The paucity of information on the pathology-

specific use of patient-centred outcomes and the heterogeneity of use justified the requirement for the standardised EMPRO evaluation.

The standardised evaluation (EMPRO) of patient-centred outcomes in LET initially assessed and collated the breadth of information available. This resulted in 15 instruments for which information was available on their metric attributes. The result of this analysis was that only four of these instruments met the baseline quality criteria for use, the quickDASH, DASH, OES and PRTEE, all of which are classified as PROMs and hence the complete absence of clinician input for their scoring, thus corresponding with the multiple levels of support for the use of PROMs in onward research. It should be noted however that deficits in each of these outcome measures were recognised, and that improvements can be made that will optimise future score interpretation. The predominant factor being the lack of clear validation in pure LET populations. Interestingly, this factor may be an aspect of many musculoskeletal PROMs validations, and attempts at standardised evaluation, where multiple pathologies are used to validate scores targeting anatomical areas (eg shoulder/hip/knee). If one were to think of analogous examples, it would be very irregular to target a PROM at all respiratory pathologies, or expect the same metric properties of mental health instruments used to assess depression and bipolar disorder. This non-pathology based application of PROMs in elbow pathology has clear ramifications on the metric assessment and inhibits the best attempts at standardised evaluation.

Following the EMPRO evaluation, a focused assessment of LET research outcomes in the UK was undertaken. This aimed to question whether, with the current levels of information, it is possible for UK-based LET research to comply with reporting standards for PROMs in trials. This identified both the misappropriation of outcome

measures and the need for formal evaluation of PROMs in UK LET populations. Validation of the PROMs was undertaken in a UK LET population sourced from primary, secondary and physiotherapy care. Owing to poor recruitment and retention this study is unable to make statements of the superiority of one PROM over the other, but it has trebled the current evidence base and offers the best available evidence that the high performing PROMs identified in the EMPRO paper do demonstrate appropriate psychometric properties in UK populations. The utility and burden of these PROMs in a UK population was also evaluated within a feasibility trial. Feedback from qualitative interviews was positive regarding the use and suitability of PROMs within a trial. The patient and public involvement group were equally positive about the use of PROMs in trials, and on reviewing the instruments, felt that the PRTEE contained items that most closely reflected their experience of LET. From the above studies, it can be recommended that within the UK, the use of the QDASH, OES or PTREE for the assessment of LET is valid and acceptable to patients, data from these studies can also ensure future compliance with the CONSORT PRO extension in UK based assessments.

The feasibility of integrating PROMs into future LET trials was assessed. Within the feasibility trial, paper booklets containing the PROMs were used, which were deemed easy to complete within the outpatient department. Participants did not feel that this was overly burdensome, PPI feedback confirmed that this would be appropriate. It is vital however to recognise the potential bias within this population who were happy to be randomised into a trial or PPI group. It remains a possibility that this group may be particularly motivated and not representative of a wider population of LET sufferers.

Although explored only to a limited degree, the use of an electronic interface should also be discussed. For matters of data storage and processing, compliance with the PROMs structure and avoidance of missing data, there are strong arguments for the use of electronic interfaces. Interestingly, however, when discussed with the PPI group, it was commented by the majority that the paper form was easier, but this may relate to the particular interface that was demonstrated. Within the validation study, though an electronic version was available, there was very poor take-up of this option. Therefore, the application of an electronic data collection for PROMs in LET cannot be recommended, studies that aspire to use this technology should undertake further feasibility work to ensure that it is acceptable to patients and valid from a psychometric standpoint.

This research is the first to quantify the utilisation of patient-centred outcomes in elbow pathology; it has identified the best-performing instruments in LET, and following the identification that they were not validated in a UK population, has expanded the knowledge base that can assist researchers and clinicians in their choice of PROM. Although it has also confirmed that it is appropriate and acceptable to patients, members of the public and experts to collect valid PROMs within a LET interventional trial, the low recruitment rate within the validation study may suggest that improved data collection techniques and/or instrument designs would optimise this further.

9.4 Intervention and delivery technique

The synthesis of this theme was informed by the literature review (chapter 1), cadaveric assessment of injection technique (chapter 6), injection consensus study (chapter 7) and feasibility RCT (chapter 8).

The assessment of injection technique, with a particular focus on the application of Platelet-Rich Plasma (PRP), was guided by the background literature review. Although numerous interventions in LET continue to be assessed, it is the application of PRP that has particular attention in the research field [114] with an almost exponential rise in utilisation in clinical practice [297]. Interestingly, this increase in utilisation is not matched by systematic reviews asserting its efficacy [119]. The identification of this potential conflict motivated a further exploration into the fundamental basis for injection delivery, the surprising conclusion being that the question “where does the injection actually distribute?” had never been explored; this question would seem to be fundamental when one is delivering an injectate thought to be locally active. This element was studied while concurrently postulating that the increased utilisation of a technology could be exploited as a research commodity. Therein, an evaluation of expert consensus in the use of PRP for LET might reveal experiential trends that could hone future research or clinical application. An example of this is the postulation that systematic reviews have been unable to answer the question “how many injections of PRP should you administer in a single clinical episode?”, due to difficulty in both running randomised controlled trials assessing this, and the complexities of synthesising information from different studies. Therefore the question was asked, “Could a collective mass of experienced PRP users have found the optimal number of injections, due to individual trial and improvement?” This technique of assessing pertinent questions relating to PRP delivery was assessed using the iterative Delphi methodology. The final component of injection delivery assessment was integrated into a feasibility trial, where the best available evidence from a literature review informed the methodology.

The cadaveric assessment of injectate distribution found no difference between 1ml and 3ml injections or between single shot or fenestrated injection delivery. The distribution of the injectate through over 96% of the CET even with the 1ml single-shot injections suggests that even this volume may be too high. This information is highly relevant for further studies investigating injection-based therapies. In the design of studies, researchers should, therefore, be able to answer two particular questions relating to their methodology. Firstly, if the efficacy of the injectates' active constituents is being assessed, can a volume above 1ml be justified, particularly if it is known that it is likely to contaminate the joint? Secondly, if volumes of 1ml or higher are used, how can the potential therapeutic effect of volumetric tissue injury be controlled? Within the consensus study it should be noted that consensus of agreement for the optimal volume was not achieved. Furthermore, the literature review did not identify studies delivering PRP at a volume of less than 1ml (<1ml was reported for Corticosteroid only [332]). In the largest study of PRP injection (intervention) vs saline injection (placebo), Krogh et al [105] identified that all groups improved, but there were no statistically significant differences between the therapies. The conclusion of the authors being that PRP is no better than placebo, however the results from the cadaveric study suggest that injection of saline, though acting as a control, should not be referred to as a "placebo". The potential therapeutic effect of high volume injection should be investigated for LET, and new designs of intervention for placebo are needed. A single pass of a needle without injection, or injection into subcutaneous tissue only, may both be options.

Results from the cadaveric study do not support the use of needle fenestration as an adjunct to improve the distribution of injectate. This finding is in contrast to the Delphi study which found that the use of needle fenestration was one of the few aspects of

PRP delivery that reached a consensus of agreement. This perceived conflict should be cautiously interpreted, wherein the fenestration may, in itself, be a useful procedure, as it may itself have a therapeutic effect that should be assessed in isolation to the injection of substrate. A study assessing needle fenestration vs surgery in LET is currently underway (Clinicaltrials.org NCT02710682); as yet no study has directly compared single shot or fenestrated delivery techniques (vs an appropriate placebo) of an injectate.

The literature review identified the lack of guidelines on the optimal production and delivery of PRP. The Delphi consensus study attempted to assess if experiential reflection while using PRP resulted in clinicians reaching similar technical conclusions, and thus using PRP in a similar way. Interestingly consensus of agreement or disagreement was only reached for 19 of the 40 statements. Hence this approach was unable to provide clear guidance on the application of PRP and highlighted the requirement for further trials to assess not only its efficacy, but the variability of its production and delivery techniques. The great benefit of an approach such as this, is that future research can now refine the research questions to correspond to particular areas of clinical equipoise.

In regard to the technical aspects of PRP delivery in clinical trials, the feasibility study assessed the ability to deliver the intervention corresponding to best available evidence and contingent on the ability to comply with reporting guidelines. Although numerous PRP injection studies have been published, none have formally reported their compliance with the reporting guidelines for interventions for biologics (MIBO) [122]. It was identified that using a commercially available system, it was possible to deliver PRP injections in a radiology outpatient setting while complying with reporting standards. The patient experience of the injection is discussed in more detail below,

but from a purely technical standpoint, the investigation of the statements identified in the Delphi study as being in equipoise is entirely possible and indeed essential if the field of biologic treatments is to progress.

This study set out to answer the question “can we rationalise the delivery of injection-based treatments?”. The cadaveric study suggests that previous injection-based therapies have used volumes and techniques that cannot be rationalised as a way of assessing a dose response to a treatment, and questions the use of injection-based placebos within trials. A technical assessment of PRP, informed through the literature review as an area of current focus in LET therapy, can feasibly be undertaken as part of an RCT while complying with reporting guidance. What was maybe more surprising, for a therapy that is becoming increasingly common, is the multitude of questions on the technical aspects of its production and delivery that were identified in the literature review. The Delphi study was unable to resolve many of these questions but can act as a starting point in pinpointing areas of lacking consensus, which should act as primary aims for future research. Ultimately, well-constructed, transparent trials are feasible and are desperately needed to justify or indeed to denounce injection therapies.

9.5 Feasibility of an interventional trial

> The synthesis of this theme was informed by the literature review (chapter 1), the UK PROMs validation study (chapter 4), the Delphi study (chapter 7) and the feasibility Randomised Controlled Trial (chapter 8).

Performing a trial in LET that is acceptable to patients, address therapies in equipoise, is methodologically transparent and repeatable, and in accordance with internationally recognised reporting standards should not be a research aspiration,

but rather the expectation. The construction of this thesis is embedded around the realisation that to fulfil this expectation additional knowledge was required. The synthesis of information discussed in the previous themes addresses the feasibility and validity of applying patient-centred outcome measures and the application of a justified injection technique. Additional information on the feasibility of a trial within this theme includes the choice of intervention for a parallel group design, which was informed through literature review and subsequently discussed in the qualitative interviews. The logistical aspects of running the trial were assessed within the quantitative assessment of the feasibility RCT and also informed through the PROMs validation study. The acceptability of the novel treatment application (in this case PRP injection) was explored through qualitative interviews and was reflected upon by the study investigators and investigated within the Delphi study.

This thesis has focused its feasibility assessment on PRP interventions in LET. A major consideration in conducting this trial was the choice of a parallel group. Although systematic reviews have called for high-quality placebo-controlled trials [40, 101], this is a challenging issue in LET injection therapy. Criticism of previously applied parallel groups in LET research was identified within the literature review, with the predominant concern being the use of corticosteroid injection that may impart a long-term negative effect. The potential confounding of any injectate substance in a volume above 1ml as a placebo arm was identified as part of the cadaveric study. The use of physiotherapy as a control group was felt to be unethical in participants with chronic LET who within our care system had all tried, and failed, physiotherapy treatment. The option of no interventional treatment, through the use of oral analgesia and advice, was not felt to be appropriate for the same reason. As the participants receiving PRP injections were not anaesthetised, undertaking a sham

procedure that mimics the injection without creating a potential bias is exceptionally difficult, due to the sensation of injection delivery. There were also concerns regarding recruitment failure if ‘placebo’ or ‘non-active control’ group were part of the randomisation, particularly in the context of treatments being available outside of a trial at allied hospitals [333]. Hence, an active control group of standard practice was used, which, as it was currently offered by the trial hospital, was open surgical debridement. The author believes that as a consequence recruitment and retention levels were high, though it is conceded that the creation of a true placebo-controlled trial may be a superior situation. Further discussion of the optimal methodology is undertaken in the future research section.

Although the target was very modest (n=12) The high recruitment and retention levels within the feasibility study contrast the poor figures within the validation study. Furthermore, the full completion of the outcome instruments within the follow-up outpatient clinic contrasts with the poor postal completion of the same questionnaires by the validation study group. Although the feasibility group were somewhat invested in the study, in that they had received a treatment, the difficulty in data collection in the validation study may be due to some of the same concerns voiced within the qualitative feedback and PPI group. The qualitative interviews and PPI feedback revealed that the items within the questionnaires were appropriate and relevant, and the participants could see the value of collecting data for the purposes of a study, yet when asked if they would wish to use the questionnaires to track their own symptoms, there was a strong feeling that this was unlikely to be helpful. When a demonstration of PROMs feedback graphs using an electronic interface was undertaken, the overall opinion of the PPI group was that data presented in this way were not particularly valuable. It could therefore be postulated that in musculoskeletal

conditions with a limited constellation of symptoms (predominantly pain with functional limitation), the utility and therefore compliance with PROMs for patient information may be limited. This may contrast with the more complex symptom patterns seen in chronic diseases and multimorbid states, where health-related quality of life is affected by a broader group of symptom domains. This information should be carefully regarded when designing larger LET trials, particularly if the treatments include non-interventional strategies. If PROMs are used as outcome measures, their delivery method should be carefully piloted to ensure participants feel they are feasible and appropriate, if electronic interfaces (to facilitate data collection) and participant facing feedback (as a motivator to improve compliance) are used, their benefit should be carefully explored.

The background literature review of LET interventions was only able to identify a limited amount of information on patient experience and adverse event reporting in interventional studies, with a single systematic review reporting injection pain as an adverse event [105]. The Delphi study, with statements generated by a group of PRP users, did not isolate injection pain as a cause for concern or safety issue. It is interesting to note that two statements regarding the use of local anaesthetic did not reach consensus, and for injection-related analgesia only paracetamol and weak opioid medication were advised. The feasibility study itself would not have identified procedural pain as a particular concern had the PROMs data been the only source of patient-centred feedback. The qualitative interview in contrast to all of the background literature, expert consensus and PROMs analysis, had one very common theme from all participants, that procedural pain was a significant issue. Although all participants would recommend the treatment to others, the pain reported at the time of injection was very significant. In the context of a feasibility trial that

aimed to comply with the laboratory-based conclusion that local anaesthesia compromises PRP effectiveness [311, 312], this finding was concerning. For clinicians delivering PRP injections (or if the findings from the cadaveric study are extrapolated, any injection of >1ml) into the common extensor tendon, should be aware that pain is a significant event and future trials should make efforts to ensure that it is quantified and reported.

This research aimed to assess the feasibility of conducting a randomised controlled interventional study in chronic LET. Guided by the evolving trends present in the LET literature, Platelet-Rich Plasma injection was selected as the novel intervention, with the parallel control group being current standard therapy for chronic LET: open surgical debridement. We have shown that it is feasible to conduct a trial with parallel groups, with acceptable recruitment and retention. It is possible to incorporate validated patient-centred outcome measures and report their use in accordance with the CONSORT-PRO. The use of biologics can also be reported according to MIBO guidelines. Qualitative assessment of patient acceptability highlights the need for pain management and clear reporting of procedural discomfort in future trials. Though uncomfortable, PRP participants' feedback uniformly agreed on a preference for injection therapies over surgery, therefore with the presented evidence of feasibility, it is vital that the research community conduct patient-centred, methodologically robust and transparently reported trials.

9.6 Limitations

This work is not without limitations, which need to be considered when interpreting results and forming conclusions.

The limitations of this work will be discussed in reference to the three overarching themes of this thesis, specific limitations relevant to the individual studies are discussed in their associated chapters. The first theme relates to the use of outcome instruments. This thesis attempts to inform the choice of outcome instrument through a sequential assessment of: identification of outcome measures, standardised evaluation and further validation. However, though this assessment was thorough in its approach, a decision was made early within the process to concentrate on patient-centred outcomes. There are numerous other outcomes that have been utilised in LET research, including strength measurements, pain provocation tests and imaging modalities including ultrasound scans and magnetic resonance imaging. Though these outcome modalities may have utility, the background literature review revealed that they have all been identified as not representative of prognosis [9, 76] or have their accuracy anchored to PROMs [86]. Therefore it would seem reasonable to concentrate exclusively on the PROMs themselves, which is in itself in concordance with international guidance on outcome evaluation in clinical effectiveness research [131, 133]. It could also be argued that the focus on outcomes was rather narrow, in that more generic tools such as a visual analogue pain scale (VAS) or generic health PROM such as the EQ5D or SF-36, could have been included in the assessment. Again, these tools may have utility, but generic health measures are recommended only as adjuncts in clinical effectiveness research [147], where a specific PROM is always recommended. Furthermore, it is likely that responsiveness of generic PROMs is poor in elbow pathology, though this has never been explicitly explored. A lack of comparative responsiveness of these generic measures was identified in the validation study (chapter 8) and has also been reported within the included PROMs development and validation studies [142, 243]. The use of simple numeric scales such

as a VAS is common within musculoskeletal research and has recently been advocated as part of an outcome set for elbow pathology [197]. However, the systematic review did not identify specific validation work using these instruments in elbow joint or pathology-specific contexts. Within the validation study the numeric pain scale was found to be poorly responsive to change.

It is also recognised that the three steps of systematic evaluation (chapters 2,3 and 4) used sequential data extraction for the same systematic search criteria. It is the author's view that though the three studies aimed to address strategically different questions, the stepwise manner in which they were conducted, and the intentionally sensitive, rather than specific search strategy, limit the risk of missing data. In an effort to gain a comprehensive view on outcome measure choice, this strategy, though novel, results in a dataset that conceivably facilitates multiple analyses of pathology-specific and cross-culturally specific assessments. Though this is dependent on rigorous data extraction (which in this scenario was co-reviewed at all stages, with concordance between reviewers tracked throughout), it is a model of PROMs assessment that may be utilised more in the future. The data from this thesis have been made open source at figshare (https://figshare.com/) to facilitate future assessment and critique.

It is recognised that the sequential methodology of the systematic review were not 'reviews within reviews', rather shared data assessing different aspects of outcome measure use, which was then supplemented by the validation study to inform an overarching aim. In this regard it is accepted that the use of systematic review is only one tool of many when assessing outcome utility and does not entirely complete the process. Other potential methodologies would involve qualitative techniques including expert reviews, cognitive interviews and focus groups. A conclusive

appraisal of LET outcomes would include some aspect of this assessment but was beyond the scope of this thesis.

The second theme undertook a synthesis of information regarding injection technique and used two particularly novel approaches, a cadaveric assessment and Delphi consensus methodology. The use of these methods provides new information that has previously proved difficult to obtain from clinical trials, but their findings do need to be interpreted with caution.

Though every effort was taken to ensure that the cadaveric samples were treated in a way that the tissue remained as representative as possible (fresh-frozen rather than embalmed, no freezing post injection, dry arthroscopy), the behaviour of cadaveric tissue to injection may be different to human tissue. The Delphi consensus study used clinician experience as a proxy for technical refinement; yet it is perfectly conceivable that clinicians did not modify their techniques or methods of patient selection, PRP preparation and delivery. Consequently, the findings should be viewed simply as a current consensus, rather than a guideline. Though it has identified areas of particular disparity, which can hone research priorities, the areas of consensus should be viewed as accepted current clinician practice, not as a proxy marker of evidence of effectiveness. These questions still require rigorous evaluation as part of a well-designed trial.

Theme three assessed the feasibility of conducting a PRP trial. Numerous trials have assessed PRP treatment, but systematic reviews have consistently criticised their methodological approach. It is recognised that the guidelines by which the reporting feasibility of the trial was assessed have only recently been published (MIBO 2017, CONSORT PRO 2013), therefore previous studies did not have such structures to

comply with. This study concludes that it is feasible to comply with such guidelines and it is likely that their prominence in the current literature will ensure that in future studies compliance is improved.

The qualitative interviews and PPI group discussions provided a wealth of important detail to the feasibility investigation. It is recognised that these investigations were limited in their scope and their representativeness may be very specific. The qualitative interviews were only conducted on the interventional (PRP) group of participants. Therefore the acceptability and treatment preference information was not balanced by those from the surgical group. Though the PRP group felt the intervention was acceptable, the authors concede that this is only one side of the discussion. The qualitative assessment utilised semi-structured interviews and a thematic approach to data analysis. Though the themes revealed reached saturation, it is recognised that alternate techniques such as focus groups and in-depth interviews may have garnered additional relevant information.

The feasibility study used outcome measures and assessed their patient acceptability, burden and data collection feasibility. This trial was conducted in parallel to the outcome measure systematic review. The outcomes for the feasibility trial were selected as they had previously been used at the same institution for an elbow trial. It is fortuitous, rather than through judgment, that the measures used were subsequently identified through the EMPRO evaluation as high performing.

Although it was found that a study of PRP vs surgery is technically feasible, two further questions must be asked that relate to the potential limitations of the findings. Firstly, is an RCT the most appropriate design for this intervention? Secondly, with information derived from the cadaveric and Delphi studies taken into account, should

more foundational research be conducted before further clinical trials? These questions will be addressed in the forthcoming sections.

9.7 Implications for clinical practice and research

Following this synthesis of information from this conducted research, the next key question should be; “in what way can these findings be operationalised in future clinical and research practice?”

The identification of four PROMs that show superior metric properties in LET can be applied to future evaluation of LET in clinical studies. This addresses the current void in information. The validity and responsiveness of these tools are adequate for their justified use in comparative research and the details on their properties mean that future studies, conducted in English language populations, can use this information to conform to CONSORT-PRO [320] reporting guidelines. However, details on the interpretability of these outcome measures, through derivation of minimal change scores, is still limited. This is of particular importance as these values are increasingly used to interpret the effect of an intervention in clinical trials [250]. Furthermore, misappropriation or extrapolation of minimal change scores from non-representative populations can have a significant impact on study conclusions [257].

It should be noted that although four PROMs have been identified, superiority of one instrument over the rest had not been confirmed. Two explanations exist, firstly that the data available are not strong enough to clearly identify the best candidate instrument, or secondly that metric properties are indeed similar and superiority will not be confirmed. As the continued synthesis of information in systematic reviews and meta-analyses continues to be frustrated by the great variety of measures available, it is essential that national societies use data from standardised

evaluations to make informed decisions on instrument choice, thereby forcing the arm of future researchers. This is beginning to occur, Hawkins et al [197] have recently produced a consensus guideline from the American Society of Shoulder and Elbow Surgeons that has made clear recommendations on instrument choice. What is concerning and frustrating however, was that these instruments were chosen through a small group expert consensus, rather than through a validated standardised evaluation such as that performed within this thesis. Furthermore, poorly performing instruments, identified in this review for LET and previously by The et al [149], continue to be recommended. Though we are unable to suggest the number one choice of instrument for LET, what is maybe clearer is that the poorly performing instruments should not continue to be utilised in clinical trials without further evidence of their validity. There is still quite some way to go before the application of the 'heritage instruments' subsidies in preference to those measures shown objectively to outperform them.

The presented assessment of injection delivery should be used to rationalise current practice. The cadaveric study suggests that in the assessment of the efficacy of injection substances, smaller volume, single shot injections should be delivered in preference to higher volume injections or fenestrated techniques. This proposition should now be tested in a clinical context. This study also concludes that the administration of "placebo" injection may be a misnomer, as the tissue destruction associated with a 1ml injection could be associated with a therapeutic benefit. Therefore, future studies should seek alternative injection methodologies, and the therapeutic effect of volumetric tissue damage should be assessed.

The findings from the Delphi study could be used as a basis on which clinicians starting to use PRP base their practice. Though, as previously stated, this is not

evidence of efficacy, the statements that reached consensus provide more of a pragmatic framework for application of this therapy than has previously been available. As the Delphi method has identified aspects of practice that did not reach consensus, this should be scrutinised and considered carefully as areas of focus for future research.

The feasibility study has identified that PROMs outcome measures are appropriate and acceptable to patients, the effect sizes observed within both the feasibility study and validation study suggest that they are sensitive to change at a magnitude that is greater than generic health measures and visual analogue scales. It is reasonable to assert therefore that they should be used as primary outcome measures in future research. The qualitative assessment has identified that patients believe PRP to be a treatment worthy of study. The quantification and reporting of procedural pain and refinement of technique and associated adjuncts aimed at reducing patient discomfort is vital for this treatment practice to continue.

9.8 Future research

The old models of research, where individuals with highly specialised expertise drove change through passionate engagement with small groups of researchers, is becoming rare. The scientific questions have now expanded to a point where they are too complex to be answered by the single expert [334], the expectation to deliver change has also shifted, with an ever-increasing focus on rapid transition of interventions from bench to clinical use [335]. The sustainability of this new approach is dependent upon one element above all others, teamwork. Collaborative research, that utilises multiple expertise, running multiple methodologies, at multiple sites, is the aspirational model of research for the 21st century. This thesis has approached

the investigation of LET treatments from a back to basics, foundational perspective, aiming to answer inherent problems that have acted as barriers to progress in the field. It was always the author's intention that these findings should not exist as a standalone research portfolio, but rather that they assist in wider collaborative efforts to understand and treat this burdensome condition. Specifically in reference to the research aims, the presented research can support future programs of work that progress the fields of outcome measurement and delivery, assessment and delivery of new therapies and the investigation and application of novel trial designs.

Within the first study of this portfolio of work, the exponential utilisation of patient-centred outcome measures in elbow research was encountered. Though the short-term goals include the identification of the best performing outcome instrument, the future of outcome assessment may look quite different. Groups such as the COMET initiative (Core Outcome Measures in Effectiveness Trials) and ICHOM (International Consortium of Health Outcome Measurement) recognise that the derivation of "Value" in healthcare will require standardised assessment of more than a pathology-specific outcome measure. PROMs will sit within this framework with other measures that quantify health behaviour, satisfaction with care, medication burden and financial burden of care, amongst others.

The way in which outcome measures are collected is also changing. This thesis acknowledges the limitations of fixed length questionnaires. The use of Item Response Theory (IRT) techniques, which utilise large question banks and statistical models to hone items on an individual basis, have the potential to hugely alter the utility of PROMs assessment. The PROMIS (Patient Reported Outcome Measurement Information System) was developed to improve outcome measurement by bringing universality to the system, allowing comparison within and

across pathologies, across cultures and to allow cross-walking of scores to the currently applied fixed length questionnaires, which may be somewhat of a holy grail of psychometrics. Publications using these instruments in the field of upper limb pathology are emerging from the USA [336, 337], with a single publication in an undefined mixture of elbow pathology [338], the forthcoming years are likely to see an emergence of this system and testing of its validity in the UK and beyond.

For the feasibility assessment of the efficacy of PRP a randomised control trial was undertaken. Though it confirmed that this was feasible, there are aspects of the trial that were encountered that suggest that it may not be the optimal design for study of this particular condition. The concern regarding an appropriate parallel group has been discussed within the literature review (chapter 1), the feasibility study (chapter 8), and as a consequence of its findings, in the cadaveric study (chapter 6). Therein two distinct problems are encountered. Firstly, there is theoretically an inability to inject a substance into the tendons of the elbow that is entirely therapeutically benign, hence creating a potential confounder; furthermore the patient's sensation of an injection (commented within the qualitative assessment) means that there will be an experiential difference between a sham injection (no injectate delivered) and a true injection, creating a bias. Secondly, the alternative use of a 'standard treatment' group carries with it the risk of bias (owing to the preference for a 'novel' minimally interventional therapy such as an injection) and a potentially high dropout rate as the 'novel' treatment is available elsewhere without randomisation (as is increasingly the case with biologics such as PRP). It is difficult to escape these risks within the traditional RCT model and although there are numerous potential trial designs that may ameliorate the highlighted issues [339], two particular methodologies may offer a

solution, a step-wedge RCT design [340], or a cohort multiple randomised controlled design [342].

In the step-wedge RCT design all groups, or clusters, of participants eventually receive the intervention, but the implementation is staggered and randomised [340]. This trial design may assist in the thorough assessment of a novel intervention that is increasingly championed, due to its patient acceptability and relative cost saving. Therein, clusters (patients at particular hospitals, or whose care is under certain consultants in this case) could have their treatment changed from an accepted standard, identified in this thesis as surgery, to the novel intervention. This trial design offers patients a single treatment, be it whatever that particular cluster has been allocated at that time. Therefore, it does not rely on individual patient recruitment and its associated potential bias [340].

It has been suggested that to address the problem encountered when comparing multiple treatments from different heterogeneous populations, application of a cohort multiple randomised controlled trial methodology may be beneficial [342]. In this design, a large observational cohort with the condition of interest is recruited, regular measurements of outcomes are undertaken, when appropriate there is identification of all eligible patients within that cohort, some of whom are randomly selected to receive the novel intervention, the outcomes are then compared between those randomly selected (novel treatment) and those not randomly selected (standard care). The consent process is designed to mirror real-world routine healthcare, in that the whole cohort are consented to collect observational data; however consent to “try” a particular intervention is sought only from those to whom it is offered [342]. This approach also has the benefit that at any time sequential or multiple randomised allocations to treatment can occur. It is vital to appreciate however, that

this approach is only possible with a robust data collection system and the use of outcome measures that are known to be valid and that do not change throughout the trial. It would therefore be particularly appropriate to utilise this trial design with the use of dimension level PROMs assessment (pain, function, quality of life etc) using a flexible system such as PROMIS.

9.9 Concluding remarks

This research aimed to optimise the assessment of interventional treatment in Lateral Elbow Tendinopathy, with a focus on injectable therapies. It was identified that for the researchers to investigate LET treatments in a robust and transparent way, a unified approach to the choice of outcome measure was needed, an ability to rationalise the technical aspects of injection treatment was necessary, and the feasibility and patient-centred acceptability of randomised trial of PRP required exploration.

A multiple-methodology approach was utilised, and the findings from individual studies were triangulated to address the overarching aim. This research can contribute to the literature by making the following recommendations: the DASH, QDASH, OES and PRTEE are the PROMs that are presently the best option for LET research, evidence of their validity in the UK has been improved and they can be recommended for use in this population; the use of high volume fenestrated injections is not required to optimise the distribution of an injectate around the common extensor tendon and this technique itself may be introducing a confounding treatment variable; there is an inconstant level of consensus on PRP preparation and delivery and further evaluation should prioritise the evaluation of dose-related effect,

and although trials of PRP injections are feasible and acceptable, patient safety and procedural pain must be recorded.

LET is not a condition that one would deem high profile, it is not on the political agenda and has not been identified as a research priority by the NIHR, patients, clinicians or carer groups [343]. Yet, it is common, painful and costly to both the individual and society and for these reasons it is worthy of our attention and our research efforts. Perhaps it is because of difficulties attaining adequate funding, commercial bias or apathy and dissatisfaction associated with our continued failing to understand and treat this condition, that certain fundamental questions in the development and evaluation of treatments have not been thoroughly scrutinised. It may also be that this condition is more complex that we have previously appreciated, that the aetiology, pathology and required treatments are highly individualised and that our current focus on unified treatment algorithms is in vain. Many exciting research ventures, from basic science to clinical trials are being formulated and undertaken, there is no doubt that breakthroughs will be discovered and treatments improved, if one thing is certain it is that we should redouble our efforts to ensure that we only produce meaningful and appropriate research into this condition. This thesis represents an effort to explore ways in which we can optimise the future evaluation of LET, to ensure that the continuum of increasing evidence is fundamentally more robust, comparable and patient-focused. It is my hope that its findings are useful for researchers and ultimately beneficial for patients.

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10 References

1 Runge F. Zur genese und behandlung des schreibekrampfes. Berl Klin Wochenschr. 1873;10:245-8.

2 Knobloch K, Gohritz A. Dr Runge: a German pioneer in sclerosing therapy in epicondylitis in 1873. British Journal of Sports Medicine. 2011;45(5):432.

3 Thurston AJ. The early history of tennis elbow: 1873 to the 1950s. ANZ Journal of Surgery. 1998;68(3):219-24.

4 Cyriax J. Tennis elbow. British Medical Journal. 1937;2(4001):559.

5 Waugh EJ. Lateral Epicondylalgia or Epicondylitis: What's in a Name? Journal of Orthopaedic and Sports Physical Therapy. 2005 Apr;35(4):201.

6 Stasinopoulos D, Johnson MI. 'Lateral elbow tendinopathy'is the most appropriate diagnostic term for the condition commonly referred-to as lateral epicondylitis. Medical hypotheses. 2006;67(6):1400-2.

7 Goldberg EJ, Abraham E, Siegel I. The surgical treatment of chronic lateral humeral epicondylitis by common extensor release. Clinical Orthopaedics and Related Research. 1988;233:208-12.

8 Viikari-Juntura E. Tenosynovitis, peritendinitis and the tennis elbow syndrome. Scandinavian journal of work, environment & health. 1984:443-9.

9 Drake ML, Ring DC. Enthesopathy of the extensor carpi radialis brevis origin: effective communication strategies. Journal of the American Academy of Orthopaedic Surgeons. 2016;24(6):365-9.

10 Verhaar J. Tennis elbow. International orthopaedics. 1994;18(5):263-7.

11 Hamilton PG. The prevalence of humeral epicondylitis: a survey in general practice. JR Coll Gen Pract. 1986;36(291):464-5.

12 Titchener AG, Tambe A, Fakis A, Smith CJ, Clark DI, Hubbard RB. Study of lateral epicondylitis (tennis elbow) using the health improvement network database. Shoulder & Elbow. 2012;4(3):209-13.

13 Walker-Bone K, Palmer KT, Reading I, Coggon D, Cooper C. Prevalence and impact of musculoskeletal disorders of the upper limb in the general population. Arthritis Rheum. 2004;51(4):642-51 DOI: 10.1002/art.20535.

14 Shiri R, Viikari-Juntura E, Varonen H, Heliövaara M. Prevalence and determinants of lateral and medial epicondylitis: a population study. American Journal of Epidemiology. 2006;164(11):1065-74.

15 Roquelaure Y, Ha C, Rouillon C, Fouquet N, Leclerc A, Descatha A, et al. Risk factors for upper-extremity musculoskeletal disorders in the working population. Arthritis Care & Research. 2009;61(10):1425-34.

16 Salaffi F, De RA, Grassi W. Prevalence of musculoskeletal conditions in an Italian population sample: results of a regional community-based study. I. The MAPPING study. Clinical and Experimental Rheumatology. 2005;23(6):819-28.

17 Sanders TL, Jr., Maradit Kremers H, Bryan AJ, Ransom JE, Smith J, Morrey BF. The epidemiology and health care burden of tennis elbow: a population-based study. American Journal of Sports Medicine. 2015;43(5):1066-71.

18 Bot S, Van der Waal J, Terwee C, Van der Windt D, Schellevis F, Bouter L, et al. Incidence and prevalence of complaints of the neck and upper extremity in general practice. Annals of the Rheumatic Diseases. 2005;64(1):118-23.

19 Hopkins C, Fu S-C, Chua E, Hu X, Rolf C, Mattila VM, et al. Critical review on the socio-economic impact of tendinopathy. Asia-Pacific Journal of Sports Medicine, Arthroscopy, Rehabilitation and Technology. 2016;4:9-20.
20 Auerbach JD, Weidner ZD, Milby AH, Diab M, Lonner BS. Musculoskeletal disorders among spine surgeons: results of a survey of the Scoliosis Research Society membership. Spine. 2011;36(26):E1715-E21.
21 Özdolap Ş, Emre U, Karamercan A, Sarikaya S, Köktürk F. Upper limb tendinitis and entrapment neuropathy in coal miners. American Journal of Industrial Medicine. 2013;56(5):569-75.
22 Kryger AI, Lassen CF, Andersen JH. The role of physical examinations in studies of musculoskeletal disorders of the elbow. Occupational and Environmental Medicine. 2007;64(11):776-81.
23 Walker-Bone K, Palmer KT, Reading I, Coggon D, Cooper C. Occupation and epicondylitis: a population-based study. Rheumatology. 2011;51(2):305-10.
24 Shiri R, Varonen H, Heliövaara M, Viikari-Juntura E. Hand dominance in upper extremity musculoskeletal disorders. The Journal of Rheumatology. 2007;34(5):1076-82.
25 Hardyck C, Petrinovich LF. Left-handedness. Psychological bulletin. 1977;84(3):385.
26 Cyriax JH. The pathology and treatment of tennis elbow. Journal of Bone and Joint Surgery (Am). 1936;18(4):921-40.
27 Nirschl RP, Pettrone F. Tennis elbow. The surgical treatment of lateral epicondylitis. Journal of Bone and Joint Surgery (Am). 1979;61(6A):832-9.
28 Boyd HB, McLeod J, Andin C. Tennis elbow. Journal of Bone and Joint Surgery (Am). 1973;55(6):1183-7.
29 Conrad R, Hooper W. Tennis elbow: Its course, conservative and surgical management. Journal of Bone and Joint Surgery (Am). 1973:1177-82. 1973:1177-82.
30 Walz DM, Newman JS, Konin GP, Ross G. Epicondylitis: pathogenesis, imaging, and treatment. Radiographics. 2010;30(1):167-84.
31 Standring S. Gray's Anatomy E-Book: The Anatomical Basis of Clinical Practice: Elsevier Health Sciences; 2015.
32 Snijders CJ, Volkers A, Mechelse K, Vleeming A. Provocation of epicondylalgia lateralis (tennis elbow) by power grip or pinching. Medicine and Science in Sports and Exercise. 1987;19(5):518-23.
33 Cohen M, da Rocha Motta Filho G. Lateral epicondylitis of the elbow. Revista Brasileira de Ortopedia (English Edition). 2012;47(4):414-20.
34 Stoeckart R, Vleeming A, Snijders C. Anatomy of the extensor carpi radialis brevis muscle related to tennis elbow. Clinical Biomechanics. 1989;4(4):210-2.
35 Nimura A, Fujishiro H, Wakabayashi Y, Imatani J, Sugaya H, Akita K. Joint capsule attachment to the extensor carpi radialis brevis origin: an anatomical study with possible implications regarding the etiology of lateral epicondylitis. Journal of Hand Surgery. 2014;39(2):219-25.
36 Bunata RE, Brown DS, Capelo R. Anatomic factors related to the cause of tennis elbow. Journal of Bone and Joint Surgery (Am). 2007;89(9):1955-63.
37 Greenbaum B, Itamura J, Vangsness C, Tibone J, Atkinson R. Extensor carpi radialis brevis. Journal of Bone and Joint Surgery (Br). 1999;81(5):926-9.

38 Regan W, Wold LE, Coonrad R, Morrey BF. Microscopic histopathology of chronic refractory lateral epicondylitis. The American Journal of Sports Medicine. 1992;20(6):746-9.
39 Kraushaar BS, Nirschl RP. Current concepts review-tendinosis of the elbow (Tennis Elbow). Clinical features and findings of histological, immunohistochemical, and electron microscopy studies. Journal of Bone and Joint Surgery (Am). 1999;81(2):259-78.
40 Buchbinder R, Johnston RV, Barnsley L, Assendelft W, Bell SN, Smidt N. Surgery for lateral elbow pain. Cochrane Database Systematic Reviews. 2011;3(3).
41 Millar NL, Murrell GA, McInnes IB. Inflammatory mechanisms in tendinopathy–towards translation. Nature Reviews Rheumatology. 2017;13(2):110.
42 Rees JD, Stride M, Scott A. Tendons–time to revisit inflammation. British Journal of Sports Medicine. 2013:bjsports-2012-091957.
43 Khan KM, Cook JL, Kannus P, Maffulli N, Bonar S. Time to abandon the "tendinitis" myth: painful, overuse tendon conditions have a non-inflammatory pathology. British Medical Journal. 2002;324(7338):626.
44 Nirschl R. Elbow tendinosis/tennis elbow. Clinics in Sports Medicine. 1992;11(4):851-70.
45 Bisset L, Coombes B, Vicenzino B. Tennis elbow. Clinical Evidence. 2011;27:27.
46 Bhabra G, Wang A, Ebert JR, Edwards P, Zheng M, Zheng MH. Lateral elbow tendinopathy: development of a pathophysiology-based treatment algorithm. Orthopaedic Journal of Sports Medicine. 2016;4(11):2325967116670635.
47 Dean BJ, Dakin SG, Millar NL, Carr AJ. Emerging concepts in the pathogenesis of tendinopathy. The Surgeon. 2017;15(6):349-54.
48 Dean BJF, Gettings P, Dakin SG, Carr AJ. Are inflammatory cells increased in painful human tendinopathy? A systematic review. British Journal of Sports Medicine. 2016;50(4):216-20.
49 Dean BJF, Snelling SJ, Dakin SG, Murphy RJ, Javaid MK, Carr AJ. Differences in glutamate receptors and inflammatory cell numbers are associated with the resolution of pain in human rotator cuff tendinopathy. Arthritis Research & Therapy. 2015;17(1):176.
50 Coombes BK, Bisset L, Vicenzino B. A new integrative model of lateral epicondylalgia. British Journal of Sports Medicine. 2009;43(4):252-8.
51 Chard M, Hazleman B. Tennis elbow—a reappraisal. Oxford University Press; 1989.
52 Nirschl RP, Sobel J. Conservative treatment of tennis elbow. The Physician and Sportsmedicine. 1981;9(6):43-54.
53 Wright A, Thurnwald P, O'Callaghan J, Smith J, Vicenzino B. Hyperalgesia in tennis elbow patients. Journal of Musculoskeletal Pain. 1994;2(4):83-97.
54 Vicenzino B, Paungmali A, Buratowski S, Wright A. Specific manipulative therapy treatment for chronic lateral epicondylalgia produces uniquely characteristic hypoalgesia. Manual Therapy. 2001;6(4):205-12.
55 Sran M, Souvlis T, Vicenzino B, Wright A. Characterisation of chronic lateral epicondylalgia using the McGill pain questionnaire, visual analog scales, and quantitative sensory tests. The Pain Clinic. 2001;13(3):251-9.

56 Pienimäki T, Tarvainen T, Siira P, Malmivaara A, Vanharanta H. Associations between pain, grip strength, and manual tests in the treatment evaluation of chronic tennis elbow. The Clinical Journal of Pain. 2002;18(3):164-70.
57 Slater H, Arendt-Nielsen L, Wright A, Graven-Nielsen T. Sensory and motor effects of experimental muscle pain in patients with lateral epicondylalgia and controls with delayed onset muscle soreness. Pain. 2005;114(1):118-30.
58 Lindenhovius A, Henket M, Gilligan BP, Lozano-Calderon S, Jupiter JB, Ring D. Injection of dexamethasone versus placebo for lateral elbow pain: a prospective, double-blind, randomized clinical trial. The Journal of Hand Surgery. 2008;33(6):909-19.
59 Bisset LM, Russell T, Bradley S, Ha B, Vicenzino BT. Bilateral sensorimotor abnormalities in unilateral lateral epicondylalgia. Archives of Physical Medicine and Rehabilitation. 2006;87(4):490-5.
60 Abbott J, Patla C, Jensen R. The initial effects of an elbow mobilization with movement technique on grip strength in subjects with lateral epicondylalgia. Manual Therapy. 2001;6(3):163-9.
61 Paungmali A, O'Leary S, Souvlis T, Vicenzino B. Naloxone fails to antagonize initial hypoalgesic effect of a manual therapy treatment for lateral epicondylalgia. Journal of Manipulative and Physiological Therapeutics. 2004;27(3):180-5.
62 Alizadehkhaiyat O, Fisher AC, Kemp GJ, Frostick SP. Pain, functional disability, and psychologic status in tennis elbow. The Clinical Journal of Pain. 2007;23(6):482-9.
63 Rojas M, Mananas MA, Muller B, Chaler J, editors. Activation of forearm muscles for wrist extension in patients affected by lateral epicondylitis. Engineering in Medicine and Biology Society, 2007 EMBS 2007 29th Annual International Conference of the IEEE; 2007: IEEE.
64 Stratford PW, Riddle DL. When Minimal Detectable Change Exceeds a Diagnostic Test–Based Threshold Change Value for an Outcome Measure: Resolving the Conflict. Physical Therapy. 2012;92(10):1338-47.
65 Mogk J, Keir P. The effects of posture on forearm muscle loading during gripping. Ergonomics. 2003;46(9):956-75.
66 Pryce JC. The wrist position between neutral and ulnar deviation that facilitates the maximum power grip strength. Journal of Biomechanics. 1980;13(6):505509-7511.
67 Lieber RL, Loren GJ, Friden J. In vivo measurement of human wrist extensor muscle sarcomere length changes. Journal of Neurophysiology. 1994;71(3):874-81.
68 Pienimäki TT, Kauranen K, Vanharanta H. Bilaterally decreased motor performance of arms in patients with chronic tennis elbow. Archives of Physical Medicine and Rehabilitation. 1997;78(10):1092-5.
69 Haahr J, Andersen J. Physical and psychosocial risk factors for lateral epicondylitis: a population based case-referent study. Occupational and Environmental Medicine. 2003;60(5):322-9.
70 Tosti R, Jennings J, Sewards JM. Lateral epicondylitis of the elbow. The American Journal of Medicine. 2013 Apr 1;126(4):357-e1.
71 Harrington JM, Carter JT, Birrell L, Gompertz D. Surveillance case definitions for work related upper limb pain syndromes. Occupational and Environmental Medicine. 1998;55(4):264-71.

72 Sluiter JK, Rest KM, Frings-Dresen MH. Criteria document for evaluating the work-relatedness of upper-extremity musculoskeletal disorders. Scandinavian Journal of Work, Environment & Health. 2001:1-102.
73 MacDermid JC, Michlovitz SL. Examination of the elbow: Linking diagnosis, prognosis, and outcomes as a framework for maximizing therapy interventions. Journal of Hand Therapy. 2006;19(2):82-97.
74 Polkinghorn BS. A novel method for assessing elbow pain resulting from epicondylitis. Journal of Chiropractic Medicine. 2002;1(3):117-21.
75 Gardner RC. 30 Tennis Elbow: Diagnosis, Pathology and Treatment: Nine Severe Cases Treated by a New Reconstructive Operation. Clinical Orthopaedics and Related Research. 1970;72:248-53.
76 Zwerus EL, Somford MP, Maissan F, Heisen J, Eygendaal D, van den Bekerom MP. Physical examination of the elbow, what is the evidence? A systematic literature review. British Journal of Sports Medicine. 2017:bjsports-2016-096712.
77 Dorf ER, Chhabra AB, Golish SR, McGinty JL, Pannunzio ME. Effect of elbow position on grip strength in the evaluation of lateral epicondylitis. The Journal of Hand Surgery. 2007;32(6):882-6.
78 Connell D, Burke F, Coombes P, McNealy S, Freeman D, Pryde D, et al. Sonographic examination of lateral epicondylitis. American Journal of Roentgenology. 2001;176(3):777-82.
79 Levin D, Nazarian LN, Miller TT, O'Kane PL, Feld RI, Parker L, et al. Lateral epicondylitis of the elbow: US findings. Radiology. 2005;237(1):230-4.
80 du Toit C, Stieler M, Saunders R, Bisset L, Vicenzino B. Diagnostic accuracy of power Doppler ultrasound in patients with chronic tennis elbow. British Journal of Sports Medicine. 2008;42(11):872-6.
81 Struijs P, Spruyt M, Assendelft W, Van Dijk C. The predictive value of diagnostic sonography for the effectiveness of conservative treatment of tennis elbow. American Journal of Roentgenology. 2005;185(5):1113-8.
82 Clarke AW, Ahmad M, Curtis M, Connell DA. Lateral elbow tendinopathy: correlation of ultrasound findings with pain and functional disability. The American Journal of Sports Medicine. 2010;38(6):1209-14.
83 Walton MJ, Mackie K, Fallon M, Butler R, Breidahl W, Zheng MH, et al. The reliability and validity of magnetic resonance imaging in the assessment of chronic lateral epicondylitis. The Journal of Hand Surgery. 2011;36(3):475-9.
84 van Kollenburg JA, Brouwer KM, Jupiter JB, Ring D. Magnetic resonance imaging signal abnormalities in enthesopathy of the extensor carpi radialis longus origin. The Journal of Hand Surgery. 2009;34(6):1094-8.
85 Krogh T, Fredberg U, Christensen R, Stengaard-Pedersen K, Ellingsen T. Ultrasonographic assessment of tendon thickness, doppler activity and bony spurs of the elbow in patients with lateral epicondylitis and healthy subjects: a reliability and agreement study. Ultraschall in der Medizin-European Journal of Ultrasound. 2013;34(05):468-74.
86 Qi L, Zhang Y-D, Yu R-B, Shi H-B. Magnetic Resonance Imaging of Patients With Chronic Lateral Epicondylitis: Is There a Relationship Between Magnetic Resonance Imaging Abnormalities of the Common Extensor Tendon and the Patient's Clinical Symptom? Medicine. 2016;95(5).

87 Dang AC, Rodner CM. Unusual compression neuropathies of the forearm, part I: radial nerve. The Journal of hand surgery. 2009;34(10):1906-14.
88 Smidt N, Van Der Windt DA, Assendelft WJ, Devillé WL, Korthals-de Bos IB, Bouter LM. Corticosteroid injections, physiotherapy, or a wait-and-see policy for lateral epicondylitis: a randomised controlled trial. The Lancet. 2002;359(9307):657-62.
89 Smidt N, Lewis M, Windt DAVD, Hay EM, Bouter LM, Croft P. Lateral epicondylitis in general practice: course and prognostic indicators of outcome. The Journal of Rheumatology. 2006;33(10):2053-9.
90 Bisset L, Beller E, Jull G, Brooks P, Darnell R, Vicenzino B. Mobilisation with movement and exercise, corticosteroid injection, or wait and see for tennis elbow: randomised trial. British Medical Journal. 2006;333(7575):939.
91 Hudak PL, Cole DC, Haines AT. Understanding prognosis to improve rehabilitation: the example of lateral elbow pain. Archives of Physical Medicine and Rehabilitation. 1996;77(6):586-93.
92 Sanders TL, Maradit Kremers H, Bryan AJ, Ransom JE, Morrey BF. Health care utilization and direct medical costs of tennis elbow: A population-based study. Sports Health. 2016;8(4):355-8.
93 Maniadakis N, Gray A. The economic burden of back pain in the UK. Pain. 2000;84(1):95-103.
94 van Tulder MW, Koes BW, Bouter LM. A cost-of-illness study of back pain in the Netherlands. Pain. 1995;62(2):233-40.
95 Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. The Spine Journal. 2008;8(1):8-20.
96 Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. The Lancet. 2010;376(9754):1751-67.
97 World Health Organization. International statistical classification of diseases and related health problems. World Health Organization; 2004.
98 World Health Organization. International classification of functioning, disability and health: ICF. Geneva: World Health Organization; 2001.
99 Coombes BK, Connelly L, Bisset L, Vicenzino B. Economic evaluation favours physiotherapy but not corticosteroid injection as a first-line intervention for chronic lateral epicondylalgia: evidence from a randomised clinical trial. British Journal of Sports Medicine. 2015:bjsports-2015-094729.
100 Groppel JL, Nirschl RP. A mechanical and electromyographical analysis of the effects of various joint counterforce braces on the tennis player. The American Journal of Sports Medicine. 1986;14(3):195-200.
101 Long L, Briscoe S, Cooper C, Hyde C, Crathorne L. What is the clinical effectiveness and cost-effectiveness of conservative interventions for tendinopathy? An overview of systematic reviews of clinical effectiveness and systematic review of economic evaluations. Health Technology Assessment (Winchester, England). 2015 Jan;19(8):1.
102 Coombes BK, Bisset L, Connelly LB, Brooks P, Vicenzino B. Optimising corticosteroid injection for lateral epicondylalgia with the addition of physiotherapy:

a protocol for a randomised control trial with placebo comparison. BMC musculoskeletal disorders. 2009;10(1):76.
103 Titchener AG, Booker SJ, Bhamber NS, Tambe AA, Clark DI. Corticosteroid and platelet-rich plasma injection therapy in tennis elbow (lateral epicondylalgia): a survey of current U.K. specialist practice and a call for clinical guidelines. British Journal of Sports Medicine. 2015;49(21):1410-3.
104 Murley A. Tennis-elbow treated with hydrocortisone acetate. The Lancet. 1954;264(6831):223-5.
105 Krogh TP, Bartels EM, Ellingsen T, Stengaard-Pedersen K, Buchbinder R, Fredberg U, et al. Comparative effectiveness of injection therapies in lateral epicondylitis: a systematic review and network meta-analysis of randomized controlled trials. The American Journal of Sports Medicine. 2013;41(6):1435-46.
106 Dong W, Goost H, Lin X-B, Burger C, Paul C, Wang Z-L, et al. Injection therapies for lateral epicondylalgia: a systematic review and Bayesian network meta-analysis. British Journal of Sports Medicine. 2016;50(15):900-8.
107 Vicenzino B, Britt H, Pollack AJ, Hall M, Bennell KL, Hunter DJ. No abatement of steroid injections for tennis elbow in Australian General Practice: A 15-year observational study with random general practitioner sampling. PloS one. 2017;12(7):e0181631.
108 Samra DJ, Orchard JW. Patterns of platelet-rich plasma use among Australasian sports physicians. BMJ Open Sport & Exercise Medicine. 2015 Nov 1;1(1):e000054.
109 Coombes BK, Bisset L, Brooks P, Khan A, Vicenzino B. Effect of corticosteroid injection, physiotherapy, or both on clinical outcomes in patients with unilateral lateral epicondylalgia: a randomized controlled trial. The Journal of the American Medical Association. 2013;309(5):461-9.
110 Degen RM, Cancienne JM, Camp CL, Altchek DW, Dines JS, Werner BC. Three or more preoperative injections is the most significant risk factor for revision surgery after operative treatment of lateral epicondylitis: an analysis of 3863 patients. Journal of Shoulder and Elbow Surgery. 2017;26(4):704-9.
111 Kachooei AR, Talaei-Khoei M, Faghfouri A, Ring D. Factors associated with operative treatment of enthesopathy of the extensor carpi radialis brevis origin. Journal of Shoulder and Elbow Surgery. 2016;25(4):666-70.
112 Murray D, Javed S, Jain N, Kemp S, Watts A. Platelet—Rich—Plasma Injections in Treating Lateral Epicondylosis: a Review of the Recent Evidence. Journal of Hand and Microsurgery. 2015;7(2):320-5.
113 Krogh TP, Fredberg U, Stengaard-Pedersen K, Christensen R, Jensen P, Ellingsen T. Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: a randomized, double-blind, placebo-controlled trial. The American Journal of Sports Medicine. 2013;41(3):625-35.
114 Murray I, LaPrade R. Platelet-rich plasma: Renewed scientific understanding must guide appropriate use. Bone and Joint Research; 2016; 92-94.
115 Murray IR, Murray AD, Geeslin AG, Goudie EB, White TO, Petrigliano FA, LaPrade RF. Infographic: we need minimum reporting standards for biologics. British Journal of Sports Medicine. 2017 Aug 22.
116 Moraes VY, Lenza M, Tamaoki MJ, Faloppa F, Belloti JC. Platelet-rich therapies for musculoskeletal soft tissue injuries. The Cochrane Library. 2014.

117 Fitzpatrick J, Bulsara M, Zheng MH. The effectiveness of platelet-rich plasma in the treatment of tendinopathy: a meta-analysis of randomized controlled clinical trials. The American Journal of Sports Medicine. 2017;45(1):226-33.
118 Ahmad Z, Brooks R, Kang SN, Weaver H, Nunney I, Tytherleigh-Strong G, et al. The effect of platelet-rich plasma on clinical outcomes in lateral epicondylitis. Arthroscopy. 2013;29(11):1851-62.
119 de Vos RJ, Windt J, Weir A. Strong evidence against platelet-rich plasma injections for chronic lateral epicondylar tendinopathy: a systematic review. British Journal of Sports Medicine. 2014;48(12):952-6.
120 Arirachakaran A, Sukthuayat A, Sisayanarane T, Laoratanavoraphong S, Kanchanatawan W, Kongtharvonskul J. Platelet-rich plasma versus autologous blood versus steroid injection in lateral epicondylitis: systematic review and network meta-analysis. Journal of Orthopaedics and Traumatology. 2016;17(2):101-12.
121 Gosens T, Mishra AK. Editorial in response to the systematic review by de Vos et al:'Strong evidence against platelet-rich plasma injections for chronic lateral epicondylar tendinopathy: a systematic review'. British Journal of Sports Medicine. 2014 Jun 1;48(12):945.
122 Murray IR, Geeslin AG, Goudie EB, Petrigliano FA, LaPrade RF. Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO): Platelet-Rich Plasma and Mesenchymal Stem Cells. Journal of Bone and Joint Surgery (Am). 2017;99(10):809-19.
123 Burn MB, Mitchell RJ, Liberman SR, Lintner DM, Harris JD, McCulloch PC. Open, Arthroscopic, and Percutaneous Surgical Treatment of Lateral Epicondylitis: A Systematic Review. Hand. 2017:1558944717701244.
124 Dunn JH, Kim JJ, Davis L, Nirschl RP. Ten-to 14-year follow-up of the Nirschl surgical technique for lateral epicondylitis. The American Journal of Sports Medicine. 2008;36(2):261-6.
125 Kroslak M, Murrell GA. Surgical treatment of lateral epicondylitis: a prospective, randomized, double blinded, placebo controlled clinical trial. Journal of Shoulder and Elbow Surgery. 2017;26(10):e328-e9.
126 Matache BA, Berdusco R, Momoli F, Lapner PL, Pollock J. A randomized, double-blind sham-controlled trial on the efficacy of arthroscopic tennis elbow release for the management of chronic lateral epicondylitis. BMC musculoskeletal disorders. 2016;17(1):239.
127 Kaska SC, Weinstein JN. Ernest Amory Codman, 1869-1940: A pioneer of evidence-based medicine: The end result idea. Spine. 1998;23(5):629-33.
128 Kaplan RS, Porter ME. How to solve the cost crisis in health care. Harvard Business Review. 2011;89(9):46-52.
129 Porter ME, Larsson S, Lee TH. Standardizing patient outcomes measurement. New England Journal of Medicine. 2016;374(6):504-6.
130 Porter ME. What is value in health care? New England Journal of Medicine. 2010;363(26):2477-81.
131 Food and Drug Administration, US Department of Health, Human Services FDA Center for Drug Evaluation, US Department of Health, Evaluation HSFCfB, US Department of Health, et al. Guidance for industry: patient-reported outcome

measures: use in medical product development to support labeling claims: draft guidance. Health and Quality of Life Outcomes. 2006;4:1-20.
132 Rolfson O, Bohm E, Franklin P, Lyman S, Denissen G, Dawson J, et al. Patient-reported outcome measures in arthroplasty registries: Report of the Patient-Reported Outcome Measures Working Group of the International Society of Arthroplasty Registries Part II. Recommendations for selection, administration, and analysis. Acta Orthopaedica. 2016;87(sup1):9-23.
133 National Institute for Healthcare and Clinical Excellence (NICE): Guide to the Methods of Technology Appraisal 2013 [Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword. (Last accessed 17/7/2018).
134 Levine DM, Morlock LL, Mushlin AI, Shapiro S, Malitz FE. The role of new health practitioners in a prepaid group practice: provider differences in process and outcomes of medical care. Medical Care. 1976:326-47.
135 Reeve BB, Wyrwich KW, Wu AW, Velikova G, Terwee CB, Snyder CF, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Quality of Life Research. 2013;22(8):1889-905.
136 Topol EJ. The patient will see you now: the future of medicine is in your hands. New York: Basic Books; 2015 Jan 6.
137 Russell EW. 2 - The nature of science. The scientific foundation of neuropsychological sssessment. Oxford: Elsevier; 2012. p. 31-46.
138 Welsing PM, Rengerink KO, Collier S, Eckert L, van Smeden M, Ciaglia A, et al. Series: Pragmatic trials and real world evidence: Paper 6. Outcome measures in the real world. Journal of Clinical Epidemiology. 2017;90:99-107.
139 McKenna SP. Measuring patient-reported outcomes: moving beyond misplaced common sense to hard science. BMC medicine. 2011;9(1):86.
140 Fayers PM, Machin D. Quality of life: the assessment, analysis and interpretation of patient-reported outcomes. New Jersey: John Wiley & Sons; 2013.
141 Gagnier JJ. Patient Report Outcome Measures in Orthopaedics. Journal of Orthopaedic Research. 2017; 35(10):2098-108.
142 Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, et al. The development and validation of a patient-reported questionnaire to assess outcomes of elbow surgery. Journal of Bone and Joint Surgery (Br). 2008;90(4):466-73.
143 Valderas JM, Alonso J. Patient reported outcome measures: a model-based classification system for research and clinical practice. Quality of Life Research. 2008;17(9):1125.
144 Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Quality of Life Research. 2010;19(4):539-49.
145 Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. British Medical Journal. 2008;337:a1655.
146 Berwick D, Hiatt H, Janeway P, Smith R. An ethical code for everybody in health care. British Medical Journal. 1997;315(7123):1633-4.

147 Devlin NJ, Appleby J. Getting the most out of PROMS. Putting health outcomes at the heart of NHS decision making. London: King's Fund; 2010.
148 Riedel K, Beaton DE. Update on the state of outcome measurement in total elbow arthroplasty research: identifying a need for consensus. Journal of Bone and Joint Surgery (Am). 2013;95(14):e97 1-8.
149 The B, Reininga IH, El Moumni M, Eygendaal D. Elbow-specific clinical rating systems: extent of established validity, reliability, and responsiveness. Journal of Shoulder Elbow Surgery. 2013;22(10):1380-94.
150 Bren L. The importance of patient-reported outcomes... it's all about the patients. FDA Consumer. 2006;40(6):26.
151 Wu AW, Kharrazi H, Boulware LE, Snyder CF. Measure once, cut twice—adding patient-reported outcome measures to the electronic health record for comparative effectiveness research. Journal of Clinical Epidemiology. 2013;66(8):S12-S20.
152 Dawson J, Doll H, Fitzpatrick R, Jenkinson C, Carr AJ. The routine use of patient reported outcome measures in healthcare settings. British Medical Journal. 2010;340:c186.
153 Alonso J, Bartlett SJ, Rose M, Aaronson NK, Chaplin JE, Efficace F, et al. The case for an international patient-reported outcomes measurement information system (PROMIS®) initiative. Health and Quality of Life Outcomes. 2013;11(1):1-5.
154 Longo UG, Franceschi F, Loppini M, Maffulli N, Denaro V. Rating systems for evaluation of the elbow. British Medical Bulletin. 2008;87:131-61.
155 Turchin DC, Beaton DE, Richards RR. Validity of observer-based aggregate scoring systems as descriptors of elbow pain, function, and disability. Journal of Bone and Joint Surgery (Am). 1998;80(2):154-62.
156 de Boer YA, Hazes JM, Winia PC, Brand R, Rozing PM. Comparative responsiveness of four elbow scoring instruments in patients with rheumatoid arthritis. The Journal of Rheumatology. 2001;28(12):2616-23.
157 Schmidt S, Ferrer M, Gonzalez M, Gonzalez N, Valderas JM, Alonso J, et al. Evaluation of shoulder-specific patient-reported outcome measures: a systematic and standardized comparison of available evidence. Journal of Shoulder and Elbow Surgery 2014;23(3):434-44.
158 Booker S, Alfahad N, Scott M, Gooding B, Wallace WA. Use of scoring systems for assessing and reporting the outcome results from shoulder surgery and arthroplasty. World Journal of Orthopedics. 2015;6(2):244.
159 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of Internal Medicine. 2009;151(4):264-9.
160 Gonçalves Bradley DC, Gibbons C, Ricci-Cabello I, Bobrovitz NJ, Gibbons EJ, Kotzeva A, et al. Routine provision of information on patient-reported outcome measures to healthcare providers and patients in clinical practice. The Cochrane Library. 2015.
161 ePROVIDE. PROQOLID Clinical Outcome Assessments Catalog. [Available from: https://eprovide.mapi-trust.org/search?form[searchText]=&form[ezxform_token]=iDnZ3IZbrQmK9ior_bMTPbCgIZ5NJTTSGw6YCl4xTmA. (Last accessed 17/07/2018).

162 Antuna S, Barco R. Essential Techniques in Elbow Surgery. Berlin: Springer; 2016.
163 Osoba D, King M. Meaningful differences. Assessing quality of life in clinical trials, methods and practice (2nd edition). Oxford: Oxford University Press; 2005. Pages 243-57.
164 Macdermid JC, Silbernagel KG. Outcome Evaluation in Tendinopathy: Foundations of Assessment and a Summary of Selected Measures. Journal of Orthopaedic & Sports Physical Therapy. 2015;45(11):950-64.
165 Morrey B, Adams R. Semiconstrained arthroplasty for the treatment of rheumatoid arthritis of the elbow. Journal of Bone and Joint Surgery (Am). 1992;74(4):479-90.
166 Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, et al. Factors associated with satisfaction in patients undergoing elbow surgery: a prospective study. Journal of Shoulder and Elbow Surgery. 2010;19(5):635-44.
167 Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, et al. Specificity and responsiveness of patient-reported and clinician-rated outcome measures in the context of elbow surgery, comparing patients with and without rheumatoid arthritis. Orthopaedics and Traumatology: Surgery & Research. 2012;98(6):652-8.
168 Morrey BF. Fracture of the radial head. The elbow and its disorders (2nd edition). Philadelphia: WB Saunders; 1993. Pages 383-404.
169 Hudak PL, Amadio PC, Bombardier C, Beaton D, Cole D, Davis A, et al. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder, and hand). American Journal of Industrial Medicine. 1996;29(6):602-8.
170 Gosling T, Blauth M, Lange T, Richter M, Bastian L, Krettek C. Outcome assessment after arthrolysis of the elbow. Archives of Orthopaedic and Trauma Surgery. 2004;124(4):232-6.
171 Angst F, John M, Pap G, Mannion AF, Herren DB, Flury M, et al. Comprehensive assessment of clinical outcome and quality of life after total elbow arthroplasty. Arthritis & Rheumatism: Arthritis Care & Research. 2005;53(1):73-82 10p.
172 Angst F, Goldhahn J, Drerup S, Kolling C, Aeschlimann A, Simmen BR, et al. Responsiveness of five outcome measurement instruments in total elbow arthroplasty. Arthritis Care Reseach. 2012;64(11):1749-55.
173 Janssen S, De Smet L. Responsiveness of the DASH questionnaire for surgically treated tennis elbow. Acta Chirurgica Belgica. 2008;108(5):583-5.
174 Altan L, Ercan I, Konur S. Reliability and validity of Turkish version of the patient rated tennis elbow evaluation. Rheumatology International. 2010;30(8):1049-54.
175 Rompe JD, Overend TJ, MacDermid JC. Validation of the Patient-Rated Tennis Elbow Evaluation questionnaire. Journal of Hand Therapy. 2007;20(1):3-10.
176 Newcomer KL, Martinez-Silvestrini JA, Schaefer MP, Gay RE, Arendt KW. Sensitivity of the Patient-rated Forearm Evaluation Questionnaire in lateral epicondylitis. Journal of Hand Therapy. 2005;18(4):400-73 8p.
177 Cacchio A, Necozione S, MacDermid JC, Rompe JD, Maffulli N, di Orio F, et al. Cross-cultural adaptation and measurement properties of the italian version of the Patient-Rated Tennis Elbow Evaluation (PRTEE) questionnaire. Phys Ther. 2012;92(8):1036-45.

178 Stasinopoulos D, Papadopoulos C, Antoniadou M, Nardi L. Greek adaptation and validation of the Patient-Rated Tennis Elbow Evaluation (PRTEE). Journal of Hand Therapy. 2015;28(3):286-90.
179 van Ark M, Zwerver J, Diercks RL, van den Akker-Scheek I. Cross-cultural adaptation and reliability and validity of the Dutch Patient-Rated Tennis Elbow Evaluation (PRTEE-D). BMC Musculoskeletal Disorders. 2014;15:270.
180 Nilsson P, Baigi A, Marklund B, Mansson J. Cross-cultural adaptation and determination of the reliability and validity of PRTEE-S (Patientskattad Utvardering av Tennisarmbage), a questionnaire for patients with lateral epicondylalgia, in a Swedish population. BMC Musculoskeletal Disorders. 2008;9:79.
181 Raven EEJ, Haverkamp D, Sierevelt IN, van Montfoort DO, Poll RG, Blankevoort L, et al. Construct Validity and Reliability of the Disability of Arm, Shoulder and Hand Questionnaire for Upper Extremity Complaints in Rheumatoid Arthritis. Journal of Rheumatology. 2008;35(12):2334-8.
182 Zimmerman NB, Kaye MB, Wilgis ES, Zimmerman RM, Dubin NH. Are standardized patient self-reporting instruments applicable to the evaluation of ulnar neuropathy at the elbow? Journal of Shoulder and Elbow Surgery. 2009 May 1;18(3):463-8.
183 Malay S, Chung KC, Grp SS. The Minimal Clinically Important Difference After Simple Decompression for Ulnar Neuropathy at the Elbow. Journal of Hand Surgery. 2013;38(4):652-9.
184 Sorensen AA, Howard D, Tan WH, Ketchersid J, Calfee RP. Minimal clinically important differences of 3 patient-rated outcomes instruments. The Journal of Hand Surgery. 2013;38(4):641-9.
185 Franchignoni F, Vercelli S, Giordano A, Sartorio F, Bravini E, Ferriero G. Minimal clinically important difference of the disabilities of the arm, shoulder and hand outcome measure (DASH) and its shortened version (QuickDASH). Journal of Orthopaedic & Sports Physical Therapy. 2014;44(1):30-9.
186 Vincent JI, MacDermid JC, King GJ, Grewal R. Validity and sensitivity to change of patient-reported pain and disability measures for elbow pathologies. Journal of Orthopaedic & Sports Physical Therapy. 2013;43(4):263-74.
187 Valderas JM, Ferrer M, Mendivil J, Garin O, Rajmil L, Herdman M, et al. Development of EMPRO: a tool for the standardized assessment of patient-reported outcome measures. Value in Health. 2008;11(4):700-8.
188 Dellon AL, Hament W, Gittelshon A. Nonoperative management of cubital tunnel syndrome An 8-year prospective study. Neurology. 1993;43(9):1673-.
189 Andrews JR, St Pierre RK, Carson Jr WG. Arthroscopy of the elbow. Clinics in Sports Medicine. 1986;5(4):653-62.
190 Celik D. Psychometric properties of the Mayo Elbow Performance Score. Rheumatology International. 2015;35(6):1015-20.
191 Celik D, Atalar AC, Demirhan M, Dirican A. Translation, cultural adaptation, validity and reliability of the Turkish ASES questionnaire. Knee Surgery, Sports Traumatology, Arthroscopy. 2013;21(9):2184-9.
192 De Boer YA, Van Den Ende CHM, Eygendaal D, Jolie IMM, Hazes JMW, Rozing PM. Clinical reliability and validity of elbow functional assessment in rheumatoid arthritis. Journal of Rheumatology. 1999;26(9):1909-17 9p.

193 de Haan J, Goei H, Schep NW, Tuinebreijer WE, Patka P, den Hartog D. The reliability, validity and responsiveness of the Dutch version of the Oxford elbow score. Journal of Orthopaedic Surgery and Research. 2011;6(1):39.
194 Ahmed S, Berzon RA, Revicki DA, Lenderking WR, Moinpour CM, Basch E, et al. The use of patient-reported outcomes (PRO) within comparative effectiveness research: implications for clinical practice and health care policy. Medical Care. 2012;50(12):1060-70.
195 Snyder CF, Jensen RE, Segal JB, Wu AW. Patient-reported outcomes (PROs): putting the patient perspective in patient-centered outcomes research. Medical care. 2013;51(8 0 3):S73.
196 Sussmann PS, Simmen BR, Goldhahn J, Sculco TP. Challenges for large orthopaedic hospitals worldwide—an ISOC position statement. HSS journal. 2010;6(1):57-60.
197 Hawkins RJ, Thigpen CA. Selection, implementation, and interpretation of patient-centered shoulder and elbow outcomes. Journal of Shoulder and Elbow Surgery. 2018 Feb 1;27(2):357-62.
198 Elmagarmid A FZ, Hammady H, Ilyas I, Khabsa M, Ouzzani M. Rayyan: a systematic reviews web app for exploring and filtering searches for eligible studies for Cochrane Reviews. In: Evidence-Informed Public Health: Opportunities and Challenges. Abstracts of the 22nd Cochrane Colloquium. 2014.
199 Powers JH, Patrick DL, Walton MK, Marquis P, Cano S, Hobart J, et al. Clinician-Reported Outcome Assessments of Treatment Benefit: Report of the ISPOR Clinical Outcome Assessment Emerging Good Practices Task Force. Value in Health. 2017;20(1):2-14.
200 Maratia S, Cedillo S, Rejas J. Assessing health-related quality of life in patients with breast cancer: a systematic and standardized comparison of available instruments using the EMPRO tool. Quality of Life Research. 2016;25(10):2467-80.
201 Garin O, Herdman M, Vilagut G, Ferrer M, Ribera A, Rajmil L, et al. Assessing health-related quality of life in patients with heart failure: a systematic, standardized comparison of available measures. Heart Failure Reviews. 2014;19(3):359-67.
202 King GJ, Richards RR, Zuckerman JD, Blasier R, Dillman C, Friedman RJ, Gartsman GM, Iannotti JP, Murnahan JP, Mow VC, Woo SL. A standardized method for assessment of elbow function. Journal of Shoulder and Elbow Surgery. 1999 Jul 1;8(4):351-4.
203 Inglis AE, Pellicci PM. Total elbow replacement. Journal of Bone and Joint Surgery (Am). 1980;62(8):1252-8.
204 Sathyamoorthy P, Kemp G, Rawal A, Rayner V, Frostick S. Development and validation of an elbow score. Rheumatology. 2004;43(11):1434-40.
205 Broberg MA, Morrey B. Results of delayed excision of the radial head after fracture. J Journal of Bone and Joint Surgery (Am). 1986;68(5):669-74.
206 Overend TJ, Wuori-Fearn JL, Kramer JF, MacDermid JC. Reliability of a patient-rated forearm evaluation questionnaire for patients with lateral epicondylitis. Journal of Hand Therapy. 1999;12(1):31-7.

207 Beaton DE, Wright JG, Katz JN, Upper Extremity Collaborative G. Development of the QuickDASH: comparison of three item-reduction approaches. Journal of Bone and Joint Surgery (Am). 2005;87(5):1038-46
208 Roles N, Maudsley R. Radial Tunnel Syndrome: Resistant Tennis Elbow as a Nerve Entrapment. Journal of Bone and Joint Surgery (Br). 1972;54(3):499-508.
209 Lowe A, Wessel J, Battié MC. Test-retest reliability, construct validity, and responsiveness of a functional pain scale for tennis elbow. Physiotherapy Canada. 2003;55(2):114-22 9p.
210 Pransky G, Feuerstein M, Himmelstein J, Katz JN, Vickers-Lahti M. Measuring functional outcomes in work-related upper extremity disorders: Development and validation of the upper extremity function scale. Journal of Occupational and Environmental Medicine. 1997;39(12):1195-202.
211 Verhaar J, Walenkamp G, Kester A, van Mameren H, van der Linden T. Lateral extensor release for tennis elbow. A prospective long-term follow-up study. Journal of Bone and Joint Surgery (Am). 1993;75(7):1034-43.
212 Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977:159-74.
213 Smith MV, Calfee RP, Baumgarten KM, Brophy RH, Wright RW. Upper extremity-specific measures of disability and outcomes in orthopaedic surgery. Journal of Bone and Joint Surgery (Am). 2012;94(3):277-85.
214 Freehill MT, Mannava S, Safran MR. Outcomes evaluation of the athletic elbow. Sports Medicine and Arthroscopy Review. 2014;22(3):e25-32.
215 Badalamente M, Coffelt L, Elfar J, Gaston G, Hammert W, Huang J, et al. Measurement scales in clinical research of the upper extremity, part 2: Outcome measures in studies of the hand/wrist and shoulder/elbow. Journal of Hand Surgery. 2013;38(2):407-12.
216 Polson K, Reid D, McNair PJ, Larmer P. Responsiveness, minimal importance difference and minimal detectable change scores of the shortened disability arm shoulder hand (QuickDASH) questionnaire. Manual Therapy. 2010;15(4):404-7.
217 Smith-Forbes EV, Howell DM, Willoughby J, Pitts DG, Uhl TL. Specificity of the minimal clinically important difference of the quick Disabilities of the Arm Shoulder and Hand (QDASH) for distal upper extremity conditions. Journal of Hand Therapy. 2016;29(1):81-8.
218 Calvert M, Blazeby J, Revicki D, Moher D, Brundage M. Reporting quality of life in clinical trials: a CONSORT extension. The Lancet. 2011;378(9804):1684-5.
219 Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine. 2000;25(24):3186-91.
220 Beirer M, Friese H, Lenich A, Crönlein M, Sandmann GH, Biberthaler P, Kirchhoff C, Siebenlist S. The Elbow Self-Assessment Score (ESAS): development and validation of a new patient-reported outcome measurement tool for elbow disorders. Knee Surgery, Sports Traumatology, Arthroscopy. 2017 Jul 1;25(7):2230-6.
221 Makhni EC, Meadows M, Hamamoto JT, Higgins JD, Romeo AA, Verma NN. Patient Reported Outcomes Measurement Information System (PROMIS) in the upper extremity: the future of outcomes reporting? Journal of Shoulder and Elbow surgery. 2017;26(2):352-7.

222 Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, et al. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value In Health. 2005;8(2):94-104.
223 McLean JM, Awwad D, Lisle R, Besanko J, Shivakkumar D, Leith J. An international, multicenter cohort study comparing 6 shoulder clinical scores in an asymptomatic population. Journal of Shoulder and Elbow Surgery. 2018;27(2):306-14.
224 Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. Journal of the American Medical Association. 1995;273(1):59-65.
225 Sousa KH, Kwok O-M. Putting Wilson and Cleary to the test: analysis of a HRQOL conceptual model using structural equation modeling. Quality of Life Research. 2006;15(4):725-37.
226 Turner L, Shamseer L, Altman DG, Schulz KF, Moher D. Does use of the CONSORT Statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane review. Systematic Reviews. 2012 Nov 29;1(1).
227 Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, et al. Comparative responsiveness and minimal change for the Oxford Elbow Score following surgery. Quality of Life Research. 2008;17(10):1257-67.
228 Poltawski L, Watson T. Measuring clinically important change with the Patient-rated Tennis Elbow Evaluation. Hand Therapy. 2011;16(3):52-7.
229 Solway S, Beaton DE, McConnell S, Bombardier C. The DASH Outcome Measure User's Manual. Toronto, Ontario: Institute for Work & Health 2002.
230 Hammond A, Prior Y, Tyson S. 172. Development and Psychometric Testing of a British English Version of the Disabilities Arm Shoulder and Hand Questionnaire. Rheumatology. 2015;54(suppl 1):i117-i.
231 Morrey BF, Sanchez-Sotelo J. The elbow and its disorders. New York: Elsevier Health Sciences; 2009.
232 Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. Journal of Clinical Epidemiology. 1993;46(12):1417-32.
233 Black N. Patient reported outcome measures could help transform healthcare. British Medical Journal. 2013;346.
234 Tyser AR, Beckmann J, Franklin JD, Cheng C, Hon SD, Wang A, et al. Evaluation of the PROMIS physical function computer adaptive test in the upper extremity. The Journal of Hand Surgery. 2014;39(10):2047-51.e4.
235 Beckmann JT, Hung M, Voss MW, Crum AB, Bounsanga J, Tyser AR. Evaluation of the Patient-Reported Outcomes Measurement Information System upper extremity computer adaptive test. The Journal of Hand Surgery. 2016;41(7):739-44.e4
236 Harris KK, Dawson J, Jones LD, Beard DJ, Price AJ. Extending the use of PROMs in the NHS—using the Oxford Knee Score in patients undergoing non-operative management for knee osteoarthritis: a validation study. British Medical Journal. 2013;3(8):e003365.
237 Kline P. An easy guide to factor analysis. Abingdon: Routledge; 2014.

238 De Vet HC, Terwee CB, Mokkink LB, Knol DL. Measurement in medicine: a practical guide. Cambridge: Cambridge University Press; 2011.
239 Guyver PM, Cattell AE, Hall MJ, Brinsden MD. Oxford elbow scores in an asymptomatic population. Annals of The Royal College of Surgeons of England. 2013;95(6):415-7.
240 Vincent J, MacDermid JC. Patient-rated tennis elbow evaluation questionnaire. Journal of Physiotherapy. 2014;60(4):240
241 Van Hout B, Janssen M, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health. 2012;15(5):708-15.
242 Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain. 1983;17(1):45-56.
243 Kennedy CA BD, Solway S, McConnell S, Bombardier C. DASH and QuickDASH Outcome measure user's manual (3rd edition): Toronto: Institute for Work & Health; 2011.
244 Mayo N. ISOQOL Dictionary of Quality of Life and Health Outcomes Measurement: ISOQOL; 2016.
245 Nunnally JC, Bernstein IH. Psychometric theory. New York: McGraw-Hill; 1994.
246 McHorney CA, Tarlov AR. Individual-patient monitoring in clinical practice: are available health status surveys adequate? Quality of Life Research. 1995;4(4):293-307.
247 Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. Medical Care. 1989;27(3):S178-S89.
248 Cohen J. A power primer. Psychological Bulletin. 1992;112(1):155.
249 Davidson M, Keating J. Patient-reported outcome measures (PROMs): how should I interpret reports of measurement properties? A practical guide for clinicians and researchers who are not biostatisticians. British Journal of Sports Medicine. 2014;48(9):792-6.
250 Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. Journal of Clinical Epidemiology. 2007;60(1):34-42.
251 Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. Controlled Clinical Trials. 1989;10(4):407-15.
252 Reade S, Spencer K, Sergeant JC, Sperrin M, Schultz DM, Ainsworth J, et al. Cloudy with a chance of pain: engagement and subsequent attrition of daily data entry in a smartphone pilot study tracking weather, disease severity, and physical activity in patients with rheumatoid arthritis. Journal of Medical Internet Research. mHealth and uHealth. 2017;5(3).
253 Tyrrell JS, Redshaw CH, Schmidt W, Williams DH. Physical activity in ankylosing spondylitis: evaluation and analysis of an eHealth tool. Journal of Innovation in Health Informatics. 2016;23(2):510-22.
254 Plaschke HC, Thillemann TM, Brorson S, Olsen BS. Outcome after total elbow arthroplasty: a retrospective study of 167 procedures performed from 1981 to 2008. Journal of Shoulder & Elbow Surgery.24(12):1982-90.

255 Beaton D, Katz J, Fossel A, Wright J, Tarasuk V, Bombardier C. Measuring the whole or the parts? Validity, reliability, and responsiveness of the DASH outcome measure in different regions of the upper extremity. Journal of Hand Therapy. 2001;14(2):128-46.
256 Leung HB, Yen CH, Tse PYT. Reliability of Hong Kong Chinese version of the Patient-rated Forearm Evaluation Questionnaire for lateral epicondylitis. Hong Kong Medical Journal. 2004;10(3):172-7.
257 Schünemann HJ, Akl EA, Guyatt GH. Interpreting the results of patient reported outcome measures in clinical trials: the clinician's perspective. Health and quality of life outcomes. 2006;4(1):62.
258 Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. Journal of Manual & Manipulative Therapy. 2009;17(3):163-70.
259 Streiner DL, Norman GR, Cairney J. Health measurement scales: a practical guide to their development and use: Oxford: Oxford University Press; 2015.
260 Sahbudin I, Peall A. SAT0420 A Survey of Tennis Elbow Treatment, What are rheumatologists recommending? Annals of the Rheumatic Diseases. 2013;72(Suppl 3):A724-A.
261 Keijsers R, van den Bekerom MP, Koenraadt KL, Bleys RL, van Dijk CN, Eygendaal D. Injection of tennis elbow: Hit and miss? A cadaveric study of injection accuracy. Knee Surgery, Sports Traumatology, Arthroscopy. 2016:1-4.
262 McAlindon TE, LaValley MP, Harvey WF, Price LL, Driban JB, Zhang M, et al. effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. Journal of the American Medical Association. 2017;317(19):1967-75.
263 Piper SL, Kramer JD, Kim HT, Feeley BT. Effects of local anesthetics on articular cartilage. The American Journal of Sports Medicine. 2011;39(10):2245-53.
264 Konin GP, Nazarian LN, Walz DM. US of the elbow: indications, technique, normal anatomy, and pathologic conditions. Radiographics. 2013;33(4):E125-E47.
265 Krogh TP, Fredberg U, Ammitzbøl C, Ellingsen T. Ultrasonographic characteristics of the common extensor tendon of the elbow in asymptomatic individuals: thickness, color doppler activity, and bony spurs. Orthopaedic Journal of Sports Medicine. 2017;5(5).
266 Ustuner E, Toprak U, Baskan B, Oztuna D. Sonographic examination of the common extensor tendon of the forearm at three different locations in the normal asymptomatic population. Surgical and Radiologic Anatomy. 2013;35(7):547-52.
267 Jaén-Díaz JI, Cerezo-López E, López-de Castro F, Mata-Castrillo M, Barceló-Galíndez JP, De la Fuente J, et al. Sonographic findings for the common extensor tendon of the elbow in the general population. Journal of Ultrasound in Medicine. 2010;29(12):1717-24.
268 Park G-Y, Kwon DR, Cho HK, Park J, Park JH. Distribution of Platelet-rich Plasma after Ultrasound-Guided Injection for Chronic Elbow Tendinopathies. Journal of Sports Science and Medicine. 2017;16:1-5.
269 Keijsers R, Turkenburg JT, Beumer A, Eygendaal D. Variation in size and location of the ecrb tendon measured with ultrasound. is blind injection of lateral epicondylitis still justified? : ITEC Medical; 2016 [Available from:

http://www.itecmedical.com/wp-content/uploads/2016/11/study-ultrasound.pdf]. (Last accessed 17/7/2018)
270 Toprak U, Baskan B, Üstüner E, Öten E, Altin L, Karademir MA, et al. Common extensor tendon thickness measurements at the radiocapitellar region in diagnosis of lateral elbow tendinopathy. Diagnostic and Interventional Radiology. 2012;18(6):566.
271 Stocker H, Harris JW. Handbook of Mathematics and Computational Science. New York: Springer; 1998.
272 Wilson JJ, Lee KS, Chamberlain C, DeWall R, Baer GS, Greatens M, et al. Intratendinous injections of platelet-rich plasma: feasibility and effect on tendon morphology and mechanics. Journal of experimental orthopaedics. 2015;2(1):5.
273 Loftus ML, Endo Y, Adler RS. Retrospective analysis of postinjection ultrasound imaging after platelet-rich plasma or autologous blood: observational review of anatomic distribution of injected material. American Journal of Roentgenology. 2012;199(4):W501-W5.
274 Belt AVD, Keg P, Dik K, Barneveld A. The correlation between the dose and distribution of intratendinous fluid injections in the flexor tendons/ligaments of the horse. Transboundary and Emerging Diseases. 1993;40(1-10):713-9.
275 Lungu E, Grondin P, Tétreault P, Desmeules F, Cloutier G, Choinière M, et al. Ultrasound-guided tendon fenestration versus open-release surgery for the treatment of chronic lateral epicondylosis of the elbow: protocol for a prospective, randomised, single blinded study. British Medical Journal open. 2018;8(6):e021373.
276 Wiegerinck JI, Reilingh ML, de Jonge MC, van Dijk CN, Kerkhoffs GM. Injection techniques of platelet-rich plasma into and around the achilles tendon a cadaveric study. The American Journal of Sports Medicine. 2011;39(8):1681-7.
277 Andia I, Latorre P, Gomez M, Burgos-Alonso N, Abate M, Maffulli N. Platelet-rich plasma in the conservative treatment of painful tendinopathy: a systematic review and meta-analysis of controlled studies. British Medical Bulletin. 2014;110(1).
278 Schnabel LV, Mohammed HO, Miller BJ, McDermott WG, Jacobson MS, Santangelo KS, et al. Platelet rich plasma (PRP) enhances anabolic gene expression patterns in flexor digitorum superficialis tendons. Journal of Orthopaedic Research. 2007;25(2):230-40.
279 McCarrel T, Fortier L. Temporal growth factor release from platelet-rich plasma, trehalose lyophilized platelets, and bone marrow aspirate and their effect on tendon and ligament gene expression. Journal of Orthopaedic Research. 2009;27(8):1033-42.
280 de Mos M, Koevoet W, van Schie HT, Kops N, Jahr H, Verhaar JA, et al. In vitro model to study chondrogenic differentiation in tendinopathy. The American Journal of Sports Medicine. 2009;37(6):1214-22.
281 Anitua E, Sánchez M, Zalduendo M, De La Fuente M, Prado R, Orive G, et al. Fibroblastic response to treatment with different preparations rich in growth factors. Cell proliferation. 2009;42(2):162-70.
282 Nourissat G, Ornetti P, Berenbaum F, Sellam J, Richette P, Chevalier X. Does platelet-rich plasma deserve a role in the treatment of tendinopathy? Joint Bone Spine. 2015;82(4):230-4.

283 Kaux JF, Bouvard M, Lecut C, Oury C, Gothot A, Sanchez M, et al. Reflections about the optimisation of the treatment of tendinopathies with PRP. Muscles, Ligaments and Tendons Journal. 2015;5(1):1-4.
284 Linstone HA, Turoff M. The Delphi method: Techniques and applications. Boston: Addison-Wesley; 1975.
285 Delbecq AL, Van de Ven AH, Gustafson DH. Group techniques for program planning: A guide to nominal group and Delphi processes. Foresman Glenview: Scott; 1975.
286 Powell C. The Delphi technique: myths and realities. Journal of Advanced Nursing. 2003;41(4):376-82.
287 Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CF, Askham J, Marteau T. Consensus development methods, and their use in clinical guideline development. Health Technology Assessment. 1998;2(3):i.
288 O'Neill S, Watson PJ, Barry S. A delphi study of risk factors for achilles tendinopathy-opinions of world tendon experts. International Journal of Sports Physical Therapy. 2016;11(5):684.
289 Eubank BH, Mohtadi NG, Lafave MR, Wiley JP, Bois AJ, Boorman RS, et al. Using the modified Delphi method to establish clinical consensus for the diagnosis and treatment of patients with rotator cuff pathology. BMC Medical Research Methodology. 2016;16(1):56.
290 Hsu C-C, Sandford BA. The Delphi technique: making sense of consensus. Practical Assessment, Research & Evaluation. 2007;12(10):1-8.
291 Williams PL, Webb C. The Delphi technique: a methodological discussion. Journal of Advanced Nursing. 1994;19(1):180-6.
292 Meshkat B, Cowman S, Gethin G, Ryan K, Wiley M, Brick A, Clarke E, Mulligan E. Using an e-Delphi technique in achieving consensus across disciplines for developing best practice in day surgery in Ireland. Journal of Hospital Administration. 2014 Jan 22;3(4):1.
293 Ludwig B. Predicting the future: Have you considered using the Delphi methodology. Journal of Extension. 1997;35(5):1-4.
294 Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. Journal of Advanced Nursing. 2000;32(4):1008-15.
295 Heiko A. Consensus measurement in Delphi studies: review and implications for future quality assurance. Technological Forecasting and Social Change. 2012;79(8):1525-36.
296 Kalaian SA, Kasim RM. Terminating sequential Delphi survey data collection. Practical Assessment, Research & Evaluation. 2012;17(5).
297 LaPrade RF, Geeslin AG, Murray IR, Musahl V, Zlotnicki JP, Petrigliano F, et al. Biologic treatments for sports injuries II think tank—current concepts, future research, and barriers to advancement, part 1: biologics overview, ligament injury, tendinopathy. The American journal of Sports Medicine. 2016;44(12):3270-83.
298 Miller LE, Parrish WR, Roides B, Bhattacharyya S. Efficacy of platelet-rich plasma injections for symptomatic tendinopathy: systematic review and meta-analysis of randomised injection-controlled trials. British Medical Journal Open Sport & Exercise Medicine. 2017;3(1)

299 DeLong JM, Russell RP, Mazzocca AD. Platelet-rich plasma: the PAW classification system. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2012;28(7):998-1009.
300 Magalon J, Chateau A, Bertrand B, Louis M, Silvestre A, Giraudo L, et al. DEPA classification: a proposal for standardising PRP use and a retrospective application of available devices. British Medical Journal Open Sport & Exercise Medicine. 2016;2(1).
301 Ehrenfest DMD, Andia I, Zumstein MA, Zhang C-Q, Pinto NR, Bielecki T. Classification of platelet concentrates (Platelet-Rich Plasma-PRP, Platelet-Rich Fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: current consensus, clinical implications and perspectives. Muscles, Ligaments and Tendons Journal. 2014;4(1):3-9.
302 Creaney L, Wallace A, Curtis M, Connell D. Growth factor-based therapies provide additional benefit beyond physical therapy in resistant elbow tendinopathy: a prospective, double-blind, randomised trial of autologous blood injections versus platelet-rich plasma injections. British Journal of Sports Medicine. 2011;45(12):966-71.
303 Stenhouse G, Sookur P, Watson M. Do blood growth factors offer additional benefit in refractory lateral epicondylitis? A prospective, randomized pilot trial of dry needling as a stand-alone procedure versus dry needling and autologous conditioned plasma. Skeletal Radiology. 2013;42(11):1515-20.
304 Glanzmann MC, Audigé L. Platelet-rich plasma for chronic lateral epicondylitis: Is one injection sufficient? Archives of Orthopaedic and Trauma Surgery. 2015;135(12):1637-45.
305 Wilson CB. Adoption of new surgical technology. British Medical Journal. 2006;332(7533):112-4.
306 McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. The Lancet. 2009;374(9695):1105-12.
307 Cook JA, McCulloch P, Blazeby JM, Beard DJ, Marinac-Dabic D, Sedrakyan A. IDEAL framework for surgical innovation 3: randomised controlled trials in the assessment stage and evaluations in the long term study stage. British Medical Journal. 2013;346:f2820.
308 Othman AMA. Arthroscopic versus percutaneous release of common extensor origin for treatment of chronic tennis elbow. Archives of Orthopaedic and Trauma Surgery. 2011;131(3):383-8.
309 Thanasas C, Papadimitriou G, Charalambidis C, Paraskevopoulos I, Papanikolaou A. Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis: a randomized controlled clinical trial. The American Journal of Sports Medicine. 2011;39(10):2130-4.
310 Mishra AK, Skrepnik NV, Edwards SG, Jones GL, Sampson S, Vermillion DA, Ramsey ML, Karli DC, Rettig AC. Efficacy of platelet-rich plasma for chronic tennis elbow: a double-blind, prospective, multicenter, randomized controlled trial of 230 patients. The American Journal of Sports Medicine. 2014 Feb;42(2):463-71.
311 Lehner C, Gehwolf R, Hirzinger C, Stephan D, Augat P, Tauber M, et al. Bupivacaine induces short-term alterations and impairment in rat tendons. The American Journal of Sports Medicine. 2013;41(6):1411-8.

312 Carofino B, Chowaniec DM, McCarthy MB, Bradley JP, Delaronde S, Beitzel K, et al. Corticosteroids and local anesthetics decrease positive effects of platelet-rich plasma: an in vitro study on human tendon cells. Arthroscopy. 2012;28(5):711-9.
313 Bausset O, Magalon J, Giraudo L, Louis M-L, Serratrice N, Frere C, et al. Impact of local anaesthetics and needle calibres used for painless PRP injections on platelet functionality. Muscles, Ligaments and Tendons Journal. 2014;4(1):18.
314 Boesen AP, Hansen R, Boesen MI, Malliaras P, Langberg H. Effect of high-volume injection, platelet-rich plasma, and sham treatment in chronic midportion Achilles tendinopathy: a randomized double-blinded prospective study. The American Journal of Sports Medicine. 2017 Jul;45(9):2034-43.
315 Ford RD, Schmitt WP, Lineberry K, Luce P. A retrospective comparison of the management of recalcitrant lateral elbow tendinosis: platelet-rich plasma injections versus surgery. Hand. 2015;10(2):285-91.
316 Karaduman M, Okkaoglu MC, Sesen H, Taskesen A, Ozdemir M, Altay M. Platelet-rich plasma versus open surgical release in chronic tennis elbow: A retrospective comparative study. Journal of Orthopaedics. 2016;13(1):10-4.
317 Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010;8(1):18.
318 Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of Internal Medicine. 2013;158(3):200-7.
319 Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. Pilot and Feasibility Studies. 2016;2(1):64.
320 Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. Journal of the American Medical Association. 2013;309(8):814-22.
321 Rabin R, Charro Fd. EQ-SD: a measure of health status from the EuroQol Group. Annals of Medicine. 2001;33(5):337-43.
322 O'Cathain A, Hoddinott P, Lewin S, Thomas KJ, Young B, Adamson J, et al. Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers. Pilot and Feasibility Studies. 2015;1(1):32.
323 Braun V, Clarke V. Using thematic analysis in psychology. Qualitative research in psychology. 2006;3(2):77-101.
324 Sullivan GM, Feinn R. Using effect size—or why the P value is not enough. Journal of Graduate Medical Education. 2012;4(3):279-82.
325 Gabel CP, Yelland M, Melloh M, Burkett B. A modified QuickDASH-9 provides a valid outcome instrument for upper limb function. BMC Musculoskeletal Disorders. 2009;10(1):161.
326 Julious SA. Sample sizes for clinical trials with normal data. Statistics in Medicine. 2004;23(12):1921-86.
327 Sealed Envelope Ltd. Power calculator for continuous outcome non-inferiority trial 2012 [Available from: https://www.sealedenvelope.com/power/continuous-noninferior/] (Last accessd 21/12/2017).
328 Merolla G, Dellabiancia F, Ricci A, Mussoni MP, Nucci S, Zanoli G, Paladini P, Porcellini G. Arthroscopic debridement versus platelet-rich plasma injection: a

prospective, randomized, comparative study of chronic lateral Epicondylitis with a nearly 2-year follow-up. Arthroscopy. 2017 Jul 1;33(7):1320-9.
329 Gaspar MP, Kane PM, Putthiwara D, Jacoby SM, Osterman AL. Predicting revision following in situ ulnar nerve decompression for patients with idiopathic cubital tunnel syndrome. Journal of Hand Surgery. 41(3):427-35.
330 Ioannidis JP, Evans SJ, Gøtzsche PC, O'neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Annals of Internal Medicine. 2004;141(10):781-8.
331 MacDermid JC. Outcome evaluation in patients with elbow pathology: issues in instrument development and evaluation. Journal of Hand Therapy. 2001;14(2):105-14.
332 Hay EM, Paterson SM, Lewis M, Hosie G, Croft P. Pragmatic randomised controlled trial of local corticosteroid injection and naproxen for treatment of lateral epicondylitis of elbow in primary care. British Medical Journal. 1999;319(7215):964-8.
333 Wartolowska K, Collins GS, Hopewell S, Judge A, Dean BJ, Rombach I, et al. Feasibility of surgical randomised controlled trials with a placebo arm: a systematic review. British Medical Journal Open. 2016;6(3):e010194.
334 Bahney CS, Bruder SP, Cain JD, Keyak JH, Killian ML, Shapiro IM, et al. Accelerating the pace of discovery in orthopaedic research: A vision toward team science. Journal of Orthopaedic Research. 2016;34(10):1673-9.
335 Hanney SR, Gonzalez-Block MA. Building health research systems: WHO is generating global perspectives, and who's celebrating national successes? Health Research Policy and Systems. 2016 Dec 28;14(1).
336 Döring A-C, Nota SP, Hageman MG, Ring DC. Measurement of upper extremity disability using the patient-reported outcomes measurement information system. Journal of Hand Surgery. 2014;39(6):1160-5.
337 Overbeek CL, Nota SP, Jayakumar P, Hageman MG, Ring D. The PROMIS physical function correlates with the QuickDASH in patients with upper extremity illness. Clinical Orthopaedics and Related Research. 2015;473(1):311-7.
338 Hung M, Voss MW, Bounsanga J, Gu Y, Granger EK, Tashjian RZ. Psychometrics of the Patient-Reported Outcomes Measurement Information System Physical Function instrument administered by computerized adaptive testing and the Disabilities of Arm, Shoulder and Hand in the orthopedic elbow patient population. Journal of Shoulder and Elbow Surgery. 2018.
339 Bernard A, Vaneau M, Fournel I, Galmiche H, Nony P, Dubernard JM. Methodological choices for the clinical development of medical devices. Medical Devices. 2014;7:325.
340 Hemming K, Haines T, Chilton P, Girling A, Lilford R. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. British Medical Journal. 2015;350:h391.
341 Torgerson DJ, Roland M. Understanding controlled trials: What is Zelen's design? British Medical Journal. 1998;316(7131):606.
342 Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. British Medical Journal. 2010;340:c1066.

343 Rangan A, Upadhaya S, Regan S, Toye F, Rees JL. Research priorities for shoulder surgery: results of the 2015 James Lind Alliance patient and clinician priority setting partnership. British Medical Journal Open. 2016;6(4):e010412.

Appendices

PRISMA checklist for the study – Clinical Rating Systems in Elbow Research – A Systematic Review Exploring Trends and Distributions of Use

Please see inserted document

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	65
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	65
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	68-70
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	70
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	72
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	71
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	71-73
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	71

• Data items	• 11	• List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	• 72
• Risk of bias in individual studies	• 12	• Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	• N/A
• Summary measures	• 13	• State the principal summary measures (e.g., risk ratio, difference in means).	• 72
• Synthesis of results	• 14	• Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	• N/A

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• Section/topic	• #	• Checklist item	• Reported on page #
• Risk of bias across studies	• 15	• Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	• N/A
• Additional analyses	• 16	• Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	• 72
• **RESULTS**			•
• Study selection	• 17	• Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	• 73
• Study characteristics	• 18	• For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	• N/A
• Risk of bias within studies	• 19	• Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	• N/A
• Results of individual studies	• 20	• For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	• 77

• Synthesis of results	• 21	• Present results of each meta-analysis done, including confidence intervals and measures of consistency.	• N/A
• Risk of bias across studies	• 22	• Present results of any assessment of risk of bias across studies (see Item 15).	• N/A
• Additional analysis	• 23	• Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	• 77-78
• **DISCUSSION**			•
• Summary of evidence	• 24	• Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	• 79
• Limitations	• 25	• Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	• 84
• Conclusions	• 26	• Provide a general interpretation of the results in the context of other evidence, and implications for future research.	• 85
• **FUNDING**			•
• Funding	• 27	• Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	• N/A

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• *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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Systematic review search strategy (Chapters 2, 3 & 4)

Medline

1. exp Elbow/
2. elbow.tw.
3. exp Elbow joint/
4. exp Tennis Elbow/
5. epicondylitis.tw.
6. common extensor origin.tw.
7. epicondylalgia.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp "Outcome Assessment (Health Care)"/
10. (Outcome? adj2 assessment).tw.
11. patient reported outcome?.tw.
12. outcome? measure?.tw.
13. exp health status/
14. health status.tw.
15. exp "quality of life"/
16. quality of life.tw.
17. (QL or QoL or HRQL or HRQoL).tw.

18. (function* adj2 (status or psychological or mental or physical or social)).tw.

19. disabilit*.tw.

20. exp "Activities of Daily Living"/

21. activities of daily living.tw.

22. (wellbeing or well being).tw.

23. exp happiness/

24. (happi* or happy).tw.

25. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24

26. assessment.tw.

27. index.tw.

28. indices.tw.

29. instrument?.tw.

30. measure?.tw.

31. profile?.tw.

32. rating?.tw.

33. report*.tw.

34. scale?.tw.

35. schedul*.tw.

36. scor*.tw.

37. exp health surveys/

38. survey?.tw.

39. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38

40. (symptom? adj2 (assessment or index or indices or instrument? or measure? or profile? or rating? or report* or scale? or schedule? or scor* or survey?)).tw.

41. 25 or 40

42. exp Self-Assessment/

43. self-assess*.tw.

44. exp Questionnaires/

45. questionnaire?.tw.

46. self report*.tw.

47. 42 or 43 or 44 or 45 or 46

48. (Validation Studies or Comparative Study).pt. or exp psychometrics/ or psychometr*.tw. or clinimetr*.tw. or clinometr*.tw. or exp observer variation/ or observer variation.tw. or exp Health Status Indicators/ or exp reproducibility of results/ or reproducib*.tw. or exp discriminant analysis/ or reliab*.tw. or unreliab*.tw. or valid*.tw. or coefficient.tw. or homogeneity.tw. or homogeneous.tw. or internal consistency.tw. or (cronbach* and (alpha or alphas)).tw. or (item and (correlation* or selection* or reduction*)).tw. or agreement.tw. or precision.tw. or imprecision.tw. or precise values.tw. or test-retest.tw. or (test and retest).tw. or (reliab* and (test or retest)).tw. or stability.tw. or interrater.tw. or inter-rater.tw. or intrarater.tw. or intra-rater.tw. or intertester.tw. or inter-tester.tw. or intratester.tw. or intra-tester.tw. or

interobserver.tw. or inter-observer.tw. or intraobserver.tw. or intraobserver.tw. or intertechnician.tw. or inter-technician.tw. or intratechnician.tw. or intra-technician.tw. or interexaminer.tw. or inter-examiner.tw. or intraexaminer.tw. or intra-examiner.tw. or interassay.tw. or inter-assay.tw. or intraassay.tw. or intra-assay.tw. or interindividual.tw. or inter-individual.tw. or intraindividual.tw. or intra-individual.tw. or interparticipant.tw. or inter-participant.tw. or intraparticipant.tw. or intra-participant.tw. or kappa.tw. or kappa*.tw. or kappas.tw. or repeatab*.tw. or ((replicab* or repeated) and (measure or measures or findings or result or results or test or tests)).tw. or concordance.tw. or (intraclass and correlation*).tw. or discriminative.tw. or known group.tw. or factor analysis.tw. or factor analyses.tw. or dimension*.tw. or subscale*.tw. or (multitrait and scaling and (analysis or analyses)).tw. or item discriminant.tw. or interscale correlation*.tw. or error.tw. or errors.tw. or individual variability.tw. or (variability and (analysis or values)).tw. or (uncertainty and (measurement or measuring)).tw. or standard error of measurement.tw. or sensitiv*.tw. or responsive*.tw. or ((minimal or minimally or clinical or clinically) and (important or significant or detectable) and (change or difference)).tw. or (small* and (real or detectable) and (change or difference)).tw. or meaningful change.tw. or ceiling effect.tw. or floor effect.tw. or Item response model.tw. or IRT.tw. or Rasch.tw. or Differential item functioning.tw. or DIF.tw. or computer adaptive testing.tw. or item bank.tw. or cross-cultural equivalence.tw.

49. 39 or 47 or 48

50. 41 and 49

51. (Oxford elbow score or Liverpool Elbow Score or Elbow Self-Assessment Score or Elbow Function Assessment or (American Shoulder and Elbow Surgeons-

elbow) or (Modified American Shoulder and Elbow Surgeons) or Mayo Elbow Performance Score or Hospital for Special Surgery score or Hospital for Special Surgery short version or patient-rated elbow evaluation or Patient-Rated Tennis Elbow Evaluation or Elbow Functional Assessment or (Disabilities of the Arm, Shoulder and Hand questionnaire) or subjective elbow value or (Broberg and Morrey) or Ewald).mp. or Pritchard.tw. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tn, dm, mf, dv, kw]

52. (OES or LES or ESAS or ASES or ASES-e or MEP or PREE or PRTEE or EFA or DASH or quickDASH).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tn, dm, mf, dv, kw]

53. 8 and 52

54. 8 and 50

55. 51 or 53 or 54

56. exp ANIMALS/ not humans.sh.

57. 55 not 56

Full list of outcome measures

In order of prevalence of use

1. MEPS (Mayo Elbow Performance Score)
2. DASH (Disabilities of the Arm Shoulder and Hand)
3. Morrey
4. QDASH (Quick Disabilities of the Arm, Shoulder and Hand)
5. PRTEE (Patient-Rated Tennis Elbow Evaluation)
6. ASES-e ((American Shoulder and Elbow Surgeons Score - elbow)
7. OES (Oxford Elbow Score)
8. Roles and Maudsley
9. Nirschl
10. HSS (Hospital for Special Surgery)
11. PREE (Patient Rated Elbow Evaluation)
12. Andrews-Carson
13. Japanese Orthopaedic Association
14. ASES (American Shoulder and Elbow Surgeons Score)
15. EFA (Elbow Functional Assessment)
16. Ewald
17. LES (Liverpool Elbow Score)

18. PREFQ (Patient-Rated Forearm Evaluation Questionnaire
19. Upper extremity functional scale
20. SECEC score
21. Verhaar
22. Bishop
23. Conway-jobe
24. Dellon
25. Levine
26. Radin and Riseborough
27. Timmerman and Andrews
28. Cassebaum
29. Figgie
30. Jupiter
31. KJOC (Keralan-Jobe Orthopaedic Clinic)
32. PRWE (Patient Rated Wrist Evaluation)
33. Tennis elbow functional scale
34. Wilson and Krout score
35. Constant
36. ESAS (Elbow Self Assessment Score)
37. Flynn

38. Grundberg and Dobson

39. McGowan

40. Michigan hand questionairre

41. PRUNE (Patient Rated Ulnar Nerve Evaluation)

42. Smith and Cooney

43. Tinvon's

44. Total elbow scoring system

45. Aitken-Rorabeck

46. Amadio

47. American Rheumatism Association

48. Broberg and Morrey

49. Cauchoix and Deburge

50. Chinease medical society hand surgery standard evaluation

51. Functional elbow score

52. Gabel and Amadio

53. Inglis and Pellicci

54. Kellgren and Lawrence

55. Khalfayan

56. Larsen

57. Leipzig

58. Modified Andrews elbow scoring system

59. Modified elbow rating system

60. Musculoskeletal Functional Assessment

61. Nestor

62. Novak

63. Pain-free Functional Index

64. Patient specific functional scale

65. PEM (Patient Evaluation Measure)

66. Pritchard

67. Sane

68. Single assessment numerical evaluation score

69. Steinberg

70. Svenlov and Adolfson

71. Wesley

72. Yasutake

PROSPERO registration

Document inserted

Evaluation of clinical rating systems in lateral epicondylar tendinopathy: a systematic review and standardised comparison of available evidence

Jonathan Evans, Ian Porter, Jaheeda Gangannaperelli, Vicky Goodwin, Nicola Fine, Christopher Smith, Jose Valderas

Citation

Jonathan Evans, Ian Porter, Jaheeda Gangannaperelli, Vicky Goodwin, Nicola Fine, Christopher Smith, Jose Valderas. Evaluation of clinical rating systems in lateral epicondylar tendinopathy: a systematic review and standardised comparison of available evidence. PROSPERO 2016 CRD42016037317 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016037317

Review question

This systematic review aims to identify clinical rating systems in lateral epicondylar tendinopathy(tennis elbow) and to evaluate the evidence supporting their psychometric properties, using a systematic and standardised comparison of available evidence.

Searches

Databases will be searched from inception.
The searches will be conducted in: MEDLINE (Ovid MEDLINE, 1948 to present & Ovid MEDLINE In-Process & Non-indexed Citations) accessed through OvidSP, Embase (Embase 1974 to present) accessed through OvidSP and CINHAL (CINHAL 1981 to present) accessed through EBSCO host.
In addition, the Cochrane Central Register of Controlled Trials (CENTRAL) will be searched, and theses will be sought via ProQuest and the Kings Fund Library Database.
The search strategy will be adapted for each database through the modification of thesaurus terms, wildcards and truncation. The search strategy will use thesaurus and free text items in a protocol designed to capture anatomical site and outcome measure domains. Terms will be adapted to the specific requirements of the database.
The anatomical site thesaurus and free text terms will be derived and cross checked with systematic reviews protocols of elbow related pathology.
Backward and forward searches will be conducted on all documents identified as relevant through Scopus (Elsevier).

Search strategy

http://medicine.exeter.ac.uk/research/healthserv/healthservicesandpolicy/projects/optimisinginterventionaltreatmentoftenniselbow/elbowoutcomemeasures/#d.en.504281

Types of study to be included

No study design restrictions.

Condition or domain being studied

Functional measurement of elbow function in adults suffering from lateral epicondylar tendinopathy
We are seeking to improve the knowledge base surrounding choice of clinical rating systems in lateral epicondylar tendinopathy research and clinical practice. We will systematically identify the available instruments and assess the utility of each instrument using a standardised evaluation.

Participants/population

Adults with lateral epicondylar tendinopathy, whose condition has been assessed using a clinical rating system.

Intervention(s), exposure(s)

Inclusion:
Articles will be eligible for inclusion if they:
- Contain information on the development process, the metric properties (reliability, validity, responsiveness to change and interpretability) or administration issues of physician or patient-led clinical rating systems for the assessment of lateral epicondylar tendinopathy;
- Or if they report on studies in which the instruments have been applied to the evaluation of outcomes.
Exclusion:
Articles will be excluded if they:
- Use generic patient-reported outcome measures;
- Use disease specific outcome measures other than elbow-specific measures;
- Lack information regarding the development process, metric properties (development, validity, reliability, responsiveness) or administrative issues;
- Are not in the English language.

Comparator(s)/control

Not applicable.

Context

The purpose of this review is to identify and systematically analyse all available clinical rating systems used in the assessment of outcomes in lateral epicondylar tendinopathy.
Clinical rating systems assess numerous domains of a disease process, they aspire to yield a summarised value that is supposed to correspond to the functional status and wellbeing experienced by the patient. They can be physician-led or patient-led, and may use combinations of questionnaires and clinical examination. They have long been used for research purposes and the number of instruments available in orthopaedics has increased substantially.
The choice of a condition specific outcome measure, for research or clinical purposes, remains very challenging. Current standards for the development and validation of such measures now allow comparison between ratings systems, however, limited systematic evidence, which gives a clear quantifiable comparison, exists in contemporary literature. The evidence for lateral epicondylar tendinopathy outcome measurement choice is limited, though numerous outcome tools have been conceived.

Primary outcome(s)

A systematic and standardised comparison of clinical rating systems in lateral epicondylar tendinopathy.

Secondary outcome(s)

None.

Data extraction (selection and coding)

Based on the above inclusion/exclusion criteria, two reviewers will independently review titles, abstracts and full text articles in a three-step process.
Titles will be included if they are topic related, for sensitivity any discrepancy between reviewers will result in the title progressing to the abstract stage. Abstracts will be reviewed based on the outlined inclusion/exclusion criteria. In the event of discrepancies, this will be resolved by discussion between reviewers, with a third reviewer if required. Full text review will follow the same process with third person arbitration if necessary.

Risk of bias (quality) assessment

The risk of bias will be minimised through the use of a standardised measurement tool - EMPRO (evaluating the measurement of patient-reported outcomes).

Strategy for data synthesis

Full text data synthesis will utilise the EMPRO (evaluating the measurement of patient-reported outcomes) tool. This is a valid and reliable tool that has previously been employed in generic and disease specific

outcome assessments. It assesses the design quality of the development process, how well the measurement performs in terms of metric properties, assessment of the administrative burden and quality of cross-cultural and linguistic comparisons. Each lateral epicondylar tendinopathy-specific outcome measure will be assigned to two reviewers. The output of the evaluation yields a linear scale from 1 (worst) to 100 (best).

Analysis of subgroups or subsets
None planned.

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Organisational affiliation of the review
University of Exeter - Institute of Health
http://medicine.exeter.ac.uk/research/healthserv/healthservicesandpolicy/projects/optimisinginterventionaltreatmentoftenniselbow/elbowoutcomemeasures/#d.en.504281

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Dr Ian Porter.
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Anticipated or actual start date
01 April 2016

Anticipated completion date
01 December 2016

Funding sources/sponsors
None

Conflicts of interest
None known

Language
English

Country
England

Stage of review
Review_Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Adult; Diagnostic Self Evaluation; Elbow; Elbow Joint; Humans; Patient Outcome Assessment; Reference Standards; Self Report

Date of registration in PROSPERO
20 April 2016

Date of publication of this version
09 February 2017

Revision note for this version
Progress update.

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note
Progress update.

Versions
20 April 2016
05 July 2016
09 February 2017

PRISMA check list for the study - Assessing patient-centered outcomes in lateral elbow tendinopathy: a systematic review and standardized comparison of clinical rating systems

Please see inserted document

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	86
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	86-87
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	88-89
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	89
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	89
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	89
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	89+71
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	89-90
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	90-93

• Data items	• 11	• List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	• 91-93
• Risk of bias in individual studies	• 12	• Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	• N/A
• Summary measures	• 13	• State the principal summary measures (e.g., risk ratio, difference in means).	• 91-93
• Synthesis of results	• 14	• Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	• 93

• Section/topic	• #	• Checklist item	• Reported on page #
• Risk of bias across studies	• 15	• Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	• N/A
• Additional analyses	• 16	• Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	• 93
• **RESULTS**			•
• Study selection	• 17	• Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	• 94-95
• Study characteristics	• 18	• For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	• 96-98
• Risk of bias within studies	• 19	• Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	• N/A
• Results of individual studies	• 20	• For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	• 96-98

• Synthesis of results	• 21	• Present results of each meta-analysis done, including confidence intervals and measures of consistency.	• N/A
• Risk of bias across studies	• 22	• Present results of any assessment of risk of bias across studies (see Item 15).	• N/A
• Additional analysis	• 23	• Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	• 99-101
• **DISCUSSION**			•
• Summary of evidence	• 24	• Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	• 102
• Limitations	• 25	• Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	• 105
• Conclusions	• 26	• Provide a general interpretation of the results in the context of other evidence, and implications for future research.	• 104-109
• **FUNDING**			•
• Funding	• 27	• Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	• N/A

•

- *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Documents included in the EMPRO

List of Included manuscripts identified and used in standardised evaluation

Instrument	Manuscript identified as reporting development or metric properties	Manuscripts identified as reporting cross-cultural adaptation in LET population	Manuscript identified as reporting instrument use (Internationally)	Manuscript identified as reporting instrument use (English speaking population)
A & C	[1]		[2] [3]	[2] [3]
ASES-e	[4] [5] [6]		[7] [8] [9] [10] [11]	[12] [10] [11] [7] [8]
DASH	[13] [14] [15] [16] [17] [18] [19] [20] [21] [6] [22] [23] [24] [25] [26] [27]	[28] [29] [30] [31] [32] [33] [34]	[35] [36] [37] [38] [39] [40] [41] [42] [43] [44] [45] [46] [47] [48] [49] [50] [51] [52] [53] [54] [55] [56] [57] [58] [59] [60] [61] [62] [63] [64] [65] [66] [67] [68] [69] [70] [71] [72] [73] [74] [75] [76] [77] [78] [79] [80] [81] [82] [83] [84] [85] [86] [87] [88] [89] [70] [90] [91] [92] [93] [94]	[35] [36] [37] [39] [41] [42] [43] [45] [46] [52] [54] [55] [59] [60] [61] [66] [68] [73] [74] [78] [79] [89] [38]
HSS	[95] [96] [27]		[97]	[97]
LES	[24]		[98]	
MEPS	[99] [4] [13] [15] [16] [27]	[100]	[101] [102] [103] [7] [104] [105] [106] [107] [108] [90] [93] [109] [110] [97] [111] [112] [113] [114] [115] [2] [71] [94]	[101] [7] [104] [106] [97] [2] [66] [113] [10]
MORREY	[116] [27]		[117] [118] [119] [94]	
Nirschl	[120] [9]		[121] [122] [8] [123] [124] [125] [126] [127] [128] [9] [129] [110] [130] [131] [132] [92]	[125] [126] [128] [133] [8] [134] [12]
OES	[13] [14] [15] [16] [135]	[136] [137] [138] [139] [140] [141]	[142] [143] [71] [144] [78]	[61] [78]

PRTEE	[145] [22] [146] [147] [23] [148] [149]	[150] [151] [152] [153] [32] [33] [34] [154] [155]	[10] [89] [156] [157] [158] [159] [160] [161] [162] [163] [164] [165] [166] [167] [168] [169] [170] [171] [172] [173] [174] [175] [176] [177] [178] [179] [180] [181] [182] [183] [184] [181] [185] [186] [187] [188] [189] [158] [190] [10] [49] [59] [93] [191] [192] [193] [194] [195] [196] [82] [131] [197]	[89] [190] [156] [157] [158] [198] [158] [199] [200] [167] [186] [171] [173] [175] [188] [179] [185] [192] [10] [59] [43]
QDASH	[201] [202] [21] [203] [204] [26] [205]	[150] [137] [30]	[129] [111] [206] [207] [208] [209] [113] [210] [211] [212] [213] [214] [215] [216] [217] [218] [219] [132]	[214] [209] [113] [212] [217]
R & M	[220] [23]	[153] [32]	[221] [222] [223] [224] [225] [119] [226] [224] [227] [228] [229] [230] [130] [211] [231] [197]	[225] [230]
TEFS	[232]		[233] [234]	
ULFI	[235]		[236] [115] [237] [238] [212]	[237] [214] [212]
Verhaar	[239]		[240] [241] [242] [243] [244] [9]	[12]

1. Andrews JR, St Pierre RK, Carson Jr WG. Arthroscopy of the elbow. Clinics in sports medicine. 1986;5(4):653-62.
2. Dzugan SS, Savoie FH, 3rd, Field LD, O'Brien MJ, You Z. Acute radial ulno-humeral ligament injury in patients with chronic lateral epicondylitis: an observational report. J Shoulder Elbow Surg. 2012;21(12):1651-5.
3. Szabo SJ, Savoie FH, Field LD, Ramsey JR, Hosemann CD. Tendinosis of the extensor carpi radialis brevis: an evaluation of three methods of operative treatment. Journal of shoulder and elbow surgery. 2006;15(6):721-7.
4. Cusick MC, Bonnaig NS, Azar FM, Mauck BM, Smith RA, Throckmorton TW. Accuracy and reliability of the Mayo Elbow Performance Score. J Hand Surg Am. 2014;39(6):1146-50 DOI: 10.1016/j.jhsa.2014.01.041.
5. King GJ, Richards RR, Zuckerman JD, Blasier R, Dillman C, Friedman RJ, et al. A standardized method for assessment of elbow function. Research Committee, American Shoulder and Elbow Surgeons. Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons [et al]. 1999;8(4):351-4.
6. MacDermid JC. Outcome evaluation in patients with elbow pathology: issues in instrument development and evaluation. Journal of Hand Therapy. 2001;14(2):105-14.
7. Garg R, Adamson GJ, Dawson PA, Shankwiler JA, Pink MM. A prospective randomized study comparing a forearm strap brace versus a wrist splint for the treatment of lateral epicondylitis. J Shoulder Elbow Surg. 2010;19(4):508-12 DOI: 10.1016/j.jse.2009.12.015.

8. Schipper ON, Dunn JH, Ochiai DH, Donovan JS, Nirschl RP. Nirschl surgical technique for concomitant lateral and medial elbow tendinosis: a retrospective review of 53 elbows with a mean follow-up of 11.7 years. Am J Sports Med. 2011;39(5):972-6 DOI: 10.1177/0363546510390452.
9. Dunn JH, Kim JJ, Davis L, Nirschl RP. Ten-to 14-year follow-up of the Nirschl surgical technique for lateral epicondylitis. The American journal of sports medicine. 2008;36(2):261-6.
10. Grewal R, MacDermid JC, Shah P, King GJ. Functional outcome of arthroscopic extensor carpi radialis brevis tendon release in chronic lateral epicondylitis. J Hand Surg Am. 2009;34(5):849-57.
11. Hechtman KS, Uribe JW, Botto-vanDemden A, Kiebzak GM. Platelet-rich plasma injection reduces pain in patients with recalcitrant epicondylitis. Orthopedics. 2011;34(2):92 DOI: 10.3928/01477447-20101221-05.
12. Dunn JH, Kim JJ, Davis L, Nirschl RP. Ten- to 14-year follow-up of the Nirschl surgical technique for lateral epicondylitis. Am J Sports Med. 2008;36(2):261-6 DOI: 10.1177/0363546507308932.
13. Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, et al. The development and validation of a patient-reported questionnaire to assess outcomes of elbow surgery. J Bone Joint Surg Br. 2008;90(4):466-73.
14. Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, et al. Comparative responsiveness and minimal change for the Oxford Elbow Score following surgery. Qual Life Res. 2008;17(10):1257-67 DOI: 10.1007/s11136-008-9409-3.
15. Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, et al. Factors associated with satisfaction in patients undergoing elbow surgery: a prospective study. J Shoulder Elbow Surg. 2010;19(5):635-44 DOI: 10.1016/j.jse.2010.02.003.
16. Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, et al. Specificity and responsiveness of patient-reported and clinician-rated outcome measures in the context of elbow surgery, comparing patients with and without rheumatoid arthritis. Orthop Traumatol-Sur. 2012;98(6):652-8 DOI: 10.1016/j.otsr.2012.05.011.
17. Gummesson C, Atroshi I, Ekdahl C. The disabilities of the arm, shoulder and hand (DASH) outcome questionnaire: longitudinal construct validity and measuring self-rated health change after surgery. BMC Musculoskelet Disord. 2003;4(1):11 DOI: 10.1186/1471-2474-4-11.
18. Hudak PL, Amadio PC, Bombardier C, Beaton D, Cole D, Davis A, et al. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder, and hand). American journal of industrial medicine. 1996;29(6):602-8.
19. Hunsaker FG, Cioffi DA, Amadio PC, Wright JG, Caughlin B. The American academy of orthopaedic surgeons outcomes instruments. J Bone Joint Surg Am. 2002;84(2):208-15.
20. Janssen S, De Smet L. Responsiveness of the DASH questionnaire for surgically treated tennis elbow. Acta Chir Belg. 2008;108(5):583-5.
21. Kachooei AR, Moradi A, Janssen SJ, Ring D. The influence of dominant limb involvement on DASH and QuickDASH. Hand (N Y). 2015;10(3):512-5 DOI: 10.1007/s11552-014-9734-7.
22. Newcomer KL, Martinez-Silvestrini JA, Schaefer MP, Gay RE, Arendt KW. Sensitivity of the Patient-rated Forearm Evaluation Questionnaire in lateral epicondylitis. Journal of Hand Therapy. 2005;18(4):400-73 8p.
23. Rompe JD, Overend TJ, MacDermid JC. Validation of the Patient-rated Tennis Elbow Evaluation Questionnaire. Journal of hand therapy : official journal of the American Society of Hand Therapists. 2007;20(1):3-10; quiz 1 DOI: 10.1197/j.jht.2006.10.003.
24. Sathyamoorthy P, Kemp G, Rawal A, Rayner V, Frostick S. Development and validation of an elbow score. Rheumatology. 2004;43(11):1434-40.

25. Schmitt JS, Di Fabio RP. Reliable change and minimum important difference (MID) proportions facilitated group responsiveness comparisons using individual threshold criteria. J Clin Epidemiol. 2004;57(10):1008-18.
26. Sorensen AA, Howard D, Tan WH, Ketchersid J, Calfee RP. Minimal clinically important differences of 3 patient-rated outcomes instruments. The Journal of hand surgery. 2013;38(4):641-9.
27. Turchin DC, Beaton DE, Richards RR. Validity of observer-based aggregate scoring systems as descriptors of elbow pain, function, and disability. The Journal of bone and joint surgery American volume. 1998;80(2):154-62.
28. Atroshi I, Gummesson C, Andersson B, Dahlgren E, Johansson A. The disabilities of the arm, shoulder and hand (DASH) outcome questionnaire: reliability and validity of the Swedish version evaluated in 176 patients. Acta Orthopaedica Scandinavica. 2000;71(6):613-8.
29. Franchignoni F, Giordano A, Sartorio F, Vercelli S, Pascariello B, Ferriero G. Suggestions for refinement of the Disabilities of the Arm, Shoulder and Hand Outcome Measure (DASH): a factor analysis and Rasch validation study. Arch Phys Med Rehabil. 2010;91(9):1370-7 DOI: 10.1016/j.apmr.2010.06.022.
30. Franchignoni F, Vercelli S, Giordano A, Sartorio F, Bravini E, Ferriero G. Minimal clinically important difference of the disabilities of the arm, shoulder and hand outcome measure (DASH) and its shortened version (QuickDASH). journal of orthopaedic & sports physical therapy. 2014;44(1):30-9.
31. Mousavi SJ, Parnianpour M, Abedi M, Askary-Ashtiani A, Karimi A, Khorsandi A, et al. Cultural adaptation and validation of the Persian version of the Disabilities of the Arm, Shoulder and Hand (DASH) outcome measure. Clin Rehabil. 2008;22(8):749-57 DOI: 10.1177/0269215508085821.
32. Nilsson P, Baigi A, Marklund B, Mansson J. Cross-cultural adaptation and determination of the reliability and validity of PRTEE-S (Patientskattad Utvardering av Tennisarmbage), a questionnaire for patients with lateral epicondylalgia, in a Swedish population. BMC Musculoskelet Disord. 2008;9:79 DOI: 10.1186/1471-2474-9-79.
33. Stasinopoulos D, Papadopoulos C, Antoniadou M, Nardi L. Greek adaptation and validation of the Patient-Rated Tennis Elbow Evaluation (PRTEE). J Hand Ther. 2015;28(3):286-90; quiz 91 DOI: 10.1016/j.jht.2014.12.005.
34. van Ark M, Zwerver J, Diercks RL, van den Akker-Scheek I. Cross-cultural adaptation and reliability and validity of the Dutch Patient-Rated Tennis Elbow Evaluation (PRTEE-D). BMC Musculoskelet Disord. 2014;15:270 DOI: 10.1186/1471-2474-15-270.
35. Davidson JH, Vandervoort A, Lessard L, Miller L. The effect of acupuncture versus ultrasound on pain level, grip strength and disability in individuals with lateral epicondylitis: a pilot study. Physiotherapy Canada. 2001;53(3):195-211 9p.
36. Melikyan EY, Shahin E, Miles J, Bainbridge LC. Extracorporeal shock-wave treatment for tennis elbow: a randomised double-blind study. Journal of Bone & Joint Surgery, British Volume. 2003;85B(6):852-5 4p.
37. Dunkow PD, Jatti M, Muddu BN. A comparison of open and percutaneous techniques in the surgical treatment of tennis elbow. Journal of Bone & Joint Surgery, British Volume. 2004;86B(5):701-4 4p.
38. Waugh EJ, Jaglal SB, Davis AM. Computer use associated with poor long-term prognosis of conservatively managed lateral epicondylalgia. The Journal of orthopaedic and sports physical therapy. 2004;34(12):770-80.
39. Waugh EJ, Jaglal SB, Davis AM, Tomlinson G, Verrier MC. Factors associated with prognosis of lateral epicondylitis after 8 weeks of physical therapy. Arch Phys Med Rehab. 2004;85(2):308-18.
40. Spacca G, Necozione S, Cacchio A. Radial shock wave therapy for lateral epicondylitis: a prospective randomised controlled single-blind study. Europa medicophysica. 2005;41(1):17-25.

41. Tasto JP, Cummings J, Medlock V, Hardesty R, Amiel D. Microtenotomy using a radiofrequency probe to treat lateral epicondylitis. Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association. 2005;21(7):851-60.
42. Thornton SJ, Rogers JR, Prickett WD, Dunn WR, Allen AA, Hannafin JA. Treatment of recalcitrant lateral epicondylitis with suture anchor repair. The American journal of sports medicine. 2005;33(10):1558-64.
43. Alizadehkhaiyat O, Fisher AC, Kemp GJ, Frostick SP. Pain, functional disability, and psychologic status in tennis elbow. Clin J Pain. 2007;0(6):482-9 DOI: 10.1097/AJP.0b013e31805f70fa.
44. Lam LK, Cheing GL. Effects of 904-nm low-level laser therapy in the management of lateral epicondylitis: a randomized controlled trial. Photomed Laser Surg. 2007;25(2):65-71 DOI: 10.1089/pho.2006.2047.
45. Brockenbrough G. No significant differences seen with steroids vs. placebo for lateral elbow pain. Orthopedics Today. 2008;28(5):63-4 2p.
46. Lindenhovius A, Henket M, Gilligan BP, Lozano-Calderon S, Jupiter JB, Ring D. Injection of dexamethasone versus placebo for lateral elbow pain: a prospective, double-blind, randomized clinical trial. J Hand Surg Am. 2008;33(6):909-19 DOI: 10.1016/j.jhsa.2008.02.004.
47. Oskarsson E, Piehl Aulin K, Gustafsson BE, Pettersson K. Improved intramuscular blood flow and normalized metabolism in lateral epicondylitis after botulinum toxin treatment. Scand J Med Sci Sports. 2009;19(3):323-8 DOI: 10.1111/j.1600-0838.2008.00804.x.
48. Akin C, Oken O, Koseoglu BF. Short-Term Effectiveness of Ultrasound Treatment in Patients with Lateral Epicondylitis: Randomized, Single-Blind, Placebo-Controlled, Prospective Study. Turk J Rheumatol. 2010;25(2):50-5 DOI: 10.5152/tjr.2010.01.
49. Emanet SK, Altan LI, Yurtkuran M. Investigation of the effect of GaAs laser therapy on lateral epicondylitis. Photomed Laser Surg. 2010;28(3):397-403 DOI: 10.1089/pho.2009.2555.
50. Gong HS, Chung MS, Kang ES, Oh JH, Lee YH, Baek GH. Musculofascial lengthening for the treatment of patients with medial epicondylitis and coexistent ulnar neuropathy. J Bone Joint Surg Br. 2010;92(6):823-7 DOI: 10.1302/0301-620X.92B6.23341.
51. Peerbooms JC, Sluimer J, Bruijn DJ, Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. Am J Sports Med. 2010;38(2):255-62.
52. Tyler TF, Thomas GC, Nicholas SJ, McHugh MP. Addition of isolated wrist extensor eccentric exercise to standard treatment for chronic lateral epicondylosis: a prospective randomized trial. J Shoulder Elbow Surg. 2010;19(6):917-22.
53. Backer M, Ludtke R, Afra D, Cesur O, Langhorst J, Fink M, et al. Effectiveness of leech therapy in chronic lateral epicondylitis: a randomized controlled trial. Clin J Pain. 2011;27(5):442-7 DOI: 10.1097/AJP.0b013e318208c95b.
54. Bellapianta J, Swartz F, Lisella J, Czajka J, Neff R, Uhl R. Randomized prospective evaluation of injection techniques for the treatment of lateral epicondylitis. Orthopedics. 2011;34(11):e708-12 DOI: 10.3928/01477447-20110922-13.
55. Carayannopoulos A, Borg-Stein J, Sokolof J, Meleger A, Rosenberg D. Prolotherapy versus corticosteroid injections for the treatment of lateral epicondylosis: a randomized controlled trial. PM R. 2011;3(8):706-15 DOI: 10.1016/j.pmrj.2011.05.011.
56. Gosens T, Peerbooms JC, van Laar W, den Oudsten BL. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. Am J Sports Med. 2011;39(6):1200-8 DOI: 10.1177/0363546510397173.

57. Othman AM. Arthroscopic versus percutaneous release of common extensor origin for treatment of chronic tennis elbow. Arch Orthop Trauma Surg. 2011;131(3):383-8 DOI: 10.1007/s00402-011-1260-2.
58. Peterson M, Butler S, Eriksson M, Svardsudd K. A randomized controlled trial of exercise versus wait-list in chronic tennis elbow (lateral epicondylosis). Ups J Med Sci. 2011;116(4):269-79.
59. Wolf JM, Ozer K, Scott F, Gordon MJ, Williams AE. Comparison of autologous blood, corticosteroid, and saline injection in the treatment of lateral epicondylitis: a prospective, randomized, controlled multicenter study. J Hand Surg Am. 2011;36(8):1269-72.
60. Agostinucci J, McLinden J, Cherry E. The effect of cryotherapy and exercise on lateral epicondylitis: a controlled randomised study. International Journal of Therapy & Rehabilitation. 2012;19(11):641-50 10p.
61. Nazar M, Lipscombe S, Morapudi S, Tuvo G, Kebrle R, Marlow W, et al. Percutaneous tennis elbow release under local anaesthesia. Open Orthop J. 2012;6:129-32.
62. Okcu G, Erkan S, Senturk M, Ozalp RT, Yercan HS. Evaluation of injection techniques in the treatment of lateral epicondylitis: a prospective randomized clinical trial. Acta Orthop Traumatol Turc. 2012;46(1):26-9.
63. Küçükşen S, Yilmaz H, Sallı A, Uğurlu H. Muscle Energy Technique Versus Corticosteroid Injection for Management of Chronic Lateral Epicondylitis: Randomized Controlled Trial With 1-Year Follow-up. 2013;94(11):2068-74.
64. Martin JI, Merino J, Atilano L, Areizaga LM, Gomez-Fernandez MC, Burgos-Alonso N, et al. Platelet-rich plasma (PRP) in chronic epicondylitis: study protocol for a randomized controlled trial. Trials. 2013;14:410 DOI: 10.1186/1745-6215-14-410.
65. Rhyou IH, Kim KW. Is posterior synovial plica excision necessary for refractory lateral epicondylitis of the elbow? Clinical orthopaedics and related research. 2013;471(1):284-90.
66. Shahid M, Wu F, Deshmukh SC. Operative treatment improves patient function in recalcitrant medial epicondylitis. Ann R Coll Surg Engl. 2013;95(7):486-8 DOI: 10.1308/003588413x13629960048479.
67. Kwon BC, Kwon YS, Bae KJ. The Fascial Elevation and Tendon Origin Resection Technique for the Treatment of Chronic Recalcitrant Medial Epicondylitis. Am J Sports Med. 2014;42(7):1731-7 DOI: 10.1177/0363546514530664.
68. Tyler TF, Nicholas SJ, Schmitt BM, Mullaney M, Hogan DE. Clinical outcomes of the addition of eccentrics for rehabilitation of previously failed treatments of golfers elbow. Int J Sports Phys Ther. 2014;9(3):365-70.
69. Valera-Garrido F, Minaya-Munoz F, Medina-Mirapeix F. Ultrasound-guided percutaneous needle electrolysis in chronic lateral epicondylitis: short-term and long-term results. Acupunct Med. 2014;32(6):446-54 DOI: 10.1136/acupmed-2014-010619.
70. Wada T, Moriya T, Iba K, Ozasa Y, Sonoda T, Aoki M, et al. Functional outcomes after arthroscopic treatment of lateral epicondylitis. J Orthop Sci. 2009;14(2):167-74.
71. Gautam VK, Verma S, Batra S, Bhatnagar N, Arora S, Verma S, et al. Platelet-rich plasma versus corticosteroid injection for recalcitrant lateral epicondylitis: clinical and ultrasonographic evaluation. Journal of Orthopaedic Surgery (10225536). 2015;23(1):1-5 p.
72. Lebiedzinski R, Synder M, Buchcic P, Polguj M, Grzegorzewski A, Sibinski M. A randomized study of autologous conditioned plasma and steroid injections in the treatment of lateral epicondylitis. International Orthopaedics. 2015;39(11):2199-203 DOI: 10.1007/s00264-015-2861-0.

73. Ruch DS, Orr SB, Richard MJ, Leversedge FJ, Mithani SK, Laino DK. A comparison of debridement with and without anconeus muscle flap for treatment of refractory lateral epicondylitis. Journal of Shoulder and Elbow Surgery. 2015;24(2):236-41 DOI: 10.1016/j.jse.2014.09.035.
74. Sevier TL, Stegink-Jansen CW. Astym treatment vs. eccentric exercise for lateral elbow tendinopathy: a randomized controlled clinical trial. PeerJ. 2015;3:e967.
75. Tetschke E, Rudolf M, Lohmann CH, Starke C. Autologous proliferative therapies in recalcitrant lateral epicondylitis. Am J Phys Med Rehabil. 2015;94(9):696-706 DOI: 10.1097/phm.0000000000000234.
76. Yadav R, Kothari SY, Borah D. Comparison of Local Injection of Platelet Rich Plasma and Corticosteroids in the Treatment of Lateral Epicondylitis of Humerus. J Clin Diagn Res. 2015;9(7):RC05-7.
77. Akkurt E, Kucuksen S, Yilmaz H, Parlak S, Salli A, Karaca G. Long term effects of high intensity laser therapy in lateral epicondylitis patients. Lasers Med Sci. 2016;31(2):249-53 DOI: 10.1007/s10103-015-1841-3.
78. Grawe BM, Fabricant PD, Chin CS, Allen AA, DePalma BJ, Dines DM, et al. Clinical Outcomes After Suture Anchor Repair of Recalcitrant Medial Epicondylitis. Orthopedics. 2016;39(1):e104-7 DOI: 10.3928/01477447-20151222-09.
79. Seng C, Mohan PC, Koh SB, Howe TS, Lim YG, Lee BP, et al. Ultrasonic Percutaneous Tenotomy for Recalcitrant Lateral Elbow Tendinopathy: Sustainability and Sonographic Progression at 3 Years. Am J Sports Med. 2016;44(2):504-10 DOI: 10.1177/0363546515612758.
80. Liu YS, Gadau M, Zhang GX, Liu H, Wang FC, Zaslawski C, et al. Acupuncture Treatment of Lateral Elbow Pain: A Nonrandomized Pilot Study. Evid Based Complement Alternat Med. 2016;2016:8182071 DOI: https://dx.doi.org/10.1155/2016/8182071.
81. Najafi M, Arazpour M, Aminian G, Curran S, Madani SP, Hutchins SW. Effect of a new hand-forearm splint on grip strength, pain, and function in patients with tennis elbow. Prosthet Orthot Int. 2016;40(3):363-8 DOI: https://dx.doi.org/10.1177/0309364615592694.
82. Palacio EP, Schiavetti RR, Kanematsu M, Ikeda TM, Mizobuchi RR, Galbiatti JA. Effects of platelet-rich plasma on lateral epicondylitis of the elbow: prospective randomized controlled trial. Revista Brasileira de Ortopedia. 2016;51(1):90-5 DOI: https://dx.doi.org/10.1016/j.rboe.2015.03.014.
83. Hsu CY, Lee KH, Huang HC, Chang ZY, Chen HY, Yang TH. Manipulation Therapy Relieved Pain More Rapidly Than Acupuncture among Lateral Epicondylalgia (Tennis Elbow) Patients: A Randomized Controlled Trial with 8-Week Follow-Up. Evid Based Complement Alternat Med. 2016;2016:3079247 DOI: https://dx.doi.org/10.1155/2016/3079247.
84. Nascimento AT, Claudio GK. Arthroscopic surgical treatment of recalcitrant lateral epicondylitis - A series of 47 cases. Revista Brasileira de Ortopedia. 2017;52(1):46-51 DOI: https://dx.doi.org/10.1016/j.rboe.2016.03.008.
85. Schoffl V, Willauschus W, Sauer F, Kupper T, Schoffl I, Lutter C, et al. Autologous Conditioned Plasma Versus Placebo Injection Therapy in Lateral Epicondylitis of the Elbow: A Double Blind, Randomized Study. Sportverletz Sportschaden. 2017;31(1):31-6 DOI: https://dx.doi.org/10.1055/s-0043-101042.
86. Yang TH, Huang YC, Lau YC, Wang LY. Efficacy of Radial Extracorporeal Shock Wave Therapy on Lateral Epicondylosis, and Changes in the Common Extensor Tendon Stiffness with Pretherapy and Posttherapy in Real-Time Sonoelastography: A Randomized Controlled Study. Am J Phys Med Rehabil. 2017;96(2):93-100 DOI: https://dx.doi.org/10.1097/PHM.0000000000000547.
87. Martinez-Cervera FV, Olteanu TE, Gil-Martinez A, Diaz-Pulido B, Ferrer-Pena R. Influence of expectations plus mobilization with movement in patient with lateral epicondylalgia: a pilot randomized controlled trial. Journal of Exercise Rehabilitation. 2017;13(1):101-9 DOI: https://dx.doi.org/10.12965/jer.1732848.424.

88. Shakeri H, Soleimanifar M, Arab AM, Hamneshin Behbahani S. The effects of KinesioTape on the treatment of lateral epicondylitis. J Hand Ther. 2017;27:27 DOI: https://dx.doi.org/10.1016/j.jht.2017.01.001.
89. Martinez-Silvestrini JA, Newcomer KL, Gay RE, Schaefer MP, Kortebein P, Arendt KW. Chronic lateral epicondylitis: comparative effectiveness of a home exercise program including stretching alone versus stretching supplemented with eccentric or concentric strengthening. Journal of Hand Therapy. 2005;18(4):411-73 11p.
90. Sauvage A, Nedellec G, Brulard C, Gaumet G, Mesnil P, Fontaine C, et al. [Arthroscopic treatment of lateral epicondylitis: a prospective study on 14 cases]. Chir Main. 2013;32(2):80-4 DOI: 10.1016/j.main.2013.02.014.
91. Oki G, Iba K, Sasaki K, Yamashita T, Wada T. Time to functional recovery after arthroscopic surgery for tennis elbow. J Shoulder Elbow Surg. 2014;23(10):1527-31 DOI: 10.1016/j.jse.2014.05.010.
92. Han SH, Lee JK, Kim HJ, Lee SH, Kim JW, Kim TS. The result of surgical treatment of medial epicondylitis: analysis with more than a 5-year follow-up. J Shoulder Elbow Surg. 2016;25(10):1704-9 DOI: https://dx.doi.org/10.1016/j.jse.2016.05.010.
93. Babaqi AA, Kotb MM, Said HG, AbdelHamid MM, ElKady HA, ElAssal MA. Short-term evaluation of arthroscopic management of tennis elbow; including resection of radio-capitellar capsular complex. J Orthop. 2014;11(2):82-6 DOI: 10.1016/j.jor.2014.04.003.
94. Jimenez I, Marcos-Garcia A, Muratore-Moreno G, Medina J. [Four surgical tips in the treatment of epicondylitis]. Rev. 2016;60(1):38-43 DOI: https://dx.doi.org/10.1016/j.recot.2015.06.001.
95. Figgie MP, Inglis AE, Mow CS, Figgie HE, 3rd. Total elbow arthroplasty for complete ankylosis of the elbow. J Bone Joint Surg Am. 1989;71(4):513-20.
96. Inglis AE, Pellicci PM. Total elbow replacement. The Journal of Bone & Joint Surgery. 1980;62(8):1252-8.
97. Coleman B, Quinlan JF, Matheson JA. Surgical treatment for lateral epicondylitis: a long-term follow-up of results. J Shoulder Elbow Surg. 2010;19(3):363-7 DOI: 10.1016/j.jse.2009.09.008.
98. Thanasas C, Papadimitriou G, Charalambidis C, Paraskevopoulos I, Papanikolaou A. Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis: a randomized controlled clinical trial. Am J Sports Med. 2011;39(10):2130-4 DOI: 10.1177/0363546511417113.
99. Morrey B, Adams R. Semiconstrained arthroplasty for the treatment of rheumatoid arthritis of the elbow. J Bone Joint Surg Am. 1992;74(4):479-90.
100. Celik D. Psychometric properties of the Mayo Elbow Performance Score. Rheumatol Int. 2015;35(6):1015-20 DOI: 10.1007/s00296-014-3201-1.
101. Baker CL, Jr., Baker CL, 3rd. Long-term follow-up of arthroscopic treatment of lateral epicondylitis. Am J Sports Med. 2008;36(2):254-60.
102. Moon YL, Jo SH, Song CH, Park G, Lee HJ, Jang SJ. Autologous bone marrow plasma injection after arthroscopic debridement for elbow tendinosis. Ann Acad Med Singapore. 2008;37(7):559-63.
103. Yan H, Cui GQ, Liu YL, Xiao J, Yang YP, Ao YF. [A randomized comparison of open and arthroscopic Nirschl debridement for refractory lateral epicondylitis]. Zhonghua Wai Ke Za Zhi. 2009;47(12):888-91.
104. Lattermann C, Romeo AA, Anbari A, Meininger AK, McCarty LP, Cole BJ, et al. Arthroscopic debridement of the extensor carpi radialis brevis for recalcitrant lateral epicondylitis. J Shoulder Elbow Surg. 2010;19(5):651-6.
105. Kim JW, Chun CH, Shim DM, Kim TK, Kweon SH, Kang HJ, et al. Arthroscopic treatment of lateral epicondylitis: comparison of the outcome of ECRB release with and without decortication. Knee Surg Sports Traumatol Arthrosc. 2011;19(7):1178-83.

106. Seitz WH, Jr., Lall A. Treatment of chronic tennis elbow with radiofrequency coblation and localized arthroscopic synovectomy. Current Orthopaedic Practice. 2012;23(6):621-4 4p.
107. Deng Y, Tang K, Li H, Zhang J, Xie M, Cao H, et al. [Short-term effectiveness of suture anchor after debridement of extensor tendon insertion for recalcitrant lateral epicondylitis]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2013;27(1):1-6.
108. Meknas K, Al Hassoni TN, Odden-Miland A, Castillejo M, Kartus J. Medium-Term Results After Treatment of Recalcitrant Lateral Epicondylitis: A Prospective, Randomized Study Comparing Open Release and Radiofrequency Microtenotomy. Orthop J Sports Med. 2013;1(4):2325967113505433 DOI: 10.1177/2325967113505433.
109. Notarnicola A, Quagliarella L, Sasanelli N, Maccagnano G, Fracella MR, Forcignano MI, et al. Effects of extracorporeal shock wave therapy on functional and strength recovery of handgrip in patients affected by epicondylitis. Ultrasound Med Biol. 2014;40(12):2830-40 DOI: 10.1016/j.ultrasmedbio.2014.07.010.
110. Behera P, Dhillon M, Aggarwal S, Marwaha N, Prakash M. Leukocyte-poor platelet-rich plasma versus bupivacaine for recalcitrant lateral epicondylar tendinopathy. J Orthop Surg (Hong Kong). 2015;23(1):6-10.
111. Lin CL, Lee JS, Su WR, Kuo LC, Tai TW, Jou IM. Clinical and ultrasonographic results of ultrasonographically guided percutaneous radiofrequency lesioning in the treatment of recalcitrant lateral epicondylitis. Am J Sports Med. 2011;39(11):2429-35 DOI: 10.1177/0363546511417096.
112. Shahid M, Wu F, Deshmukh SC. Operative treatment improves patient function in recalcitrant medial epicondylitis. The Annals of The Royal College of Surgeons of England. 2013;95(7):486-8.
113. Barnes DE, Beckley JM, Smith J. Percutaneous ultrasonic tenotomy for chronic elbow tendinosis: a prospective study. J Shoulder Elbow Surg. 2015;24(1):67-73 DOI: 10.1016/j.jse.2014.07.017.
114. Ertem K, Ergen E, Yologlu S. Functional outcomes of arthroscopic treatment of lateral epicondylitis. Acta Orthop Traumatol Turc. 2015;49(5):471-7 DOI: 10.3944/aott.2015.15.0048.
115. Yoon JP, Chung SW, Yi JH, Lee BJ, Jeon IH, Jeong WJ, et al. Prognostic Factors of Arthroscopic Extensor Carpi Radialis Brevis Release for Lateral Epicondylitis. Arthroscopy. 2015;31(7):1232-7 DOI: 10.1016/j.arthro.2015.02.006.
116. Broberg MA, Morrey B. Results of delayed excision of the radial head after fracture. J Bone Joint Surg Am. 1986;68(5):669-74.
117. Seegenschmiedt MH, Keilholz L, Martus P, Kuhr M, Wichmann G, Sauer R. [Epicondylopathia humeri. The indication for, technic and clinical results of radiotherapy]. Epicondylopathia humeri Indikation, Technik, klinische Ergebnisse der Radiotherapie. 1997;173(4):208-18.
118. Seegenschmiedt MH, Keilholz L. Epicondylopathia humeri (EPH) and peritendinitis humeroscapularis (PHS): evaluation of radiation therapy long-term results and literature review. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 1998;47(1):17-28.
119. Rubenthaler F, Wiese M, Senge A, Keller L, Wittenberg RH. Long-term follow-up of open and endoscopic Hohmann procedures for lateral epicondylitis. Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association. 2005;21(6):684-90.
120. Nirschl R. Elbow tendinosis/tennis elbow. Clinics in sports medicine. 1992;11(4):851-70.
121. Baskurt F, Ozcan A, Algun C. Comparison of effects of phonophoresis and iontophoresis of naproxen in the treatment of lateral epicondylitis. Clinical rehabilitation. 2003;17(1):96-100.

122. Connell DA, Ali KE, Ahmad M, Lambert S, Corbett S, Curtis M. Ultrasound-guided autologous blood injection for tennis elbow. Skeletal radiology. 2006;35(6):371-7.
123. Weber T, Kabelka B. Noninvasive monopolar capacitive-coupled radiofrequency for the treatment of pain associated with lateral elbow tendinopathies: 1-year follow-up. PM R. 2012;4(3):176-81 DOI: 10.1016/j.pmrj.2011.11.003.
124. Stenhouse G, Sookur P, Watson M. Do blood growth factors offer additional benefit in refractory lateral epicondylitis? A prospective, randomized pilot trial of dry needling as a stand-alone procedure versus dry needling and autologous conditioned plasma. Skeletal radiology. 2013;42(11):1515-20.
125. Organ SW, Nirschl RP, Kraushaar BS, Guidi EJ. Salvage surgery for lateral tennis elbow. The American journal of sports medicine. 1997;25(6):746-50.
126. Edwards SG, Calandruccio JH. Autologous blood injections for refractory lateral epicondylitis. The Journal of hand surgery. 2003;28(2):272-8.
127. Jindal N, Gaury Y, Banshiwal RC, Lamoria R, Bachhal V. Comparison of short term results of single injection of autologous blood and steroid injection in tennis elbow: a prospective study. J Orthop Surg Res. 2013;8(1):10.
128. Nirschl RP, Rodin DM, Ochiai DH, Maartmann-Moe C, Group D-A-S. Iontophoretic administration of dexamethasone sodium phosphate for acute epicondylitis. A randomized, double-blinded, placebo-controlled study. The American journal of sports medicine. 2003;31(2):189-95.
129. Kazemi M, Azma K, Tavana B, Rezaiee Moghaddam F, Panahi A. Autologous blood versus corticosteroid local injection in the short-term treatment of lateral elbow tendinopathy: a randomized clinical trial of efficacy. Am J Phys Med Rehabil. 2010;89(8):660-7 DOI: 10.1097/PHM.0b013e3181ddcb31.
130. Cho BK, Kim YM, Kim DS, Choi ES, Shon HC, Park KJ, et al. Mini-open muscle resection procedure under local anesthesia for lateral and medial epicondylitis. Clin Orthop Surg. 2009;1(3):123-7 DOI: 10.4055/cios.2009.1.3.123.
131. Dilek B, Batmaz I, Sariyildiz MA, Sahin E, Ilter L, Gulbahar S, et al. Kinesio taping in patients with lateral epicondylitis. J Back Musculoskeletal Rehabil. 2016;29(4):853-8 DOI: https://dx.doi.org/10.3233/BMR-160701.
132. Soeur L, Desmoineaux P, Devillier A, Pujol N, Beaufils P. Outcomes of arthroscopic lateral epicondylitis release: Should we treat earlier? Orthop Traumatol Surg Res. 2016;102(6):775-80 DOI: https://dx.doi.org/10.1016/j.otsr.2016.05.017.
133. Connell DA, Ali KE, Ahmad M, Lambert S, Corbett S, Curtis M. Ultrasound-guided autologous blood injection for tennis elbow. Skeletal radiology. 2006;35(6):371-7.
134. Stenhouse G, Sookur P, Watson M. Do blood growth factors offer additional benefit in refractory lateral epicondylitis? A prospective, randomized pilot trial of dry needling as a stand-alone procedure versus dry needling and autologous conditioned plasma. Skeletal radiology. 2013;42(11):1515-20.
135. Guyver PM, Cattell AE, Hall MJ, Brinsden MD. Oxford elbow scores in an asymptomatic population. Ann R Coll Surg Engl. 2013;95(6):415-7 DOI: 10.1308/003588413X13629960048352.
136. de Haan J, Schep N, Tuinebreijer W, Patka P, den Hartog D. Rasch analysis of the Dutch version of the Oxford elbow score. Patient Relat Outcome Meas. 2011;2:145-9 DOI: 10.2147/PROM.S22257.
137. de Haan J, Goei H, Schep NW, Tuinebreijer WE, Patka P, den Hartog D. The reliability, validity and responsiveness of the Dutch version of the Oxford elbow score. J Orthop Surg Res. 2011;6:39 DOI: 10.1186/1749-799X-6-39.
138. Ebrahimzadeh MH, Kachooei AR, Vahedi E, Moradi A, Mashayekhi Z, Hallaj-Moghaddam M, et al. Validity and cross-cultural adaptation of the persian version of the oxford elbow score. Int J Rheumatol. 2014;2014:381237 DOI: 10.1155/2014/381237.

139. Plaschke HC, Jørgensen A, Thillemann TM, Brorson S, Olsen BS. Validation of the Danish version of the Oxford elbow score. Danish Medical Journal. 2013;60(10).
140. Marquardt J, Schottker-Koniger T, Schafer A. [Validation of the German version of the Oxford Elbow Score : A cross-sectional study]. Orthopade. 2016;45(8):695-700 DOI: https://dx.doi.org/10.1007/s00132-016-3292-3.
141. Yosmaoglu HB, Dogan D, Sonmezer E. The reliability and validity of the Turkish version of the Oxford Elbow Score. Journal of Orthopaedic Surgery. 2016;11(1):95 DOI: https://dx.doi.org/10.1186/s13018-016-0429-3.
142. Tahririan MA, Moayednia A, Momeni A, Yousefi A, Vahdatpour B. A randomized clinical trial on comparison of corticosteroid injection with or without splinting versus saline injection with or without splinting in patients with lateral epicondylitis. Journal of Research in Medical Sciences. 2014;19(9):813-8.
143. Nazar M, Lipscombe S, Morapudi S, Tuvo G, Kebrle R, Marlow W, et al. Percutaneous tennis elbow release under local anaesthesia. Open Orthop J. 2012;6:129-32.
144. Carulli C, Tonelli F, Innocenti M, Gambardella B, Muncibi F, Innocenti M. Effectiveness of extracorporeal shockwave therapy in three major tendon diseases. J. 2016;17(1):15-20 DOI: https://dx.doi.org/10.1007/s10195-015-0361-z.
145. Chung B, Wiley JP. Validity, responsiveness and reliability of the Patient-Rated Tennis Elbow Evaluation. Hand Therapy. 2010;15(3):62-8 7p DOI: 10.1258/ht.2010.010014.
146. Overend TJ, Wuori-Fearn JL, Kramer JF, MacDermid JC. Reliability of a patient-rated forearm evaluation questionnaire for patients with lateral epicondylitis. Journal of Hand Therapy. 1999;12(1):31-7.
147. Poltawski L, Watson T. Measuring clinically important change with the Patient-rated Tennis Elbow Evaluation. Hand Therapy. 2011;16(3):52-7.
148. Stratford P, Levy DR, Gauldie S, Levy K, Miseferi D. Extensor carpi radialis tendonitis: a validation of selected outcome measures. Physiotherapy Canada. 1987;39(4):250-5 6p.
149. Vincent J, MacDermid JC. Patient-rated tennis elbow evaluation questionnaire. J Physiother. 2014;60(4):240 DOI: 10.1016/j.jphys.2014.08.002.
150. Altan L, Ercan I, Konur S. Reliability and validity of Turkish version of the patient rated tennis elbow evaluation. Rheumatol Int. 2010;30(8):1049-54 DOI: 10.1007/s00296-009-1101-6.
151. Blanchette MA, Normand MC. Cross-cultural adaptation of the patient-rated tennis elbow evaluation to Canadian French. J Hand Ther. 2010;23(3):290-9; quiz 300 DOI: 10.1016/j.jht.2010.01.003.
152. Cacchio A, Necozione S, MacDermid JC, Rompe JD, Maffulli N, di Orio F, et al. Cross-cultural adaptation and measurement properties of the italian version of the Patient-Rated Tennis Elbow Evaluation (PRTEE) questionnaire. Phys Ther. 2012;92(8):1036-45 DOI: 10.2522/ptj.20110398.
153. Leung HB, Yen CH, Tse PYT. Reliability of Hong Kong Chinese version of the Patient-rated Forearm Evaluation Questionnaire for lateral epicondylitis. Hong Kong medical journal = Xianggang yi xue za zhi / Hong Kong Academy of Medicine. 2004;10(3):172-7.
154. Kaux JF, Delvaux F, Schaus J, Demoulin C, Locquet M, Buckinx F, et al. Cross-cultural adaptation and validation of the Patient-Rated Tennis Elbow Evaluation Questionnaire on lateral elbow tendinopathy for French-speaking patients. J Hand Ther. 2016;29(4):496-504 DOI: https://dx.doi.org/10.1016/j.jht.2016.06.007.

155. Farazdaghi MR, Mansoori A, Vosoughi O, Kordi Yoosefinejad A. Evaluation of the reliability and validity of the Persian version of Patient-Rated Elbow Evaluation questionnaire. Rheumatol Int. 2017;37(5):743-50 DOI: https://dx.doi.org/10.1007/s00296-016-3605-1.
156. Connell D, Datir A, Alyas F, Curtis M. Treatment of lateral epicondylitis using skin-derived tenocyte-like cells. British journal of sports medicine. 2009;43(4):293-8.
157. Paoloni JA, Murrell GA, Burch RM, Ang RY. Randomised, double-blind, placebo-controlled clinical trial of a new topical glyceryl trinitrate patch for chronic lateral epicondylosis. Br J Sports Med. 2009;43(4):299-302 DOI: 10.1136/bjsm.2008.053108.
158. Radpasand M, Owens E. Combined multimodal therapies for chronic tennis elbow: pilot study to test protocols for a randomized clinical trial. J Manipulative Physiol Ther. 2009;32(7):571-85.
159. Tarhan S, Unlu Z, Ovali GY, Pabuscu Y. Value of Ultrasonography on Diagnosis and Assessment of Pain and Grip Strength in Patients with Lateral Epicondylitis. Turk J Rheumatol. 2009;24(3):123-30.
160. Amro A, Diener I, Bdair WO, Hameda IM, Shalabi AI, Ilyyan DI. The effects of Mulligan mobilisation with movement and taping techniques on pain, grip strength, and function in patients with lateral epicondylitis. Hong Kong Physiotherapy Journal. 2010;28(1):19-23.
161. Clarke AW, Ahmad M, Curtis M, Connell DA. Lateral Elbow Tendinopathy Correlation of Ultrasound Findings With Pain and Functional Disability. The American journal of sports medicine. 2010;38(6):1209-14.
162. Blanchette MA, Normand MC. Augmented soft tissue mobilization vs natural history in the treatment of lateral epicondylitis: a pilot study. J Manipulative Physiol Ther. 2011;34(2):123-30 DOI: 10.1016/j.jmpt.2010.12.001.
163. Blanchette M-A, Normand MC. Impairment assessment of lateral epicondylitis through electromyography and dynamometry. Journal of the Canadian Chiropractic Association. 2011;55(2):96-106 11p.
164. Creaney L, Wallace A, Curtis M, Connell D. Growth factor-based therapies provide additional benefit beyond physical therapy in resistant elbow tendinopathy: a prospective, single-blind, randomised trial of autologous blood injections versus platelet-rich plasma injections. British journal of sports medicine. 2011:bjsports82503.
165. Gonzalez-Iglesias J, Cleland JA, del Rosario Gutierrez-Vega M, Fernandez-de-las-Penas C. Multimodal management of lateral epicondylalgia in rock climbers: a prospective case series. J Manipulative Physiol Ther. 2011;34(9):635-42 DOI: 10.1016/j.jmpt.2011.09.003.
166. Ajimsha MS, Chithra S, Thulasyammal RP. Effectiveness of myofascial release in the management of lateral epicondylitis in computer professionals. Arch Phys Med Rehabil. 2012;93(4):604-9 DOI: 10.1016/j.apmr.2011.10.012.
167. Chourasia AO, Buhr KA, Rabago DP, Kijowski R, Irwin CB, Sesto ME. Effect of lateral epicondylosis on grip force development. J Hand Ther. 2012;25(1):27-36; quiz 7 DOI: 10.1016/j.jht.2011.09.003.
168. Forogh B, Khalighi M, Javanshir MA, Ghoseiri K, Kamali M, Raissi G. The effects of a new designed forearm orthosis in treatment of lateral epicondylitis. Disabil Rehabil Assist Technol. 2012;7(4):336-9 DOI: 10.3109/17483107.2011.635330.
169. Ilieva EM, Minchev RM, Petrova NS. Radial shock wave therapy in patients with lateral epicondylitis. Folia Med (Plovdiv). 2012;54(3):35-41.
170. Kim LJ, Choi H, Moon D. Improvement of Pain and Functional Activities in Patients with Lateral Epicondylitis of the Elbow by Mobilization with Movement: a Randomized, Placebo-Controlled Pilot Study. J Phys Ther Sci. 2012;24(9):787-90.

171. Chourasia AO, Buhr KA, Rabago DP, Kijowski R, Lee KS, Ryan MP, et al. Relationships Between Biomechanics, Tendon Pathology, and Function in Individuals With Lateral Epicondylosis. J Orthop Sport Phys. 2013;43(6):368-78 DOI: 10.2519/jospt.2013.4411.
172. Krogh TP, Fredberg U, Stengaard-Pedersen K, Christensen R, Jensen P, Ellingsen T. Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: a randomized, double-blind, placebo-controlled trial. Am J Sports Med. 2013;41(3):625-35 DOI: 10.1177/0363546512472975.
173. Rabago D, Lee KS, Ryan M, Chourasia AO, Sesto ME, Zgierska A, et al. Hypertonic dextrose and morrhuate sodium injections (prolotherapy) for lateral epicondylosis (tennis elbow): results of a single-blind, pilot-level, randomized controlled trial. Am J Phys Med Rehabil. 2013;92(7):587-96.
174. Shin KM, Kim JH, Lee S, Shin MS, Kim TH, Park HJ, et al. Acupuncture for lateral epicondylitis (tennis elbow): study protocol for a randomized, practitioner-assessor blinded, controlled pilot clinical trial. Trials. 2013;14:174 DOI: 10.1186/1745-6215-14-174.
175. Shiple BJ. How effective are injection treatments for lateral epicondylitis? Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine. 2013;23(6):502-3.
176. Arik HO, Kose O, Guler F, Deniz G, Egerci OF, Ucar M. Injection of autologous blood versus corticosteroid for lateral epicondylitis: a randomised controlled study. J Orthop Surg (Hong Kong). 2014;22(3):333-7.
177. Lee S, Ko Y, Lee W. Changes in pain, dysfunction, and grip strength of patients with acute lateral epicondylitis caused by frequency of physical therapy: a randomized controlled trial. J Phys Ther Sci. 2014;26(7):1037-40.
178. Singh A, Gangwar DS, Singh S. Bone marrow injection: A novel treatment for tennis elbow. J Nat Sci Biol Med. 2014;5(2):389-91 DOI: 10.4103/0976-9668.136198.
179. Coombes BK, Bisset L, Vicenzino B. Cold hyperalgesia associated with poorer prognosis in lateral epicondylalgia: a 1-year prognostic study of physical and psychological factors. Clin J Pain. 2015;31(1):30-5 DOI: 10.1097/ajp.0000000000000078.
180. Murtezani A, Ibraimi Z, Vllasolli TO, Sllamniku S, Krasniqi S, Vokrri L. Exercise and Therapeutic Ultrasound Compared with Corticosteroid Injection for Chronic Lateral Epicondylitis: A Randomized Controlled Trial. Ortop Traumatol Rehabil. 2015;17(4):351-7 DOI: 10.5604/15093492.1173377.
181. Tosun HB, Gumustas S, Agir I, Uludag A, Serbest S, Pepele D, et al. Comparison of the effects of sodium hyaluronate-chondroitin sulphate and corticosteroid in the treatment of lateral epicondylitis: a prospective randomized trial. J Orthop Sci. 2015;20(5):837-43 DOI: 10.1007/s00776-015-0747-z.
182. Qi L, Zhang Y-D, Yu R-B, Shi H-B. Magnetic Resonance Imaging of Patients With Chronic Lateral Epicondylitis: Is There a Relationship Between Magnetic Resonance Imaging Abnormalities of the Common Extensor Tendon and the Patient's Clinical Symptom? Medicine. 2016;95(5):1-5 p DOI: 10.1097/md.0000000000002681.
183. Faes M, van den Akker B, de Lint JA, Kooloos JGM, Hopman MTE. Dynamic extensor brace for lateral epicondylitis. Clinical orthopaedics and related research. 2006;442:149-57.
184. Nilsson P, Thom E, Baigi A, Marklund B, Mansson J. A prospective pilot study of a multidisciplinary home training programme for lateral epicondylitis. Musculoskeletal Care. 2007;5(1):36-50 DOI: 10.1002/msc.97.
185. Bergin MJG, Hirata R, Mista C, Christensen SW, Tucker K, Vicenzino B, et al. Movement evoked pain and mechanical hyperalgesia after intramuscular injection of nerve growth factor: A model of sustained elbow pain. Pain Medicine. 2015;16(11):2180-91.
186. Coombes BK, Bisset L, Vicenzino B. Thermal hyperalgesia distinguishes those with severe pain and disability in unilateral lateral epicondylalgia. The Clinical journal of pain. 2012;28(7):595-601.

187. Dabholkar AS, Kalbande VM, Yardi S. Neural Tissue Mobilisation Using ULTT2b and Radial Head Mobilisation v/s Exercise Programme in Lateral Epicondylitis. Indian Journal of Physiotherapy and Occupational Therapy. 2013;7(4):247.
188. Maffulli G, Hemmings S, Maffulli N. Assessment of the effectiveness of extracorporeal shock wave therapy (ESWT) for soft tissue injuries (assert): an online database protocol. Translational medicine@ UniSa. 2014;10:46.
189. Massy-Westropp N, Simmonds S, Caragianis S, Potter A. Autologous blood injection and wrist immobilisation for chronic lateral epicondylitis. Advances in orthopedics. 2012;2012.
190. Tonks JH, Pai SK, Murali SR. Steroid injection therapy is the best conservative treatment for lateral epicondylitis: a prospective randomised controlled trial. International Journal of Clinical Practice. 2007;61(2):240-6.
191. Alizadehkhaiyat O, Fisher AC, Kemp GJ, Frostick SP. Pain, functional disability, and psychologic status in tennis elbow. The Clinical journal of pain. 2007;23(6):482-9.
192. Coombes BK, Connelly L, Bisset L, Vicenzino B. Economic evaluation favours physiotherapy but not corticosteroid injection as a first-line intervention for chronic lateral epicondylalgia: evidence from a randomised clinical trial. BJSM online. 2016;50(22):1400-5 DOI: https://dx.doi.org/10.1136/bjsports-2015-094729.
193. Segretin F, Paris G, Cheriet S, Delarue Y. Rehabilitation and auto-exercises protocol in patients with chronic lateral epicondylitis: 6 months follow-up. Ann Phys Rehabil Med. 2016;59S:e109 DOI: https://dx.doi.org/10.1016/j.rehab.2016.07.243.
194. Amroodi MN, Mahmuudi A, Salariyeh M, Amiri A. Surgical Treatment of Tennis Elbow; Minimal Incision Technique. Arch. 2016;4(4):366-70.
195. Merolla G, Dellabiancia F, Ricci A, Mussoni MP, Nucci S, Zanoli G, et al. Arthroscopic Debridement Versus Platelet-Rich Plasma Injection: A Prospective, Randomized, Comparative Study of Chronic Lateral Epicondylitis With a Nearly 2-Year Follow-Up. Arthroscopy. 2017;19:19 DOI: https://dx.doi.org/10.1016/j.arthro.2017.02.009.
196. Guo YH, Kuan TS, Chen KL, Lien WC, Hsieh PC, Hsieh IC, et al. Comparison Between Steroid and 2 Different Sites of Botulinum Toxin Injection in the Treatment of Lateral Epicondylalgia: A Randomized, Double-Blind, Active Drug-Controlled Pilot Study. Arch Phys Med Rehabil. 2017;98(1):36-42 DOI: https://dx.doi.org/10.1016/j.apmr.2016.08.475.
197. Capan N, Esmaeilzadeh S, Oral A, Basoglu C, Karan A, Sindel D. Radial Extracorporeal Shock Wave Therapy Is Not More Effective Than Placebo in the Management of Lateral Epicondylitis: A Double-Blind, Randomized, Placebo-Controlled Trial. Am J Phys Med Rehabil. 2016;95(7):495-506 DOI: https://dx.doi.org/10.1097/PHM.0000000000000407.
198. Tong C, Bertouch JVJV, Katrib A, Joshua F. Power Doppler ultrasound in lateral epicondylitis. Internal Medicine Journal. 2009;39:A40.
199. Clarke AW, Ahmad M, Curtis M, Connell DA. Lateral elbow tendinopathy: correlation of ultrasound findings with pain and functional disability. Am J Sports Med. 2010;38(6):1209-14 DOI: 10.1177/0363546509359066.
200. Creaney L, Wallace A, Curtis M, Connell D. Growth factor-based therapies provide additional benefit beyond physical therapy in resistant elbow tendinopathy: a prospective, single-blind, randomised trial of autologous blood injections versus platelet-rich plasma injections. Br J Sports Med. 2011;45(12):966-71 DOI: 10.1136/bjsm.2010.082503.
201. Beaton DE, Wright JG, Katz JN, Upper Extremity Collaborative G. Development of the QuickDASH: comparison of three item-reduction approaches. J Bone Joint Surg Am. 2005;87(5):1038-46 DOI: 10.2106/JBJS.D.02060.

202. Fan ZJ, Smith CK, Silverstein BA. Assessing validity of the QuickDASH and SF-12 as surveillance tools among workers with neck or upper extremity musculoskeletal disorders. Journal of Hand Therapy. 2008;21(4):354-65.
203. Polson K, Reid D, McNair PJ, Larmer P. Responsiveness, minimal importance difference and minimal detectable change scores of the shortened disability arm shoulder hand (QuickDASH) questionnaire. Manual therapy. 2010;15(4):404-7.
204. Smith-Forbes EV, Howell DM, Willoughby J, Pitts DG, Uhl TL. Specificity of the minimal clinically important difference of the quick Disabilities of the Arm Shoulder and Hand (QDASH) for distal upper extremity conditions. J Hand Ther. 2016;29(1):81-8 DOI: 10.1016/j.jht.2015.09.003.
205. Stover B, Silverstein B, Wickizer T, Martin DP, Kaufman J. Accuracy of a disability instrument to identify workers likely to develop upper extremity musculoskeletal disorders. Journal of occupational rehabilitation. 2007;17(2):227-45.
206. Solheim E, Hegna J, Oyen J. Extensor tendon release in tennis elbow: results and prognostic factors in 80 elbows. Knee Surg Sports Traumatol Arthrosc. 2011;19(6):1023-7 DOI: 10.1007/s00167-011-1477-1.
207. Mardani-Kivi M, Karimi-Mobarakeh M, Karimi A, Akhoondzadeh N, Saheb-Ekhtiari K, Hashemi-Motlagh K, et al. The effects of corticosteroid injection versus local anesthetic injection in the treatment of lateral epicondylitis: a randomized single-blinded clinical trial. Arch Orthop Trauma Surg. 2013;133(6):757-63 DOI: 10.1007/s00402-013-1721-x.
208. Solheim E, Hegna J, Oyen J. Arthroscopic versus open tennis elbow release: 3- to 6-year results of a case-control series of 305 elbows. Arthroscopy. 2013;29(5):854-9 DOI: 10.1016/j.arthro.2012.12.012.
209. Wang A, Breidahl W, Mackie KE, Lin Z, Qin A, Chen J, et al. Autologous tenocyte injection for the treatment of severe, chronic resistant lateral epicondylitis: a pilot study. Am J Sports Med. 2013;41(12):2925-32.
210. Otoshi K, Takegami M, Sekiguchi M, Onishi Y, Yamazaki S, Otani K, et al. Chronic hyperglycemia increases the risk of lateral epicondylitis: the Locomotive Syndrome and Health Outcome in Aizu Cohort Study (LOHAS). Springerplus. 2015;4:407 DOI: 10.1186/s40064-015-1204-3.
211. Trentini R, Mangano T, Repetto I, Cerruti P, Kuqi E, Trompetto C, et al. Short- to mid-term follow-up effectiveness of US-guided focal extracorporeal shock wave therapy in the treatment of elbow lateral epicondylitis. Musculoskelet Surg. 2015;99 Suppl 1:S91-7 DOI: 10.1007/s12306-015-0361-4.
212. Wang A, Mackie K, Breidahl W, Wang T, Zheng MH. Evidence for the Durability of Autologous Tenocyte Injection for Treatment of Chronic Resistant Lateral Epicondylitis: Mean 4.5-Year Clinical Follow-up. Am J Sports Med. 2015;43(7):1775-83 DOI: 10.1177/0363546515579185.
213. Kocyigit F, Kuyucu E, Kocyigit A, Herek DT, Savkin R, Aslan UB, et al. Association of real-time sonoelastography findings with clinical parameters in lateral epicondylitis. Rheumatol Int. 2016;36(1):91-100 DOI: 10.1007/s00296-015-3356-4.
214. Walton MJ, Mackie K, Fallon M, Butler R, Breidahl W, Zheng MH, et al. The reliability and validity of magnetic resonance imaging in the assessment of chronic lateral epicondylitis. The Journal of hand surgery. 2011;36(3):475-9.
215. Glanzmann MC, Audige L. Platelet-rich plasma for chronic lateral epicondylitis: is one injection sufficient? Arch Orthop Trauma Surg. 2015;135(12):1637-45 DOI: 10.1007/s00402-015-2322-7.
216. Solheim E, Hegna J, Oyen J, Inderhaug E. Arthroscopic Treatment of Lateral Epicondylitis: Tenotomy Versus Debridement. Arthroscopy. 2016;32(4):578-85 DOI: https://dx.doi.org/10.1016/j.arthro.2015.10.008.
217. Shillito M, Soong M, Martin N. Radiographic and Clinical Analysis of Lateral Epicondylitis. J Hand Surg [Am]. 2017;2017:12 DOI: https://dx.doi.org/10.1016/j.jhsa.2017.03.016.

218. Kwon BC, Kim JY, Park KT. The Nirschl procedure versus arthroscopic extensor carpi radialis brevis debridement for lateral epicondylitis. J Shoulder Elbow Surg. 2017;26(1):118-24 DOI: https://dx.doi.org/10.1016/j.jse.2016.09.022.
219. Gulabi D, Uysal MA, Akca A, Colak I, Cecen GS, Gumustas S. USG-guided injection of corticosteroid for lateral epicondylitis does not improve clinical outcomes: a prospective randomised study. Arch Orthop Trauma Surg. 2017;137(5):601-6 DOI: https://dx.doi.org/10.1007/s00402-017-2657-3.
220. Roles N, Maudsley R. RADIAL TUNNEL SYNDROME Resistant Tennis Elbow as a Nerve Entrapment. Journal of Bone & Joint Surgery, British Volume. 1972;54(3):499-508.
221. Perlick L, Gassel F, Zander D, Schmitt O, Wallny T. [Comparison of results of results of medium energy ESWT and Mittelmeier surgical therapy in therapy refractory epicondylitis humeri radialis]. Vergleich der Ergebnisse der mittelenergetischen ESWT und der operativen Therapie in der Technik nach Mittelmeier bei der therapieresistenten Epicondylitis humeri radialis. 1999;137(4):316-21.
222. Rompe JD, Riedel C, Betz U, Fink C. Chronic lateral epicondylitis of the elbow: a prospective study of low-energy shockwave therapy and low-energy shockwave therapy plus manual therapy of the cervical spine. Archives of Physical Medicine & Rehabilitation. 2001;82(5):578-82.
223. Haake M, Konig IR, Decker T, Riedel C, Buch M, Muller HH, et al. Extracorporeal shock wave therapy in the treatment of lateral epicondylitis : a randomized multicenter trial. The Journal of bone and joint surgery American volume. 2002;84-A(11):1982-91.
224. Pannier S, Masquelet AC. [Treatment of epicondylitis by deep fasciotomy of the extensor carpi radialis brevis and supinator: a review of 18 cases]. Traitement de l'epicondylalgie par aponevrotomie profonde de l'extensor carpi radialis brevis et du supinator: une serie de 18 cas. 2002;88(6):565-72.
225. Furia JP. Safety and efficacy of extracorporeal shock wave therapy for chronic lateral epicondylitis. American journal of orthopedics (Belle Mead, NJ). 2005;34(1):13-9.
226. Decker T, Kuhne B, Gobel F. [Extracorporeal shockwave therapy (ESWT) in epicondylitis humeri radialis. Short-term and intermediate-term results]. Extrakorporale Stosswellentherapie (ESWT) bei Epicondylitis humeri radialis Kurz- und mittelfristige Ergebnisse. 2002;31(7):633-6.
227. Vulpiani MC, Nusca SM, Vetrano M, Ovidi S, Baldini R, Piermattei C, et al. Extracorporeal shock wave therapy vs cryoultrasound therapy in the treatment of chronic lateral epicondylitis. One year follow up study. Muscles Ligaments Tendons J. 2015;5(3):167-74.
228. Haake M, Jensen K, Prinz H, Willenberg T. [Design of a multicenter study for assessing the effectiveness of extracorporeal shockwave therapy in epicondylitis humeri radialis]. Design einer Multizenterstudie zum Wirksamkeitsnachweis der Extrakorporalen Stosswellentherapie (ESTW) bei Epicondylitis humeri radialis. 2000;138(2):99-103.
229. Ozkut AT, Kilincoglu V, Ozkan NK, Eren A, Ertas M. [Extracorporeal shock wave therapy in patients with lateral epicondylitis]. Acta Orthop Traumatol Turc. 2007;41(3):207-10.
230. Wang AW, Erak S. Fractional lengthening of forearm extensors for resistant lateral epicondylitis. ANZ J Surg. 2007;77(11):981-4 DOI: 10.1111/j.1445-2197.2007.04294.x.
231. Montalvan B, Le Goux P, Klouche S, Borgel D, Hardy P, Breban M. Inefficacy of ultrasound-guided local injections of autologous conditioned plasma for recent epicondylitis: results of a double-blind placebo-controlled randomized clinical trial with one-year follow-up. Rheumatology (Oxford). 2016;55(2):279-85 DOI: https://dx.doi.org/10.1093/rheumatology/kev326.
232. Lowe A, Wessel J, Battié MC. Test-retest reliability, construct validity, and responsiveness of a functional pain scale for tennis elbow. Physiotherapy Canada. 2003;55(2):114-22 9p.

233. Nagrale AV, Herd CR, Ganvir S, Ramteke G. Cyriax physiotherapy versus phonophoresis with supervised exercise in subjects with lateral epicondylalgia: a randomized clinical trial. J Man Manip Ther. 2009;17(3):171-8 DOI: 10.1179/jmt.2009.17.3.171.
234. Viswas R, Ramachandran R, Korde Anantkumar P. Comparison of effectiveness of supervised exercise program and Cyriax physiotherapy in patients with tennis elbow (lateral epicondylitis): a randomized clinical trial. ScientificWorldJournal. 2012;2012:939645.
235. Pransky G, Feuerstein M, Himmelstein J, Katz JN, Vickers-Lahti M. Measuring functional outcomes in work-related upper extremity disorders: Development and validation of the upper extremity function scale. Journal of Occupational and Environmental Medicine. 1997;39(12):1195-202 DOI: 10.1097/00043764-199712000-00014.
236. Rompe JD, Decking J, Schoellner C, Theis C. Repetitive low-energy shock wave treatment for chronic lateral epicondylitis in tennis players. American Journal of Sports Medicine. 2004;32(3):734-43 10p.
237. Pettrone FA, McCall BR. Extracorporeal shock wave therapy without local anesthesia for chronic lateral epicondylitis. Journal of Bone & Joint Surgery, American Volume. 2005;87-A(6):1297-304 8p.
238. Ozturan KE, Yucel I, Cakici H, Guven M, Sungur I. Autologous blood and corticosteroid injection and extracoporeal shock wave therapy in the treatment of lateral epicondylitis. Orthopedics. 2010;33(2):84-91 DOI: 10.3928/01477447-20100104-09.
239. Verhaar J, Walenkamp G, Kester A, Van Mameren H, Van der Linden T. Lateral extensor release for tennis elbow. A prospective long-term follow-up study. J Bone Joint Surg Am. 1993;75(7):1034-43.
240. Svernlov B, Adolfsson L. Non-operative treatment regime including eccentric training for lateral humeral epicondylalgia. Scandinavian journal of medicine & science in sports. 2001;11(6):328-34.
241. Svernlov B, Adolfsson L. Outcome of release of the lateral extensor muscle origin for epicondylitis. Scand J Plast Reconstr Surg Hand Surg. 2006;40(3):161-5 DOI: 10.1080/02844310500491492.
242. Krischek O, Pompe JD, Hopf C, Vogel J, Herbsthofer B, Nafe B, et al. [Extracorporeal shockwave therapy in epicondylitis humeri ulnaris or radialis--a prospective, controlled, comparative study]. Die extrakorporale Stosswellentherapie bei Epicondylitis humeri ulnaris oder radialis--Eine prospektive, kontrollierte, vergleichende Studie. 1998;136(1):3-7.
243. Isikan UE, Sarban S, Kocabey Y. [The results of open surgical treatment in patients with chronic refractory lateral epicondylitis]. Kronik, konservatif tedaviye direncli lateral epikondilitte acik cerrahi tedavi sonuclari. 2005;39(2):128-32.
244. Ozden R, Uruc V, Doğramaci Y, Kalaci A, Yengil E. Management of tennis elbow with topical glyceryl trinitrate. Acta Orthop Traumato. 2013;48(2):175-80.

EMPRO Attribute and individual item scores for each outcome instrument.

Item scores graded from 4 (strongly agree) to 1 (strongly disagree or no information).

Attributes and Items	A&C	ASES-e	DASH	HSS	LES	MEPS	Morrey	Nirschl	OES	PRTEE	qDASH	R&M	TEFS	ULFI	Verhaar
CONCEPTUAL AND MEASUREMENT MODEL															
Concept of measurement stated	3	4	4	2	3	4	3	4	4	4	4	1	3	3	2
Obtaining and combining items described	1	3	4	1	4	1	1	1	4	1	3	1	2	3	1
Rationality for dimensionality and scales	1	2	3	1	1	1	1	1	3	2	4	1	1	2	1
Involvement of the target population	1	2	3	1	4	1	1	1	4	2	2	1	2	3	1
Scale variability described and adequate	1	1	3	2	2	2	2	2	3	3	3	1	3	3	1
Level of measurement described	2	1	3	2	3	2	2	1	3	1	3	1	2	3	1
Procedures for deriving scores	2	1	3	1	3	2	2	2	4	3	4	1	1	3	1
ATTRIBUTE SCORE	19.0	33.3	76.2	14.3	61.9	28.6	23.8	23.8	85.7	42.9	76.2	0.0	33.3	61.9	4.8
RELIABILITY: Internal consistency															
Data collection methods described	1	1	3	1	3	1	1	1	4	3	3	1	1	3	1
Cronbach's alpha adequate	1	1	4	1	4	1	1	1	4	4	4	1	2	3	1

IRT estimates provided	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Testing in different populations	1	1	2	1	3	1	1	1	2	4	3	1	1	2	1
ATTRIBUTE SCORE	0.0	0.0	50.0	0.0	58.3	0.0	0.0	0.0	58.3	66.7	58.3	0.0	8.3	41.7	0.0
RELIABILITY: Reproducibility															
Data collection methods described	1	3	4	1	2	2	1	1	3	4	3	1	4	1	1
Test-retest and time interval adequate	1	1	4	1	2	2	1	1	2	3	3	1	4	1	1
Reproducibility coefficients adequate	1	4	4	1	2	1	1	1	4	4	4	1	4	1	1
IRT estimates provided	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
ATTRIBUTE SCORE	0.0	41.7	75.0	0.0	25.0	16.7	0.0	0.0	50.0	66.7	58.3	0.0	75.0	0.0	0.0
VALIDITY															
Content Validity adequate	1	2	4	1	4	1	1	2	2	1	3	1	1	3	1
Construct/critereon validity adequate	2	3	3	3	3	4	3	1	4	3	4	2	4	3	1
Sample composition described	1	1	1	3	3	1	3	1	2	4	2	2	2	2	1
Prior hypothesis stated	1	4	3	1	1	4	1	1	4	4	3	1	2	2	1
Rational for criterion validity	1	1	1	1	1	1	1	1	1	1	4	1	1	1	1
Tested in different populations	1	1	3	1	3	1	1		1		3			2	
ATTRIBUTE SCORE	5.6	33.3	50.0	22.2	50.0	33.3	22.2	6.7	44.4	53.3	72.2	13.3	33.3	38.9	0.0
RESPONSIVENESS															
Adequacy of methods	2	1	4	1	2	4	1	1	4	4	4	2	4	4	1

Description of estimated magnitude of change	2	1	4	1	1	4	1	1	4	3	4	3	2	3	1
Comparison of stable and unstable groups	1	1	1	1	1	1	1	1	2	3	3	1	1	1	1
ATTRIBUTE SCORE	22.2	0.0	66.7	0.0	11.1	66.7	0.0	0.0	77.8	77.8	88.9	33.3	44.4	55.6	0.0
INTERPRETABILITY															
Rational of external criteria	1	1	4	1	1	2	2	1	3	3	4	1	2	1	1
Description of interpretation strategies	1	1	3	1	1	1	1	1	3	3	4	1	2	1	1
How data should be reported stated	1	1	2	1	1	2	1	1	3	1	1	1	1	1	1
ATTRIBUTE SCORE	0.0	0.0	66.7	0.0	0.0	22.2	11.1	0.0	66.7	44.4	66.7	0.0	22.2	0.0	0.0
BURDEN: Respondent															
Skills and time needed	1	1	3	2	3	1	2	1	2	2	2	1	1	2	1
Impact on respondents	1	1	4	1	2	1	1	1	3	3	3	1	1	1	1
Not suitable circumstances	1	1	4	1	1	1	1	1	2	3	3	1	1	1	1
ATTRIBUTE SCORE	0.0	0.0	88.9	11.1	33.3	0.0	11.1	0.0	44.4	55.6	55.6	0.0	0.0	11.1	0.0
BURDEN: Administrative															
Resources Required	1	1	4	3	4	1	2	1	4	4	3	1	1	1	1
Time required	1	1	1	1	4	1	1	1	4	1	1	1	1	1	1
Training and expertise needed	1	1	1	1	1	1	1	1	4	1	2	1	1	1	1

Burden of score calculation	2	1	4	2	3	3	2	1	4	4	4	1	1	2	1
ATTRIBUTE SCORE	8.3	0.0	50.0	25.0	66.7	16.7	16.7	0.0	100.0	50.0	50.0	0.0	0.0	8.3	0.0
OVERALL SCORE	**N/A**	**21.67**	**66.90**	**N/A**	**36.27**	**33.49**	**N/A**	**N/A**	**66.59**	**57.02**	**72.46**	**N/A**	**41.67**	**39.60**	**N/A**

PRISMA checklist for the study - Patient-Centred Outcomes in Lateral Elbow Tendinopathy: A Systematic Review of Available Evidence in UK Populations

Please see the inserted document

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	109
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	109
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	109-110
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	111
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	111
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	111+71
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	112
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	112-113

• Data items	• 11	• List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	• 112-113
• Risk of bias in individual studies	• 12	• Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	• N/A
• Summary measures	• 13	• State the principal summary measures (e.g., risk ratio, difference in means).	• 112
• Synthesis of results	• 14	• Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	• N/A

• **Section/topic**	• #	• **Checklist item**	• **Reported on page #**
• Risk of bias across studies	• 15	• Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	• N/A
• Additional analyses	• 16	• Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	• 113
• **RESULTS**			•
• Study selection	• 17	• Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	• 113
• Study characteristics	• 18	• For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	• 117-120
• Risk of bias within studies	• 19	• Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	• N/A

• Results of individual studies	• 20	• For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	• 117-120
• Synthesis of results	• 21	• Present results of each meta-analysis done, including confidence intervals and measures of consistency.	• N/A
• Risk of bias across studies	• 22	• Present results of any assessment of risk of bias across studies (see Item 15).	• N/A
• Additional analysis	• 23	• Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	• 120
• **DISCUSSION**			•
• Summary of evidence	• 24	• Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	• 121
• Limitations	• 25	• Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	• 123
• Conclusions	• 26	• Provide a general interpretation of the results in the context of other evidence, and implications for future research.	• 124
• **FUNDING**			•
• Funding	• 27	• Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	• N/A

•

• *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Documents included in the UK-specific evaluation

1. Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, et al. The development and validation of a patient-reported questionnaire to assess outcomes of elbow surgery. J Bone Joint Surg Br. 2008;90(4):466-73.
2. Sathyamoorthy P, Kemp G, Rawal A, Rayner V, Frostick S. Development and validation of an elbow score. Rheumatology. 2004;43(11):1434-40.
3. Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, et al. Comparative responsiveness and minimal change for the Oxford Elbow Score following surgery. Qual Life Res. 2008;17(10):1257-67.
4. Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, et al. Specificity and responsiveness of patient-reported and clinician-rated outcome measures in the context of elbow surgery, Orthopaedics & Traumatology: Surgery & Research 98.6 (2012): 652-658.
5. Poltawski L, Watson T. Measuring clinically important change with the Patient-rated Tennis Elbow Evaluation. Hand Therapy. 2011;16(3):52-7.
6. Melikyan EY, Shahin E, Miles J, Bainbridge LC. Extracorporeal shock-wave treatment for tennis elbow. Bone & Joint Journal. 2003;85(6):852-5.
7. Dunkow PD, Jatti M, Muddu BN. A comparison of open and percutaneous techniques in the surgical treatment of tennis elbow. Bone & Joint Journal. 2004;86(5):701-4.
8. Connell DA, Ali KE, Ahmad M, Lambert S, Corbett S, Curtis M. Ultrasound-guided autologous blood injection for tennis elbow. Skeletal radiology. 2006;35(6):371-7.
9. Alizadehkhaiyat O, Fisher AC, Kemp GJ, Frostick SP. Pain, functional disability, and psychologic status in tennis elbow. The Clinical Journal of Pain. 2007;23(6):482-9.
10. Connell D, Datir A, Alyas F, Curtis M. Treatment of lateral epicondylitis using skin-derived tenocyte-like cells. British Journal of Sports Medicine. 2009;43(4):293-8.
11. Clarke AW, Ahmad M, Curtis M, Connell DA. Lateral Elbow Tendinopathy Correlation of Ultrasound Findings With Pain and Functional Disability. The American Journal of Sports Medicine. 2010;38(6):1209-14.
12. Creaney L, Wallace A, Curtis M, Connell D. Growth factor-based therapies provide additional benefit beyond physical therapy in resistant elbow tendinopathy: a prospective, double-blind, randomised trial of autologous blood injections versus platelet-rich plasma injections. British Journal of Sports Medicine. 2011;45(12):966-71.
13. Nazar M, Lipscombe S, Morapudi S, Tuvo G, Kebrle R, Marlow W, et al. Percutaneous tennis elbow release under local anaesthesia. Open Orthop J. 2012;6:129-32.
14. Stenhouse G, Sookur P, Watson M. Do blood growth factors offer additional benefit in refractory lateral epicondylitis? A prospective, randomized pilot trial of dry needling as a stand-alone procedure versus dry needling and autologous conditioned plasma. Skeletal Radiology. 2013;42(11):1515-20.
15. Maffulli G, Hemmings S, Maffulli N. Assessment of the effectiveness of extracorporeal shock wave therapy (ESWT) for soft tissue injuries (assert): an online database protocol. Translational medicine@ UniSa. 2014;10:46.
16. Tonks JH, Pai SK, Murali SR. Steroid injection therapy is the best conservative treatment for lateral epicondylitis: a prospective randomised controlled trial. International Journal of Clinical Practice. 2007;61(2):240-6.

Participant questionnaire evaluation booklet

Please see the Inserted document

Research supported by: BESS British Elbow & Shoulder Society | University of Exeter Medical School | Royal Devon and Exeter NHS Foundation Trust

Participant Number: _____

Questionnaire Pack

Please tick		
1 [ ]	2 [ ]	3 [ ]
Day 1	1 week	8 weeks

The following questionnaires are included in this pack:

1. **Oxford Elbow Score (OES)**
2. **quick Disabilities of the Arm, Shoulder and Hand (qDASH)**
3. **Patient Rated Tennis Elbow Evaluation (PRTEE)**
4. **PROMIS Upper limb and Pain questionnaire (PROMIS)**
5. **EuroQol five dimensions questionnaire (EQ-5D)**
6. **Visual Analogue Scale of Pain and Function (VAS)**
7. **Global Change Criteria (GCC)**

Please complete as many questions as you can, if however, you feel you are unable to answer a question, for whatever reason, please leave it blank.

Once you have completed all the questionnaire sets – Please post them to us using the pre-paid envelope.

Please complete the following information and then the questionnaires.

Name			
Date of Birth		**Day Month Year**	
Weight (Kg or Stone)		**Height (Cms or Ft+Inches)**	
Profession			
Dominant arm		**Right [ ] Left [ ]**	
Arm affected with Tennis Elbow		**Right [ ] Left [ ]**	
How long have you had Tennis Elbow		**Months Years**	
Today's Date		**Day Month Year**	

Thank you once again for your time and participation

The Oxford Elbow Score

PROBLEMS WITH YOUR ELBOW

Tick (✓) one box for every question.

1. During the past 4 weeks...

Have you had difficulty lifting things in your home, such as putting out the rubbish, because of your elbow problem?

No difficulty	A little bit of difficulty	Moderate difficulty	Extreme difficulty	Impossible to do
☐	☐	☐	☐	☐

2. During the past 4 weeks...

Have you had difficulty carrying bags of shopping, because of your elbow problem?

No difficulty	A little bit of difficulty	Moderate difficulty	Extreme difficulty	Impossible to do
☐	☐	☐	☐	☐

3. During the past 4 weeks...

Have you had any difficulty washing yourself all over, because of your elbow problem?

No difficulty	A little bit of difficulty	Moderate difficulty	Extreme difficulty	Impossible to do
☐	☐	☐	☐	☐

4. During the past 4 weeks...

Have you had any difficulty dressing yourself, because of your elbow problem?

No difficulty	A little bit of difficulty	Moderate difficulty	Extreme difficulty	Impossible to do
☐	☐	☐	☐	☐

5. During the past 4 weeks...

Have you felt that your elbow problem is "controlling your life"?

No, not at all	Occasionally	Some days	Most days	Every day
☐	☐	☐	☐	☐

6. During the past 4 weeks...

How much has your elbow problem been "on your mind"?

Not at all	A little of the time	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

7. During the past 4 weeks...

Have you been troubled by pain from your elbow in bed at night**?**

Not at all	1 or 2 nights	Some nights	Most nights	Every night
☐	☐	☐	☐	☐

8. During the past 4 weeks...

How often has your elbow pain interfered with your sleeping?

Not at all	Occasionally	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

9. During the past 4 weeks...

How much has your elbow problem interfered with your usual work or everyday activities?

Not at all	A little bit	Moderately	Greatly	Totally
☐	☐	☐	☐	☐

10. During the past 4 weeks...

Has your elbow problem limited your ability to take part in leisure activities that you enjoy doing?

No, not at all	Occasionally	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

11. During the past 4 weeks...

How would you describe the <u>worst pain</u> you have from your elbow?

No pain	Mild pain	Moderate pain	Severe pain	Unbearable
☐	☐	☐	☐	☐

12. During the past 4 weeks...

How would you describe the pain you <u>usually</u> have from your elbow?

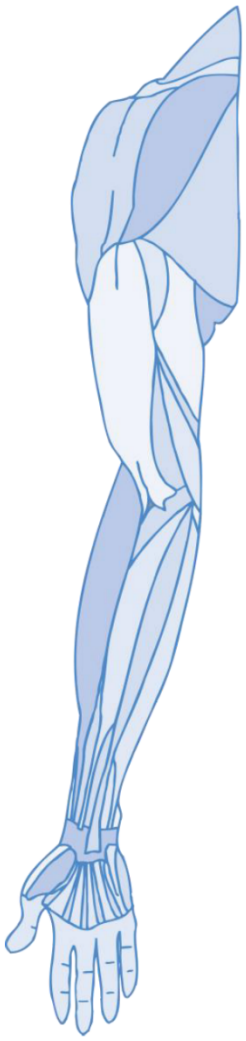
No pain	Mild pain	Moderate pain	Severe pain	Unbearable
☐	☐	☐	☐	☐

Finally, please check back that you have answered each question.

Thank you very much.

THE Quick DASH OUTCOME MEASURE

British English



INSTRUCTIONS

This questionnaire asks about your symptoms as well as your ability to do certain activities.

Please answer every question, based on your condition in the last week, by circling the appropriate number.

If you did not do an activity in the last week, please give your best guess which response would be most accurate.

It doesn't matter which hand or arm you use to do the activity; please answer based on your ability regardless of how you do the task.

British English translation courtesy of: Prof Alison Hammond[1], Dr Yeliz Prior[1], Prof Sarah Tyson[2]
[1] Centre for Health Sciences Research, University of Salford;
[2] Centre for Long term Conditions Research, University of Manchester, UK.

QuickDASH

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	*MILD DIFFICULTY*	*MODERATE DIFFICULTY*	*SEVERE DIFFICULTY*	*UNABLE*
1. Open a tight or new jar	1	2	3	4	5
2. Do heavy household jobs (e.g. wash windows, clean floors)	1	2	3	4	5
3. Cary a shopping bag or briefcase	1	2	3	4	5
4. Wash your back	1	2	3	4	5
5. Use a knife to cut food	1	2	3	4	5
6. Recreational activities which require you to take some force or impact through your arm, shoulder or hand (e.g. golf, hammering, tennis etc)	1	2	3	4	5

	NOT AT ALL	*SLIGHTLY*	*MODERATELY*	*QUITE A BIT*	*EXTREMELY*
7. During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family. friends, neighbours or groups? *(circle number)*	1	2	3	4	5

	NOT LIMITED AT ALL	*SLIGHTLY LIMITED*	*MODERATELY LIMITED*	*VERY LIMITED*	*UNABLE*
8. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? *(circle number)*	1	2	3	4	5

Please rate the severity of the following symptoms in the last week *(circle number)*	*NONE*	*MILD*	*MODERATE*	*SEVERE*	*EXTREME*
9. Arm, shoulder or hand pain	1	2	3	4	5
10. Tingling (pins and needles) in your arm, shoulder or hand	1	2	3	4	5

	NO DIFFICULTY	*MILD DIFFICULTY*	*MODERATE DIFFICULTY*	*SEVERE DIFFICULTY*	*SO MUCH DIFFICULTY THAT I CAN'T SLEEP*
11. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)*	1	2	3	4	5

QuickDASH DISABILITY/SYMPTOM SCORE = [(sum of n responses)–1] x 25 (where n is the number of completed responses)
n

A QuickDASH score may <u>not</u> be calculated if there is greater than 1 missing item.

Quick DASH

WORK MODULE -

The following questions ask about the impact of your arm, shoulder or hand problem on your ability to work (including home-making if that is your main work role).

Please indicate what your job / work is: _____

❑ I do not work (you may skip this section).

Please circle the number that best describes your physical ability in the past week.

Did you have any difficulty:	*NO DIFFICULTY*	*MILD DIFFICULTY*	*MODERATE DIFFICULTY*	*SEVERE DIFFICULTY*	*UNABLE*
1. Doing your work in your usual way?	1	2	3	4	5
2. Doing your usual work because of arm, shoulder or hand pain?	1	2	3	4	5
3. Doing your work as well as you would like?	1	2	3	4	5
4. Spending your usual amount of time doing your work?	1	2	3	4	5

SPORTS/PERFORMING ARTS MODULE

The following questions relate to the impact of your arm, shoulder or hand problem on playing *your musical instrument or sport or both*. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you.

Please indicate the sport or instrument which is most important to you: _____

❑ I do not play a sport or an instrument. (You may skip this section).

Please circle the number that best describes your physical ability in the past week.

Did you have an difficulty:	*NO DIFFICULTY*	*MILD DIFFICULTY*	*MODERATE DIFFICULTY*	*SEVERE DIFFICULTY*	*UNABLE*
1. Playing your instrument or sport in your usual way?	1	2	3	4	5
2. Playing your musical instrument or sport because of arm, shoulder or hand pain?	1	2	3	4	5
3. Playing your instrument or sport as well as you would like?	1	2	3	4	5
4. Spending your usual amount of time practising or playing your instrument or sport?	1	2	3	4	5

PATIENT-RATED TENNIS ELBOW EVALUATION

*The questions below will help us understand the amount of difficulty you have had with your arm in the past week. You will be describing your **average** arm symptoms **over the past week** on a scale 0-10. Please provide an answer for all questions. If you did not perform an activity because of pain or because you were unable ,then you should circle a "10". If you are unsure please estimate to the best of your ability. Only leave items blank if you never perform that activity. Please indicate this by drawing a line completely through the question.*

1. PAIN in your affected arm

*Rate the average amount of pain in your arm **over the past week** by circling the number that best describes your pain on a scale from 0-10. A **zero** (0) means that you **did not have any pain** and a **ten** (10) means that you had **the worst pain imaginable.***

RATE YOUR PAIN: No Pain											Worst Imaginable
When your are at rest	0	1	2	3	4	5	6	7	8	9	10
When doing a task with repeated arm movement	0	1	2	3	4	5	6	7	8	9	10
When carrying a plastic bag of groceries	0	1	2	3	4	5	6	7	8	9	10
When your pain was at its least	0	1	2	3	4	5	6	7	8	9	10
When your pain was at its worst	0	1	2	3	4	5	6	7	8	9	10

2. FUNCTIONAL DISABILITY

A. SPECIFIC ACTIVITIES

*Rate the **amount of difficulty** you experienced performing each of the tasks listed below, over the past week, by circling the number that best describes your difficulty on a scale of 0-10. A zero (0) means you did not experience any difficulty and a **ten (10)** means it was **so difficult you were unable to do it at all**.*

	No Difficulty										Unable To Do
Turn a doorknob or key	0	1	2	3	4	5	6	7	8	9	10
Carry a grocery bag or briefcase by the handle	0	1	2	3	4	5	6	7	8	9	10
Lift a full coffee cup or glass of milk to your mouth	0	1	2	3	4	5	6	7	8	9	10
Open a jar	0	1	2	3	4	5	6	7	8	9	10
Pull up pants	0	1	2	3	4	5	6	7	8	9	10
Wring out a washcloth or wet towel	0	1	2	3	4	5	6	7	8	9	10

B. USUAL ACTIVITIES

*Rate the **amount of difficulty** you experienced performing your **usual** activities in each of the areas listed below, over the past week, by circling the number that best describes your difficulty on a scale of 0-10. By "usual activities", we mean the activities that you performed **before** you started having a problem with your arm. A **zero** (0) means you did not experience any difficulty and a **ten** (10) means it was so difficulty you were unable to do any of your usual activities.*

1. Personal activities (dressing, washing)	0	1	2	3	4	5	6	7	8	9	10
2. Household work (cleaning, maintenance)	0	1	2	3	4	5	6	7	8	9	10
3. Work (your job or everyday work)	0	1	2	3	4	5	6	7	8	9	10
4. Recreational or sporting activities	0	1	2	3	4	5	6	7	8	9	10

Comments:

Upper Extremity – Short Form 7a

Please respond to each question or statement by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA14r1	Are you able to carry a heavy object (over 10 pounds /5 kg)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA34	Are you able to wash your back?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA36	Are you able to put on and take off a coat or jacket?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB13	Are you able to carry a shopping bag or briefcase?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB28r1	Are you able to lift 10 pounds (5 kg) above your shoulder?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB34	Are you able to change a light bulb overhead?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFM16	Are you able to pass a 20-pound (10 kg) turkey or ham to other people at the table?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

16 October 2016

Pain Interference – Short Form 6a

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ12	How much did pain interfere with the things you usually do for fun?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ36	How much did pain interfere with your enjoyment of social activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2 June 2016

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

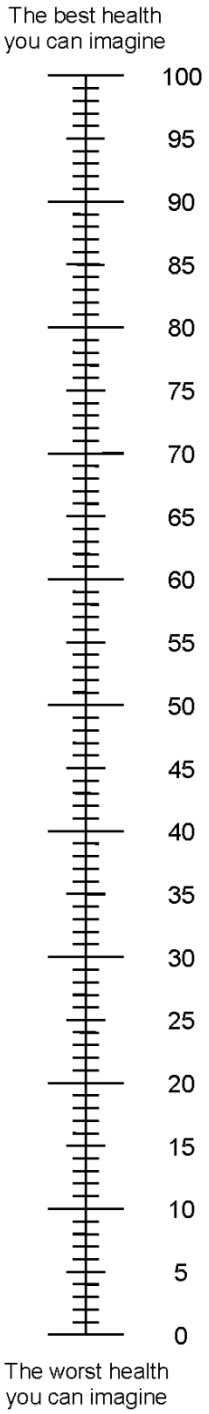
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Numeric Rating Scale

If a zero (0) means “no pain” and a ten (10) means “pain as bad as it could be” on this scale of 0 to 10 what is your level of pain?

Put an ’X’ through that number

0	1	2	3	4	5	6	7	8	9	10

Global Rating of Change

If you are completing questionnaire 2 (1 week after the first questionnaire) or questionnaire 3 (8 weeks after the first questionnaire) please complete the following:

1. How is the **pain** in your elbow now, compared with the last time you filled out this questionnaire?

Please tick a box

-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5

Very much worse — Unchanged — Completely recovered

2. How is the **function** of your elbow now, compared with the last time you filled out this questionnaire?

Please tick a box

-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5

Very much worse — Unchanged — Completely recovered

On behalf of the whole research team - Thank you for completing this Questionnaire

Please store your questionnaires safely until you have completed Questionnaire set 3

If this is Questionnaire 3
Please post your responses to the research team using the pre-paid, pre-addressed envelope.

Participant patient information sheet and participant instructions

Research supported by:

people's lives?

To thank you for your involvement, you will receive a £10 Love2Shop voucher which can be used at over 20,000 shops, restaurants and attractions.

Research supported by:

<u>If your Tennis Elbow has bothered you at all within the last month, we would really like you to help us with our study.</u>

By completing a set of specialist questionnaires you will help us identify:

1. **Which questionnaire best reflects how Tennis Elbow affects you**
2. **Which questionnaire changes when your condition changes**
3. **What your score means compared to other people with Tennis Elbow**

What is the purpose of this study?

Tennis Elbow is very common. It affects people of all ages and all occupations (from desk workers to bricklayers, and occasionally, tennis players). Even though it is common, and can cause significant patient distress and work-related sickness, we are still trying to find the best treatments. When we study Tennis Elbow, it is really important that we have a way of accurately measuring the pain and functional problems you experience.

This study is attempting to use a set of specialist questionnaires known as Patient-Reported Outcome Measures (PROMs). They have been designed to accurately measure how elbow problems affect patients' lives. They have not been tested on UK patients with Tennis Elbow.

Why have I been approached?

You have been identified by your Physiotherapist or Consultant as suffering from Tennis Elbow.

Who is organising the study?

This study has been organised by the University of Exeter Medical School. The study is being supported by the British Elbow and Shoulder Society (BESS) and the Royal Devon and Exeter Hospital Foundation Trust.

What will happen if I participate?

If you are happy to participate in this study, we would like you to complete the attached Consent Form and post it back to us using the pre-paid envelope or return it to the researcher if they are with you in person.

- Once we have received those we will send you 3 sets of questionnaires.
- Each set of questionnaires takes an average of 20 minutes to complete.
- The questionnaires ask some basic information about you (height, weight, profession and how long tennis elbow has bothered you) and then there are different questionnaires that ask you about your pain and symptoms.
- We will ask you to complete the questionnaire as soon as you receive them, then in 1 week later, then 8 weeks after that.
- Once the questionnaires are completed, we would like you to return them to us for analysis.
- There is also the option of completing a short electronic questionnaire on the Internet. This new system uses a large set of questions, using your previous answer it predicts the most relevant next question. No participant details are required and it on average less than 2 minutes to complete.

Do I have to take part?

You are under no obligation to take part. If you do not participate, your care or any future care you receive will not be affected in any way.

What are the possible benefits of taking part?

We know that the best way to truly understand a medical condition is with the input of patients. Your participation will greatly help the way we measure the effect of treatments and design healthcare services for Tennis Elbow sufferers.

Will what is found out about me be kept confidential?

The results of the questionnaires are only being used for research and will be confidential. They will not become part of your medical record and will not be discussed with your General Practitioner, Physiotherapist or Consultant.

Where will my personal information from this study be stored?

The information you provide, in the form of personal contact details and questionnaire answers, will be stored on an Encrypted University of Exeter computer. This will only be accessed by the research team. We will store your personal information for 6 months, to allow us to send you questionnaires during your participation in the study. The research data will be anonymised and will be stored for 10 years.

What will happen to the results of the study?

The results will be published in journals and publications which will help other researchers and healthcare professionals be informed about the work we have done. You will be able to obtain a copy of the research on request by contacting Jon Evans via email on j.evans3@exeter.ac.uk and a summary of the results will be published on the study website (available at http://bit.ly/2cPZDWl)
Your name and any identifiable details will not be included in the published articles.

How and when will I receive the shopping voucher?

The research team would like to offer you a £10 shopping voucher to thank you for completing the questionnaires. Once the research team receive the three questionnaires we have asked you to complete, we will post the voucher to you.

Who has reviewed the study?

The East of Scotland Research Ethics Service REC 2, which has responsibility for scrutinising all proposals for research on humans, has examined the proposal and has raised no objections from the point of view of research ethics. It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from the University of Exeter and Royal Devon and Exeter Foundation Trust, whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

Who else is taking part?

We will be asking for participants from GP practices, physiotherapy clinics and specialist elbow surgery clinics. We are doing this to be able to assess the whole spectrum of Tennis Elbow symptoms.

If you have a concern about any aspect of this study, you should ask the Patient Advice and Liaison Service (PALS team) who can be contacted on 01392 402093 or rde-tr.PALS@nhs.net. They will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through Patient Advice and Liaison Service at RD&E. If your concerns are about the way in which the study is being conducted then please contact the R&D department at the RD&E on research@rdeft.nhs.uk.
On behalf of the study team and the members of BESS thank you for taking the time to read this information sheet.

What to get involved? Here's what to do:

Complete the attached Consent Form

Post it back to us using the pre-paid envelope

The 3 sets of questionnaires will be sent to you in the post

Complete the questionnaires and return them using the pre-paid envelope

Once we receive the questionnaires we will post you a £10 Love2Shop voucher to thank you for your support.

Love2shop Vouchers are the UK's leading multi-retailer gift voucher. They can be redeemed in over 20,000 stores, restaurants and attractions.

If you have any further questions or require clarification please feel free to contact

Jon Evans
University of Exeter Medical School
Health Service Research Group
Smeall Building, Room JS03 St Lukes Campus
Exeter
EX1 2LU

Email: j.evans3@exeter.ac.uk
Tel: 01392 722750

Research supported by:

Participant Instructions

Thank you once again for participating in this study

- **Please follow the steps below**
- **Please answer all the questions as honestly as possible**
- **You may find some questions repetitive as some parts of the questionnaires are similar**
- **If you feel that you are unable to answer a question, for whatever reason, please leave it blank**

1. 1 week after completing the 1st questionnaire Complete questionnaire 2
2. 8 weeks after completing the 1st questionnaire Complete questionnaire 3
3. Post them back to us using pre-paid envelope

You also have to opportunity to complete a new Internet based questionnaire

If you would like to do this, when you complete a paper questionnaire please also log on to:

https://www.assessmentcenter.net/ac1/Assessments/TennisElbowUK

When you are asked for your Participant Number, please use the one on the top of your paper questionnaire

Primary Care	• Honiton Surgery Group, Marlpits Ln, Honiton EX14 2NY • Claremont Medical Practice, Exmouth Health Centre, Claremont Grove, Exmouth EX8 2JF • St Leonards Medical Practice, Athelstan Rd, St Leonards, Exeter EX1 1SB • Whipton Branch Surgery, 10 Whipton Village Rd, Exeter EX4 8AR • Somerset Partnership NHS Foundation Trust (SOMPAR), 2nd Floor, Mallard Court, Express Park, Bristol Rd, Bridgwater TA6 4RN
Secondary Care	• Royal Devon and Exeter NHS foundation trust, Barrack Rd, Exeter EX2 5DW • Plymouth Hospitals NHS Trust, Derriford Rd, Crownhill, Plymouth PL6 8DH • Torbay and South Devon NHS foundation trust, Lowes Bridge, Torquay TQ2 7AA
Physiotherapy	• Exmouth Hospital, Claremont Grove, Exmouth, Devon, EX8 2JN • Honiton Hospital, Marlpitts Road, EX14 2DE • Axminster Hospital, Chard Road, Axminster. Devon. Ex13 5DU • Crediton Hospital, Western Rd, Crediton EX17 3NH • Franklyn Community Hospital, Franklyn Dr, Exeter EX2 9HS • Torbay and South Devon NHS foundation trust, Lowes Bridge, Torquay TQ2 7AA • Somerset Partnership NHS Foundation Trust (SOMPAR), 2nd Floor, Mallard Court, Express Park, Bristol Rd, Bridgwater TA6 4RN

Ethical approval and Health Research Authority approval for the study - A Comparative Assessment of Patient Reported Outcome Measures for Lateral Elbow Tendinopathy in a UK Population

Please see the inserted documents

TAyside medical Science Centre
Residency Block Level 3
George Pirie Way
Ninewells Hospital and Medical School
Dundee DD1 9SY

Mr Jonathan Evans
MD Student - University of Exeter
Student - University of Exeter
Health Service and Policy Research Group
Smeall JS03 St Lukes Campus
EX1 2LU

Date: 3 March 2017
Your Ref:
Our Ref: LR/AG17/ES/0017
Enquiries to: Arlene Grubb
Direct Line: 01382 383848
Email: eosres.tayside@nhs.net

Dear Mr Evans

Study title: **Patient-Led Treatment in Lateral Epicondylar Tendinopathy –A feasibility trial assessing outcome measurement reliability, validity, and responsiveness in England**
REC reference: **17/ES/0017**
Protocol number: **1617/010**
IRAS project ID: **213445**

Thank you for your letter of 27 February 2017, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact please contact hra.studyregistration@nhs.net outlining the reasons for your request. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

You should notify the REC once all conditions have been met (except for site approvals

from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).
Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.
There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	Version	Date	
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity]	1	14 November 2016	
IRAS Application Form [IRAS_Form_31012017]		31 January 2017	
IRAS Checklist XML [Checklist_02022017]		02 February 2017	
IRAS Checklist XML [Checklist_27022017]		27 February 2017	
Letter from funder [British Elbow and Shoulder society funder letter]	1	03 August 2016	
Letter from sponsor [Sponsorship Confirmation]	1	13 December 2016	
Letters of invitation to participant [Invitation letter]	1	22 November 2016	
Other [Flowchart instructions to participant - Secondary care and Physio]	2	22 November 2016	
Other [HRA statement of activities]	1	07 December 2016	
Other [HRA schedule of events - GP]	1	07 December 2016	
Other [HRA schedule of events - Secondary care and Physio]	1	07 December 2016	
Other [Assessment centre - PROMIS questionnaire - Preview]	1	22 November 2016	
Other [PROMIS question bank - Pain]	1		
Other [PROMIS question bank - Upper extremity function]		16 October 2016	
Other [Patient Information - Secondary Care and Physio]	3	01 February 2017	
Other [Co supervisor CV - Chris Smith]	1	01 February 2017	
Other [Co supervisor CV - Vicki Goodwin]	1	01 February 2017	
Other [Co supervisor CV - Rod Taylor]	1	01 February 2017	
Other [Patient Information - Secondary Care and Physio]	3	23 February 2017	
Other [HRA statement of activities]	2	23 February 2017	
Other [HRA Statement of Activities (Secondary Care)]	1	23 February 2017	
Other [Ethics review response]	2	27 February 2017	
Participant consent form [Participant Consent]	3	01 February 2017	
Participant consent form [Participant Consent]	4	23 February 2017	
Participant information sheet (PIS) [Participant Information - GP]	3	01 February 2017	
Participant information sheet (PIS) [Participant Information - GP]	3	23 February 2017	
Referee's report or other scientific critique report [Scientific review support]	1	11 November 2016	
Research protocol or project proposal [Protocol]	3	01 November 2016	
Research protocol or project proposal [Protocol]		23 February 2017	
Summary CV for Chief Investigator (CI) [JPEvans CV]	1	07 December 2016	
Summary CV for student [Student short CV]		07 December 2016	
Summary CV for supervisor (student research) [Supervisor short CV]			
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Flowchart instructions to participants]	2	22 November 2016	
Validated questionnaire [Questionnaire Set]			
Validated questionnaire [Questionnaire Set]	4	23 February 2017	

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

Notifying substantial amendments
Adding new sites and investigators
Notification of serious breaches of the protocol
Progress and safety reports
Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our RES Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

17/ES/0017	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

Arlene Gubb

Dr Stuart Paterson
Alternative Vice Chair

Email: eosres.tayside@nhs.net

Enclosures: "After ethical review – guidance for researchers" [SL-AR2]

Copy to: Mrs Gail Seymour

Miss Lisa Treeby, Royal Devon & Exeter NHS Foundation Trust

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

TAyside medical Science Centre
Residency Block Level 3
George Pirie Way
Ninewells Hospital and Medical School
Dundee DD1 9SY

Mr Jonathan Evans
MD Student - University of Exeter
Student - University of Exeter
Health Service and Policy Research Group
Smeall JS03 St Lukes Campus
EX1 2LU

Date: 14 August 2017
Your Ref:
Our Ref: LR/17/ES/0017
Enquiries to: Mrs Lorraine Reilly
Direct Line: 01382 383878
Email: eosres.tayside@nhs.net

Dear Mr Evans

Study title:	**Patient-Led Treatment in Lateral Epicondylar Tendinopathy –A feasibility trial assessing outcome measurement reliability, validity, and responsiveness in England**
REC reference:	**17/ES/0017**
Protocol number:	**1617/010**
Amendment number:	**AM03 (for REC reference only)**
Amendment date:	**18 July 2017**
IRAS project ID:	**213445**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

- The Sub-committee thanked the research team for their responses and for amending the consent form with removal of statement 8 'I understand that I will receive a £10 Love2shop voucher one the questionnaires have been returned to the research team' as it was not applicable to the consent.
- The Sub-committee also noted the changes to the title on page 1 and information regarding storage of personal and research data information to the PIS.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Letters of invitation to participant [GP]	2	09 August 2017
Notice of Substantial Amendment (non-CTIMP)	AM03	18 July 2017
Other [Covering Email]		18 July 2017

Other [Response to additional information]		09 August 2017
Other [Email response to further info]		11 August 2017
Other [Response to further information]		14 August 2017
Participant consent form	6	09 August 2017
Participant information sheet (PIS) [Physio & Secondary Care (highlighted changes]	7	09 August 2017
Participant information sheet (PIS) [GP (highlighted changes)]	8	09 August 2017
Research protocol or project proposal [highlighted]	6	18 July 2017

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

17/ES/0017:	**Please quote this number on all correspondence**

Yours sincerely

L Reilly

Dr Roberta Littleford
Chair

E-mail: eosres.tayside@nhs.net

Enclosures: List of names and professions of members who took part in the review

Copy to: Miss Lisa Treeby, Royal Devon & Exeter NHS Foundation Trust
Mrs Gail Seymour

East of Scotland Research Ethics Service REC 2

Attendance at Sub-Committee of the REC meeting on 09 August 2017

Committee Members:

Name	Profession	Present	Notes
Dr Roberta Littleford	Assistant Director, Tayside Clinical Trials Unit	Yes	Chair
Mrs Lorna McLeish	Retired Genetic Counsellor	Yes	

Also in attendance:

Name	Position (or reason for attending)
Mrs Lorraine Reilly	REC Manager

NHS
Health Research Authority

Mr Jonathan Evans
MD Student - University of Exeter
Student - University of Exeter
Health Service and Policy Research Group
Smeall JS03 St Lukes Campus
EX1 2LU

Email: hra.approval@nhs.net

16 March 2017 – Reissued 17 May 2017

Dear Mr Evans,

Letter of HRA Approval

Study title:	**Patient-Led Treatment in Lateral Epicondylar Tendinopathy – A feasibility trial assessing outcome measurement reliability, validity, and responsiveness in England**
IRAS project ID:	**213445**
Protocol number:	**1617/010**
REC reference:	**17/ES/0017**
Sponsor	**University of Exeter Medical School**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

IRAS project ID	213445

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **213445**. Please quote this on all correspondence.

Yours sincerely

Alex Thorpe
Senior Assessor

Email: hra.approval@nhs.net

Copy to: *Mrs Gail Seymour, Sponsor's representative*
Miss Lisa Treeby, Royal Devon & Exeter NHS Foundation Trust, Lead R&D Contact
NIHR CRN Portfolio Applications Team

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity]	1	14 November 2016
IRAS Application Form [IRAS_Form_31012017]		31 January 2017
IRAS Application Form XML file [IRAS_Form_31012017]		31 January 2017
IRAS Checklist XML [Checklist_27022017]		27 February 2017
Letter from funder [British Elbow and Shoulder society funder letter]	1	03 August 2016
Letter from sponsor [Sponsorship Confirmation]	1	13 December 2016
Letters of invitation to participant [Invitation letter]	1	22 November 2016
Other [Patient Information - Secondary Care and Physio]	2	22 November 2016
Other [Flowchart instructions to participant - Secondary care and Physio]	2	22 November 2016
Other [HRA schedule of events - GP]	1	16 March 2017
Other [Assessment centre - PROMIS questionnaire - Preview]	1	22 November 2016
Other [PROMIS question bank - Pain]	1	
Other [PROMIS question bank - Upper extremity function]		16 October 2016
Other [Patient Information - Secondary Care and Physio]	3	01 February 2017
Other [Co supervisor CV - Chris Smith]	1	01 February 2017
Other [Patient Information - Secondary Care and Physio]	4	23 February 2017
Other [HRA statement of activities]	2	16 March 2017
Other [HRA Statement of Activities (Secondary Care)]	1	16 March 2017
Other [Ethics review response]	2	27 February 2017
Other [Co supervisor CV - Vicki Goodwin]	1	01 February 2017
Other [Co supervisor CV - Rod Taylor]	1	01 February 2017
Participant consent form [Participant Consent]	4	23 February 2017
Participant information sheet (PIS) [Participant Information - GP]	3	23 February 2017
Referee's report or other scientific critique report [Scientific review support]	1	11 November 2016
Research protocol or project proposal [Protocol]	3	01 November 2016
Summary CV for Chief Investigator (CI) [JPEvans CV]	1	07 December 2016

Summary CV for student [Student short CV]		07 December 2016
Summary CV for supervisor (student research) [Supervisor short CV]		
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Flowchart instructions to participants]	2	22 November 2016
Validated questionnaire [Questionnaire Set]		
Validated questionnaire [Questionnaire Set]	4	23 February 2017

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations, capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Mrs Gail Seymour
g.m.seymour@exeter.ac.uk
01392726621

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	The IRAS form originally submitted did not list participating sites in Part C. The applicant provided a draft IRAS form which listed the sites and participant identification centres that are intended to participate.
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	Two sets of Statement of Activities and Schedule of Events have been provided for the two site types participating in this study. The researcher intends for these to act as the agreement between the sponsor and site, for sites that are in England.

Section	HRA Assessment Criteria	Compliant with Standards	Comments
4.2	Insurance/indemnity arrangements assessed	Yes	Design and management of the study is covered by the sponsor's insurance policy. Conduct while on NHS premises will be covered by NHS indemnity. Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this research study.
4.3	Financial arrangements assessed	Yes	Funding will be provided as described in the Statement of Activities.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	The applicant has explained that contact details are required in order to follow up participants. Identifiers will not be entered onto the electronic questionnaire which will be stored in the USA.
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.
Due to the involvement of PIC sites, participating NHS organisations in England **will be expected to formally confirm their capacity and capability to host this research**. • Following issue of this letter, participating NHS organisations in England may now confirm to the sponsor their capacity and capability to host this research, when ready to do so. How capacity and capacity will be confirmed is detailed in the *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* section of this appendix. • The Assessing, Arranging, and Confirming document on the HRA website provides further information for the sponsor and NHS organisations on assessing, arranging and confirming capacity and capability.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).
The student researcher will be undertaking the majority of research activities. GCP training is not a generic training expectation, in line with the HRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
The student will not have direct and unsupervised access to participants. HR arrangements should not be required. If, however, the student does not already have a contractual arrangement with a site and enters the premises for the purpose of patient contact, then a Letter of Access and appropriate Occupational Health checks would be required.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.

Search strategy for Delphi study

Medline

1	Platelet-Rich Plasma/
2	Blood Transfusion, Autologous/
3	(platelet rich adj3 (plasma or therap* or fibrin)).tw
4	(PRP or PRF).tw.
5	((platelet adj3 (gel or concentrate)) or buffy layer).tw.
6	or/1-5
7	tendinitis.sh.
8	elbow.sh.
9	elbow joint.sh.
10	8 or 9
11	7 and 10
12	tennis elbow.sh.
13	11 or 12
14	epicondylitis.tw.
15	elbow.tw.
16	13 or 14 or 15
17	6 and 16
18	exp cohort studies/
19	cohort$.tw.
20	controlled clinical trial.pt.
21	epidemiologic methods/
22	limit 21 to yr=1966-1989
23	exp case-control studies/
24	(case$ and control$).tw.
25	or/18-20,22-24
26	"randomized controlled trial".pt.
27	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
28	(retraction of publication or retracted publication).pt.
29	or/26-28
30	(animals not humans).sh.
31	((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.
32	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.
33	29 not (30 or 31 or 32)
34	(review or review, tutorial or review, academic).pt.
35	(medline or medlars or embase or pubmed or cochrane).tw,sh.
36	(scisearch or psychinfo or psycinfo).tw,sh.
37	(psychlit or psyclit).tw,sh.
38	cinahl.tw,sh.
39	((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
40	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
41	(pooling or pooled or mantel haenszel).tw,sh.

42 (peto or dersimonian or der simonian or fixed effect).tw,sh.
43 (retraction of publication or retracted publication).pt.
44 or/35-43
45 34 and 44
46 meta-analysis.pt.
47 meta-analysis.sh.
48 (meta-analys$ or meta analys$ or metaanalys$).tw,sh.
49 (systematic$ adj5 review$).tw,sh.
50 (systematic$ adj5 overview$).tw,sh.
51 (quantitativ$ adj5 review$).tw,sh.
52 (quantitativ$ adj5 overview$).tw,sh.
53 (quantitativ$ adj5 synthesis$).tw,sh.
54 (methodologic$ adj5 review$).tw,sh.
55 (methodologic$ adj5 overview$).tw,sh.
56 (integrative research review$ or research integration).tw.
57 or/46-56
58 45 or 57
59 25 or 33 or 58
60 17 and 59

Delphi Primary Questions for Round 1

1. Which patient factors affect your decision to offer PRP as a treatment option? (e.g. age, gender, co-morbidities, occupation, high/low demand activities)

2. Which symptoms or signs would prompt you to consider PRP as a treatment option? (e.g. pain characteristics, symptom duration or examination findings)

3. Do you think there are any contraindications to PRP treatment? (e.g. co-morbidities, symptom or site specific pathology, previous conservative, pharmacological, injection or surgical interventions)

4. What is your opinion on the minimum and maximum concentration of platelets?

5. What is your opinion on the minimum and maximum volume of PRP?

6. Do you have a preference over leucocyte concentration?

7. Do you consider a preferred spin protocol (time, speed)?

8. What is your opinion on the use of anticoagulants (including additives used) as part of PRP preparation?

9. What is your opinion on PRP activation (including additives used) prior to administration?

10. Are there further PRP constituents or processing techniques you feel contribute to your choice of PRP preparation?

11. Do you consider an optimal, or cut-off time (in mins/hours) between processing and delivery of PRP?

12. What is your opinion on the use of local anaesthetic prior to PRP delivery?

13. Do you have a preferential needle size?

14. What is your opinion on the use of adjunct imaging (e.g. Ultrasound) in the delivery of PRP?

15. What is your opinion on injection technique (e.g. fenestration/peppering, single pass)?

16. What is your opinion on the number and frequency of PRP injections that should be administered for a single clinical episode?

17. What is your opinion on the use of immobilisation and/or activity modification?

18. What is your opinion on the administration and/or avoidance of analgesics?

19. How do you judge the outcome of PRP injections?

20. What is your opinion on repeated PRP administration, if the primary treatment was unsuccessful?

21. We would also like to invite you to provide any additional opinions on the use/preparation or delivery of PRP use in Lateral Epicondylar Tendinopathy

Delphi Secondary round feedback example

Document inserted

Round 2

Individual

Summary

Evans, Jonathan

Report

Dear ……

Thank you so much for your participation in this study assessing the level of consensus in Platelet-Rich Plasma (PRP) use in Lateral Epicondylar Tendinopathy. We have had a fantastic International response from both researchers and clinical users.

Please see your individual report for round 2 of the Delphi questionnaire process.

We would ask you to carefully read your results, and compare your scores with the group scores summarised in the graphs.

In keeping with the Delphi methodology, we would like to see if there is any convergence of opinion following this feedback. The validity of the consensus measurements will be greatly enhanced if you would be kind enough to complete the questionnaire a second time, giving you the opportunity to change your responses.

Please place your new score in the column on the right.

Please note that two statements have been altered following the synthesis of the groups free texts comments during the previous round. Please score the new statement.

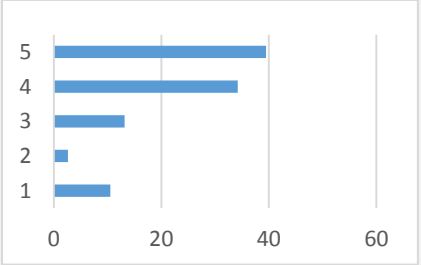
Once complete, please email this back to us using address j.evans3@exeter.ac.uk.

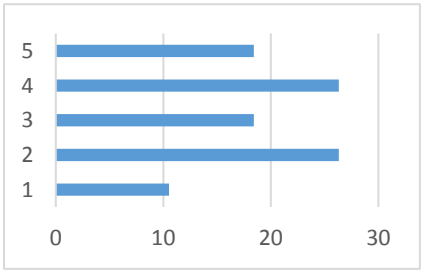
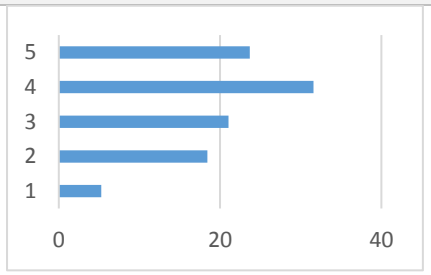
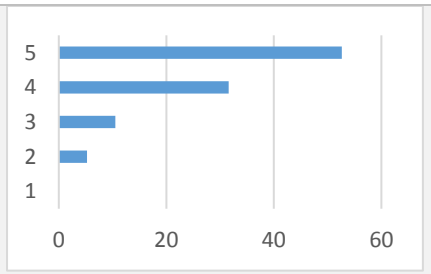
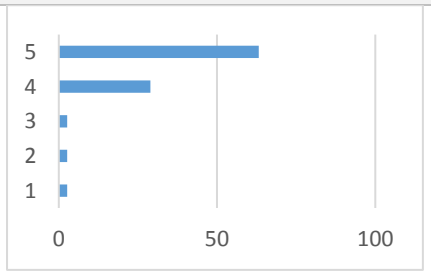
We will, of course, update you on the group responses following this final round of questionnaires.

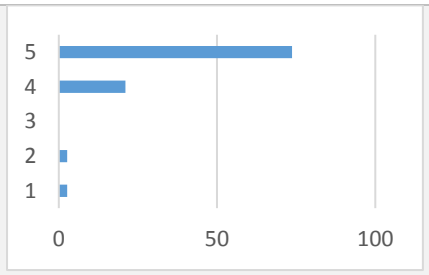
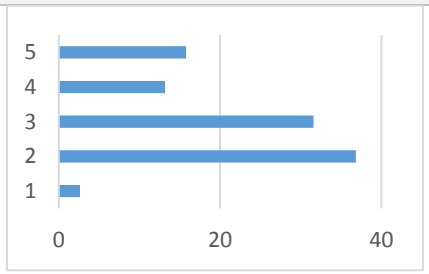
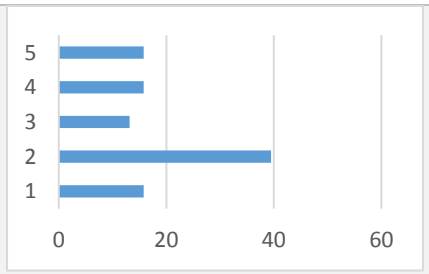
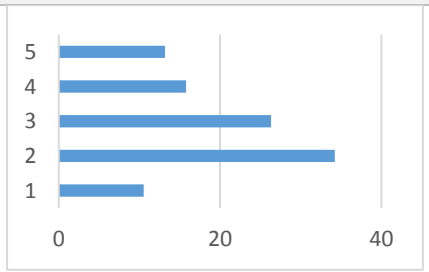
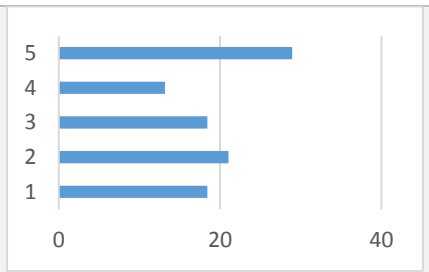
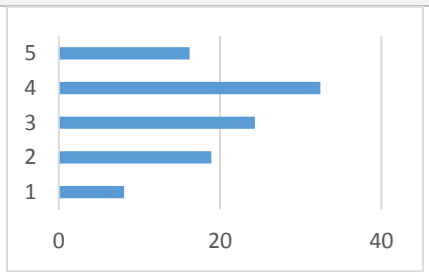
Kindest Regards,

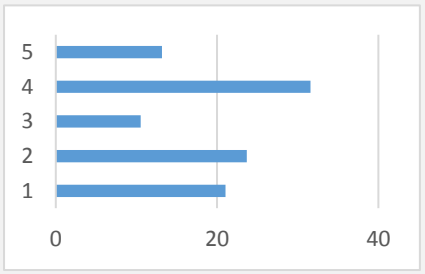
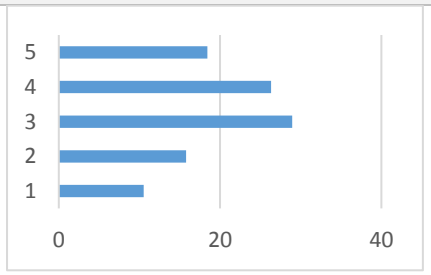
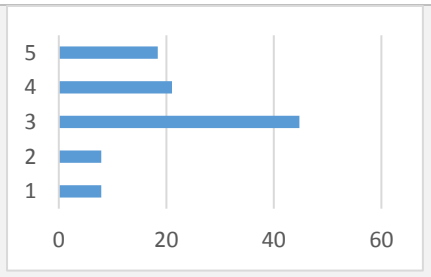
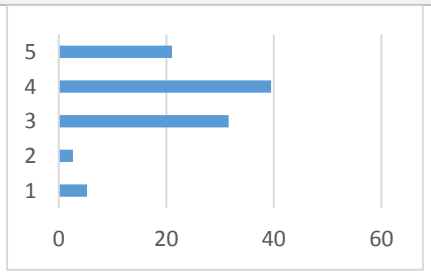
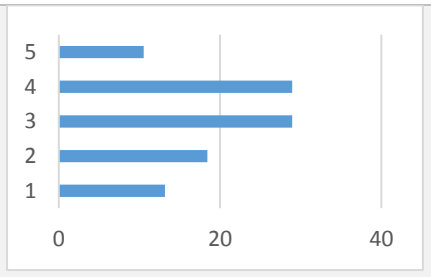
Jon Evans

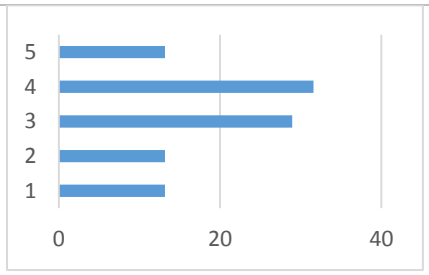
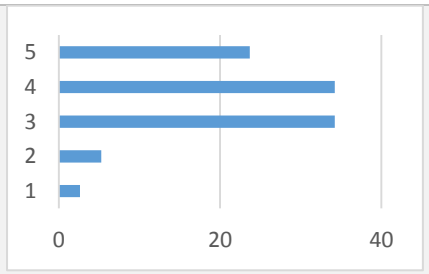
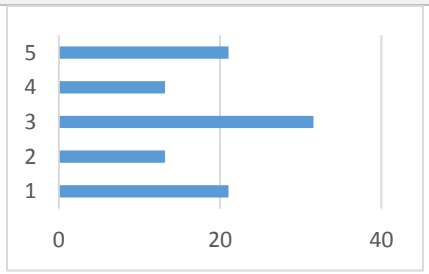
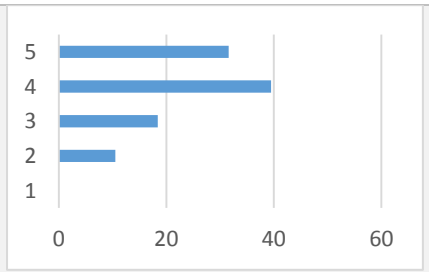
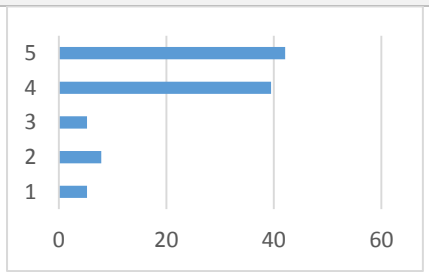
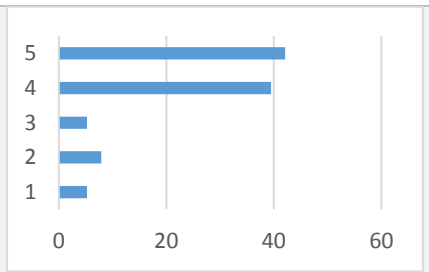
Orthopaedic Registrar and Post Graduate Researcher
Health Service and Policy Research Group
j.evans3@exeter.ac.uk Tel: +44(0)1392 722750
University of Exeter Medical School,
Room JS03, Smeall Building, St Luke's Campus,
Magdalen Road, Exeter, United Kingdom, EX1 2L

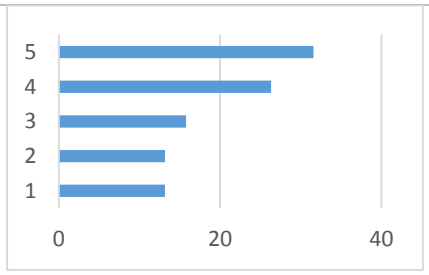
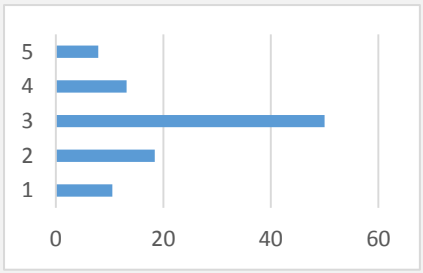
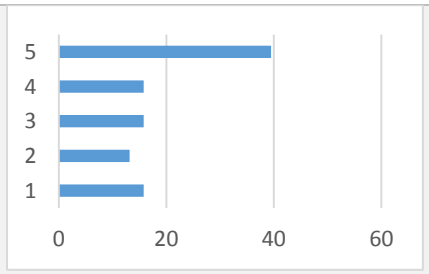
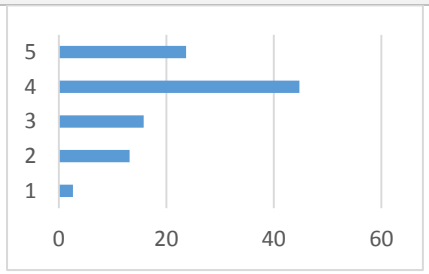
	Statement	Your Score	Group Scores 5 = Strongly agree 4 = Agree 3 = Neither agree or disagree 2 = Disagree 1 = Strongly disagree	New Score
Patient Selection	**1. PRP should only be considered in patients presenting with characteristic tennis elbow pain (lateral elbow pain exacerbated by wrist extension).**	5		

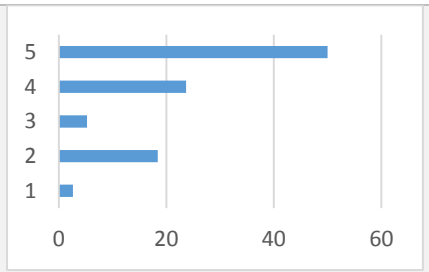
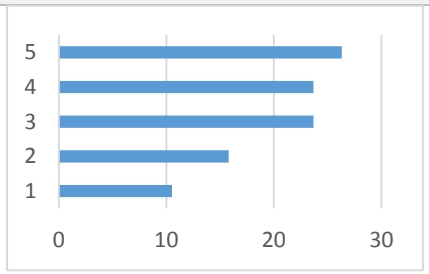
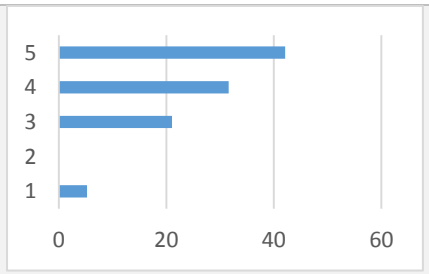
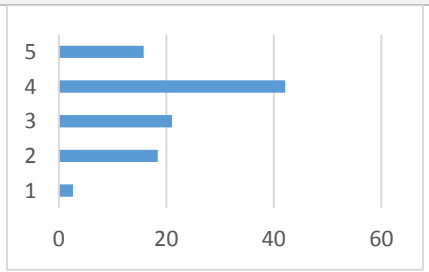
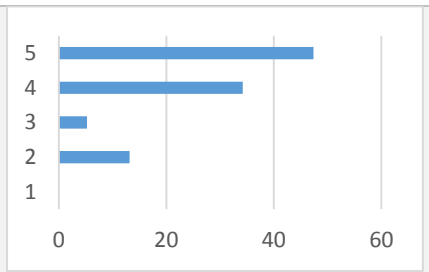
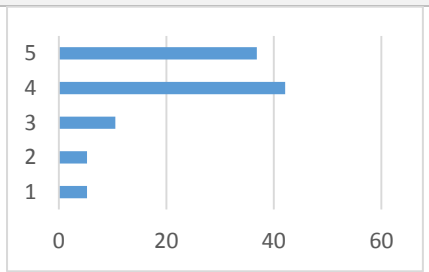
	2. PRP should only be considered following 6 months of conservative therapy. **Question modified due to free text comments.** **See below:**	2		/
	PRP should only be considered following 3 months of conservative therapy			New Score
	3. PRP should only be considered in patients who are experiencing considerable intrusion into their activities of daily life.	4		
	4. PRP treatment can be considered in patients over the age of 18, with no upper age limit.	5		
	5. PRP treatment can be considered in patients with manual or sedentary occupations.	5		

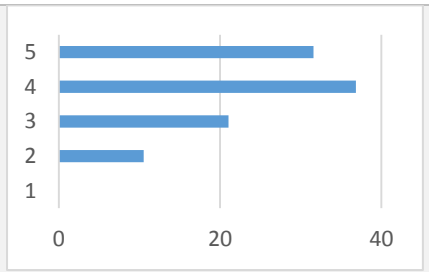
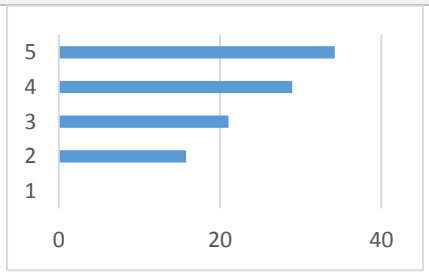
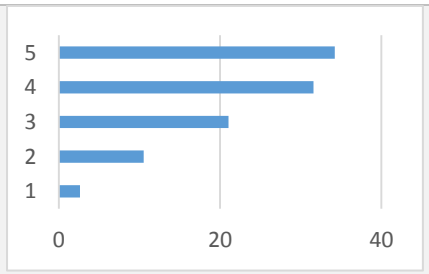
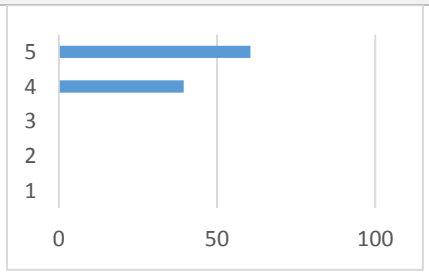
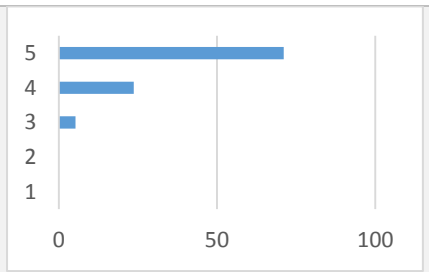
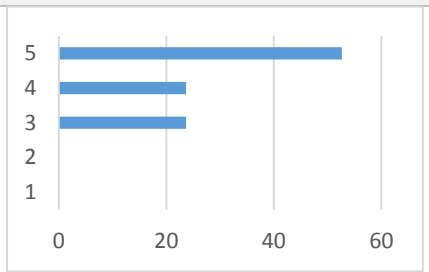
	6. PRP treatment can be considered in both high demand (e.g. sports people) and low demand (e.g. office worker) patients.	5		
	7. PRP is contraindicated in patients with a coagulopathy.	2		
Contraindications	**8. PRP is contraindicated in patients with large wrist extensor tendon tears.**	1		
	9. PRP is contraindicated in patients taking anticoagulant medication.	1		
	10. PRP is contraindicated in patients with a dependence on Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).	1		
	11. PRP is contraindicated in patients with known thrombocytopenia (less than 150,000 platelets per microlitre of whole blood).	1		

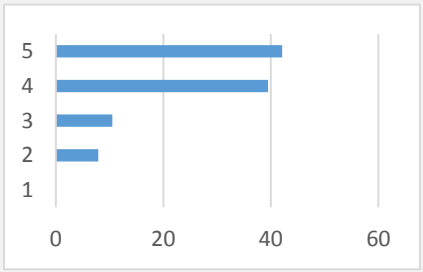
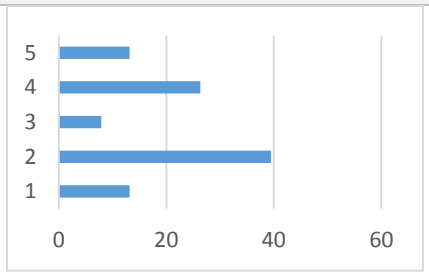
	12. PRP is contraindicated in patients who have received a steroid injection for treatment of their Lateral Epicondylar Tendinopathy, within 3 months of the intended PRP treatment date.	4		
Platelet-Rich Plasma Formulation	**13. The minimum recommended platelet concentration of injected PRP is 2x baseline.**	1		
	14. The maximum recommended platelet concentration of injected PRP is 5x baseline.	3		
	15. The minimum recommended volume of PRP is 1ml.	5		
	16. The maximum recommended volume of PRP is 3mls.	5		

	17. Leukocyte deplete PRP is the recommended formulation.	1		
	18. A single spin cycle of 20 minutes or less is recommended.	5		
	19. The addition of an anticoagulant to the whole blood sample is recommended prior to PRP preparation.	1		
	20. PRP activation, through the addition of additives prior to its administration, is not required.	5		
	21. Once processed, PRP should be administered within 30mins.	5		
Administration	**22. Local anaesthetic should be administered to the skin and subcutaneous tissue.**	4		

	23. Local anaesthesia should not be administered to the tendon.	1		
	24. A 19g needle is the recommended minimum size used to administer PRP. **Question modified due to free text comments.** **See below:**	1		/
	A 19g is the recommended MAXIMUM size used to administer PRP.			New score
	25. Ultrasound guidance should be utilised in all PRP injections for Lateral Epicondylar Tendinopathy.	3		
	26. Needle fenestration is recommended over a single injection technique.	5		

Administration Strategy	**27. Following the first administration of PRP, the patient should be reassessed to discern the need for repeated administration.**	5		
	28. A maximum of 3 administrations is recommended for each episode of Lateral Epicondylar Tendinopathy.	5		
	29. If symptoms recur following a successful course of treatment, PRP injection can be reattempted.	5		
	30. Surgery is recommended for patients in whom PRP treatment is not effective.	2		
Post-injection Management	**31. Immobilisation of the elbow following injection is not necessary.**	2		
	32. Light loads should be avoided for the first 48 hours following injection.	4		

	33. Heavy loads should be avoided for 6 weeks.	4		
	34. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should be avoided for 1 week prior to PRP administration.	3		
	35. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should be avoided for at least 2 weeks following injection.	5		
	36. Acetaminophen (Paracetamol) and weak opioid-based analgesia can be offered as required following PRP administration.	5		
Post-injection Assessment	**37. Clinical assessment is recommended to assess the outcome of PRP administration.**	5		
	38. A Visual Analogue Pain Score (VAS) should be collected in addition to clinical assessment.	5		

	39. A validated Patient-Reported Outcome Measure (PROM) (e.g. PRTEE, DASH, OES) should be collected in addition to clinical assessment.	5		
	40. Resolution of tendinosis on US or MRI can be utilised to assess outcome.	4		

Please add any further comment below:

Thank you so much for your continued participation.

We will contact you in due course with the results of this final round of questions.

Ethics approval for the study - Platelet-Rich-Plasma Injection in Lateral Elbow Tendinopathy: Exploring Expert Consensus with the Delphi Method

Document inserted

UNIVERSITY OF EXETER | MEDICAL SCHOOL

University of Exeter Medical School
Research Ethics Committee

Certificate of Ethical Approval

Research Institute/Centre: Institute of Health Research

Title of Project: Platelet-Rich-Plasma Injection Technique in Lateral Epicondylar Tendinopathy - Exploring consensus with the Delphi Method

Name(s) of Project Research Team member(s): Jonathan Evans, Christopher Smith, Professor Jose Valderas, Dr Vicki Goodwin and Professor Rod Taylor

Project Contact Point: Jonathan Evans

This project has been approved for the period

From: November 2016

To: November 2017

University of Exeter Medical School
Research Ethics Committee approval reference: Nov16/B/105

Signature:

Date: 4 November 2016

Name of Co-chair:
Rob Anderson, PhD

Your attention is drawn of the attached paper "Guidance for Researchers when Ethics Committee approval is given", which reminds the researcher of information that needs to be observed when Ethics Committee approval is given.

Application Reference Number 16/09/105

Ethical approval for the study - A Feasibility Randomised, Controlled Trial of Platelet-Rich Plasma injection vs Surgery for Chronic Lateral Elbow Tendinopathy

Document inserted

NHS
Health Research Authority
South West - Exeter Research Ethics Committee
Whitefriars
Level 3
Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1335
Fax:0117 342 0445

25 February 2016

Mr Chris Smith
Orthopaedic Consultant
Royal Devon and Exeter Hospital
Princess Elizabeth Orthopaedic Centre
Royal Devon and Exeter Hospital
Barrack Road, Exeter
EX2 5DW

Dear Mr Smith

Study title:	**Platelet Rich Plasma vs Open Surgery in the Treatment of Chronic Lateral Epicondylar Tendonopathy (Tennis Elbow)A Pilot Randomized Control Trial**
REC reference:	**16/SW/0007**
IRAS project ID:	**179045**

Thank you for your letter of 10 February 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mrs Naazneen Nathoo, nrescommittee.southwest-exeter@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).
Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Cover Letter]	1	10 February 2016
GP/consultant information sheets or letters [GP letter]	1	25 September 2015
Instructions for use of medical device [CE mark]		04 November 2015
IRAS Checklist XML [Checklist_01122015]		01 December 2015
IRAS Checklist XML [Checklist_10022016]		10 February 2016
Non-validated questionnaire [Pain Log]	1	25 September 2015
Participant consent form [Consent]	2	05 February 2016
Participant information sheet (PIS) [Patient Information]	3	05 February 2016
REC Application Form [REC_Form_01122015]		01 December 2015
Research protocol or project proposal [Study Protocol]		04 November 2015
Summary CV for Chief Investigator (CI) [CV]		04 November 2015
Validated questionnaire [OES]	1	04 November 2015
Validated questionnaire [DASH]	1	04 November 2015
Validated questionnaire [PRTEE]	1	04 November 2015

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements
The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

16/SW/0007	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp. **Dr Denise Sheehan**
Chair

Email:nrescommittee.southwest-exeter@nhs.net

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: *Mr Chris Gardner*
Ms Joanne Lowe, Royal Devon And Exeter NHS Foundation Trust

Patient information sheet and consent form for the PRP vs Surgery feasibility RCT

Document inserted

Patient

Royal Devon and Exeter NHS
NHS Foundation Trust

Information Sheet

A Randomised Controlled Trial of Interventions for Tennis Elbow

You have been invited to take part in a research study. Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information and discuss it with your friends and relatives if you wish. Please ask us if there is anything that is not clear or if you would like more information and please take your time to decide whether or not you wish to take part.

What is the purpose of this study?

Tennis Elbow is a common condition. There are two treatments provided by hospitals when the symptoms are longstanding. These are injection of a concentrated form of your own blood called Platelet-Rich-Plasma (PRP) or a

surgical procedure called an Open Debridement. The first is conducted in the outpatient clinic and the second requires attendance for a day-case surgical procedure. No study has compared the two procedures to ascertain if one is better than the other.

Why am I being chosen?

You have been found to have chronic tennis elbow.

We give you this diagnosis as you have had pain on the outside of the elbow for a long time. It is also likely that the treatments you have tried have not made you any better.

Though tennis elbow often improves by itself, in a small number of people the symptoms persist and do not get better with pain killers or physiotherapy. Patients tell us that the pain often interferes with their job and their ability to do things around the home. In this case surgery or injections are sometimes recommended by your surgeon.

These treatments are designed to reduce your pain and increase the amount of activity you can do.

There is evidence that injection of Platelet-Rich-Plasma or Surgery can rapidly improve your pain. Both of these treatments are used both in the UK and the rest of the world.

Platelet-rich-plasma is a form of your own blood that has been taken by injection. It is then concentrated and injected into the area of your arm that is painful. It is thought that this kick-starts healing in this area. Surgery involves removing the tissue around your elbow that is causing you the pain.

Until now the normal treatment at the Royal Devon and Exeter Hospital has been surgery. Though common in other hospitals in the UK, this is the first time we will be using PRP injections at the Royal Devon and Exeter Hospital.

Who is organising the study?

The Chief Investigator is Mr Chris Smith, Consultant Shoulder Surgeon at the Royal Devon and Exeter Hospital. Patients from all of the elbow surgeons are being invited to take part in this study.

Will anyone be paid?

No patients are being paid to take part in this study.

There is no commercial sponsorship of this study. The staff involved are receiving their normal salary with no other benefits.

We are receiving a small grant of £10,000 which covers the cost of running the study.

What will happen if I participate?

If you agree to participate you will be randomly assigned to either receive PRP injections or surgery.

The only difference to your management will be that you will either attend hospital as a day patient for a surgical procedure that requires a general anaesthetic, or the outpatient department to have the injection procedure. The injection is given

twice. They will be given a week apart which will require 2 visits to the outpatient department..

Both procedures take approximately 1 hour to complete.

If any other condition is discovered during either procedure it will be discussed with you and then treated routinely.

We will follow-up your progress following your treatment. We would like you to attend an outpatient appointment at 6 weeks, 3 months, 6 months and 1 year after your treatment. This is 2 or 3 extra appointments than we would normally do after Tennis Elbow treatment.

At each follow-up appointment we will examine you and ask you to complete 4 questionnaires that ask about your symptoms and allow us to track your progress. The questionnaires should take around 10 minutes to complete at each clinic visit.

Do I have to take part?

No. Please remember that if you take part in this study it is entirely voluntary and that if you decide to take part you are free to leave the study at any time without having to give a reason as to why you wish to do so. If you decide not to take part,

this will in no way affect your future medical care. If you decide to take part you will have this information sheet to keep and you will be asked to sign a consent form that indicates that you have agreed to take part and that you understand that you can withdraw from this study at any time.

What are the possible benefits of taking part?

You will help us understand more about the most appropriate way to treat tennis elbow – a common condition in the general population.

What are the risks of taking part?

We do not think there are any increased risks associated with participation in this research project. Both treatments are common and safe.

Will what is found out about me be kept confidential?

All information collected about you during this study will be kept confidential in the same way that all of your medical notes are. Confidentiality, privacy and

anonymity will be ensured in the collection, storage and publication of any data that this trial generates in accordance with current regulations.

What will happen to the results of the study?

The results will be published in journals and publications which will help other surgeons become better informed about the work we have done. This will help influence their practice so that they too can treat Tennis Elbow with a greater understanding. You will be able to obtain a copy of the research on request by contacting 01392- 403560 and asking for Sian Gallacher. You name and details will not be included in the published articles.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called the NRES Committee South West -Exeter, to protect your interests. This study has been reviewed and given favourable opinion by the NRES Committee South West – Plymouth and Cornwall.

Who else is taking part?

12 people are being asked to take part. 6 randomised platelet-rich-plasma injection and 6 randomised for surgery. These are people who match the project's selection criteria. No-one, either the patients or the research team is being paid to take part. The study is a pilot study and will hopefully lead on to further work in this area.

Contact for further information:

If you have a concern about any aspect of this study, you should ask to the Patient Advice and Liaison Service (PALS team) who can be contacted on 01392 402093 or rde-tr.PALS@nhs.net. They will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through Patient Advice and Liaison Service at RD&E. If your concerns are about the way in which the study is being conducted then please contact the R&D department at the RD&E on research@rdeft.nhs.uk.

Thank you:

Thank you for taking the time to read this information sheet. You will receive a copy of what you have signed/read as well as the contact details of the research team. See below.

If you have any further questions or require clarification please feel free to contact:

Mr Chris Smith, Chief Investigator, via the Hospital on 01392 411611.

Mrs Sian Gallacher, Surgical care Practitioner. 07798-893517.

Royal Devon and Exeter NHS
NHS Foundation Trust

Certificate of Consent

Title of study:	Platlet Rich Plasma VS Open Surgery in the Treatment of Chronic Lateral Epicondylar Tendonopathy (Tennis Elbow) A Pilot Randomised Control Trial
Name of Principal Investigator:	Mr C D Smith
Centre/Site number:	Royal Devon & Exeter NHS Foundation Trust
Study number:	1510155
REC approval number:	16/SW/0007
Participant ID:	

PLEASE INITIAL THE BOXES IF YOU AGREE WITH EACH SECTION:

1. I have read the information sheet dated…….…… for the above study and have been given a copy to keep. I have had the opportunity to ☐

consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the Research Team only, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. I understand that the information will be kept confidential. ☐

4. I understand that my Doctor will be informed of my participation and also if any of the results of tests done as part of the research are important for my health. ☐

5. I understand that I will not benefit financially if this research leads to the development of a new treatment or test. ☐

6. I know how to contact the research team if I need to. ☐

7. I agree to participate in this study ☐

- _____ _____ _____
- Name of Patient Date Signature
- _____ _____ _____

- Name of Person
- taking consent Date Signature taking consent

Topic guide for qualitative data

PRP vs Surgery RCT feasibility trial: Interview topic guide – Intervention arm

Introduction

Thank you for agreeing to be interviewed today. The interview is to find out about the care you received as part of the tennis elbow trial. Everything you say will be treated as strictly confidential. The information you provide will be useful in helping us design new Tennis elbow trials including improvements on the one you have been involved in. Are you happy for me to turn on the recorder?

Background

- Tell me briefly how long and how bad your tennis elbow was prior to being referred to the hospital?
    - Prompt: Duration, activities, work interference, pain level 0-10
- What treatments had you previously received?
    - Prompt: injections, physio, over the counter etc
        - If injections – type/number

Expectations and decisions to seek referral to secondary care

- What made you decide to seek referral to secondary care (hospital consultant)?
    - Prompt: GP advice, personally sought, allied health care professional opinion, friends/family members opinion.
- What were your expectations about what the consultant would offer you?
    - Prompt: Were you aware of surgery as a treatment for tennis elbow? Did you know a trial was taking place? Where you aware that injections were an option?

Expectations and decisions to participate in the PRP trial

- What did you think when it was mentioned that a trial was being run?
    - Prompt: Did it make you feel reassured/anxious?
- How did it make you feel that the trial treatments were surgery or PRP injection?
    - Prompt: Do you think this is a fair comparison? Were the reasons for comparing these two treatments explained to you? Did you have a strong preference of treatment?
- How do you feel about being randomised to the PRP treatment?
    - Prompt: What were your initial thoughts? Would you have rather been given the surgery at that stage?
- Do you feel you have an understanding of how/why PRP works?
    - Was it explained to you? Have you read around the subject – what have you found out independently?

Experience of care as part of the trial

- How did you find the injection process?

    - Prompt: Did you feel safe? Was the injection process explained to you? Did you feel prepared for the injection?
- Can you tell me how the injection felt?
    - Prompt: Can you describe the discomfort? How bad was the pain out of 10? What this more/less than expected?
- How did you feel straight after the injection?
    - How comfortable were you? Did you feel safe to go home straight away? Did you have someone with you? Was this necessary?
- How did you feel in the first 48 hours after the injection?
    - How was the pain level? Did you use the sling? Did you take pain killers? How much did you use the arm?
- How did you feel in the first 5-7 day after the injection?
    - How was the pain level? Did you use the sling? Did you take pain killers? How much did you use the arm?
- How do you feel these experiences differ from having surgery?
    - How do you feel about having an anaesthetic? How do you feel about the recommendation not to use the arm for 6 weeks and no driving?

Experience of follow-up

- Has the injection worked? Is so how long did it take to be effective? If not, have your symptoms changed?
    - How long till you were pain free? How long did you modify your activities? Did you follow the rehab protocol you were given?

- Were you able to return to the work and social activities that you had hoped to?

- How did you find the experience of being part of a trial?
    - Did you mind the extra appointments? Did you mind the questionnaires? Could this process have been improved (postal/electronic/telephone communication or follow/up)?
- Would you recommend this treatment?
    - Would you have the same treatment again? Would you rather have surgery?

- What have you told your friends and family about the injection?
- What would you say to someone undergoing this treatment?

Further comments/ improvements that could be made

Thank you [Turn off recorder]

Example transcript from patient interview

Interview 1

Interviewer: [00:00] Fantastic, and so, if we just go right back to your experience of your tennis elbow, could you just tell me briefly how long you di—you'd had your tennis elbow prior to being referred to hospital?

Participant: [00:10] Um, it started [00:12] april last year.

Interviewer: [00:13] Okay, fine, fine, and in terms of how it was interfering with your life at that time, just tell me briefly what you were and weren't able to do and how bad the pain was.

Participant: [00:24] Um, it was [00:25] the lack of sleep really.

Interviewer: [00:26] Oh.

Participant: [00:26] Um, I could sleep for about an hour and a half at the time, and then the pain would wake [00:30] me up, and then, I would probably get to sleep again, and that would happen all through the night for about [00:36] [crosstalk]

Interviewer: [00:36] Really? Okay.

Participant: [00:37] Um, so that was probably the worst part of it really.

Interviewer: [00:39] Yeah, okay, fine, fine.

Participant: [00:40] Um, yeah, it just interfered with everyday life because the job that I did.

Interviewer: [00:43] Yeah.

Participant: [00:43] It, everything was just painful and uncomfortable really.

Interviewer: [00:46] Yeah, absolutely, okay. Um, what treatments did you try previously, before coming to hospital?

Participant: [00:51] Um, I tried, um, [00:54] non steroidals but they didn't touch it

Interviewer: [00:55] Mm hm.

Participant: [00:56] And, um, I had steroid injections, which didn't touch it either.

Interviewer: [01:00] Did you just have the one steroid injection then?

Participant: [01:02] Yeah, yeah, I wouldn't let her do it a second time [01:04]

Interviewer: [01:04] [crosstalk] Really? [laughs] Okay, fine, but that didn't make any difference at all, not even [01:08] [crosstalk]

Participant: [01:08] It, they di-, I just hurt, but if it made any difference, I would have done it again, but it made no difference [01:12] at all.

Interviewer: [01:12] No difference at all, okay, fine, fine, and that was just done by the GP? They didn't use ultrasound or anything like that?

Participant: [01:20] No, no, it was just done by my GP.

Interviewer: [01:22] Just done by the GP, fine, fine. So, what was it that made you seek referral to hospital? Was it, was it your idea, or your GP's idea? How did it come about?

Participant: [01:30] Um, I went—I had a week off, and the pain was just worse, and my friend kept on [01:36] at me all the time cuz I was in such pain.

Interviewer: [01:38] Mm.

Participant: [01:38] And the [01:38] [inaudible] came back and actually saw the [01:40] nurse at the medical center.

Interviewer: [01:41] Okay.

Participant: [01:42]He said, "I think you need to do something." He said, "I'd like you to have an X-ray, but I don't think they're gonna find anything."

Interviewer: [01:47] Hm.

Participant: [01:48] And, so, I had an X-ray for and went back to my gp to ask for some steroids 20 [01:49] and she said, "No, [01:53] this has gone on too long, we need to refer you know.

Interviewer: [01:54] [crosstalk] too far, fine, fine, and what were your expectations about coming [02:00] to the hospital to see the consultant? Were you aware of any particular treatments that you would have been keep on trying or anything like that?

Participant: [02:06] Uh, well, doing the job I do, I [02:08] had sort of been online [02:10] see what [02:10] sort of treatments there were. I had read about PRP [02:12]

Interviewer: [02:11] Mm, [crosstalk]

Participant: [02:13] Um, they were doing it in London a lot, but I think [02:15] somewhere like that that.

Interviewer: [02:16] Mm.

Participant: [02:16] Um, so, I'd read about that, but [02:17] it sounded quite good [02:18] because you don't have to have an anaesthetic [02:19].

Interviewer: [02:20] Yeah, fine.

Participant: [02:21] I don't really like anaesthetics but—and I saw [02:22] that there was the surgery that you could do [02:23] [inaudible] what was gonna be offered really.

Interviewer: [02:27] Fine, fine, were you aware that we doing a trial at all or was that [02:30] [crosstalk]?

Participant: [02:30] No. Not until I came the first time I saw whoever it was I saw [02:34] [phonetic]

Interviewer: [02:35] Fine, fine, and what did you think when they mentioned that there was a trial being run?

Participant: [02:39] Yeah, I was quite interested cuz, again, because of what I do, it, you know—people don't put themselves forward [02:44]your never going to know [02:45] [inaudible]

Interviewer: [02:46] Mm.

Participant: [02:46] And to be fair the pain was so bad I was up for trying anything.

Interviewer: [02:49] Mm, fair enough, and—and what did you think about the fact where you were comparing surgery and this PRP? Did you think it was a fair comparison? You thought it was an appropriate type of question that we were asking?

Participant: [03:00] Yeah, apparently, [03:00] because I'd been on the internet recently [03:01] [crosstalk]

Interviewer: [03:00] Mm, yeah.

Participant: [03:02] They—they—they [03:02] and it was the comparison with the steroid injection that they were doing [03:03] wasn't it and the PRP [03:06]

Interviewer: [03:06] Yeah, yeah.

Participant: [03:07] Um, well, it seemed a bit different cuz we felt it—it cost we use steroid injections quite a lot [03:11] and it is quite short term.

Interviewer: [03:12] Yeah.

Participant: [03:13] Um, I know—I know that [03:16] tennis elbow is supposed to be self regulating [03:17] and that after [03:18] a certain length of time it sorts itself out anyway.

Interviewer: [03:18] Mm, mm, you think so. Mm.

Participant: [03:21] Um, but I was bit like, "If anything can make this go quicker, then I'll a have a go, and this PRP is the way to go, and [03:26] if that's what I can have [03:28] and avoid having surgery, then that's what I want to do [03:30] [inaudible]

Interviewer: [03:28] Mm. Sure, and, um, y—you're obviously a much more knowledgeable patient than most, [laughs] but how did you feel when you got randomized to the PRP? Were you reassured and happy that that was the treatment you were gonna be given?

Participant: [03:43] Yeah, cuz that was the—the was, uh—during the reading and stuff, that [03:46] [crosstalk] my treatment of choice from—from my reading, and that was [03:48] [crosstalk] what I preferred.

Interviewer: [03:46] Mm. Mm.

Participant: [03:51] So, it was quite nice to see the [03:53] treatment was going to be PRP.

Interviewer: [03:54] Fair enough, good, good, and although this is—is in its infancy, what—do you manage to get any [04:00] information from the internet about how the PRP worked and why?

Participant: [04:04] Yes, cuz there's—I can't think what hospital it was, but one of the hospitals came up with quite a lot of information, and it talked about how it worked, and—

Interviewer: [04:10] Mm.

Participant: [04:11] Um, cuz they use a lot of sports—other sports injuries that may [04:14] [phonetic] [04:15] [crosstalk]

Interviewer: [04:15] Yeah, they do, mm hm.

Participant: [04:16] Yeah, and, um, it just [04:19] sounded to me, if you can avoid messing around new joints, then it's gotta be a good thing, really.

Interviewer: [04:24] Yeah, absolutely, good, and so, tell me about the injection itself. Uh, how did feel [04:30] about the injection process, in terms of the safety and how it was explained? Did you feel prepared for the injection?

Participant: [04:35] Yes, yeah, well, I was prepared for how much it was gonna hurt.

Interviewer: [04:38] Mm.

Participant: [04:39] And—which probably is a good thing.

Interviewer: [04:40] Mm.

Participant: [04:41] And I thought that the recovery after the first one was much quicker [04:46] [crosstalk] [it was time to] [04:47] [phonetic] go home cuz I booked a couple days of work, thinking it was gonna be that sore, and actually, to be fair, it was fine.

Interviewer: [04:47] Yup.

Participant: [04:55] The first time was fine. I didn't have any issues with that at all.

Interviewer: [04:57] Okay.

Participant: [04:58] And it was the second one [05:00] that was the bummer, really.

Interviewer: [05:00] Really.

Participant: [05:01] Yeah.

Interviewer: [05:02] Okay, and tell me about the recovery from that one.

Participant: [05:05] Um, the recovery was a good couple of hours post-injection. It was still incredibly painful — really, really sore — um, and I—I—I don't think I'm a wimp, but it was [05:17] really painful.

Interviewer: [05:17] Mm.

Participant: [05:19] Um, and it a couple of days before my arm felt comfortable to use normally.

Interviewer: [05:23] Really? Yeah.

Participant: [05:25] And—and it—it lasted about four to six weeks. It—it [05:28] started more comfortable. [05:30] It's not very comfortable at the moment.

Interviewer: [05:32] No, okay, okay, cuz that—the pain, I think, that you experienced during the injection, as we discussed before, was this—this all bit—a bit of learning curve for all of us, and we're surprised at—that it is quite as painful, and in terms of the pain that you experienced, how bad was it out of ten, if you were to give it a score? Maybe [05:50] [crosstalk]

Participant: [05:50] When you did it, it was [05:51] [crosstalk]

Interviewer: [05:51] Yeah, mm.

Participant: [05:52] Eleven.

Interviewer: [05:53] Really?

Participant: [05:54] Yeah.

Interviewer: [05:54] [crosstalk]

Participant: [05:55] And I—I—I don't like to think that I, you know—I think I'm quite—I can cope [06:00] with that, but, yeah, I could have got up and walked away from that one.

Interviewer: [06:02] Yeah, absolutely, no, and I think you [06:05] [crosstalk]

Participant: [06:05] And I don't know if that was just me or whether other people have said the same.

Interviewer: [06:07] The other people have said exactly the same. Yeah.

Participant: [06:09] Yeah.

Interviewer: [06:10] And that's it. It's been a bit of a surprise to us of how uncomfortable it's been, and I think, like I said to you, most people have said, with the benefit of hindsight and [06:19] You know they probably still would have had the injection, but it makes us a bit uncomfortable that it's caused you so much discomfort, you know. So—

Participant: [06:27] Yeah, uh, I've think I said it to you before, but [is it definitely all right if] [06:30] it was the other way round, if I'd had that much pain the first time I'm not sure I would come back for the second one.

Interviewer: [06:32] Yeah. I think that's absolutely—well, that's very [06:36] [crosstalk]

Participant: [06:36] That's human nature, isn't it?

Interviewer: [06:39] Of course.

Participant: [06:39] Um, and probably the fact that it didn't—it was uncomfortable when it was done the first place time [06:43] cuz it was [06:44] certainly far worse the second time..

Interviewer: [06:43] Mm. Sure, and what do you think about how all these experiences would differ [where you're] [06:50] were you having the operation? So you think you would have been more comfortable, or do you have any [06:58] [crosstalk] idea of how the surgery would have been?

Participant: [06:58] Well, I imagine it probably would have been [07:00] more painful for a longer length of time cuz any sort of surgery tends to be [07:04] [crosstalk] cuz you've got ripped tissues to repair.

Interviewer: [07:04] Mm, yeah, yeah, it does.

Participant: [07:07] And, and when you start making holes in anything, it's gonna take a while to recover.

Interviewer: [07:11] Mm.

Participant: [07:12] And—and at least I could go back to work and—and do relatively normal stuff. So—

Interviewer: [07:18] Sure.

Participant: [07:19] And you [07:19] [inaudible] for six-week recovery period, which, to me, is an awful long time not be able to do [07:23] [crosstalk] normal duties at work.

Interviewer: [07:23] Yeah. Absolutely, all right. So, how long did you think it was until [07:30] you felt there was a difference from the injection in a positive way?

Participant: [07:34] Um, with the second one, I would say probably about four—about a month or so.

Interviewer: [07:38] Mm.

Participant: [07:38] And it—it—it—because you suddenly realize that you can do stuff and it's not hurting [07:41].

Interviewer: [07:42] Yeah, sure, okay. So, how quickly did you find that you returned to doing things that you—would have otherwise caused you [07:50] quite a lot of discomfort?

Participant: [07:56] Uh, I wanna say about six weeks. I was [07:57] [crosstalk] experie—I was asking other people to do stuff [08:00] [crosstalk] at work.

Interviewer: [07:57] About six weeks. Yeah, sure. Okay, good, good.

Participant: [08:03] Because I could get away with asking other people to do it, I did.

Interviewer: [08:06] Yeah, of course.

Participant: [08:07] I could do it, but I always knew I had done it, if that makes sense.

Interviewer: [08:10] Mm, absolutely, and, um, to finish, really, how did you find the experience of being part of trial, in terms of the fact we'd done extra appointments for you, you filled loads of questionnaires, and—do you think anything about that process could have been improved or you would have done differently?

Participant: [08:26] No, not really, um, I appreciate that, if you don't do the—the—the pain [08:30] scoring stuff um, again, when [you're used to] [08:30] [phonetic] doing pain scoring at work, [08:32] [crosstalk] that wasn't, you know, [very bad] [08:35] [phonetic]

Interviewer: [08:32] Yeah.

Participant: [08:37] Um, no, I think it was all very good [08:38] [inaudible] save [08:39] [phonetic] me. Everybody has been really helpful. Um—

Interviewer: [08:43] good.

Participant: [08:44] My only concern is my left elbow is very painful, [08:45] [crosstalk] you know?

Interviewer: [08:45] Yes, [laughs] yes.

Participant: [08:48] [laughs] [inaudible from laughter] that one really.

Interviewer: [08:47] [laughs] I think—I think [08:49] [inaudible] mentioned in your—your recent appointment. Yeah, we'd sort of need to see how things go with that, but, um, there's, you know—if you do have problems with that, you should get in touch, you know, if it's getting worse and worse [09:00] and worse and we're—we're [09:01] [crosstalk]

Participant: [09:01] Yeah, [09:01] [inaudible] that just because, as a rule, I don't carry shopping home because that's what I find—still find quite uncomfortable, [09:09] [crosstalk] carrying, you know, shopping.

Interviewer: [09:09] Mm.

Participant: [09:11] Um, and today, actually, it would be easier to carry it in my right hand, which is my treated arm cuz my left arm, uh—my left arm is getting that painful there.

Interviewer: [09:19] Mm, okay, well, yeah, I've—well, we'll see how we go. [laughs] See how we go. Um, I suppose, ultimately, in terms of this treatment, would you have the same thing again if you were offered [09:30] [crosstalk] it again?

Participant: [09:30] Yeah.

Interviewer: [09:31] You would?

Participant: [09:32] Yes.

Interviewer: [09:33] Good, and what have you told your friends and family about it?

Participant: [09:36] Yeah, no, um, obviously, especially, my—my work colleagues at work are all really interested in it and somewhat [09:42] [crosstalk]

Interviewer: [09:41] Mm.

Participant: [09:43] And, um, no, yeah, I, I would do it again. I would prefer this sort of thing to surgery, and I was, as I've said [09:49] [crosstalk] to that before, [09:50] then if you get [09:51] tennis elbow then, if you have to [09:53] opportunity to try that, then I would try it.

Interviewer: [09:49] Yeah. You would? Good, well, that's, that's positive to finish on. I think, that's—that's really helpful.

Participant: [10:00] You might need to hit me over the head with a mallet to inject it [10:01] [crosstalk]

Interviewer: [10:01] [laughs] Well, that is the question. So, were you to be offered it but we'd say, this time, we'd give you an anesthetic, would you go for that, or do you think that negates the positive side of it [10:13] [crosstalk]

Participant: [10:13] Um, I think that will be, for me, personally, [10:15] [inaudible] the anesthetic [10:17] [crosstalk] that I wouldn't really want to do.

Interviewer: [10:17] Mm.

Participant: [10:19] Maybe, um, I think there's, like, mild sedation, like, when you go to the dentist [10:22] and have stuff like that.

Interviewer: [10:22] Yup.

Participant: [10:24] I'd probably do that. I wouldn't want local cuz, to me, if you put a local in, by the time [10:30] you've got the local in, you [10:31] might have well have done it.

Interviewer: [10:31] Yeah, absolutely, yup.

Participant: [10:33] So, to me, that's how I look at it.

Interviewer: [10:34] Mm.

Participant: [10:35] Um, I wouldn't really want the [10:36] GA to do it and if I had to man-up and do it again, I'd man-up and do it again, but [10:40] [inaudible from laughter]

Interviewer: [10:40] [laughs] All right.

Participant: [10:41] But, you know, there's different sorts of people, isn't there?

Interviewer: [10:43] Yeah, exactly, that's absolutely right. Great, is there anything else you can think of, [10:46] [phonetic] that you'd like to mention?

Participant: [10:50] No, I don't think so. Like, the—the only thing I find now is—is that I find that it's more painful, but it's not doing anything and [10:56] [crosstalk] less painful to—to use it, but it's [10:59] more when its at rest [inaudible] [crosstalk] and stuff, but it [11:00] [crosstalk] other than that, eh.

Interviewer: [10:56] Yeah. And it stiffens up. Yeah, we'll see how you, see how you go, but, uh, look, I think I've said to you before that I think the surgical people tend to experience exactly the same at this stage, with this stiffness in their activity, and it still causes [11:15] [crosstalk] them a problem, and—

Participant: [11:15] Yeah. And that's the thing with surgery, isn't it? [11:19] Then I assume they have to have physical therapy to get them up and working [11:21][inaudible] uh, after doing all that.

Interviewer: [11:21] Absolutely, yeah.

Participant: [11:23] And then, that's just more time, isn't it, where it's actually—I've not really lost any time [11:28] out of my either working life [11:30] or my normal life really.

Interviewer: [11:31] No. No, you were able to get working straight away [11:32] [crosstalk]

Participant: [11:32] [crosstalk] normal.

Interviewer: [11:34] Yeah, absolutely, great, lovely, well, thanks for talking, [11:37] [phonetic] That was really helpful. Well, [11:38] [crosstalk]

Participant: [11:38] [crosstalk]

Interviewer: [11:39] Uh, we'll document all that down and scratch our heads and have a think about it.

Coding Matrix

Coding Matrix – Domains and Themes

Symptoms	**Interference**	**Knowledge**
Pre-procedural pain Procedural pain Post-procedural pain Stiffness Numbness/tingling	Pre-procedure interference with work Pre-procedure interference with lifestyle Pre-procedure interference with sleep Post-procedure interference with work Post-procedure interference with lifestyle Post-procedure interference with sleep	Knowledge of new treatments Instigation of referral Expectations of referral Knowledge of trial Sources of information Expectation of treatment
Reflection	**Managing symptoms**	
Burden of being in a trial Being in a trial Recommendation or not of treatment Safety If randomised to surgery Improvements	Pre treatment Post Treatment	

Codes from qualitative analysis

Qualitative Summary Document

Research questions

1. What was the participant experience of the intervention (PRP)?
2. What was the participant experience of the trial?
3. Is PRP an acceptable and appropriate intervention for further study?

Themes directly associated with Question 1

Procedural

Procedural pain

Experience of health professionals

Safety

Post Procedural

Post-procedural pain

Post-procedural treatments

Post-procedure interference with quality of life

Themes directly associated with Question 2

Knowledge of trial

Reflection on being in a trial

Burden of being in a trial

Reflection on possibly being randomised to surgery

Improvements

Themes directly associated with Question 3

Procedural pain

Safety

Repeat treatment

Recommendation or not of treatment

Coding explanation

Procedural pain

Pain caused by the injection itself.

Experience of health professionals

The behaviours of health professionals and experience of the patient at the time of delivery of the injection.

Safety

The perceived safety of the environment and procedures surrounding the delivery of the injection and the direct post-injection time period.

Post-procedural pain

The pain experienced by the patients in the days and months following the injection and the interval between the first and second injection.

Post-procedural treatments

The use and experience of analgesia, slings, ice packs etc by the patient, both advised by health professionals and self-administered.

Post-procedure interference with quality of life

The patient experience of the impact of the intervention on their quality of life.

Reflection on being in a trial

The patient's own reflections on the process of being part of a trail.

Burden of being in a trial

The patients views on the burden of extra follow-up appointments and data collection through the use of questionnaires.

Reflection on possibly being randomised to surgery

The patient's reflection on how they would have felt had they been randomised to the surgical arm of the trial.

Improvements

The patient's opinion on any improvements that could be made in a further similar trial. This includes procedural improvements, patient information and post procedural care.

Repeat treatment

The patients views on being offered the treatment again in the future.

Recommendation or not of treatment

The patient's assessment of whether or not they would recommend the treatment to a friend or family member and what advise they would give this person.

Feasibility Randomised Controlled Trial - checklists

Please see inserted documents

CONSORT – Pilot and Feasibility checklist

CONSORT – PRO extension items checklist

MIBO checklist

TiDiER checklist

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	204
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	204
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	206-208
	2b	Specific objectives or research questions for pilot trial	207-208
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	208
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	209
	4b	Settings and locations where the data were collected	209
	4c	How participants were identified and consented	209
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	210-213
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	213-214
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N/A
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	N/A
Sample size	7a	Rationale for numbers in the pilot trial	209
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	210
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	210
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	210

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	210
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
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Recruitment	14a	Dates defining the periods of recruitment and follow-up	215
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Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	216
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	216
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	N/A
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	217-229
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	223-227
	19a	If relevant, other important unintended consequences	N/A
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	233
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	233
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	229-232
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	233
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	208
Protocol	24	Where the pilot trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	209
	26	Ethical approval or approval by research review committee, confirmed with reference number	208

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.
*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Table 1. Information for Reporting Randomized Controlled Trials With Patient reported Outcomes

Section/Topic	Item	CONSORT 2010 Statement Checklist Item	PRO-Specific Extensions Are Prefaced by the letter *P*	Page
		Title and Abstract		
	1a	Identification as a randomized trial in the title		
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[b]	P1b: The PRO should be identified in the abstract as a primary or secondary outcome	204
		Introduction		207
Background and objectives	2a	Scientific background and explanation of rationale	Including background and rationale for PRO assessment	
	2b	Specific objectives or hypotheses	P2b: The PRO hypothesis should be stated and relevant domains identified, if applicable	207
		Methods		
Trial design	3a	Description of trial design (such as parallel, factorial), including allocation ratio		
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		
Participants	4a	Eligibility criteria for participants	Not PRO-specific, unless the PROs were used in eligibility or stratification criteria	
	4b	Settings and locations where the data were collected		
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered		
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	P6a: Evidence of PRO instrument validity and reliability should be provided or cited if available including the person completing the PRO and methods of data collection (paper, telephone, electronic, other)	213
	6b	Any changes to trial outcomes after the trial commenced, with reasons		
Sample size	7a	How sample size was determined	Not required for PRO unless it is a primary study outcome	
	7b	When applicable, explanation of any interim analyses and stopping guidelines		
		Randomization		
Sequence generation	8a	Method used to generate the random allocation sequence		
	8b	Type of randomization; details of any restriction (such as blocking and block size)		
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned		
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions		
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		
	11b	If relevant, description of the similarity of interventions		
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	P12a: Statistical approaches for dealing with missing data are explicitly stated	N/A
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		
		Results		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	The number of PRO outcome data at baseline and at subsequent time points should be made transparent	219
	13b	For each group, losses and exclusions after randomization, together with reasons		
Recruitment	14a	Dates defining the periods of recruitment and follow-up		
	14b	Why the trial ended or was stopped		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Including baseline PRO data when collected	219
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Required for PRO results	216
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, the estimated effect size, and its precision (such as 95% confidence interval)	For multidimensional PRO results from each domain and time point	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	Including PRO analyses, where relevant	220-222
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)		
		Discussion		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	P20/21: PRO–specific limitations and implications for generalizability and clinical practice	232
Generalizability	21	Generalizability (external validity, applicability) of the trial findings		
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	PRO data should be interpreted in relation to clinical outcomes including survival data, where relevant	232
		Other Information		
Registration	23	Registration number and name of trial registry		
Protocol	24	Where the full trial protocol can be accessed, if available		
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders		

MIBO Platelet Rich Plasma

Section / Topic	Item number	Checklist item	Reported on Page No
Study design	1	Study conducted in accordance with CONSORT (RCT), STROBE (cohort, case-control or cross-sectional) or PRISMA (meta-analysis) guidelines	208
	2	Relevant institutional and ethical approval	208
Recipient details	3	Recipient demographics (including age and gender)	216
	4	Comorbidities (including underlying diabetes, blood dyscrasia, inflammatory conditions, pre-existing joint pathology and smoking status)	215
	5	Current anti-inflammatory or anti-platelet medications	216
Injury details	6	Diagnosis (including relevant grading system and chronicity)	216
	7	Results of any pre-operative imaging	215
	8	Previous surgical or biological treatments for current injury	215
Intervention	9	Intervention described sufficiently to enable replication	211-212
	10	Operative findings	218
Whole blood processing	11	Whole blood storage environment (including concentration and volume of anticoagulant, temperature and light exposure)	211-212
Whole blood characteristics	12	Whole blood platelet, differential leukocyte and red cell analysis of all samples	Not undertaken
PRP processing	13	PRP processing described sufficiently to enable replication (including commercial kit details and Spin protocol)	211-212
	14	Platelet recovery rate of protocol	211-212
	15	PRP storage temperature and light exposure	211-212
	16	Time between blood drawing, PRP processing, activation and delivery	211-212
PRP characteristics	17	PRP format (for example liquid, gel, membrane)	211
	18	PRP platelet, differential leukocyte and red cell analysis of all samples	212-217
Activation	19	Activation described sufficiently to enable replication (including volume and concentration of activating agent)	211
Delivery	20	Point of delivery (intraoperative and/or postoperative or serial)	211
	21	PRP delivery described sufficiently to enable replication (including volume delivered, concomitant use of stem cells or cytokines, and details of carrier or scaffold)	217
Post-operative care	22	Rehabilitation protocol sufficiently described to enable replication (including immobilization and physical therapy)	212
Outcome	23	Outcome assessments include functional outcomes and recording of complications (including infection and need for further surgery). If performed radiographic outcomes, physical examination findings, return to activities and satisfaction.	218-222

TIDieR
Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	211	
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	207	
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	211	
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	211	
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	212	
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	211-212	
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	212	

	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	211	
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	211	
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A	
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	224	
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	217	

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).
‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).