Protocol for a prognostic systematic review

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Title
Prognostic models for the outcome of conservative treatment including physiotherapy in adults with rotator cuff disorders: a systematic review

1. Background and rationale
1.1. Description of disease
Shoulder complaints rank among the commonest musculoskeletal disorders and are frequently seen in medical and physiotherapy practice (Feleus et al. 2008; Karels et al. 2006; Kooijman et al. 2013). Disorders related to the structures within the subacromial space, i.e. the rotator cuff and the subacromial-subdeltoid bursae, have consistently been reported to form the largest subgroup (44% to 89%) of shoulder disorders in clinical practice (Kooijman et al. 2013; van der Windt et al. 1995; van der Windt et al. 1996; Virta et al. 2012). The rotator cuff, a deep cuff of four tendons around the shoulder, is often involved in a progressive degenerative continuum (Cook & Purdam 2009; Lewis 2010). Widely used diagnostic labels for disorders related to the rotator cuff include “subacromial pain”, “shoulder impingement” or “rotator cuff disease”. These encompass a wide range of structural pathologies from rotator cuff tendinopathy to partial or full-thickness rotator cuff tears. The overall prevalence of rotator cuff tears in the general population has been reported as > 40% (Reilly et al. 2006), and is strongly associated with increasing age (Beaudreuil et al. 2007). Rotator cuff-related disorders can significantly impair shoulder function and health-related quality of life (Ryliskis et al. 2009), and can lead to prolonged sick leave (Virta et al. 2012).

1.2. Diagnosis
Clinical signs and symptoms associated with rotator cuff disorders include pain in the shoulder with movements of the arm or at rest, pain-related impairment of shoulder
function and, in more advanced cases (specifically in the presence of a rotator cuff tear), abnormalities on tests of rotator cuff function and integrity (Hanchard et al. 2013). Verification of the presence of a rotator cuff tear requires diagnostic imaging (e.g. ultrasonography (US), magnetic resonance imaging (MRI)) (Lenza et al. 2013; Smith et al. 2011).

1.3. Treatment

Current international guidelines for the management of rotator cuff disorders recommend conservative treatment as the first-line treatment, with surgery reserved for non-responders (Beaudreuil et al. 2010; Haute Autorité de Santé 2005; Robb et al. 2009; American Academy of Orthopaedic Surgeons 2011), or for patients with full-thickness rotator cuff tears, in whom early consideration of surgery is commonly recommended.

A variety of conservative and surgical options is available (Braun et al. 2013; Gebremariam et al. 2011; Littlewood et al. 2011; Hanratty et al. 2012; Seida et al. 2010). Conservative treatment usually consists of medical care (e.g. advice, oral medication, corticosteroid injections) as well as physiotherapy (e.g. exercises, manual therapy). Surgical treatment options include a variety of arthroscopic, mini-open or open approaches to subacromial decompression, debridement or repair. Surgical intervention is a more invasive approach, and not without risk such as infection and iatrogenic injury. Even though the overall rate of complications of rotator cuff surgery appears to be low, shoulder arthroscopic procedures also carry a small but real potential for life-threatening complications (Marecek & Saltzman 2010; Randelli et al. 2012).

1.4. What is known

Despite the available range of treatment options the published literature on the management of rotator cuff disorders reflects a considerable uncertainty about the specific indications for any treatment, whether conservative or surgical (Beaudreuil et al. 2010; Haute Autorité de Santé 2005; Robb et al. 2009; American Academy of Orthopaedic Surgeons 2011). A growing number of studies provide evidence that both conservative and surgical approaches can lead to successful outcomes in patients with any rotator cuff disorder, but there is a paucity of direct comparisons. As yet, only a small number of studies have investigated the comparative effectiveness
of conservative versus surgical treatment (Braun et al. 2013; Dorrestijn et al. 2009; Gebremariam et al. 2011; Tashjian 2013; Kukkonen et al. 2014). Overall, these studies provide no evidence for any clinically relevant differences in outcomes between conservative and surgical treatment. Nonetheless, there is a well-documented increase in the rates of surgical interventions for rotator cuff disorders in many countries (Colvin et al. 2012; Svendsen et al. 2012; Yu et al. 2010).

1.5. Prognostic research and rationale for the planned review

Unnecessary surgery is obviously undesirable, but so is ineffective conservative treatment. It would consequently benefit both patients and health care providers if likely responders and, by corollary, non-responders to conservative interventions, could be identified at the commencement of their care pathway. Early identification would help preserve patients from unnecessary or prolonged suffering, reduce uncertainty and anxiety and limit exposure to the risk of surgery. Also, optimization of treatment selection would save time and effort of both patients and health professionals, and would promote the optimal distribution of available resources.

The importance of predicting which patients will respond to particular treatments has recently been recognised, prompting an increased interest in musculoskeletal prognostic research (Stanton et al. 2010). There has been a corresponding and timely development in related prognostic research methodology, including prognostic models to guide treatment decisions (Moons et al. 2009; PROGRESS 2013; Cochrane Prognosis Methods Group 2013). Prognostic models, which are derived from combinations of multiple prognostic factors (a prognostic factor being “any measure that, among people with a given health condition, is associated with a subsequent clinical outcome”, (PROGRESS 2013)), aim to predict the risk of future clinical outcomes in patients or healthy people. Research on individual prognostic models encompasses three phases: 1) the development of a model (including its internal validation); 2) the external validation of the model; and 3) the investigation of the clinical impact of the model (Steyerberg et al. 2013).

To our knowledge, this is the first systematic review to synthesize the available evidence on prognostic models for the outcome of physiotherapy in adults with rotator cuff disorders.
2. Objectives
This review aims to identify, evaluate and synthesize the available research on prognostic models for the outcome conservative treatment including physiotherapy in adults with shoulder pain and coexistent rotator cuff disorders. By this, we aim to provide a concise resource to facilitate clinical decision-making but also to identify any research gaps.

3. Methods:
3.1. General
This protocol was developed in the light of current methodological recommendations by the Cochrane Prognosis Methods Group (Cochrane Prognosis Methods Group 2013) and the PROGgnosis RESearch Strategy (PROGRESS) Partnership (PROGRESS 2013) as well as related relevant publications (e.g. (Altman 2001; Altman 2009; Bouwmeester et al. 2012; Geersing et al. 2012; Hayden et al. 2006; Hayden et al. 2009; Hayden et al. 2013; Hemingway et al. 2013; Huguet et al. 2013; Steyerberg et al. 2013). This review protocol will be registered in the international Prospective Register of Systematic Reviews, PROSPERO (PROSPERO 2013).

3.2. Criteria for selecting studies for this review
3.2.1. Types of studies
This review will include primary studies specifically designed to explore prognostic models for the outcome of conservative treatment including physiotherapy in adults with rotator cuff disorders. According to the PROGRESS partnership (PROGRESS 2013), prognostic models „utilise multiple prognostic factors in combination to predict the risk of future clinical outcomes in individual patients“. Inclusion will encompass all phases of prognostic model research (PROGRESS 2013; Steyerberg et al. 2013), i.e. any studies designed to develop, validate or assess the clinical impact of prognostic models. We will consider any longitudinal research designs, but inclusion will be restricted to prospective studies, including randomised controlled trials (RCTs). Inclusion will also be restricted to study reports published in English, as our resources do not allow for inclusion of reports in other languages (but see 3.3.2. for approach to searches regardless of language, and documentation of findings).
3.2.2. Types of participants
We will include studies on populations of adult patients (age ≥ 18 years) who have a diagnosis of a non-traumatic rotator cuff disorder. We define a rotator cuff disorder as shoulder pain that is related to an impairment or dysfunction of the rotator cuff tendons (supraspinatus, infraspinatus, teres minor or subscapularis). Diagnoses of tendinitis, tendonitis, tendinopathy or tear, as applied to these tendons, are our explicit focus. We will also include studies whose inclusion criteria are symptoms or mechanisms consistent with rotator cuff disorders e.g. subacromial pain, or subacromial or shoulder impingement. We will not actively seek studies concentrating on subacromial–subdeltoid bursitis per se although, due to its intimate relationship to the rotator cuff, incidental involvement of this bursa may well occur in our population of interest.

We will include research on the full spectrum of rotator cuff disorders as defined above, and as diagnosed by clinical examination and/or diagnostic imaging (e.g. ultrasonography (US), magnetic resonance imaging (MRI) or magnetic resonance arthrography (MRA)). We define a non-traumatic disorder as a disorder that is considered unrelated to a substantial trauma involving the shoulder (e.g. shoulder dislocation). No restrictions will be made on the duration or severity of symptoms at the time of baseline assessment. We will include studies regardless of the setting of care (e.g. primary or secondary care, inpatient or outpatient settings).

We will exclude studies focusing on patients who are pain-free or have trauma-related conditions. We will also exclude studies on disorders of the long head of biceps or calcific tendinitis. Ideally, included studies will specifically exclude other potential sources of shoulder pain (e.g. frozen (contracted) shoulder, glenoid labrum pathologies, previous substantial shoulder trauma, previous surgery at the affected shoulder, neck disorders, multisite musculoskeletal pain, relevant systemic diseases and disorders, or neurologic disorders). Studies in which 85% or more of participants satisfy our criteria will also be included. We anticipate that in some studies there will be insufficient characterisation of participants (e.g. other potential causes of shoulder pain might not be considered). The impact of including these studies will be evaluated by sensitivity analyses.
3.2.3. **Types of interventions**

Inclusion will be restricted to studies evaluating conservative treatment including physiotherapy with or without adjunctive medical treatment (e.g. advice, oral analgesics, steroid injections) as part of a non-surgical care pathway. We define physiotherapy as any type of exercises and/or manual mobilisation as commonly supplied by physiotherapists. Additional physical therapy modalities (e.g. electrotherapy, thermotherapy) may be an additional part of the physiotherapy treatment, but only if supplied as a supplement to exercises and/or manual mobilisation. Adjunctive treatments that are usually not considered core elements of physiotherapy practice (e.g. acupuncture or osteopathic musculoskeletal interventions) are permissible. Studies on non-surgical interventions that do not include physiotherapy (e.g. corticosteroid injections alone) will be excluded. No restrictions will be made on the duration or frequency of the physiotherapy. Studies with two or more groups, in which any other non-surgical, surgical or no treatment is compared with non-surgical treatment including physiotherapy, will only be considered if there is separate prognostic modelling for the latter.

3.2.4. **Types of prognostic factors**

We will include studies that model potential prognostic factors elicited at the baseline assessment. We anticipate that these factors will typically include demographic (e.g. age or shoulder function), clinical (e.g. measures of symptom severity) or diagnostic imaging (e.g. type of structural rotator cuff defect) characteristics. Studies modelling potential prognostic factors that were not elicited from the baseline assessment will be excluded.

3.2.5. **Types of outcomes**

Primary outcomes addressed by this review will be

- Pain
- Shoulder disability (as measured by patient-reported outcome measures (PROMs, e.g. Shoulder Pain and Disability Index or Western Ontario Rotator Cuff Index))
- Adverse events

Secondary outcomes will be

- Health-related quality of life (HrQoL)
• Sick leave (i.e. time off work due to the shoulder problem)
• Global perceived change (GPC)
• Structural progression from no tear or partial tears to full-thickness tears (as determined by US, MRI or MRA)

Any eligible study must present a prognostic model in relation to at least one of these outcomes. Ideally, study authors should provide information on the psychometric properties of all measurements used.

3.2.6. Types of analysis
For inclusion, studies must include or evaluate a prognostic model of multiple prognostic factors, but no restriction will be placed on the phase (modelling, validation or evaluation of impact) or the type of analysis. Details will be documented.

3.3. Search methods for identification of studies
3.3.1. Search strategy
Acknowledging the known difficulties with the retrieval of prognostic model research in electronic databases (Geer sing et al. 2012; Walker-Dilks et al. 2008), we have given careful attention to the development of a sensitive search strategy with which we expect to detect most of the available prognostic model studies that are relevant to our review question. The final search strategy was informed by a preliminary strategy that we had developed in 2011 preparatory to a prognostic study in the field. We have revised and updated this strategy for the purpose of the present review. We tested multiple combinations of search terms for the population, interventions, comparisons, prognostic factors and outcomes, but decided on a broad strategy including only search terms relating to or describing the population and interventions. The final selection of search terms was informed by findings from test searches, as well as by the experience of previous searches for two intervention systematic reviews in the field (Braun & Hanchard 2010; Braun et al. 2013). We further tested various available search filters for the identification of prognostic research (e.g. Altman 2001; Geersing et al. 2012; Haynes et al. 2005; Wilczynski & Haynes 2004; Wilczynski & Haynes 2005; Walker-Dilks et al. 2008). For the Medline search we will use a recently developed and validated search string for clinical prediction models studies by Geersing et al. (2013, with a small supplement) but, due to concerns about the currency and performance of some of the available filters, we decided to
search without such filters in the other databases. See Appendix for the Medline (EBSCO format) strategy.

We will search the following electronic databases: Medline (PubMed), Embase, Cochrane CENTRAL, Cinahl and PEDro. We will further search the WHO International Clinical Trials Registry Platform (ICTRP). We are aware of the relevance of further sources such as citation indices, hand searches and grey literature, but our resources do not allow for their consideration for this review. The databases’ “related articles” functions will be applied to all relevant findings. We will further search the bibliographies of relevant articles and existing systematic reviews. Even though inclusion will be restricted to publications in the English language (see also 3.2.1.), we will search regardless of language and document any findings in other languages. We will incorporate the findings from our previous (2011) searches.

3.3.2. Search and selection process

The process of study selection will follow current methodological guidelines (Higgins & Green 2011) and will be documented by a PRISMA flow diagram (Moher et al. 2010). One author (CB) will conduct the searches and two authors (CB, NH) will independently perform study selection. The findings will then be compared. In case of disagreement, consensus will be sought through discussion, or through involvement of a third independent researcher. Reasons will be given for all final exclusions.

3.4. Data collection and analyses

3.4.1. Data collection

Two researchers (CB, NH) will independently collect data using a piloted data extraction form. Data extraction will include the following key items:

- Publication details: e.g. authors, year of publication
- Study design: type of study and phase of research (i.e. model development, external validation or investigations of clinical impact)
- Study characteristics: e.g. year and place of study, setting (primary or secondary care, inpatient or outpatient)
- Sample size and sample size justification
- Population characteristics: type of rotator cuff disorder, inclusion/exclusion criteria, sample characteristics (e.g. age, sex, employment)
- Intervention characteristics: e.g. content, duration, dosage, compliance
• Duration of follow-up, losses to follow-up
• Outcomes: primary and secondary outcomes, outcome measurements
• Prognostic factors: numbers, definitions and details of factors and factor measurements
• Analyses: details of methods of multivariable prognostic modelling (including any adjustments and methods of dealing with missing data)
• Results for each outcome: final statistical model(s), predictive performance/accuracy statistics with their confidence intervals. All prognostic factors considered in the analyses will be presented regardless of “statistical significance”.

Where necessary, we will attempt to contact study authors for unreported study details and data. We will not impute missing data.

3.4.2. Assessment of study quality and risk of bias
We will use the Prediction Model Studies Risk of Bias Tool (PROBAST 2013) for the assessment of risk of bias in the included prognostic model studies. We have been in contact with Robert Wolff (a member of the PROBAST steering group) on the use of this new instrument (Wolff 2013). Publication of the instrument is planned for the first half of 2014. The PROBAST tool is being developed to assess risk of bias in prediction model studies and includes the following five key domains: 1) participant selection, 2) outcome, 3) predictors, 4) sample size and flow, 5) analysis. Depending on the stage of development of PROBAST at the time when we will assess the studies for our review, we will either use the current pre-final version, or the final version. We will conduct supplementary risk of bias assessments for other study types, using appropriate instruments (e.g. the Cochrane Collaboration’s risk of bias tool (Higgins & Green 2011) for RCTs investigating the clinical impact of a prognostic model).

Risk of bias will be assessed independently by two researchers (CB, NH). In case of disagreement, consensus will be sought through discussion, or through involvement of a third independent researcher.

3.4.4. Analysis and synthesis
We will provide a narrative summary of the findings of all included studies and for each outcome. In particular, this will include the presentation of all prognostic factors included in the final prognostic model, specification of the prognostic model, its actual outcome as well as its prognostic accuracy. We are planning to categorize the results by the type of cuff disorder (non-tear populations (rotator cuff tendinitis/"subacromial impingement"/"subacromial pain"), PTT, FTT, or mixed populations), and by type of treatment (physiotherapy alone versus physiotherapy plus adjunctive medical treatment). Should we decide on any other categorisation, we will note this and provide a rationale. We will synthesise the results in consideration of the phase of research, i.e. according to if (and how) the presented models have been externally validated or tested for clinical impact.

If a sufficient number of good quality studies on the same prognostic model are available, we will summarise the performance of the model through a meta-analysis. If appropriate, exploratory meta-regression will be performed to assess sub-group and continuous covariate effects (such as type of disorder, sex or treatment parameters).

Acknowledgements
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Declarations of interest
The authors are currently involved in an ongoing (non-funded) study aimed at developing a prognostic model for the outcome of conservative treatment including physiotherapy in adults with partial-thickness rotator cuff tears.

4. References


Appendix: Example search strategy: Medline (compatible with EBSCO)

Prognosis research filter: Geersing et al. (2012) (clinical prediction models studies, Ingui filter OR update (S3 OR S4))

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<td><strong>S1</strong></td>
<td>((MH “Shoulder” OR MH “Shoulder Pain” OR shoulder) AND (MH Tendinopathy OR (“soft tissue” OR tendon* OR tendin* OR imping* OR rotator OR cuff).ti,ab)) OR (supraspinatus OR infraspinatus OR “teres minor” OR subscapularis OR „rotator cuff“ OR subacromial”).ti,ab OR MH “Shoulder Impingement Syndrome” OR MH “Rotator Cuff”</td>
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<tr>
<td><strong>S2</strong></td>
<td>MH “Physical Therapy Modalities+” OR MH “Rehabilitation+” OR (“physical therap**” or physiotherap* OR exercis* OR ”manual therap**” OR ”manipulative therap**” OR mobilis* or rehab* OR conservative* OR non-operat* OR nonoperat* OR non-surg* OR nonsurg*).ti,ab</td>
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<td><strong>S3</strong></td>
<td>validat* OR TI predict*.ti OR rule* OR (predict* AND (outcome* OR risk* OR model*))) OR ((history OR variable* OR criteria OR scor* OR characteristic* OR finding* OR factor*) AND (predict* OR model* OR decision* OR identif* OR prognos*)) OR (decision* AND (model* OR clinical* OR MH “Logistic Models”)) OR (prognostic AND (history OR variable* OR criteria OR scor* OR characteristic* OR finding* OR factor* OR model*))</td>
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<td><strong>S4</strong></td>
<td>stratification OR MH &quot;ROC Curve&quot; OR discrimination OR discriminate OR c-statistic OR “c statistic” OR area under the curve OR AUC OR calibration OR indices OR algorithm OR multivariable</td>
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<td><strong>S5</strong></td>
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