



STUDY PROTOCOL

REVISED The Adolescent Knee Pain (AK-Pain) prognostic tool: protocol for a prospective cohort study [version 2; peer review: 2 approved]

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Abstract

Background: One in three children and adolescents experience knee pain. Approximately one in two adolescents with knee pain will continue to experience pain even five years later and have low quality of life. The general practitioner (GP) is the first point of contact for children and adolescents with knee pain in Denmark. There is a variety of treatments being delivered in general practice, despite similar symptoms and patients' characteristics. This suggests a need to support the GPs in identifying those at high risk of a poor outcome early on, in order to better allocate resources. The aim of this study is to develop a user-friendly prognostic tool to support GPs' management of children and adolescents' knee pain.

Methods: A preliminary set of items in the prognostic tool were identified using systematic reviews and meta-analysis of individual participant data. Following feedback from GPs and children and adolescents on the content and understanding, the tool was piloted and implemented in general practice. A cohort of approximately 300 children and adolescents (age 8-19 years old) is being recruited from general practices (recruitment period, July 2019 – June 2020). Clinically meaningful risk groups (e.g. low/medium/high) for the recurrence/persistence of knee pain (at 3 and 6 months) will be identified.

Discussion: If successful, this prognostic tool will allow GPs to gain insights into the likely prognosis of adolescents with knee pain and subsequently provide the first building blocks towards stratified care, where treatments will be matched to the patients' prognostic profile. This has the potential to improve the recovery of children and adolescents from knee pain, to improve the allocation of resources in primary care, and to avoid the decline in physical activity and potential associated health and social consequences due to adolescent knee pain.

Registration: Registered with ClinicalTrials.gov on 24 June 2019 (ID [NCT03995771](https://clinicaltrials.gov/ct2/show/study/NCT03995771)).

Keywords

Prognosis, Prognostic factor, Adolescent, Knee pain

Open Peer Review

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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED Amendments from Version 1

The article has been amended following the reviewers comments.

The main changes concerned:

- In the introduction, the link to stratified care and to aligned treatments based on the risk was stressed more.
- A clearer explanation of the eligibility and recruitment of participants was provided.
- A clearer explanation of the process of collection of the data was provided.
- A figure showing the process of recruitment and retainment of participants was provided (Figure 1).
- A clearer explanation of the process that has led to the development of the tool was provided.
- A clearer explanation of the study piloting process was provided.
- A clearer description of the outcome of the study was provided.
- An updated and clearer statistical analysis plan was provided.
- In the discussion, a part about the future stages of the wider research program for the use of the tool for providing stratified care was added.

Any further responses from the reviewers can be found at the end of the article

Background

One in three adolescents experience knee pain¹. Knee pain is associated with low quality of life and lower sporting ability compared to adolescents without knee pain¹. In addition to the impact on the individual adolescents, knee pain has an impact on their family² and an economic impact, due to both direct (e.g. primary care visits, community services use, medication use) and indirect (e.g. parental productivity work loss and days off work) costs^{3,4}. Adolescent knee pain (AKP) was once thought to be innocuous and self-limiting, but new data has challenged this assumption⁵. A recent prospective cohort study demonstrated that 40% of adolescents with knee pain still experienced knee pain even after five years⁵. Knee pain is linked to both health and social consequences^{5,6}. Children and adolescents with knee pain are likely to reduce their sport participation, which may have implications for overall health in later life (e.g. higher adiposity, impaired sleep)^{1,7-10}. For some adolescents it results in school absence^{8,11} and for one in seven it affects their choice of job or career^{5,12}.

While there is a large body of knowledge on adult knee pain¹³⁻¹⁵, less is known in children and adolescents^{7,16}. Potential prognostic factors for a poor outcome in AKP include female sex, high leisure time sport participation, low health-related quality of life, high baseline frequency of knee pain⁶. These preliminary prognostic factors have been identified from single studies and have never been replicated in independent cohorts. Therefore, there is a need to further test and replicate these prognostic factors in other studies in order to confirm this preliminary evidence, also in contexts such as primary care.

Children and adolescents with knee pain commonly consult their general practitioner (GP), who is their first point of contact and who discuss with them and their caregivers the

different treatment options (e.g. referral to a specialist, education on how to manage knee pain, or exercises). This is largely based on clinical experience as there is a lack of clinical practice guidelines and original research on the management of AKP. This may result in heterogeneous care, unnecessary over-medicalization^{17,18} and large differences in treatments, despite presenting with similar symptoms and characteristics.

One potential option to support clinical decision making is to develop decision aids such as prognostic tools. These tools often consist of items with prognostic value that can be asked during the clinical consultation or completed prior to the consultation, and can be used to stratify patients depending on their prognosis¹⁹ and subsequently the best targeted treatment based on the prognostic profile can be offered the patient. In the case of a child or adolescent with knee pain, different treatments or recommendations (e.g. short education session, modification of physical activity levels, exercise, use of painkillers, referral to a specialist) might be provided depending on the risk of a poor prognosis. Examples of prognostic tools that have already been developed include the Keele STarT Back Screening Tool (SBST) for lower back pain in adults²⁰ or the Pediatric Pain Screening Tool (PPST) for general pediatric pain¹⁹. However, a prognostic tool to be used specifically for the prognosis of AKP in primary care has not been developed yet. The development of a prognostic tool for AKP would fill this gap and provide supporting information to guide GPs in their clinical decision towards a stratified care based on the category of risk for AKP (derived from the patients' individual characteristics).

Methods

Aim of the study

The aim of this study is to develop and test a prognostic tool for AKP to be used in general practice.

Study design

This study is designed as a prospective cohort study and the protocol follow The Recommendations for Interventional Trials (SPIRIT) 2013; the [completed checklist](#) can be accessed at the Harvard Dataverse online repository²¹.

Study setting

Participants will be recruited from general practices in Denmark, with data collected from July 2019 until June 2020.

Recruitment strategy

The recruitment strategy for the project has been developed together with experienced GPs and researchers within the field of general practice to ensure feasibility of recruitment and high generalisability. The recruitment includes two stages; the recruitment of GPs and the recruitment of participants.

Eligibility and recruitment of GPs

GPs working in the North Denmark Region and Odense area in Denmark are eligible for inclusion. These areas were chosen for logistic reasons, but more regions (e.g. Central

Denmark Region, Copenhagen area) may be added if recruitment is slower than anticipated. To obtain enough GPs involved in the study, efforts will be done to comply with the Solberg's seven R-factors for recruiting medical groups for research (i.e. relationship, reputation, requirements, reward, reciprocity, resolute behaviour and respect)²². First, contact will be made with GPs in order to ask them their availability to join the research. The first contact will be brief, but informative. Second, introductory meetings will be held with GPs and their staff (i.e. secretaries and nurses) to confer the importance, contents and goals of the study, information regarding the participants' eligibility criteria and to plan the recruitment of participants. After the beginning of participant recruitment, regular meetings with the GPs and their staff will be held during the follow-up in order to monitor the recruitment rate of participants and support them in recruitment (e.g. if changes are needed to the strategy used at their clinic).

Eligibility and recruitment of participants

Children and adolescents who consult their GP because of knee pain (of both traumatic and non-traumatic origin) during a period of recruitment of at least 6 months (start in July 2019) are eligible for inclusion. Children and adolescents will have to be between 8 and 19 years old. The age of 8 is considered to be the lowest age for the children to be able to complete a pain questionnaire or a pain chart without adult guidance²³ (provided that the questions are properly worded by taking into account the age-related cognitive abilities^{24,25}), and the age of 19 is defined as the upper limit for the period of adolescence by the World Health Organization²⁶. The following exclusion criteria will be assessed and applied by the person in charge of recruiting the participants (i.e. either the GP or a member of the staff):

- Age below 8 years old or over 19 years old
- Consultation for musculoskeletal pain only in a body region different from the knee
- Pain originated from specific non-musculoskeletal conditions (e.g. cancer, infections)
- Child is vulnerable (e.g. he/she has experienced a recent trauma and the distress may have an impact on the self-report making it not valid)²⁴
- Inability to take part to the study because of inability to understand the questionnaire (i.e. participants who have issues with Danish language or have learning difficulties)

Participants will be recruited from general practices on the basis of consultation for knee pain. In Denmark, consultations with the GP are booked beforehand, which allows the GP and the GP's staff to know in advance what the patient is consulting for. The study will be introduced to the caregivers and children before the consultation by a person working at the general practice (e.g. the GP/nurse/secretary). If patients meet the inclusion criteria for being eligible into the study (e.g. patient aged between 8 and 19 years old who consult for knee pain)

and agree to participate, they will be provided with the study material (i.e. prognostic tool to be completed). However, if the GP was made aware of the issue of the presence of knee pain during a consultation regarding other health issues, the questionnaire will be completed after the consultation. In the primary stages of the study the person in charge of recruiting participants will be assisted in recruitment by the primary investigator of this study (A.A.) or by a research assistant who will attend the participating general practices.

Complementary recruitment strategies that might be applied to maximize the recruitment rate are the advertisement of the study through social media (e.g. Facebook, Twitter, Snapchat) and through explicative posters displayed at the participating general practices. In this case, it will be screened that participants have been seen by their GP within the last week and knee pain was part of the consultation. These complementary strategies will be applied if less than approximately 100 participants in 3 months will be recruited.

To encourage participation, children and adolescents will be offered two cinema tickets to take part to the study. The first ticket will be given at baseline, when children and adolescents decide to take part in the study and return the questionnaire. The second ticket will be given when the participants have completed the follow-up (e.g. provided information at both the 3-month and 6-month follow-up points).

Data collection

Data will be collected through a questionnaire delivered at the general practice to children and adolescents who consult for knee pain (available as *Extended data*²⁷). The questionnaire will be either paper-based or collected with the support of a tablet through a link to the REDcap web application for online surveys²⁸ depending on the GPs' preference for data collection. A further recruitment through social media might be applied to complement the baseline collection of data, with data collected through a questionnaire home-mailed or delivered with an e-mail with a link to the web application for online surveys.

Outcomes will be collected by questionnaires. The adolescent can choose to do this self-reported or caregiver-reported (through an e-mail with a link to the web application for online surveys or text message) at follow-up (two time points: 3-month and 6-month follow-up). The questionnaires will include questions about pain characteristics (e.g. severity of pain, period free of knee pain, disability and activity limitations due to pain^{29,30}) taken from previously validated pain questionnaires or pain scales. The questionnaire also includes a question about who the person replying to the questionnaire is (i.e. child alone/caregiver/child together with the caregiver). In order to limit loss to follow-up, an e-mail/text message reminder will be sent to participants if they do not complete the follow-up questionnaire within one week from the day when they are supposed to reply (i.e. 3-month and 6-month follow-up). A second reminder will be sent one week after the first reminder if they still will not have completed the follow-up questionnaire. Reasons for loss to follow-up will be assessed by

contacting through a phone call/e-mail/text message those participants who do not reply to 3 consecutive follow-up reminders and asking about reasons for leaving the study.

Recruitment and retainment of participants

The process of recruitment and retainment of participants in the study (data collection start date: July 2019 – end date: June 2020) is described in the following flow diagram (Figure 1).

Development of the tool

Prognostic factors for knee pain in children and adolescents that can be measured in the context of general practice were identified from a review of the current literature on the topic³¹. The review

included 26 prospective studies, of which 4 focused on knee pain. These 4 studies included schoolchildren 12–19 years old from Denmark (3 studies) and 10–12 years old from Finland. Initially, the most important domains for the prognosis of knee pain and the specific items to be included in the tool were selected based on the review but also from the strength of association from previous studies identified within the literature and from meta-analysis of individual participant data. Prognostic factors for knee pain identified within the review³¹ were increasing age, pain frequency, practicing sport more than 2 times/week and low quality of life (second question of item 9 within the tool). Other factors that were identified from the wider literature and meta-analysis of individual participant data (PROSPERO ID CRD42019116861) were knee pain characteristics (pain duration,

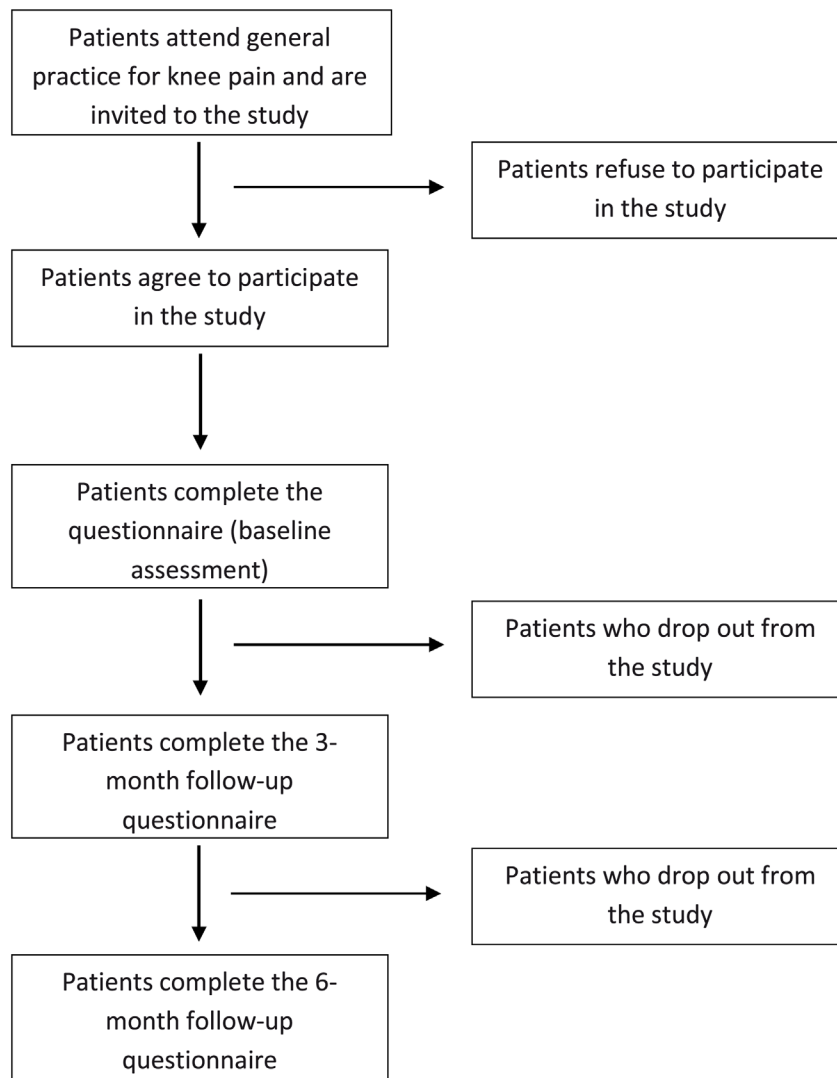


Figure 1. Recruitment and retainment of participants in the study.

traumatic/non-traumatic pain onset, limitations in daily activities due to knee pain, presence of knee pain in one knee or both knees), presence of pain in other body sites, gender, sleep, smoking, psychological factors, parental history of pain. During this stage, great emphasis was given to include only the most necessary factors considering the ultimate use of the prognostic tool (i.e. it should be used in a reasonable time of a consultation within general practice). Items relative to the specific prognostic factors were initially selected from validated scales when possible (e.g. regarding pain characteristics, limitation in daily activities, sport participation, psychological factors, sleep), or from previous studies. When multiple items within a scale or multiple scales were available for a prognostic factor, the relevant literature on the topic was identified and discussed at meetings with GPs and staff working at the Center of General Practice at Aalborg University in order to select the most appropriate items within the possible options. For example, the sleep item was selected from the self-reported Pediatric Quality of Life Inventory, one question of the psychological factor item from the Pain Catastrophizing Scale for Children, one question of the psychological factor item and the item relative to limitations in daily activities from the EuroQol Five-Dimensional Questionnaire Youth version. Following previous tools developed for pain in children and adolescents^{19,29,32}, items were properly worded for the age and properly framed with respect to the response options (e.g. direction, time intervals, avoiding double-barrelled items). A process of forward-backward translation of each item from Danish to English was applied to ensure that the items worded in Danish were conceptually equivalent to the items worded in English which were selected from previous studies or validated tools.

Study piloting

This project included a stage where the prognostic tool was piloted, which included a development, testing and implementation stage. After the initial development stage described above, the prognostic tool was tested with volunteer participants (n = 14) recruited through advertisement of the study on Facebook. Children and adolescents who were interested in the study (or their caregivers) contacted the primary investigator of this study (A.A.) for taking part in the test, and a date was arranged for testing the tool and carrying out cognitive interviews with a research assistant (T.S.). The test and cognitive interviews were carried out either in person at the Center for General Practice at Aalborg University or through Skype. The initial version of the tool was delivered to participants and asked to be completed, and the time needed for completion was assessed. After completion of the tool, cognitive interviews were carried out to assess the appropriateness, comprehensibility, wording and potential lack of items relating to the prognosis of knee pain, as previously done for other tools that evaluated pain status in children and adolescents^{29,32–34}. The questionnaire for cognitive interviews is available as *Extended data*³⁵. The aim was to improve the face, construct and content validity of the tool at this stage. This is especially important considering that a worse outcome can result if there is a lack of communication between the GP and the child about the knee pain characteristics and the factors related to knee pain assessed within the tool³⁶. After receiving

feedback through cognitive interviews, the prognostic tool was implemented to reach the optimal final version to be used in the data collection stage (Figure 2; also available as *Extended data*²⁷ together with the English version). Participants were given a cinema ticket as a reward for participating in the cognitive interviews.

Stability of the tool

A pilot study to assess the stability of the prognostic tool³³ in children and adolescents pre- and post- consultation was carried out. Children and adolescents who consulted primary care and their caregivers were given the prognostic tool (together with the informed consent) to be completed in the waiting room of the general practice before the consultation. Subsequently, after the consultation with the general practitioner, children and their caregivers were asked to complete the prognostic tool again in order to assess the stability of the tool parameters and the general practitioner's influence on the parameters (e.g. pain perception and psychological factors) assessed with the tool. Differences in reporting were assessed by means of K-statistics for categorical variables and intra-class correlation coefficient for continuous variable (e.g. age). Results, which are available as *Extended data*³⁷, showed K-statistics values above 0.80 (range from 0.66 to 1) for most items, showing good stability. Only the item relative to helplessness had a value below 0.70 (K-statistics = 0.66), which is considered the minimum standard for reliability³³.

Outcome

The outcome measure will be the recurrence/persistence of activity-limiting knee pain (i.e. defined as participants reporting yes to having pain that is limiting activities in the same knee) at follow-up³⁰. Participants will be asked about continuity of their knee pain (i.e. “do you still have knee pain?” and, if they reply “no”, “when did your stop having knee pain?”), to enable the distinction between recurrence (on/off knee pain episodes between baseline and follow-up) and persistence (continuous knee pain from baseline to follow-up) of knee pain. The primary end-point that will be collected is the recurrence/persistence of activity-limiting knee pain at 3-month follow-up, while the secondary end-point is the recurrence/persistence of activity-limiting knee pain at 6-month follow-up

In addition, previous studies have shown an effect of the treatment received on the change in risk group for the recurrence/persistence of pediatric pain³⁸ and on the change in pain and function³⁹. Therefore, an additional outcome measure that will be assessed include the treatment effectiveness on the recurrence/persistence of knee pain.

Statistics

A statistical analysis plan for the development of the final prognostic tool prior to recruitment has been developed. The analysis plan includes the following stages:

1. Descriptive analysis of the collected data, with results presented as means with SDs and as percentages.

Adolescent knee pain prognostic tool	
Disse spørgsmål handler om dine knæ smerter. Sæt kryds i den boks som bedst beskriver hvordan du har det, eller skriv i tekstboksen. Hvis du er i tvivl, så bedes du svare så godt du kan. Spørgsmålene står i venstre side, og svarmulighederne i højre side af skemaet.	
1. Hvor gammel er du?	(_____)
2. Er du en pige eller en dreng?	<input type="checkbox"/> Pige <input type="checkbox"/> Dreng
3. Har du ondt i det ene knæ eller begge knæ?	<input type="checkbox"/> Kun det ene knæ (højre knæ) <input type="checkbox"/> Kun det ene knæ (venstre knæ) <input type="checkbox"/> Begge knæ
4. Hvor lang tid har du haft ondt i knæet? Hvis du har ondt i begge knæ skal du svare ud fra det knæ hvor smerterne har varet længst	<input type="checkbox"/> under 3 måneder <input type="checkbox"/> 3– 6 måneder <input type="checkbox"/> 6–12 måneder <input type="checkbox"/> mere end 12 måneder (hvor mange år? _____)
5. Hvordan startede dine knæsmerter? Hvis du har ondt i begge knæ skal du svare ud fra det knæ hvor smerterne har varet længst	<input type="checkbox"/> Kom pludseligt (f.eks. da jeg fik en skade) <input type="checkbox"/> Kom gradvist (f.eks. langsomt over en længere periode)
6. Hvor ofte oplever du dine knæsmerter? Hvis du har ondt i begge knæ skal du svare ud fra det knæ hvor smerterne har varet længst	<input type="checkbox"/> Sjældent <input type="checkbox"/> Månedligt <input type="checkbox"/> Ugentligt <input type="checkbox"/> Mere end en gang om ugen <input type="checkbox"/> Næsten dagligt
7. Har du ondt andre steder i kroppen som gør at du ikke kan deltage i dine normale aktiviteter (leg i skolegården, sport og lignende)? I dette spørgsmål menes andre steder end knæet	<input type="checkbox"/> Nej <input type="checkbox"/> Ja. Marker venligst hvor. Du må gerne afkrydse mere end et område: <input type="checkbox"/> Hovedet <input type="checkbox"/> Ryg eller nakke <input type="checkbox"/> Skulder <input type="checkbox"/> Albuen <input type="checkbox"/> Håndled eller hånden <input type="checkbox"/> Underbenet <input type="checkbox"/> Låret <input type="checkbox"/> Bækken (badebudsområdet) <input type="checkbox"/> Ankel, hælen eller foden <input type="checkbox"/> Andet (_____)
8. Under hver overskrift bedes du sætte kryds i DEN kasse, der bedst beskriver hvordan dine knæsmerter påvirker de ting du laver på en normal dag (f.eks., gå i skole, hobbyer, sport, være sammen med venner eller familie) Hvis du har ondt i begge knæ skal du svare ud fra det knæ hvor smerterne har varet længst	<input type="checkbox"/> Jeg har ingen problemer med at udføre mine sædvanlige aktiviteter <input type="checkbox"/> Jeg har lidt problemer med at udføre mine sædvanlige aktiviteter <input type="checkbox"/> Jeg har nogle problemer med at udføre mine sædvanlige aktiviteter <input type="checkbox"/> Jeg har store problemer med at udføre mine sædvanlige aktiviteter <input type="checkbox"/> Jeg kan ikke udføre mine sædvanlige aktiviteter
9. Hvor enig er du i dette udsagn "Når jeg har ondt, er det forfærdeligt og jeg tror aldrig det bliver bedre" Sæt kryds i den kasse som bedst beskriver hvordan du har det i dag. Ængstelig/deprimeret svarer til at være ked af det (det handler om hvordan du har det, og ikke nødvendigvis på grund af dine smerter)	<input type="checkbox"/> Overhovedet ikke <input type="checkbox"/> Lidt <input type="checkbox"/> I nogen grad <input type="checkbox"/> Meget <input type="checkbox"/> Rigtig meget <input type="checkbox"/> Jeg er ikke ængstelig eller deprimeret <input type="checkbox"/> Jeg er lidt ængstelig eller deprimeret <input type="checkbox"/> Jeg er i nogen grad ængstelig eller deprimeret <input type="checkbox"/> Jeg er meget ængstelig eller deprimeret <input type="checkbox"/> Jeg er ekstremt ængstelig eller deprimeret
10. Har din mor eller stedmor ofte ondt i kroppen? (dette kan både være ondt i hovedet, ryggen, skulderen eller andre steder) Har din far eller stedfar ofte ondt i kroppen? (dette kan både være ondt i hovedet, ryggen, skulderen eller andre steder)	<input type="checkbox"/> Nej <input type="checkbox"/> Ja <input type="checkbox"/> Nej <input type="checkbox"/> Ja
11. Hvor mange gange per uge deltager du typisk i sport (udover idræt i skolen)? Hvilken type sport? (feks håndbold, fodbold, svømning, løb). Du må gerne skrive mere end en sport.	<input type="checkbox"/> Aldrig <input type="checkbox"/> 1 gange/uge <input type="checkbox"/> 2 gange/uge <input type="checkbox"/> 3 gange/uge <input type="checkbox"/> 4 gange/uge <input type="checkbox"/> 5 gange/uge <input type="checkbox"/> 6 gange/uge <input type="checkbox"/> 7 eller flere gange/uge (_____)
12. Har du røget cigaretter I de sidste 4 uger?	<input type="checkbox"/> Nej <input type="checkbox"/> Ja
13. Hvor enig er du i dette udsagn "Jeg har problemer med at sove" (det behøver ikke nødvendigvis være på grund af smerter)	<input type="checkbox"/> Aldrig <input type="checkbox"/> Næsten aldrig <input type="checkbox"/> Nogle gange <input type="checkbox"/> Ofte <input type="checkbox"/> Næsten altid

Figure 2. Adolescent Knee Pain prognostic tool.

2. Assessment of potential floor and ceiling effects of the items included in the prognostic tool. This will be done by checking that for those items that represent an ordinal or categorical variable with more than two potential response categories, the responses given are not skewed towards the top or bottom extreme of the scales (e.g. a ceiling or floor effect is present if >15% of the respondents report the lowest/highest score of the scale^{30,33,40}).
3. We will estimate the knee pain prognosis (i.e. recurrence/persistence of knee pain, dichotomous outcome) at 3-month and 6-month follow-up by means of multiple logistic regression to estimate ORs and 95% confidence intervals for each item included in the tool. This allows to assess the independent effects of each item and will inform on which factors are most related to the prognosis of knee pain (only the items that will show a statistically significant contribution to the model will be selected). This will also provide an insight on the scores of the prognostic tool (both overall and for subscales) to be applied for the creation of the initial risk groups. Alternatively, the RR will be estimated if another linear model analysis will be carried out. In addition, a potential option is to apply different weights to the items based on the strength of association.
4. Discriminant validity of the prognostic score will be assessed by using receiver operating characteristics (ROC) curves and by calculating the area under the curve (AUC) for the overall score and subscales of the prognostic tool.
5. Data from this sample will be used for the creation of risk groups for the recurrence/persistence of knee pain on the basis of cut-off scores identified using the ROC curves. Weights based on the strength of association identified with the multiple logistic regression might be applied. The initial idea is to have two or three risk groups (e.g. low/medium/high), which have to be clinically meaningful. More importance will be given to the sensitivity of the tool over the specificity. This means that in the presence of different cut-off scores for the inclusion of patients in the high-risk group, the cut-off that will allow to identify the majority of those with a bad prognostic outcome will be chosen. This will be done to avoid the misclassification of patients at high-risk in the medium or low-risk group.
6. Assessment of the predictive ability of the risk groups defined at baseline by calculating the sensitivity, specificity and negative and positive likelihood ratios (LRs) against the primary and secondary outcome (i.e. 3-month and 6-month recurrence/persistence of knee pain; disability/activities limitation due to knee pain).
7. Assessment of the potential influence of non-modifiable patients' characteristics on the predictive ability of the risk groups defined at baseline by stratifying the former analysis by age groups, sex and traumatic/non-traumatic onset.

Sample size

A sample size of minimum 300 participants from at least 20 general practices for the development of the tool has been estimated. This estimate was based on the following factors; the sample size required for the development of other prognostic tools^{19,20}, the annual consultation prevalence for knee pain in children and adolescents in general practice, the size of general practices, the number of items in the tool and the rule of thumb of at least 10 events for variable (or items within the prognostic tool)³³.

Previous studies have shown an annual consultation prevalence of 104–200 per 10,000 registered persons in children aged 3 to 19 years old^{41–43}. Several potential scenarios about participants' recruitment were hypothesized by considering the lowest and the highest annual consultation prevalence. These scenarios were calculated on a conservative estimate of 30% study participation rate. This is a worst-case scenario, and this approach was taken in order to have a safe recruitment that will provide enough children and adolescents for the development of the tool. These calculations resulted in an estimate of at least 20 general practices needed for recruiting the participants to the study (the estimate changes depending on the annual consultation prevalence considered and the size of the general practices; full calculations are available on request to the authors). In addition, if the recruitment from general practices will provide a low number of participants, a complementary recruitment through social media will be performed in order to achieve a total sample size of at least 300 children. In this case, sensitivity analysis would be performed to check for any potential difference in characteristics between the sample recruited through general practices and social media.

Data completeness, quality and security

The participant submitted responses will be automatically registered in a database using the REDCap. Handling of data will comply to the General Data Protection Regulation and the concomitant local data handling instructions for Center of General Practice at Aalborg University. Data will be stored at a server at Aalborg University, this will ensure a safe and legal handling of data. The accuracy of the data will be checked through screening of data outliers and potentially "wrong" or "strange" data will be identified and corrected. In order to obtain a "full analysis set" for the project, participants will have to provide data from baseline through the 3-month and 6-month follow-up, which will allow to estimate the short-term and long-term knee pain prognosis. Data completeness (i.e. completion and accuracy of data forms) will be monitored and actions will be taken to overcome potential problems such as missing data⁴⁴. In case of baseline missing data, the missing observation will be replaced by means of an imputation process (e.g. multiple imputation by chained equation) depending on the number of missing observations (i.e. multiple imputation is usually performed when the percentage of missing data is low). A sensitivity analysis will also be carried out in order to compare results between the analysis carried out on the dataset with missing observation (complete-case analysis) and the multiple imputed dataset (multiple imputation analysis). A backup copying of the dataset will be performed daily.

Access to data

The final dataset will be accessed by A.A., M.S.R., M.B.J. and S.H..

Protocol amendments

Any future protocol amendments or changes will be made publicly visible in the clinical trial registration, and clearly described in the subsequent reporting of the results.

Dissemination

The present study will provide data on the prognosis for knee pain in children and adolescents who present to primary care. In addition, this study will provide data on the usability of a prognostic tool to allocate children and adolescents to a category of risk for knee pain recurrence or persistence and consequently provide them with the best targeted treatment. The study results will be disseminated at scientific conferences and through appropriate scientific journals. General practitioners, children and caregivers participating into the study will be regularly provided with feedback about the ongoing study as well.

All authors of this current paper (AA, SH, MBJ, MSR) will be involved in the production of manuscripts originating from this study.

Ethics approval and consent to participate

Ethical approval for the study and for the pilot study was sought by sending an enquiry to the Scientific Ethics Committee for Region North Jutland, together with a brief description of the study. The response obtained from the Scientific Ethics Committee stated that ethical approval was not needed, as the study implied the use of a questionnaire survey and did not imply any type of intervention on participants. Written informed consent will be obtained by the adolescents if aged 15 years old or more, otherwise from the caregivers. Participants who will become 15 years old during the transition from baseline to follow-up will be asked to provide consent themselves when contacted at follow-up.

Discussion

The objective of this study is to develop a user-friendly prognostic tool (Adolescent Knee Pain prognostic tool), which will be the first one to be used to support the GPs' management of AKP. Within this study, the preliminary prognostic factors for AKP identified in the literature and included in the initial version of the tool will be tested. Those prognostic factors that will prove to be independently significantly associated with a poor AKP prognosis and will contribute to the prognostic model will be included in the final version of the tool. The tool will enable the identification of different subgroups of patients who seek primary care for AKP according to their risk of recurrence or persistence of knee pain at 3-month and 6-month follow-up.

Limitations

A limitation is that it might be argued that specific knee pain conditions (e.g. patellofemoral pain, Osgood-Schlatter) might be characterized by different prognostic courses. However,

the accurate diagnosis of specific knee pain conditions in the primary care context might be challenging, and this tool was conceived for enquiring general questions regarding AKP. Second, this tool might not be applicable to health-care systems of countries where there might be a different categorization of primary care and secondary care or where GPs might not be the sole gatekeeper of primary care provision⁴⁵. Third, there might be difficulties in recruiting 300 participants with AKP from general practices, and although alternative recruitment strategies have been planned (i.e. through social media), this might produce selection bias⁴⁶.

Strengths

First, primary care is the place where the majority of health care is delivered⁴⁷, and consequently the development of a tool to be used within this setting has the potential to have a significant impact in real-life.

Second, the prognostic tool includes items about factors that are specific to the AKP prognosis (e.g. pain duration, knee pain frequency) and therefore would be more sensitive than other more general pain tools. This is important considering that misclassification of patients might potentially lead to undertreat those misclassified as low-risk and overtreat those misclassified as high-risk⁴⁸.

Third, the subgroup of patients who refer to primary care is usually characterized by a different severity of symptoms compared to general population, second or tertiary care samples, as proposed by the iceberg theory of disease⁴⁹⁻⁵¹. Hence, this research has the opportunity to provide information on the predictive ability of a prognostic tool in primary care compared to studies carried out within other care settings (e.g. the PPST was validated in tertiary care settings^{19,52}), as it has previously been observed a difference in the efficacy of risk prediction potentially because of differences in patients case mix⁵³.

Fourth, this prognostic tool is short (only 13 prognostic factors assessed overall) and quick to use (tests during the piloting of the tool showed that on average approximately three minutes and a half are needed to complete the tool) and includes factors that can be easily collected during a consultation with a GP. Finally, the tool is easy to be delivered and properly worded to be understandable by children and adolescents, as it was implemented following their feedback during cognitive interviews.

Use of the tool for providing stratified care

The use of this tool can potentially improve the understanding of the AKP prognosis and identify specific categories of risk of a poor prognosis. However, the care needed will differ among patients with AKP. Some of them will only need conservative management (e.g. education on how to manage knee pain, modification or avoidance of physical activity), while others will need a referral to a specialist (e.g. a physiotherapist, a rheumatologist). If it will prove to perform adequately (i.e. in terms of sensitivity, specificity, positive and negative likelihood ratio), this tool will inform on the likely prognosis of AKP and potentially

guide the GPs in providing a targeted stratified care according to the risk of recurrence or persistence of AKP at 3-month and 6-month follow-up. The use of this tool can potentially significantly change the use of resources and increase the primary care efficiency by allocating resources to those who need them most. The development of this tool fits within a wider research program, which overall aim is to provide a stratified approach to primary care management of child and adolescent knee pain that can result in clinical and economic benefits compared with current best practice. Therefore, future perspectives include the use of this tool in a randomized controlled trial, which will investigate whether subgrouping patients using the tool, combined with targeted treatment, is more clinically effective (i.e. it will reduce long-term disability from knee pain) and cost-effective compared to best current care. In addition, there is scope for performing future qualitative studies to assess the GPs' behavioral change when using the tool (e.g. changes in referral to physical therapy, diagnostic tests and medication prescriptions).

Trial status

Name of registry: ClinicalTrials.gov

Registration number: NCT03995771

Date of registration: 24/06/2019

Date of start of recruitment: 01/07/2019

Expected date of recruitment conclusion: 30/06/2020

Trial URL: <https://clinicaltrials.gov/ct2/show/NCT03995771?term=NCT03995771&rank=1>.

Data availability

Underlying data

No underlying data are associated with this article.

Extended data

Harvard Dataverse: Dataset to test the stability of the prognostic tool. <https://doi.org/10.7910/DVN/SMQRKA>³⁷.

This project contains the dataset generated when testing the stability of the tool.

Harvard Dataverse: Questionnaire for cognitive interviews. <https://doi.org/10.7910/DVN/UT1MGD>³⁵.

This project contains the Danish- and English-language questionnaire for cognitive interviews.

Harvard Dataverse: Final questionnaire. <https://doi.org/10.7910/DVN/QKWOOT>²⁷.

This project contains the final Danish- and English-language questionnaire for data collection.

Reporting guidelines

Harvard Dataverse: SPIRIT checklist for 'The Adolescent Knee Pain (AK-Pain) prognostic tool: protocol for a prospective cohort study'. <https://doi.org/10.7910/DVN/SIO5WG>²¹.

Extended data and completed reporting guidelines checklist are available under the terms of the [Creative Commons Zero "No rights reserved"](https://creativecommons.org/licenses/by/4.0/) data waiver (CC0 1.0 Public domain dedication).

Author contributions

AA planned the overall study protocol and all other authors (SH, MBJ and MSR) provided clinical advice and contributed to the refinement of the protocol. AA led the writing of this study protocol paper, and all other authors (SH, MBJ and MSR) contributed equally with comments and critical revision to the manuscript. All authors read and approved the final manuscript.

Acknowledgments

We would like to thank all the GPs and their staff who agreed to take part to the project and research assistant Tagrid Salim (T.S.) for carrying out the cognitive interviews. We would also like to thank all the children and adolescents (and their families) who took part in the piloting of the prognostic tool and provided valuable advice for the improvement of the tool.

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The authors have successfully addressed my previous comments and I feel the paper has improved in terms of content and clarity. I have no further comments and wish the team well in their endeavours to development a knee pain based prognostic model for children and adolescents.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Psychology, Psychometrics, Epidemiology, Musculoskeletal

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 27 January 2020

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Many thanks for the opportunity to review this protocol paper that reports on the rationale and methodology of testing an adolescent knee pain prognostic tool. The protocol is generally well written, and the proposed project to develop a prognostic tool is much needed within the child and adolescent musculoskeletal community. However I do feel some points within the paper require greater clarity and have set out a number of recommendations that I feel would improve the content and presentation of this paper.

1. Whilst the authors have aptly discussed the rationale for a prognostic tool within the introduction and briefly touch upon stratified care, I feel they need also mention what this means in terms of aligned treatments based on the risk (i.e. the pathway for stratified patients), a little bit more on this would benefit the introduction.
2. In the exclusion criteria the authors mention participants will be excluded if they have an inability to understand the questionnaire, is this a language issue, or for those with learning difficulties, or both, I think the authors might wish to expand on this a little more to give examples.
3. The authors state that both parents will be approached before the consultation, does that then require that both parents be present as this won't often be the case (parent working, single parent etc), also more fundamental is the issue of "before the consultation", if this is the case how do they know that the knee pain is not referred pain from the spine for example or that whilst the child/adolescent has knee pain that they may also discuss other issues within the consultation and the focus is on those other issues? I might add that the child may be looked after by someone who is not the parent (family member) and perhaps the term "caregiver" should also be used when the term parent is used?
4. The authors describe complementary recruitment strategies to work alongside primary care recruitment, I think the use of wider recruitment strategy is good considering the low participation rate of children within primary care to MSK studies. However, whilst the authors have stipulated that children/adolescents will be reminded of the premise for participation, i.e. that participants have been seen by their GP for knee pain, how will this be confirmed? Furthermore, the authors have not explained the timeline for this, for example the recruitment within GP practices is at the time of consultation, however social media recruitment does not state a criteria of when they should have consulted. One of the key prognostic markers for adult MSK pain is time since onset, here you may have potentially two distinct groups, one who have consulted (not clear whether this will be the first consultation or a subsequent visit), and those via social media at presumably post consultation (but not stipulated as to what time period criteria is acceptable, is it a week, month, year etc), this presents issues of case mix, and at the very least the authors would have to collect information about timing of consultations (and timing of when patient first experienced pain) to factor into their analysis.
5. I think the offer of cinema tickets is a good incentive, however would it not be better to offer a family ticket or at least two tickets as a child would most likely go on their own?
6. For the data collection section, I wonder if a diagram might be helpful here as it is not fully clear, does the GP collect the data post consultation, will they (GPs) have time to do this, the authors mention previously that the child/adolescent will be approached to complete the tool before consultation, so does this mean they fill in the tool before consultation and then other information post consultation? The authors should be aware that pre-consultation may reveal different responses to a post-consultation (e.g. reductions in fear avoidance for parent/child due to reassurance from GP etc), this point also relates to point 4 above where alternative recruitment

strategies may be used that could lead to different responses due to different timings?

7. When discussing the outcomes, the authors describe that outcomes will be collected by a combination of self-report or parent report, firstly this doesn't make sense because of the inclusion of "or" as that implies either, whereas it is described as a combination. Does this mean that there will be a choice in who fills in the questionnaire, should it not be self-report AND parent report, or is this related to age and access to online social media platforms where parents/caregivers would have to complete, I think this needs to be explained, and again the researchers should collect information on who fills in the questionnaire as there are differences between proxy and self-report.
8. Participant timeline, is table 1 needed, I think it is clear that there will be an assessment at baseline and follow up at 3 months and 6 months for each participant, I don't think a diagram is needed for that? I feel a recruitment flow diagram would be a much better inclusion for this paper.
9. The authors discuss the development of the items for the tool, I think a little more should be said about this, for example is this the information within the review (ref 31) or additional literature, also as this is a generation of the candidate items for a prognostic tool it would be good to give some detail (e.g. how many studies within the review, what sort of populations, were they all prospective studies etc). In addition the authors discuss the situation where multiple items or multiple scales were present for items, I feel this whole sentence could do with expansion, what is meant by multiple items and multiple scales, do you mean prognostic factors that have been measured using multiple items/scales? Give some examples and how a multiple scale construct is then reduced to a single question, how was this done?
10. Within the study piloting section, the authors mention the process of improving face, construct, content validity, stressing the importance of this should a GP make an inaccurate diagnosis, I have some concern about this statement as it suggests that the questions asked about pain via the tool are in some way involved in diagnosis, this is surely not the case, can the authors explain what they mean?
11. In the stability of the tool section the authors state that children were referred to primary care because of their knee pain, who is it then who refers children to primary care, what is the process for this as this may be a factor to be considered (e.g. how long does it take for a person to be referred to primary care, who does the referral, how are decisions made on a referral etc), I thought it was that the child/parent/caregiver attends primary care?
12. I am slightly confused about the test-retest parameters, from what is written it appears that the test was done pre and post consultation (i.e. within the same day, perhaps within the same hour), this timeline is too short, the point of test/retest is to ensure that the participants would not remember the responses to the questions asked, so for example the next week, to then ensure that the responses are consistent, I am not convinced this current test stacks up, and any differences would likely be via information received within the consultation (influencing different responses) rather than the actual difference coming from inconsistency in the measure (for example a GP offering reassuring information).
13. I feel for the general readership it would be helpful to have the tool in English within the paper, and when I tracked down the English version I could see it has 12 questions, whereas the one in the current paper has 13 questions?

14. The secondary outcome is the same as the primary outcome, with the only difference being time, could the authors clarify whether this is actually a secondary outcome or just a different time period for the same primary outcome measure?
15. The authors state that the statistical analysis plan can be found elsewhere, this protocol paper should include the full statistical analysis plan rather than have a signpost to another protocol, can the authors include the full details in this paper (and if they have then they don't need to reference another protocol).
16. The authors discuss potential floor and ceiling effects, can the authors say a little more about this as presumably some risk items would only identify those at extremes (i.e. at risk) in any case? This is particularly true of items that can identify those at high risk, they may only account for a small proportion of the population with a number of items giving an additive high risk score?
17. Will the authors examine both each individual item but also within a model (multivariable) to test the independent effects of each item as some many have overlapping qualities (will they also examine redundant items); also will the authors consider model fit (e.g. explained variance) within their analysis?
18. Point 5 in the statistical plan is not explained well, could the authors say a little more about the identification of cut off scores and what criteria will be used to decide on this (i.e. are these independently generated from other sample or this one, what determines a poor outcome, if determined from this cohort it will make external validity more problematic), also if more will be given to sensitivity of the tool, how will this factor in the development of risk groups? Also it might be beneficial for the authors to compare risk groups in terms of the baseline characteristics and test across those to give further discriminant information, and in addition it might be worth considering construct validity by comparing to any existing measures, for example this measure could be compared to the generic PPST?
19. The discussion might benefit more by describing the potential for the tool in terms of the assistance to clinicians, for example within the study will the research consider how clinicians feel about the tool and whether they feel it would be useful, also what is not clear at present is the potential pathways that are available as defined by risk, do the proposed risk groups have an aligned pathway already for example, if so what might that look like and if not how will these be developed?

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Psychology, Psychometrics, Epidemiology, Musculoskeletal

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 15 Feb 2020

Alessandro Andreucci, Aalborg University, Aalborg, Denmark

Dear Editorial Team, F1000 Research,

We were delighted that the Reviewers of our recent submission " The Adolescent Knee Pain (AK-Pain) prognostic tool: protocol for a prospective cohort study" (ID: 21740) provided us with their very helpful feedback on our paper. This has given us the opportunity to apply changes that have led to an improvement of the paper.

Reviewer 1

Many thanks for the opportunity to review this protocol paper that reports on the rationale and methodology of testing an adolescent knee pain prognostic tool. The protocol is generally well written, and the proposed project to develop a prognostic tool is much needed within the child and adolescent musculoskeletal community. However I do feel some points within the paper require greater clarity and have set out a number of recommendations that I feel would improve the content and presentation of this paper.

Response: We thank the reviewer for the valuable feedback provided. We have addressed the comments and changed the manuscript (changes are underlined in the text), which we feel is now improved. Individual responses for each specific comment are outlined below.

1. Whilst the authors have aptly discussed the rationale for a prognostic tool within the introduction and briefly touch upon stratified care, I feel they need also mention what this means in terms of aligned treatments based on the risk (i.e. the pathway for stratified patients), a little bit more on this would benefit the introduction.

Response: We thank the reviewer for the comment and have now amended the introduction by providing more information on the aligned treatments based on the risk.

The text (Introduction section) now reads "One potential option to support clinical decision making is to develop decision aids such as prognostic tools. These tools often consist of items with prognostic value that can be asked during the clinical consultation or completed prior to the consultation. Thereby patients can be stratified depending on their prognosis (19) and subsequently the best targeted treatment based on the prognostic profile can be offered the patient. In the case of a child or adolescent with knee pain, different treatments or recommendations (e.g. short education session, modification of physical activity levels, exercise, use of painkillers, referral to a specialist) might be provided depending on the risk of a poor prognosis. Examples of prognostic tools that have already been developed include the Keele STarT Back Screening Tool (SBST) for lower back pain in adults (20) or the Pediatric Pain Screening Tool (PPST) for general pediatric pain (19)."

2. In the exclusion criteria the authors mention participants will be excluded if they have an inability to understand the questionnaire, is this a language issue, or for those with learning difficulties, or both, I think the authors might wish to expand on this a little more to give examples.

Response: Participants are meant to be excluded if they have either language issues or learning difficulties.

The text (section Methods, Eligibility and recruitment of participants) now reads “Inability to take part in the study due to an inability to understand the questionnaire (i.e. participants who have issues with Danish language or have learning difficulties)”

3. The authors state that both parents will be approached before the consultation, does that then require that both parents be present as this won't often be the case (parent working, single parent etc), also more fundamental is the issue of “before the consultation”, if this is the case how do they know that the knee pain is not referred pain from the spine for example or that whilst the child/adolescent has knee pain that they may also discuss other issues within the consultation and the focus is on those other issues? I might add that the child may be looked after by someone who is not the parent (family member) and perhaps the term “caregiver” should also be used when the term parent is used?

Response: In Denmark, the general practitioner and his/her staff know in advance if the person is consulting for knee pain based on the booking. However, the general practitioner might also be made aware of the knee pain problem during a consultation regarding other issues. In this case, the questionnaire will be filled out after the consultation. As the reviewer correctly pointed out however, the knee pain might be referred from other body sites (e.g. spine), and we acknowledge that this is a limitation of our study.

We have amended the text and made it clearer. The text (section Methods - Eligibility and recruitment of participants) now reads “Participants will be recruited from general practices on the basis of consultation for knee pain. In Denmark, consultations with the GP are booked beforehand, which allows the GP and the GP's staff to know in advance what the patient is consulting for. The study will be introduced to the caregivers and children before the consultation by a person working at the general practice (e.g. the GP/nurse/secretary). If patients meet the inclusion criteria for being eligible into the study (e.g. patient aged between 8 and 19 years old who consult for knee pain) and agree to participate, they will be provided with the study material (i.e. prognostic tool to be completed). However, if the GP was made aware of the issue of the presence of knee pain during a consultation regarding other health issues, the questionnaire will be completed after the consultation.”

4. The authors describe complementary recruitment strategies to work alongside primary care recruitment, I think the use of wider recruitment strategy is good considering the low participation rate of children within primary care to MSK studies. However, whilst the authors have stipulated that children/adolescents will be reminded of the premise for participation, i.e. that participants have been seen by their GP for knee pain, how will this be confirmed? Furthermore, the authors have not explained the timeline for this, for example the recruitment within GP practices is at the time of consultation, however social media recruitment does not state a criteria of when they should have consulted. One of the key prognostic markers for adult MSK pain is time since onset, here you may have potentially two distinct groups, one who have consulted (not clear whether this will be the first consultation or a subsequent visit), and those via social media at presumably post consultation (but not stipulated as to what time period criteria is acceptable, is it a week, month,

year etc), this presents issues of case mix, and at the very least the authors would have to collect information about timing of consultations (and timing of when patient first experienced pain) to factor into their analysis.

Response: We thank the reviewer for the very insightful comment.

Our plan is to include only those who have consulted within one week. In addition, sensitivity analysis will be applied by comparing results of those recruited in primary care and those recruited through social media to assess potential differences related to case mix. Regarding timing of when patient first experienced pain, this is already assessed with item number 4 of the prognostic tool.

We have amended the text and made it clearer. The text (section Methods - Eligibility and recruitment of participants) now reads “Complementary recruitment strategies that might be applied to maximize the recruitment rate are the advertisement of the study through social media (e.g. Facebook, Twitter, Snapchat) and through explicative posters displayed at the participating general practices. In this case, it will be screened that participants have been seen by their GP within the last week and knee pain was part of the consultation.”

5. I think the offer of cinema tickets is a good incentive, however would it not be better to offer a family ticket or at least two tickets as a child would most likely go on their own?

Response: Although the idea of offering a family ticket or at least two tickets is good, unfortunately we were limited in our choice by financial constrictions. This is why we can offer only one cinema ticket at baseline and one cinema ticket at follow-up, and unfortunately it is not possible to change this strategy now as the study is already on-going.

6. For the data collection section, I wonder if a diagram might be helpful here as it is not fully clear, does the GP collect the data post consultation, will they (GPs) have time to do this, the authors mention previously that the child/adolescent will be approached to complete the tool before consultation, so does this mean they fill in the tool before consultation and then other information post consultation? The authors should be aware that pre-consultation may reveal different responses to a post-consultation (e.g. reductions in fear avoidance for parent/child due to reassurance from GP etc), this point also relates to point 4 above where alternative recruitment strategies may be used that could lead to different responses due to different timings?

Response: We thank the reviewer for the very insightful comment.

Data collection will occur before the consultation and will be facilitated by the general practitioner's staff (e.g. nurse, secretary), with the tool to be fully completed before consultation. However, as pointed out at point 3 above, the knee pain problem might not be cited as the primary reason for consultation, and the GP only made aware of it during the consultation. In this case, the tool will be completed after the consultation. Being aware of the potential differences in parameters pre-consultation vs. post-consultation we assessed the stability of the tool, which showed good stability of the tool parameters before and after consultation with the general practitioner, as described in section “Methods – Stability of the tool”.

7. When discussing the outcomes, the authors describe that outcomes will be collected by a combination of self-report or parent report, firstly this doesn't make sense because of the inclusion of “or” as that implies either, whereas it is described as a combination. Does this mean that there will be a choice in who fills in the questionnaire, should it not be self-report AND parent report, or is this related to age and access to online social media platforms where parents/caregivers would

have to complete, I think this needs to be explained, and again the researchers should collect information on who fills in the questionnaire as there are differences between proxy and self-report.

Response: We thank the reviewer for the comment. The outcome will be collected by questionnaires that will be sent through an e-mail with a link to the web application for online surveys or text message. Within the questionnaire, there are also questions about name, surname and contact information (e-mail and phone number) and about who the person replying to the questionnaire is (i.e. child alone/caregiver/child together with the caregiver). This allows us to know if the person replying is the caregiver or the child/adolescent.

We have amended the text and made it clearer. The text (section Methods – Data collection) now reads: “Outcomes will be collected by questionnaires. The adolescent can choose to do this self-reported or caregiver-reported (through an e-mail with a link to the web application for online surveys or text message) at follow-up (two time points: 3-month and 6-month follow-up). The questionnaire also includes a question about who the person replying to the questionnaire is (i.e. child alone/caregiver/child together with the caregiver)”

8. Participant timeline, is table 1 needed, I think it is clear that there will be an assessment at baseline and follow up at 3 months and 6 months for each participant, I don't think a diagram is needed for that? I feel a recruitment flow diagram would be a much better inclusion for this paper.

Response: We have replaced table 1 with a recruitment flow diagram and modified the text, which now reads “The process of recruitment and retainment of participants in the study (data collection start date: July 2019 – end date: June 2020) is described in the following flow diagram (figure 1).”

9. The authors discuss the development of the items for the tool, I think a little more should be said about this, for example is this the information within the review (ref 31) or additional literature, also as this is a generation of the candidate items for a prognostic tool it would be good to give some detail (e.g. how many studies within the review, what sort of populations, were they all prospective studies etc). In addition the authors discuss the situation where multiple items or multiple scales were present for items, I feel this whole sentence could do with expansion, what is meant by multiple items and multiple scales, do you mean prognostic factors that have been measured using multiple items/scales? Give some examples and how a multiple scale construct is then reduced to a single question, how was this done?

Response: We thank the reviewer for the insightful comment.

Items to be included in the prognostic tool were selected based on a combination of those initially identified with the review (31), of the wider literature on child and adolescent musculoskeletal pain

and from meta-analysis of individual participant data (PROSPERO ID CRD42019116861). This allowed us to include also other potential factors that were not previously assessed in the studies identified in the review but were found to be associated with the prognosis of general musculoskeletal pain in other studies and might therefore result as significant contributors to the prognostic model. Regarding the situation where multiple items or multiple scales were present for items relative to the prognostic factors, single items were selected from the most appropriate scales.

We have now modified the text (Section Methods - Development of the tool) and made it clearer. The text now reads:

“Prognostic factors for knee pain in children and adolescents that can be measured in the context of general practice were identified from a review of the current literature on the topic (29). The review included 26 prospective studies, of which 4 focused on knee pain. These 4 studies included schoolchildren 12-19 years old from Denmark (3 studies) and 10-12 years old from Finland. Initially, the most important domains for the prognosis of knee pain and the specific items to be included in the tool were selected based on the review but also from strength of association from previous studies identified within the literature and from meta-analysis of individual participant data. Prognostic factors for knee pain identified within the review (29) were increasing age, pain frequency, practicing sport more than 2 times/week and low quality of life (second question of item 9 within the tool). Other factors that were identified from the wider literature and meta-analysis of individual participant data (PROSPERO ID CRD42019116861) were knee pain characteristics (pain duration, traumatic/non-traumatic pain onset, limitations in daily activities due to knee pain, presence of knee pain in one knee or both knees), presence of pain in other body sites, gender, sleep, smoking, psychological factors, parental history of pain. During this stage, great emphasis was given to include only the most necessary factors considering the ultimate use of the prognostic tool (i.e. it should be used in a reasonable time of a consultation within general practice). Items relative to the specific prognostic factors were initially selected from validated scales when possible (e.g. regarding pain characteristics, limitation in daily activities, sport participation, psychological factors, sleep), or from previous studies. When multiple items within a scale or multiple scales were available for a prognostic factor, the relevant literature on the topic was identified and discussed at meetings with GPs and staff working at the Center of General Practice at Aalborg University in order to select the most appropriate items within the possible options. For example, the sleep item was selected from the self-reported Pediatric Quality of Life Inventory, one question of the psychological factor item from the Pain Catastrophizing Scale for Children, one question of the psychological factor item and the item relative to limitations in daily activities from the EuroQol Five-Dimensional Questionnaire Youth version.”

10. Within the study piloting section, the authors mention the process of improving face, construct, content validity, stressing the importance of this should a GP make an inaccurate diagnosis, I have some concern about this statement as it suggests that the questions asked about pain via the tool are in some way involved in diagnosis, this is surely not the case, can the authors explain what they mean?

Response: The aim of the study piloting was to improve the comprehensibility and wording of the questions included in the tool, so that adolescents would provide information about the parameters related to the knee pain prognosis that were as close as possible to the real values and therefore limit potential misreporting. As the reviewer correctly pointed out, the tool is not conceived as a replacement of the diagnosis made by the general practitioner, but only as a support for understanding the prognosis together with the clinical examination.

We have now modified the text and made it clearer. The text (section Methods – Study piloting) now reads:

“The aim was to improve the face, construct and content validity of the tool at this stage. This is especially important considering that a worse outcome can result if there is a lack of communication between the GP and the child about the knee pain characteristics and the factors related to knee pain assessed within the tool (33).”

11. In the stability of the tool section the authors state that children were referred to primary care because of their knee pain, who is it then who refers children to primary care, what is the process for this as this may be a factor to be considered (e.g. how long does it take for a person to be referred to primary care, who does the referral, how are decisions made on a referral etc), I thought it was that the child/parent/caregiver attends primary care?

Response: We have amended the imprecision in the text, as we actually meant the child/adolescent who consult primary care for knee pain. We have modified the text, which now reads “Children and adolescents who consulted primary care and their caregivers were given the prognostic tool (together with the informed consent) to be completed in the waiting room of the general practice before the consultation.”

12. I am slightly confused about the test-retest parameters, from what is written it appears that the test was done pre and post consultation (i.e. within the same day, perhaps within the same hour), this timeline is too short, the point of test/retest is to ensure that the participants would not remember the responses to the questions asked, so for example the next week, to then ensure that the responses are consistent, I am not convinced this current test stacks up, and any differences would likely be via information received within the consultation (influencing different responses) rather than the actual difference coming from inconsistency in the measure (for example a GP offering reassuring information).

Response: We thank the reviewer for the comment and acknowledge the inaccuracy in the language used within the text. As pointed out by the reviewer, the GP might influence the perception of certain parameters related to pain (i.e. psychological factors, pain duration) through the discussion occurring during the consultation. In order to test if responses to the questions asked were influenced by the consultation with the GP (and to estimate the difference in responses), the stability of the tool before and after the consultation was tested and results showed good stability. However, as the reviewer correctly pointed out, this cannot be considered a test-retest as the time frame between the two measurements was too short. We have amended the text, (Section Methods – Stability of the tool) which now reads “A pilot study to assess the stability of the prognostic tool (31) in children and adolescents pre- and post- consultation was carried out.”

13. I feel for the general readership it would be helpful to have the tool in English within the paper, and when I tracked down the English version I could see it has 12 questions, whereas the one in the current paper has 13 questions?

Response: The English version, with 13 questions is accessible at:
<https://doi.org/10.7910/DVN/QKWOOT>

14. The secondary outcome is the same as the primary outcome, with the only difference being time, could the authors clarify whether this is actually a secondary outcome or just a different time

period for the same primary outcome measure?

Response: We thank the reviewer for the comment and have amended the imprecision in the text. In our study, the outcome is the same is collected at two endpoints. We decided to consider the knee pain prognosis at 3-month as the primary endpoint and the knee pain prognosis at 6 months as a secondary endpoint.

We have modified the text (Section Methods – Outcome), which now reads “The outcome measure will be the recurrence/persistence of activity-limiting knee pain (i.e. defined as participants reporting yes to having pain that is limiting activities in the same knee) at follow-up (28). Participants will be asked about continuity of their knee pain (i.e. “do you still have knee pain?” and, if they reply “no”, “when did your stop having knee pain?”), to enable the distinction between recurrence (on/off knee pain episodes between baseline and follow-up) and persistence (continuous knee pain from baseline to follow-up) of knee pain. The primary end-point that will be collected is the recurrence/persistence of activity-limiting knee pain at 3-month follow-up, while the secondary end-point is the recurrence/persistence of activity-limiting knee pain at 6-month follow-up”

15. The authors state that the statistical analysis plan can be found elsewhere, this protocol paper should include the full statistical analysis plan rather than have a signpost to another protocol, can the authors include the full details in this paper (and if they have then they don't need to reference another protocol).

Response: We have now corrected the text (section Methods – Statistics), inserted the full analysis plan within this paper and deleted the reference to the other protocol.

16. The authors discuss potential floor and ceiling effects, can the authors say a little more about this as presumably some risk items would only identify those at extremes (i.e. at risk) in any case? This is particularly true of items that can identify those at high risk, they may only account for a small proportion of the population with a number of items giving an additive high risk score?

Response: We thank the reviewer for the very insightful comment. As correctly pointed out by the reviewer, for items that represent an ordinal or categorical variable with more than two potential response categories (for example 5 categories), the responses given might be only the top or bottom extreme of the scales. For example, this might happen for items related to psychological factors and sleep. In this case, participants with higher levels of anxiety/depression, helplessness or sleep problems would most likely fall in the high-risk category. A potential option to account for this is to initially test the independent effect of each item by means of multiple logistic regression, include those items that show a significant contribution to the model and subsequently apply different weights based on the strength of association. For example, a combination of the different items can be used to identify the scores for defining the risk groups (i.e. low/medium/high) and if items that identify only a small proportion of the population (e.g. high levels of psychological factors or sleep problems) are associated with a high risk of a bad prognosis, they can be selected and used to give an additive high-risk score.

17. Will the authors examine both each individual item but also within a model (multivariable) to test the independent effects of each item as some many have overlapping qualities (will they also examine redundant items); also will the authors consider model fit (e.g. explained variance) within their analysis?

Response: We thank the reviewer for the comment. The plan is to test the independent effect of each item by means of multiple logistic regression and include only those items that show a significant contribution to the model. Therefore, the items that will not show a significant contribution will be excluded. In addition, items might be weighted differently based on the strength of association.

We have modified the text (section Methods – Statistics), which now reads: “We will estimate the knee pain prognosis (i.e. recurrence/persistence of knee pain, dichotomous outcome) at 3-month and 6-month follow-up by means of multiple logistic regression to estimate ORs and 95% confidence intervals for each item included in the tool. This allows to assess the independent effects of each item and will inform on which factors are most related to the prognosis of knee pain (only the items that will show a statistically significant contribution to the model will be selected). This will also provide an insight on the scores of the prognostic tool (both overall and for subscales) to be applied for the creation of the initial risk groups. Alternatively, the RR will be estimated if another linear model analysis will be carried out. In addition, a potential option is to apply different weights to the items based on the strength of association.”

18. Point 5 in the statistical plan is not explained well, could the authors say a little more about the identification of cut off scores and what criteria will be used to decide on this (i.e. are these independently generated from other sample or this one, what determines a poor outcome, if determined from this cohort it will make external validity more problematic), also if more will be given to sensitivity of the tool, how will this factor in the development of risk groups? Also it might be beneficial for the authors to compare risk groups in terms of the baseline characteristics and test across those to give further discriminant information, and in addition it might be worth considering construct validity by comparing to any existing measures, for example this measure could be compared to the generic PPST?

Response: We thank the reviewer for the insightful comment and provide some clarifications on this point.

At each follow-up time-point, a poor outcome is defined as the presence of activity-limiting knee pain. As the cut-off scores will be generated by using data of this sample, the prognostic model developed within this cohort will have to be externally validated with another cohort in the future. Regarding sensitivity, we stated that more importance will be given to sensitivity of the tool, meaning that we will choose cut-off scores for the definition of risk groups that will allow to identify the majority of those with a potential bad prognosis in the high risk group, and rule out from the group those with a good prognosis.

In addition, despite comparing the prognostic tool to the pediatric pain screening tool might be an option, it should be taken into account that the pediatric pain screening tool was validated in a tertiary care clinic and may operate differently in a primary care setting, which is where our prognostic tool is meant to operate. Therefore, the comparison might result in a poor match between risk group categories of the two tools due to differences in the severity of the sample used to develop the tools.

We have modified the text, which now reads: “Data from this sample will be used for the creation of risk groups for the recurrence/persistence of knee pain, on the basis of cut-off scores identified using the ROC curves. Weights based on the strength of association identified with the multiple logistic regression might be applied. The initial idea is to have two or three risk groups (e.g. low/medium/high), which have to be clinically meaningful. More importance will be given to the

sensitivity of the tool over the specificity. This means that in the presence of different cut-off scores for the inclusion of patients in the high-risk group, the cut-off that will allow to identify the majority of those with a bad prognostic outcome will be chosen. This will be done to avoid the misclassification of patients at high-risk in the medium or low-risk group."

19. The discussion might benefit more by describing the potential for the tool in terms of the assistance to clinicians, for example within the study will the research consider how clinicians feel about the tool and whether they feel it would be useful, also what is not clear at present is the potential pathways that are available as defined by risk, do the proposed risk groups have an aligned pathway already for example, if so what might that look like and if not how will these be developed?

Response: We thank the reviewer for the insightful comment and provide some clarifications on this point.

There are other steps that will follow the development of this tool. As the reviewer highlights, there are additional steps to be completed before implementing the tool. This includes 1) an external validation of the tool 2) developing the matched care pathways 3) mixed-methods studies to understand how the tool should look and operate in the context of general practice, and 4) subsequent clinical trials to test the impact of the tool. A cluster randomized controlled trial will be performed where patients will be randomized to stratified care provided by using the tool or to the best current care, and differences in clinical outcomes will be assessed. The original idea is to provide targeted treatments to the three risk groups. For example, patients in the low risk group might be provided with an initial short patient education session and given a leaflet that reinforces the information given by the GP. For the medium risk group, strengthening exercises and load management might be delivered, while for the high-risk group a tailored treatment might be delivered that will target also psychological factors. However, these are only initial suggested treatments, and additional treatments might be developed depending on the items that will prove to be significantly associated with a bad prognosis (e.g. potential further treatments might be advices regarding having a good sleep hygiene). Regarding assistance to the clinician, this tool together with another tool for the knee pain diagnosis, will be part of a package (decision tool) that will assist clinicians in the diagnosis and treatment of knee pain. Future qualitative studies will be needed to assess the GPs' behaviour when using the tool.

We have now modified the text and added this part to the section "Use of the tool for providing stratified care":

"The development of this tool fits within a wider research program, which overall aim is to provide a stratified approach to primary care management of child and adolescent knee pain that can result in clinical and economic benefits compared with current best practice. Therefore, future perspectives include the use of this tool in a randomized controlled trial, which will investigate whether subgrouping patients using the tool, combined with targeted treatment, is more clinically effective (i.e. it will reduce long- term disability from knee pain) and cost-effective compared to best current care. In addition, there is scope for performing future qualitative studies to assess the GPs' behavioral change when using the tool (e.g. changes in referral to physical therapy, diagnostic tests and medication prescriptions)"

Reviewer 2

Thank you for giving me the opportunity to review this well described paper about development and test of a prognostic tool for knee pain in adolescence. A very important area. I am very pleased to see the incorporation of psychosocial aspect in the pain.

I was wondering about the use of the word Ængstelig/deprimeret (anxious/depressed). Do children aged 8 and a bit older understand that word? Would it be better to use the word bekymret (worried) instead?

In the statistics section; you write that you will stratify by traumatic/non-traumatic onset. Why do they choose to do so?

I think this paper is well written and described and I therefore have no further comments. I am looking forward the seeing the results.

Response: We thank the reviewer for the valuable feedback provided. We have addressed the comments, and individual responses for each specific comment are outlined below.

1. I was wondering about the use of the word Ængstelig/deprimeret (anxious/depressed). Do children aged 8 and a bit older understand that word? Would it be better to use the word bekymret (worried) instead?

We thank the reviewer for the insightful comment.

The item used to ask about the psychological status was taken from the validated Danish version of the EQ-5d. However, because of the same concern regarding understanding the word Ængstelig/deprimeret, we asked children and adolescents during the cognitive interviews if they had any problems with this word. As it was difficult for some of the younger children to understand this word, we decided to add a note explaining what Ængstelig/deprimeret means. The note was “Ængstelig/deprimeret svarer til at være ked af det (det handler om hvordan du har det, og ikke nødvendigvis på grund af dine smerter)” (In English, anxious/depressed corresponds to be sad – it’s about how you feel and not necessarily because of your knee pain). After adding the note, children did not have further problems with the word.

1. In the statistics section; you write that you will stratify by traumatic/non-traumatic onset. Why do they choose to do so?

We thank the reviewer for the insightful comment.

The reason why we decided to stratify analysis by traumatic/non-traumatic onset is that previous research has indicated clear differences in the prognosis depending on the type of knee pain onset in both children and adults (please see references below).

If the stratification will provide very different prognostic results, it might be possible to use this factor for a quick initial discrimination between low risk vs. medium/high-risk of a bad prognosis.

References:

El-Metwally A. Lower Limb Pain in a Preadolescent Population: Prognosis and Risk Factors for Chronicity--A Prospective 1- and 4-Year Follow-up Study. *Pediatrics*. 2005;116(3):673-681. doi:10.1542/peds.2004-1758

Belo JN, Berger MY, Koes BW, Bierma-Zeinstra SMA. Prognostic factors in adults with knee pain in general practice. *Arthritis Care Res*. 2009;61(2):143-151. doi:10.1002/art.2441

Competing Interests: There are no competing interests to be declared.

Reviewer Report 27 January 2020

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Signe Fuglkjær Møller

Hartvigsen and Hein Back Centre and Sports Clinic, Odense, Denmark

Thank you for giving me the opportunity to review this well described paper about development and test of a prognostic tool for knee pain in adolescence. A very important area. I am very pleased to see the incorporation of psykosocial aspect in the pain.

I was wondering about the use of the word Ængstelig/deprimeret (anxious/depressed). Do children aged 8 and a bit older understand that word? Would it be better to use the word bekymret (worried) instead?

In the statistics section; you write that you will stratify by traumatic/non-traumatic onset. Why do they choose to do so?

I think this paper is well written and described and I therefore have no further comments. I am looking forward the seeing the results.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: musculoskeletal health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 15 Feb 2020

Alessandro Andreucci, Aalborg University, Aalborg, Denmark

Dear Editorial Team, F1000 Research,

We were delighted that the Reviewers of our recent submission " The Adolescent Knee Pain (AK-Pain) prognostic tool: protocol for a prospective cohort study" (ID: 21740) provided us with their very helpful feedback on our paper. This has given us the opportunity to apply changes that have led to an improvement of the paper.

Reviewer 1

Many thanks for the opportunity to review this protocol paper that reports on the rationale and methodology of testing an adolescent knee pain prognostic tool. The protocol is generally well written, and the proposed project to develop a prognostic tool is much needed within the child and adolescent musculoskeletal community. However I do feel some points within the paper require greater clarity and have set out a number of recommendations that I feel would improve the content and presentation of this paper.

Response: We thank the reviewer for the valuable feedback provided. We have addressed the comments and changed the manuscript (changes are underlined in the text), which we feel is now improved. Individual responses for each specific comment are outlined below.

1. Whilst the authors have aptly discussed the rationale for a prognostic tool within the introduction and briefly touch upon stratified care, I feel they need also mention what this means in terms of aligned treatments based on the risk (i.e. the pathway for stratified patients), a little bit more on this would benefit the introduction.

Response: We thank the reviewer for the comment and have now amended the introduction by providing more information on the aligned treatments based on the risk.

The text (Introduction section) now reads "One potential option to support clinical decision making is to develop decision aids such as prognostic tools. These tools often consist of items with prognostic value that can be asked during the clinical consultation or completed prior to the consultation. Thereby patients can be stratified depending on their prognosis (19) and subsequently the best targeted treatment based on the prognostic profile can be offered the patient. In the case of a child or adolescent with knee pain, different treatments or recommendations (e.g. short education session, modification of physical activity levels, exercise, use of painkillers, referral to a specialist) might be provided depending on the risk of a poor prognosis. Examples of prognostic tools that have already been developed include the Keele STarT Back Screening Tool (SBST) for lower back pain in adults (20) or the Pediatric Pain Screening Tool (PPST) for general pediatric pain (19)."

2. In the exclusion criteria the authors mention participants will be excluded if they have an inability to understand the questionnaire, is this a language issue, or for those with learning difficulties, or both, I think the authors might wish to expand on this a little more to give examples.

Response: Participants are meant to be excluded if they have either language issues or learning difficulties.

The text (section Methods, Eligibility and recruitment of participants) now reads "Inability to take

part in the study due to an inability to understand the questionnaire (i.e. participants who have issues with Danish language or have learning difficulties)”

3. The authors state that both parents will be approached before the consultation, does that then require that both parents be present as this won't often be the case (parent working, single parent etc), also more fundamental is the issue of “before the consultation”, if this is the case how do they know that the knee pain is not referred pain from the spine for example or that whilst the child/adolescent has knee pain that they may also discuss other issues within the consultation and the focus is on those other issues? I might add that the child may be looked after by someone who is not the parent (family member) and perhaps the term “caregiver” should also be used when the term parent is used?

Response: In Denmark, the general practitioner and his/her staff know in advance if the person is consulting for knee pain based on the booking. However, the general practitioner might also be made aware of the knee pain problem during a consultation regarding other issues. In this case, the questionnaire will be filled out after the consultation. As the reviewer correctly pointed out however, the knee pain might be referred from other body sites (e.g. spine), and we acknowledge that this is a limitation of our study.

We have amended the text and made it clearer. The text (section Methods - Eligibility and recruitment of participants) now reads “Participants will be recruited from general practices on the basis of consultation for knee pain. In Denmark, consultations with the GP are booked beforehand, which allows the GP and the GP's staff to know in advance what the patient is consulting for. The study will be introduced to the caregivers and children before the consultation by a person working at the general practice (e.g. the GP/nurse/secretary). If patients meet the inclusion criteria for being eligible into the study (e.g. patient aged between 8 and 19 years old who consult for knee pain) and agree to participate, they will be provided with the study material (i.e. prognostic tool to be completed). However, if the GP was made aware of the issue of the presence of knee pain during a consultation regarding other health issues, the questionnaire will be completed after the consultation.”

4. The authors describe complementary recruitment strategies to work alongside primary care recruitment, I think the use of wider recruitment strategy is good considering the low participation rate of children within primary care to MSK studies. However, whilst the authors have stipulated that children/adolescents will be reminded of the premise for participation, i.e. that participants have been seen by their GP for knee pain, how will this be confirmed? Furthermore, the authors have not explained the timeline for this, for example the recruitment within GP practices is at the time of consultation, however social media recruitment does not state a criteria of when they should have consulted. One of the key prognostic markers for adult MSK pain is time since onset, here you may have potentially two distinct groups, one who have consulted (not clear whether this will be the first consultation or a subsequent visit), and those via social media at presumably post consultation (but not stipulated as to what time period criteria is acceptable, is it a week, month, year etc), this presents issues of case mix, and at the very least the authors would have to collect information about timing of consultations (and timing of when patient first experienced pain) to factor into their analysis.

Response: We thank the reviewer for the very insightful comment.

Our plan is to include only those who have consulted within one week. In addition, sensitivity analysis will be applied by comparing results of those recruited in primary care and those recruited

through social media to assess potential differences related to case mix. Regarding timing of when patient first experienced pain, this is already assessed with item number 4 of the prognostic tool.

We have amended the text and made it clearer. The text (section Methods - Eligibility and recruitment of participants) now reads “Complementary recruitment strategies that might be applied to maximize the recruitment rate are the advertisement of the study through social media (e.g. Facebook, Twitter, Snapchat) and through explicative posters displayed at the participating general practices. In this case, it will be screened that participants have been seen by their GP within the last week and knee pain was part of the consultation.”

5. I think the offer of cinema tickets is a good incentive, however would it not be better to offer a family ticket or at least two tickets as a child would most likely go on their own?

Response: Although the idea of offering a family ticket or at least two tickets is good, unfortunately we were limited in our choice by financial constrictions. This is why we can offer only one cinema ticket at baseline and one cinema ticket at follow-up, and unfortunately it is not possible to change this strategy now as the study is already on-going.

6. For the data collection section, I wonder if a diagram might be helpful here as it is not fully clear, does the GP collect the data post consultation, will they (GPs) have time to do this, the authors mention previously that the child/adolescent will be approached to complete the tool before consultation, so does this mean they fill in the tool before consultation and then other information post consultation? The authors should be aware that pre-consultation may reveal different responses to a post-consultation (e.g. reductions in fear avoidance for parent/child due to reassurance from GP etc), this point also relates to point 4 above where alternative recruitment strategies may be used that could lead to different responses due to different timings?

Response: We thank the reviewer for the very insightful comment.

Data collection will occur before the consultation and will be facilitated by the general practitioner's staff (e.g. nurse, secretary), with the tool to be fully completed before consultation. However, as pointed out at point 3 above, the knee pain problem might not be cited as the primary reason for consultation, and the GP only made aware of it during the consultation. In this case, the tool will be completed after the consultation. Being aware of the potential differences in parameters pre-consultation vs. post-consultation we assessed the stability of the tool, which showed good stability of the tool parameters before and after consultation with the general practitioner, as described in section “Methods – Stability of the tool”.

7. When discussing the outcomes, the authors describe that outcomes will be collected by a combination of self-report or parent report, firstly this doesn't make sense because of the inclusion of “or” as that implies either, whereas it is described as a combination. Does this mean that there will be a choice in who fills in the questionnaire, should it not be self-report AND parent report, or is this related to age and access to online social media platforms where parents/caregivers would have to complete, I think this needs to be explained, and again the researchers should collect information on who fills in the questionnaire as there are differences between proxy and self-report.

Response: We thank the reviewer for the comment. The outcome will be collected by questionnaires that will be sent through an e-mail with a link to the web application for online surveys or text message. Within the questionnaire, there are also questions about name, surname and contact information (e-mail and phone number) and about who the person replying to the

questionnaire is (i.e. child alone/caregiver/child together with the caregiver). This allows us to know if the person replying is the caregiver or the child/adolescent.

We have amended the text and made it clearer. The text (section Methods – Data collection) now reads: “Outcomes will be collected by questionnaires. The adolescent can choose to do this self-reported or caregiver-reported (through an e-mail with a link to the web application for online surveys or text message) at follow-up (two time points: 3-month and 6-month follow-up). The questionnaire also includes a question about who the person replying to the questionnaire is (i.e. child alone/caregiver/child together with the caregiver)”

8. Participant timeline, is table 1 needed, I think it is clear that there will be an assessment at baseline and follow up at 3 months and 6 months for each participant, I don't think a diagram is needed for that? I feel a recruitment flow diagram would be a much better inclusion for this paper.

Response: We have replaced table 1 with a recruitment flow diagram and modified the text, which now reads “The process of recruitment and retainment of participants in the study (data collection start date: July 2019 – end date: June 2020) is described in the following flow diagram (figure 1).”

9. The authors discuss the development of the items for the tool, I think a little more should be said about this, for example is this the information within the review (ref 31) or additional literature, also as this is a generation of the candidate items for a prognostic tool it would be good to give some detail (e.g. how many studies within the review, what sort of populations, were they all prospective studies etc). In addition the authors discuss the situation where multiple items or multiple scales were present for items, I feel this whole sentence could do with expansion, what is meant by multiple items and multiple scales, do you mean prognostic factors that have been measured using multiple items/scales? Give some examples and how a multiple scale construct is then reduced to a single question, how was this done?

Response: We thank the reviewer for the insightful comment.

Items to be included in the prognostic tool were selected based on a combination of those initially identified with the review (31), of the wider literature on child and adolescent musculoskeletal pain and from meta-analysis of individual participant data (PROSPERO ID CRD42019116861). This allowed us to include also other potential factors that were not previously assessed in the studies identified in the review but were found to be associated with the prognosis of general musculoskeletal pain in other studies and might therefore result as significant contributors to the prognostic model. Regarding the situation where multiple items or multiple scales were present for items relative to the prognostic factors, single items were selected from the most appropriate scales.

We have now modified the text (Section Methods - Development of the tool) and made it clearer. The text now reads:

“Prognostic factors for knee pain in children and adolescents that can be measured in the context of general practice were identified from a review of the current literature on the topic (29). The review included 26 prospective studies, of which 4 focused on knee pain. These 4 studies included schoolchildren 12-19 years old from Denmark (3 studies) and 10-12 years old from Finland. Initially, the most important domains for the prognosis of knee pain and the specific items to be included in the tool were selected based on the review but also from strength of association from previous studies identified within the literature and from meta-analysis of individual participant data. Prognostic factors for knee pain identified within the review (29) were increasing age, pain frequency, practicing sport more than 2 times/week and low quality of life (second question of item 9 within the tool). Other factors that were identified from the wider literature and meta-analysis of individual participant data (PROSPERO ID CRD42019116861) were knee pain characteristics (pain duration, traumatic/non-traumatic pain onset, limitations in daily activities due to knee pain, presence of knee pain in one knee or both knees), presence of pain in other body sites, gender, sleep, smoking, psychological factors, parental history of pain. During this stage, great emphasis was given to include only the most necessary factors considering the ultimate use of the prognostic tool (i.e. it should be used in a reasonable time of a consultation within general practice). Items relative to the specific prognostic factors were initially selected from validated scales when possible (e.g. regarding pain characteristics, limitation in daily activities, sport participation, psychological factors, sleep), or from previous studies. When multiple items within a scale or multiple scales were available for a prognostic factor, the relevant literature on the topic was identified and discussed at meetings with GPs and staff working at the Center of General Practice at Aalborg University in order to select the most appropriate items within the possible options. For example, the sleep item was selected from the self-reported Pediatric Quality of Life Inventory, one question of the psychological factor item from the Pain Catastrophizing Scale for Children, one question of the psychological factor item and the item relative to limitations in daily activities from the EuroQol Five-Dimensional Questionnaire Youth version.”

10. Within the study piloting section, the authors mention the process of improving face, construct, content validity, stressing the importance of this should a GP make an inaccurate diagnosis, I have some concern about this statement as it suggests that the questions asked about pain via the tool are in some way involved in diagnosis, this is surely not the case, can the authors explain what they mean?

Response: The aim of the study piloting was to improve the comprehensibility and wording of the questions included in the tool, so that adolescents would provide information about the parameters related to the knee pain prognosis that were as close as possible to the real values and therefore limit potential misreporting. As the reviewer correctly pointed out, the tool is not conceived as a replacement of the diagnosis made by the general practitioner, but only as a support for understanding the prognosis together with the clinical examination.

We have now modified the text and made it clearer. The text (section Methods – Study piloting) now reads:

“The aim was to improve the face, construct and content validity of the tool at this stage. This is especially important considering that a worse outcome can result if there is a lack of communication between the GP and the child about the knee pain characteristics and the factors related to knee pain assessed within the tool (33).”

11. In the stability of the tool section the authors state that children were referred to primary care because of their knee pain, who is it then who refers children to primary care, what is the process for this as this may be a factor to be considered (e.g. how long does it take for a person to be referred to primary care, who does the referral, how are decisions made on a referral etc), I thought it was that the child/parent/caregiver attends primary care?

Response: We have amended the imprecision in the text, as we actually meant the child/adolescent who consult primary care for knee pain. We have modified the text, which now reads “Children and adolescents who consulted primary care and their caregivers were given the prognostic tool (together with the informed consent) to be completed in the waiting room of the general practice before the consultation.”

12. I am slightly confused about the test-retest parameters, from what is written it appears that the test was done pre and post consultation (i.e. within the same day, perhaps within the same hour), this timeline is too short, the point of test/retest is to ensure that the participants would not remember the responses to the questions asked, so for example the next week, to then ensure that the responses are consistent, I am not convinced this current test stacks up, and any differences would likely be via information received within the consultation (influencing different responses) rather than the actual difference coming from inconsistency in the measure (for example a GP offering reassuring information).

Response: We thank the reviewer for the comment and acknowledge the inaccuracy in the language used within the text. As pointed out by the reviewer, the GP might influence the perception of certain parameters related to pain (i.e. psychological factors, pain duration) through the discussion occurring during the consultation. In order to test if responses to the questions asked were influenced by the consultation with the GP (and to estimate the difference in responses), the stability of the tool before and after the consultation was tested and results showed good stability. However, as the reviewer correctly pointed out, this cannot be considered a test-retest as the time frame between the two measurements was too short. We have amended the text, (Section Methods – Stability of the tool) which now reads “A pilot study to assess the stability of the prognostic tool (31) in children and adolescents pre- and post- consultation was carried out.”

13. I feel for the general readership it would be helpful to have the tool in English within the paper, and when I tracked down the English version I could see it has 12 questions, whereas the one in the current paper has 13 questions?

Response: The English version, with 13 questions is accessible at:
<https://doi.org/10.7910/DVN/QKWOOT>

14. The secondary outcome is the same as the primary outcome, with the only difference being time, could the authors clarify whether this is actually a secondary outcome or just a different time period for the same primary outcome measure?

Response: We thank the reviewer for the comment and have amended the imprecision in the text. In our study, the outcome is the same is collected at two endpoints. We decided to consider the knee pain prognosis at 3-month as the primary endpoint and the knee pain prognosis at 6 months as a secondary endpoint.

We have modified the text (Section Methods – Outcome), which now reads “The outcome measure will be the recurrence/persistence of activity-limiting knee pain (i.e. defined as participants reporting yes to having pain that is limiting activities in the same knee) at follow-up (28). Participants will be asked about continuity of their knee pain (i.e. “do you still have knee pain?” and, if they reply “no”, “when did your stop having knee pain?”), to enable the distinction between recurrence (on/off knee pain episodes between baseline and follow-up) and persistence (continuous knee pain from baseline to follow-up) of knee pain. The primary end-point that will be collected is the recurrence/persistence of activity-limiting knee pain at 3-month follow-up, while the secondary end-point is the recurrence/persistence of activity-limiting knee pain at 6-month follow-up”

15. The authors state that the statistical analysis plan can be found elsewhere, this protocol paper should include the full statistical analysis plan rather than have a signpost to another protocol, can the authors include the full details in this paper (and if they have then they don't need to reference another protocol).

Response: We have now corrected the text (section Methods – Statistics), inserted the full analysis plan within this paper and deleted the reference to the other protocol.

16. The authors discuss potential floor and ceiling effects, can the authors say a little more about this as presumably some risk items would only identify those at extremes (i.e. at risk) in any case? This is particularly true of items that can identify those at high risk, they may only account for a small proportion of the population with a number of items giving an additive high risk score?

Response: We thank the reviewer for the very insightful comment. As correctly pointed out by the reviewer, for items that represent an ordinal or categorical variable with more than two potential response categories (for example 5 categories), the responses given might be only the top or bottom extreme of the scales. For example, this might happen for items related to psychological factors and sleep. In this case, participants with higher levels of anxiety/depression, helplessness or sleep problems would most likely fall in the high-risk category. A potential option to account for this is to initially test the independent effect of each item by means of multiple logistic regression, include those items that show a significant contribution to the model and subsequently apply different weights based on the strength of association. For example, a combination of the different items can be used to identify the scores for defining the risk groups (i.e. low/medium/high) and if items that identify only a small proportion of the population (e.g. high levels of psychological factors or sleep problems) are associated with a high risk of a bad prognosis, they can be selected and used to give an additive high-risk score.

17. Will the authors examine both each individual item but also within a model (multivariable) to test the independent effects of each item as some many have overlapping qualities (will they also examine redundant items); also will the authors consider model fit (e.g. explained variance) within their analysis?

Response: We thank the reviewer for the comment. The plan is to test the independent effect of each item by means of multiple logistic regression and include only those items that show a significant contribution to the model. Therefore, the items that will not show a significant contribution will be excluded. In addition, items might be weighted differently based on the strength of association.

We have modified the text (section Methods – Statistics), which now reads: “We will estimate the knee pain prognosis (i.e. recurrence/persistence of knee pain, dichotomous outcome) at 3-month and 6-month follow-up by means of multiple logistic regression to estimate ORs and 95% confidence intervals for each item included in the tool. This allows to assess the independent effects of each item and will inform on which factors are most related to the prognosis of knee pain (only the items that will show a statistically significant contribution to the model will be selected). This will also provide an insight on the scores of the prognostic tool (both overall and for subscales) to be applied for the creation of the initial risk groups. Alternatively, the RR will be estimated if another linear model analysis will be carried out. In addition, a potential option is to apply different weights to the items based on the strength of association.”

18. Point 5 in the statistical plan is not explained well, could the authors say a little more about the identification of cut off scores and what criteria will be used to decide on this (i.e. are these independently generated from other sample or this one, what determines a poor outcome, if determined from this cohort it will make external validity more problematic), also if more will be given to sensitivity of the tool, how will this factor in the development of risk groups? Also it might be beneficial for the authors to compare risk groups in terms of the baseline characteristics and test across those to give further discriminant information, and in addition it might be worth considering construct validity by comparing to any existing measures, for example this measure could be compared to the generic PPST?

Response: We thank the reviewer for the insightful comment and provide some clarifications on this point.

At each follow-up time-point, a poor outcome is defined as the presence of activity-limiting knee pain. As the cut-off scores will be generated by using data of this sample, the prognostic model developed within this cohort will have to be externally validated with another cohort in the future. Regarding sensitivity, we stated that more importance will be given to sensitivity of the tool, meaning that we will choose cut-off scores for the definition of risk groups that will allow to identify the majority of those with a potential bad prognosis in the high risk group, and rule out from the group those with a good prognosis.

In addition, despite comparing the prognostic tool to the pediatric pain screening tool might be an option, it should be taken into account that the pediatric pain screening tool was validated in a tertiary care clinic and may operate differently in a primary care setting, which is where our prognostic tool is meant to operate. Therefore, the comparison might result in a poor match between risk group categories of the two tools due to differences in the severity of the sample used to develop the tools.

We have modified the text, which now reads: “Data from this sample will be used for the creation of risk groups for the recurrence/persistence of knee pain, on the basis of cut-off scores identified using the ROC curves. Weights based on the strength of association identified with the multiple logistic regression might be applied. The initial idea is to have two or three risk groups (e.g. low/medium/high), which have to be clinically meaningful. More importance will be given to the sensitivity of the tool over the specificity. This means that in the presence of different cut-off scores for the inclusion of patients in the high-risk group, the cut-off that will allow to identify the majority of those with a bad prognostic outcome will be chosen. This will be done to avoid the misclassification of patients at high-risk in the medium or low-risk group.”

19. The discussion might benefit more by describing the potential for the tool in terms of the

assistance to clinicians, for example within the study will the research consider how clinicians feel about the tool and whether they feel it would be useful, also what is not clear at present is the potential pathways that are available as defined by risk, do the proposed risk groups have an aligned pathway already for example, if so what might that look like and if not how will these be developed?

Response: We thank the reviewer for the insightful comment and provide some clarifications on this point.

There are other steps that will follow the development of this tool. As the reviewer highlights, there are additional steps to be completed before implementing the tool. This includes 1) an external validation of the tool 2) developing the matched care pathways 3) mixed-methods studies to understand how the tool should look and operate in the context of general practice, and 4) subsequent clinical trials to test the impact of the tool. A cluster randomized controlled trial will be performed where patients will be randomized to stratified care provided by using the tool or to the best current care, and differences in clinical outcomes will be assessed. The original idea is to provide targeted treatments to the three risk groups. For example, patients in the low risk group might be provided with an initial short patient education session and given a leaflet that reinforces the information given by the GP. For the medium risk group, strengthening exercises and load management might be delivered, while for the high-risk group a tailored treatment might be delivered that will target also psychological factors. However, these are only initial suggested treatments, and additional treatments might be developed depending on the items that will prove to be significantly associated with a bad prognosis (e.g. potential further treatments might be advices regarding having a good sleep hygiene). Regarding assistance to the clinician, this tool together with another tool for the knee pain diagnosis, will be part of a package (decision tool) that will assist clinicians in the diagnosis and treatment of knee pain. Future qualitative studies will be needed to assess the GPs' behaviour when using the tool.

We have now modified the text and added this part to the section "Use of the tool for providing stratified care":

"The development of this tool fits within a wider research program, which overall aim is to provide a stratified approach to primary care management of child and adolescent knee pain that can result in clinical and economic benefits compared with current best practice. Therefore, future perspectives include the use of this tool in a randomized controlled trial, which will investigate whether subgrouping patients using the tool, combined with targeted treatment, is more clinically effective (i.e. it will reduce long- term disability from knee pain) and cost-effective compared to best current care. In addition, there is scope for performing future qualitative studies to assess the GPs' behavioral change when using the tool (e.g. changes in referral to physical therapy, diagnostic tests and medication prescriptions)"

Reviewer 2

Thank you for giving me the opportunity to review this well described paper about development and test of a prognostic tool for knee pain in adolescence. A very important area. I am very pleased to see the incorporation of psychosocial aspect in the pain.

I was wondering about the use of the word Ængstelig/deprimeret (anxious/depressed). Do children aged 8 and a bit older understand that word? Would it be better to use the word bekymret (worried) instead?

In the statistics section; you write that you will stratify by traumatic/non-traumatic onset. Why do they choose to do so?

I think this paper is well written and described and I therefore have no further comments. I am looking forward the seeing the results.

Response: We thank the reviewer for the valuable feedback provided. We have addressed the comments, and individual responses for each specific comment are outlined below.

1. I was wondering about the use of the word Ængstelig/deprimeret (anxious/depressed). Do children aged 8 and a bit older understand that word? Would it be better to use the word bekymret (worried) instead?

We thank the reviewer for the insightful comment.

The item used to ask about the psychological status was taken from the validated Danish version of the EQ-5d. However, because of the same concern regarding understanding the word Ængstelig/deprimeret, we asked children and adolescents during the cognitive interviews if they had any problems with this word. As it was difficult for some of the younger children to understand this word, we decided to add a note explaining what Ængstelig/deprimeret means. The note was “Ængstelig/deprimeret svarer til at være ked af det (det handler om hvordan du har det, og ikke nødvendigvis på grund af dine smerter)” (In English, anxious/depressed corresponds to be sad – it’s about how you feel and not necessarily because of your knee pain). After adding the note, children did not have further problems with the word.

1. In the statistics section; you write that you will stratify by traumatic/non-traumatic onset. Why do they choose to do so?

We thank the reviewer for the insightful comment.

The reason why we decided to stratify analysis by traumatic/non-traumatic onset is that previous research has indicated clear differences in the prognosis depending on the type of knee pain onset in both children and adults (please see references below).

If the stratification will provide very different prognostic results, it might be possible to use this factor for a quick initial discrimination between low risk vs. medium/high-risk of a bad prognosis.

References:

El-Metwally A. Lower Limb Pain in a Preadolescent Population: Prognosis and Risk Factors for Chronicity--A Prospective 1- and 4-Year Follow-up Study. *Pediatrics*. 2005;116(3):673-681. doi:10.1542/peds.2004-1758

Belo JN, Berger MY, Koes BW, Bierma-Zeinstra SMA. Prognostic factors in adults with knee pain in general practice. *Arthritis Care Res*. 2009;61(2):143-151. doi:10.1002/art.2441

Competing Interests: There are no competing interests to be declared.

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