Adolescent Knee Pain (AK-Pain) prognostic tool study protocol

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Revision history

1.0 → 1.1 (section 2.8, 2.10, 2.11 and 2.12 have been modified on 15th of June 2019)

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1. Introduction

1.1. Background and rationale for the study

Knee pain is experienced by 33% of adolescents [1], and the prognosis of knee pain is often unfavorable, with approximately 50% of adolescents still reporting knee pain after 1 or 2 years [1,2]. Common child and adolescent knee pain includes a variety of conditions (e.g. patellofemoral pain, patella tendinopathy, fat pad impingement, Osgood-Schlatter and Sinding-Larsen-Johansson disease), with specific treatments provided (e.g. education, activity modification, flexibility and strengthening exercises, cryotherapy, orthoses, patellar taping, medications) depending on the condition [3,4]. Knee pain is linked to both health and social consequences [3]. Children and adolescents with knee pain are more likely to reduce their sport participation, with following issues regarding the overall health (e.g. poor cardiovascular health, higher adiposity, impaired sleep) [1,5–8], to have a higher rate of school absence [6,9] and to be affected in the choice and performance of future work activities [10,11]. Knee pain in children and adolescents has also an economic impact, which include 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 [12,13]. Knee pain in childhood and adolescence may also persist in adulthood; previous studies have shown that a high proportion of them experience recurrence of symptoms over up to 20 years of follow-up [14,15], and adolescent knee pain might be a precursor of adult knee conditions such as knee osteoarthritis [16–19]. While there is a body of research on adult knee pain [20–22], less is known in children and adolescents, who are a distinct population compared to adults with different physiology and psychosocial development [5,23]. Potential prognostic factors for knee pain identified in previous studies conducted in adolescents include female gender, high leisure time sport

participation, low health-related quality of life, high baseline frequency of knee pain [2]. A proportion of children and adolescents with knee pain will consult the general practitioner because of their condition; previous research has shown an annual consultation prevalence for knee pain in children and adolescents of 119 [24] - 200 [25] per 10,000 registered persons.

Once patients have consulted for their knee pain, general practitioners are left with the difficult task of figuring out how their patient's condition can progress (i.e. if the patient will get better or not) in order to provide them with the best care [26,27]. This include avoiding overdiagnosis (i.e. identification of a pathological state which will not result in a future poor outcome but might lead to unnecessary over-medicalization) and taking into account the patient's entire biological, psychological and social context [27].

General practitioners can be aided in the decision process by prognostic tools, which are tools that are used to stratify patients and match them to specific treatments depending on their risk of recurrence or persistence of a condition. This type of tools can help clinicians to identify subgroups of patients with different risk of recurrence or persistence of a pain condition depending on a prognostic score derived from a combination of individual prognostic factors [28]. Examples of prognostic tools that have already been developed include the Keele STarT Back Screening Tool (SBST) for back pain in adults [29] or the Pediatric Pain Screening Tool (PPST) for general pediatric pain [28]. However, a prognostic tool to be used specifically for the prognosis of knee pain in children and adolescents in primary care has not been developed yet, as the PPST included physical and psychosocial items that can be applied to general musculoskeletal and non-musculoskeletal pain conditions and it was validated in tertiary care settings [28,30]. Therefore, the development of a pediatric knee pain prognostic tool will fill this gap and will enable general practitioners to provide stratified care by tailoring the best targeted treatment to patients with

knee pain according to the category of risk. In summary, the development of a prognostic tool for child and adolescent knee pain within a primary care setting is important for three reasons:

1. First, primary care is the place where the majority of health care is delivered [31], and consequently research carried out within this setting has the potential to have a significant impact in real-life.
2. Second, a prognostic tool developed for knee pain will include items about factors that are specific to the prognosis of knee pain (e.g. pain duration, previous history of knee pain) and therefore would be more sensitive than other more general pediatric pain tools, such as the PPST. This is important considering that misclassification of patients might potentially lead to undertreat those misclassified as low-risk and overtreat those misclassified as high-risk [32].
3. 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 disease [33–35], and it is recommended that prognostic tools are validated in different care settings [36]. Therefore, 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 samples of care settings, as it has previously been observed a difference in the efficacy of risk prediction potentially because of differences in patients case mix [37].

1.2. Aim of the study

The overall aim of this study is to develop and test a prognostic tool for knee pain in children and adolescents to be used in general practice.

1.3. Importance of this study

The importance of this study lies in the fact that the development of a prognostic tool for children and adolescents with knee pain will allow general practitioners to categorize them according to their category of risk and consequently provide them the best targeted treatment.

1.4. Specific objectives of the study

1) Identification of prognostic factors for knee pain in children and adolescents
    a) Review of prognostic factors for knee pain in children and adolescents from current literature
    b) Selection of prognostic factors to be included in the prognostic tool
2) Development of a prognostic model
    a) Development of the questions to be included in the prognostic tool
    b) Discussion about the questions wording with GPs
    c) Identification of the most suitable form to deliver the prognostic tool
3) Piloting the prognostic tool and recruitment procedures
    a) Testing the prognostic tool at the general practices
        i) Assess time taken to use the prognostic tool

ii) Assess quality/acceptability of the prognostic tool (e.g. content of the questions and domains included, acceptability and understanding of the questions used, acceptability of the delivery of the tool, face validity, construct validity, criterion validity)

b) Assess participants' recruitment processes

i) Assess baseline response (e.g. ratio between children who participated in the study over all those who consulted for knee pain as recorded with codes for consultation) and reasons for non-participation

c) Improvement of the prognostic tool and of the recruitment procedures

4) Recruitment of children and adolescents and collection and analysis of the data

a) Description of the sample characteristics

b) Assess the predictive ability of the prognostic tool

i) Sensitivity

ii) Specificity

c) Assess baseline response and reasons for non-participation

d) Assess loss to follow-up and reasons for dropping out of the study where possible

5) Cost-effectiveness of the study (optional depending on time availability)

a) Assess the workload for GPs, researchers and administrative staff

b) Assess the time needed to deliver the tool in general practice and identification of alternative solutions to deliver the tool (e.g. by using iPads etc)

c) Assess satisfaction of the participants and general practitioners with the study

d) Evaluation of the effectiveness and suitability of this study in light of the resources available in general practice

1.5. Study design

Prospective cohort study. Data will be collected at baseline through a questionnaire delivered at the general practice if the primary recruitment strategy will be applied. Otherwise, the baseline collection of the data will occur through a questionnaire home-mailed or delivered through a survey internet link if a strategy of recruitment through social media will be applied (please see section 2.7.2 for a description of the recruitment strategies). Outcomes will be collected by questionnaires either self-reported or parent-reported (collected through e-mail or text messages) at follow-up.

2. Methods

2.1. Study Setting

The aim is to collect data from general practices based in Denmark (with a potential complementary recruitment occurring through social media). For logistic reasons the recruitment will initially focus on large practices (populations around 10.000 each). However, smaller practices may be included too. For a calculation of the number of practices required to carry out the project please see section 2.5.

2.2. Participants and eligibility criteria

Children and adolescents who consult their general practitioner because of their knee pain (of both traumatic and non-traumatic origin) during a period of recruitment of 6 months (starting in July 2019) are eligible for inclusion.

2.2.1. Inclusion criteria:

- Age 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 guidance [38] (provided that the questions are properly worded by taking into account the age-related cognitive abilities [39,40]), and the age of 19 is defined as the upper limit for the period of adolescence by the World Health Organization [41].

2.2.2. Exclusion criteria:

- 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 by different 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) [39]
- Inability to take part to the study because of inability to understand or comply

2.3. Outcome measures

The primary outcome measure will be the recurrence/persistence of activity-limiting knee pain (i.e. yes/no pain that is limiting activities in the same knee) at 3-month follow-up [42]. Participants will also be asked about continuity of their knee pain (i.e. "how long have you been free of 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. A secondary outcome measure that will be collected is the recurrence/persistence of activity-limiting knee pain at 6-month follow-up.

Previous studies have shown an effect of the treatment received on the change in risk group for the recurrence/persistence of pediatric pain [43] and on the change in pain and function [44]. Therefore, an additional outcome measure that might potentially be assessed include the treatment effectiveness on the recurrence/persistence of knee pain (provided that there will be the possibility to collect data on the treatment given). For practical reasons, it might be considered assessing this additional outcome on a subsample of children and adolescents.

2.4. Participant timeline

Examples of potential participants' timeline are described in table 1.

Table 1. Participants' timeline														
	Year	2019						2020						
	Stage	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
	Baseline participant recruitment													
Child n°1	Baseline assessment													
	3-month follow-up													
	6-month follow-up													
Child n°2	Baseline assessment													
	3-month follow-up													
	6-month follow-up													
Child n°3	Baseline assessment													
	3-month follow-up													
	6-month follow-up													
Child n°4	Baseline assessment													
	3-month follow-up													
	6-month follow-up													
Child n°5	Baseline assessment													
	3-month follow-up													
	6-month follow-up													
Child n°6	Baseline assessment													
	3-month follow-up													
	6-month follow-up													

2.5. Sample size

The sample size for the development of the Pediatric Pain Screening Tool included 321 children aged 8-18 years old [28]. A minimum of 100 subjects is required for a stable variance-covariance matrix [45], and following the rule of thumb of at least 10 events for variable (or items within the prognostic tool) [45], around 300 individuals would be necessary for a maximum of 30 items included in the tool. However, in case of presence of binary predictors with low prevalence, ≥20 events per variable would be necessary [46] (this would consequently lower the number of items that it is possible to include in the prognostic tool).

Previous studies have shown an annual consultation prevalence of 104 - 200 per 10,000 registered persons in children aged 3 to 19 years old [24,25,47]. Here below, different potential scenarios about participants' recruitment are described. These scenarios are calculated on a conservative estimate of 30% study participation rate. This is a worst-case scenario, and this approach is taken in order to have a safe recruitment that will provide us with enough children and adolescents for the development of the tool.

Based on the prevalence estimate of 119 [24] per 10,000 registered persons (which is a likely prevalence for children aged 8-19), at least 168 general practices of a medium size of 5000 individuals each will be needed to recruit at least 300 participants at baseline (provided that 30% of all children aged 8-19 with a consultation for knee pain during a period of 6 month decide to take part in the study). This means that the overall target population includes 840.000 persons (168*5000) registered in general practices, which corresponds to 1/7 of the whole Danish population. Indeed, among these 840.000 persons, approximately 168.000 (20%) will be aged between 8 and 19 years old and 1,999 (119 per 10,000 registered persons) of these young people will have a consultation for knee pain in one year. Of these, 999 will have a consultation in a 6-

month period (which is the duration of the baseline recruitment). If 30% of these children decide to take part in the study, there will be data on 300 children aged 8-19 at baseline.

However, for the development of the START-BACK screening tool 244 patients were identified, of which only 131 (54%) returned the baseline questionnaire and 107 (82%) agreed to further contact [29]. Therefore, if we aimed at only 100 children aged 8-19 years old with a consultation for knee pain in a 6-month period and by keeping the same proportions shown above (i.e. only 30% baseline participation rate), only 56 general practices of a medium size of 5000 individuals each would be needed (corresponding to a target population of 280.000 individuals, of which 56.000 aged 8-19 years old). A target of 100 children would enable approximately 30 individuals in each prognostic risk group (low/medium/high).

Conversely, based on the highest prevalence estimate (200 per 10,000 registered persons) and considering a 30% participation rate into the study, 33 general practices of a medium size of 5000 individuals each would be needed (corresponding to a target population of 165.000 individuals, of which 33.000 aged 8-19 years old) to recruit at least 100 children. To recruit at least 300 children, 100 general practices of a medium size of 5000 individuals each would be needed (corresponding to a target population of 500.000 individuals, of which 100.000 aged 8-19 years old). Alternatively, it might be possible to target fewer bigger general practices (e.g. 18 general practices of a medium size of 10.000 individuals to recruit 100 children).

In addition, if only 100 children will be recruited from general practices, it might be possible to perform an extra recruitment through social media that would complement the group of children recruited through general practices, 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.

2.6. Development of the tool

Clinically meaningful prognostic factors for knee pain in children and adolescents were identified from a review of the current literature on the topic. 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 strength of association from previous studies identified within the literature and from meta-analysis of individual participant data. Additional factors were included after discussion with general practitioners that agreed to take part to the study and staff working at the Center for General Practice at Aalborg University. During this stage, great emphasis was given to include only the most necessary factors taking in mind that the prognostic tool 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 where possible (e.g. regarding pain characteristics, limitation in daily activities, sport participation, psychological factors). 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 general practitioners and staff working at the Center of General Practice at Aalborg University in order to select the most appropriate items within the possible options. Following previous tools developed for pain in children and adolescents [28,48,49], items were properly worded for the age and properly framed with respect to the response options (e.g. direction, time intervals, avoiding double-barreled items).

The initial version of the tool was tested and implemented during the pilot stage (great emphasis was given to the cognitive interviews that were carried out with children and adolescents), until reaching a final version that will be used for the collection of the data, as further described below in section 2.8.6. The outline of the final tool is provided in the figure below:

Knæ project

Disse spørgsmål handler om dine knæsmerter. 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.

	Navn	
1.	Hvor gammel er du?	(_____)
2.	Er du en pige eller en dreng?	☐ Pige ☐ Dreng
3.	Har du ondt i det ene knæ eller begge knæ?	☐ Kun det ene knæ (højre knæ) ☐ Kun det ene knæ (venstre knæ) ☐ 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	☐ under 3 måneder ☐ 3– 6 måneder ☐ 6–12 måneder ☐ 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	☐ Kom pludseligt (f.eks. da jeg fik en skade) ☐ 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	☐ Sjældent ☐ Månedligt ☐ Ugentligt ☐ Mere end en gang om ugen ☐ 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	☐ Nej ☐ Ja. Marker venligst hvor. Du må gerne afkrydse mere end et område: ☐ Hovedet ☐ Ryg eller nakke ☐ Skulder ☐ Albuen ☐ Håndled eller hånden ☐ Underbenet ☐ Låret ☐ Bækken (badebuksområdet) ☐ Ankel, hælen eller foden ☐ 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	☐ Jeg har ingen problemer med at udføre mine sædvanlige aktiviteter ☐ Jeg har lidt problemer med at udføre mine sædvanlige aktiviteter ☐ Jeg har nogle problemer med at udføre mine sædvanlige aktiviteter ☐ Jeg har store problemer med at udføre mine sædvanlige aktiviteter ☐ 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)	☐ Overhovedet ikke ☐ Lidt ☐ I nogen grad ☐ Meget ☐ Rigtig meget ☐ Jeg er ikke ængstelig eller deprimeret ☐ Jeg er lidt ængstelig eller deprimeret ☐ Jeg er i nogen grad ængstelig eller deprimeret ☐ Jeg er meget ængstelig eller deprimeret ☐ 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)	☐ Nej ☐ Ja ☐ Nej ☐ 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.	☐ Aldrig ☐ 1 gange/uge ☐ 2 gange/uge ☐ 3 gange/uge ☐ 4 gange/uge ☐ 5 gange/uge ☐ 6 gange/uge ☐ 7 eller flere gange/uge (_____)

12.	Har du røget cigaretter I de sidste 4 uger?	☐ Nej ☐ Ja
13.	Hvor enig er du i dette udsagn ”Jeg har problemer med at sove” (det behøver ikke nødvendigvis være på grund af smerter)	☐ Aldrig ☐ Næsten aldrig ☐ Nogle gange ☐ Ofte ☐ Næsten altid

2.7. Recruitment procedures

The recruitment strategy involves different stages (see figure 2), which include both the general practitioners' and the participants' recruitment. These stages are outlined below:

2.7.1. Recruitment and involvement of general practices into the study

This stage involves the recruitment of general practitioners. It is important to recruit enough general practitioners in order to have an adequate number of participants to the study (section 2.5). Insufficient recruitment can result in a limitation in power and generalizability of the study [50]. In order to obtain enough general practitioners involved in the study, efforts were done to comply with the Solberg's seven R-factors [50]. These factors include the relationship between recruiters and general practitioners, the reputation of recruiters, the requirements for study participation, the reward for participating to the study, reciprocity between what is provided by recruiters and what is expected by participants, resolute behavior of recruiters and respect between recruiters and participants [50]. Several sub-stages are included within the stage of recruitment of general practitioners:

1. Getting in touch with the general practitioners in order to ask them their availability to join the research (large clinics of general practitioners are preferred). The first contact was brief but informative. General practitioners were contacted by:
    - In-person presentations at general practitioners' professional meetings
    - Cold calls to practices identified using local telephone books
    - Exploiting previous relationships between our general practitioners and their colleagues
    - Distributing flyers with the description of the study to general practitioners

2. Introductory meetings with general practitioners, the secretaries and nurses to confer the importance, contents and goals of the study.

   Goals to be achieved with these meeting:

   - General practitioners and their staff's understanding of the importance of the study.
   - General practitioners and their staff's understanding of the recruitment methods.
   - General practitioners and their staff's trust in the study and confidence in communicating research to their patients.
   - General practitioners and their staff will have to feel morally rewarded by taking part in this research.

3. Meeting for the implementation of the recruitment strategy with general practitioners and their staff

   - General practitioners were asked to help us advertising the study to other general practitioners.
   - General practitioners were involved in the design of tailored recruitment procedures (i.e. in the initial brainstorming meetings and during the piloting stage of the recruitment) and as a source of feedback in the process of recruitment.
   - Definition of the specific workload for each member of the study (e.g. researchers, general practitioners and their staff).

4. Beginning of recruitment after implementation of the recruitment strategy
    - A collaboration agreement and a data handling agreement with general practitioners was signed in order to avoid potential breach of data confidentiality and privacy.
5. Regular follow-up meetings with the general practitioners and the recruitment staff will be held in order to monitor the recruitment rate
    - Feedback about recruitment achievements will regularly be provided to the general practitioners and their staff. The recruitment rates from every practice will be monitored and every month an e-mail will be sent to each general practitioner who takes part in the study to provide them with statistics of both the overall and individual recruitment rate. If the number of participants recruited is lower than the expected rate (which will vary depending on the practice size), practices will be contacted to discuss reasons for the low participant rate [51].

2.7.2. Participant recruitment

Simple and broad entry criteria (described above in section 2.2) will be applied, in order to get as many participants as possible. A combination of strategies (please see figure 3), which are described below, has been taken into consideration.

The primary participant recruitment strategy will be the recruitment occurred at general practices on the day of consultation for knee pain (called "warm recruitment" within this document).

1. Warm recruitment. This method involves the invitation to join the study directly when children and adolescents have a consultation for knee pain at the general practice. If they agree to participate to the study, they will be provided with the study material (i.e. prognostic tool to be completed). In case children decide not to participate, the reason for non-participation will be asked from a list of options.

Alternative recruitment strategies that might be applied in order to maximize the recruitment rate

1. Advertisement of the study through social media (e.g. Facebook, Twitter, Snapchat).
2. Advertisement of the study through explicative posters that will be displayed at the participating general practices.

2.7.3. Strategies to increase baseline participation and limit loss to follow-up

In order to promote baseline participation and limit loss to follow-up from the study, children will be given two cinema tickets if they decide to take part in the study. The first ticket will be given at baseline, when children decide to take part in the study and after returning the questionnaire, and the second ticket will be given only if the children will have completed the follow-up (e.g. provided

information at both the 3-month and 6-month follow-up points). The ethics committee was be informed about the cinema tickets to be given to participants and approved this method.

Figure 2

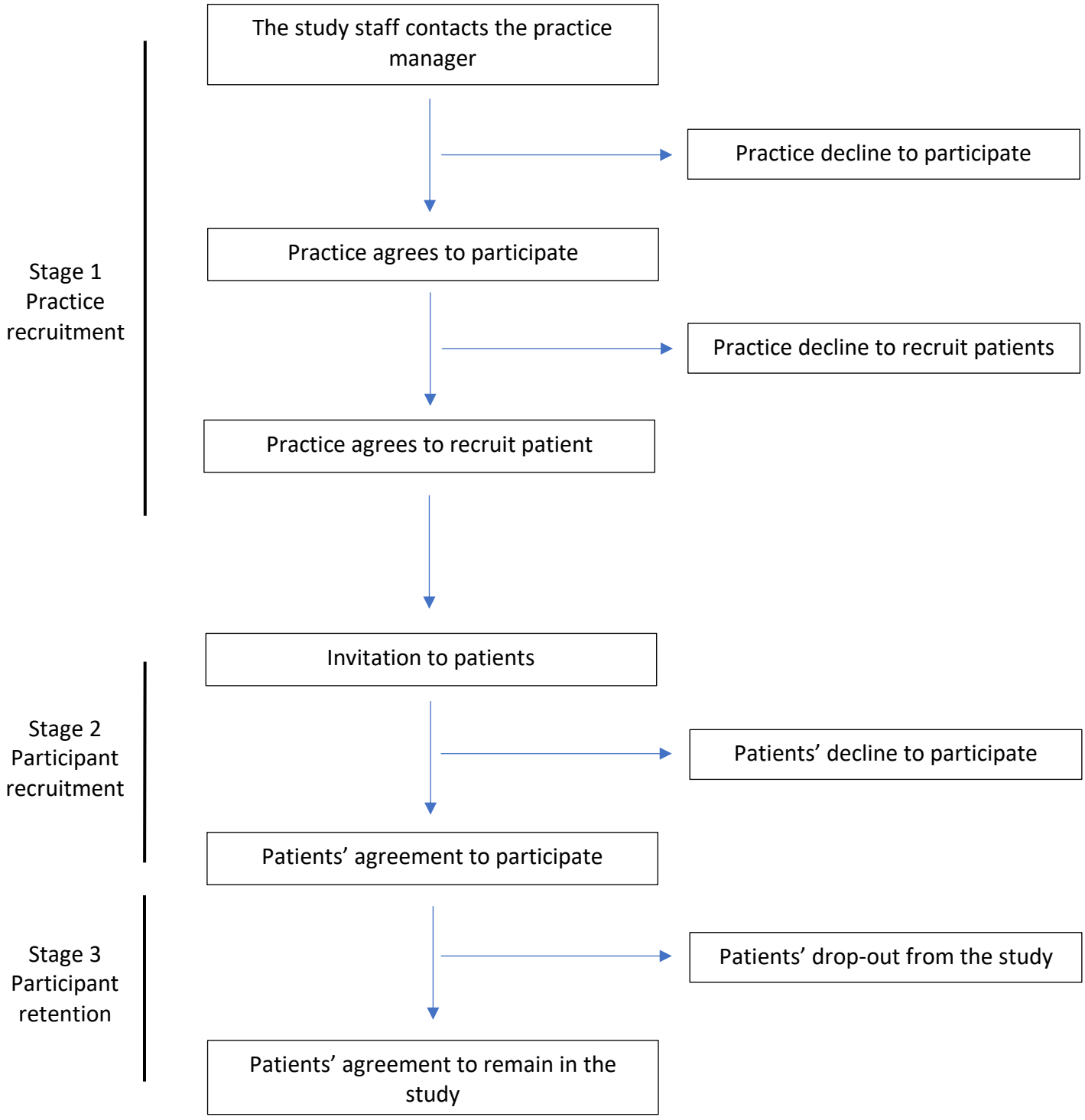
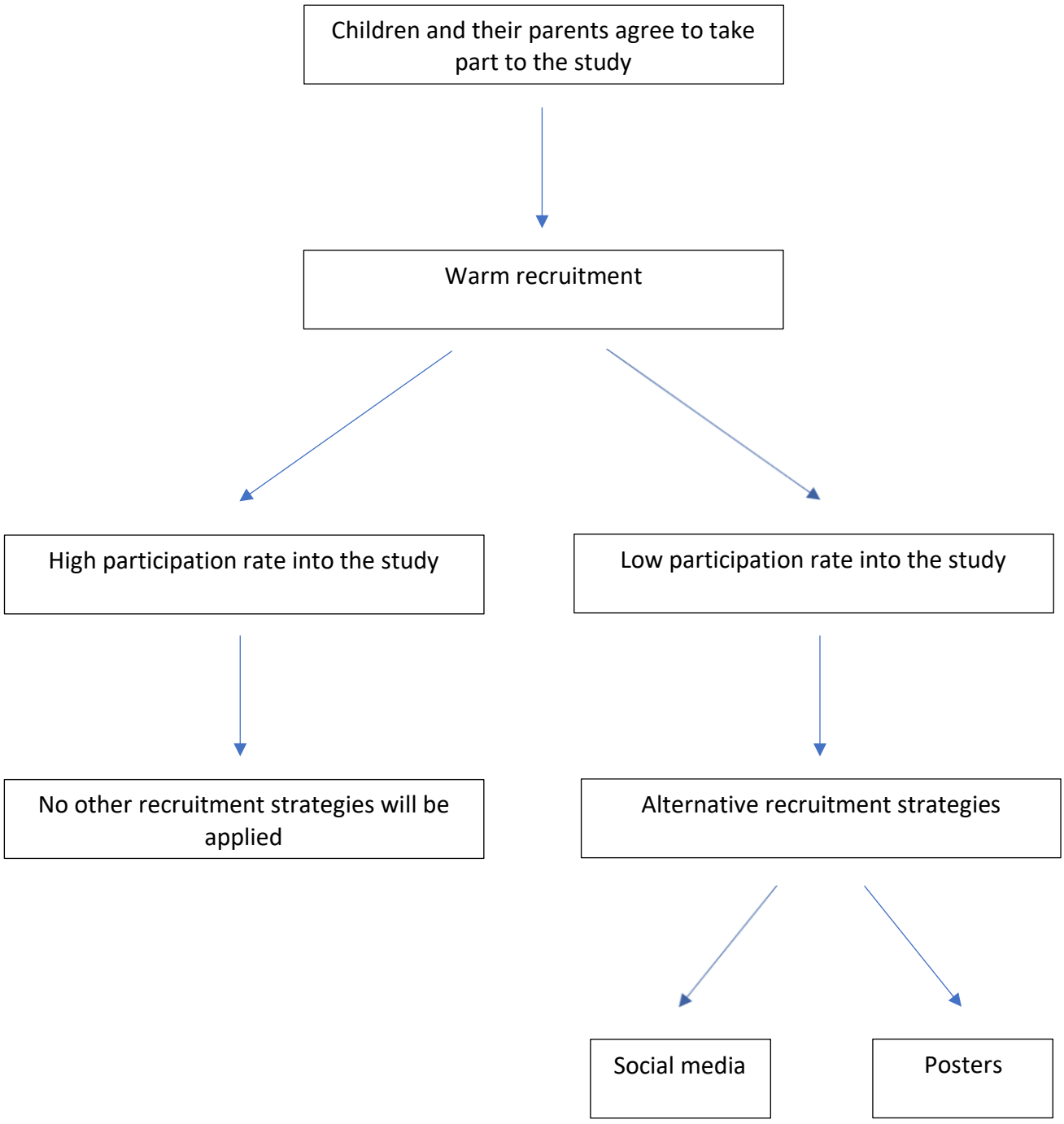

The study staff contacts the practice manager
Practice decline to participate
Practice agrees to participate
Practice decline to recruit patients
Practice agrees to recruit patient
Stage 1 Practice recruitment
Invitation to patients
Patients' decline to participate
Patients' agreement to participate
Stage 2 Participant recruitment
Patients' drop-out from the study
Patients' agreement to remain in the study
Stage 3 Participant retention

Figure 3


Children and their parents agree to take part to the study
Warm recruitment
High participation rate into the study
Low participation rate into the study
No other recruitment strategies will be applied
Alternative recruitment strategies
Social media
Posters

2.8. Data collection methods

2.8.1. Tool delivery at baseline

Data will be collected at baseline by means of a questionnaire (either with a paper-based questionnaire or collected with the support of a tablet) directly at the general practice when children and adolescents consult for knee pain. Alternatively, the questionnaire will be delivered at home or through a survey delivered with an internet link after that the children or their parents agreed to take part to the study if an alternative recruitment strategy will be applied (e.g. social media recruitment). In this case, children and their parents will be given the opportunity to choose between providing data through a paper-based questionnaire or a questionnaire delivered with an internet link.

2.8.2. Collection of data during follow-up

Data will be collected during follow-up from the children or parents through a questionnaire email-based or to be completed by text messages depending on the participants' preference. The questionnaire will include questions about pain characteristics (e.g. severity of pain, period free of knee pain, disability and activity limitations due to pain [42,48]) and about who is the person replying to the questionnaire (child alone/parent alone/child together with the parent). These questions will be taken from previously validated pain questionnaires or pain scales. Data collected at 3-month follow-up will be used to assess the primary outcome of the study, and data collected at 6-month follow-up will be used to assess the secondary outcome. 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. A second reminder

will be sent one week after the first reminder if they still will not have completed the follow-up questionnaire.

2.8.3. Information about non-participation to the study and loss to follow-up

Information about reasons for baseline non-participation to the study (e.g. participant is too busy or not interested in the topic, or the participant has been considered not suitable to take part in the study by the general practitioner, or the general practitioner is too busy) will be collected by the person in charge of inviting the children to join the study. Information about reasons for baseline non-participation together with other data regarding non-participants (e.g. number, age, gender) will be used to describe the process of selection of participants [51].

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.

2.8.4. Pain assessment

Parents are involved in both the decision of seeking healthcare for musculoskeletal pain and in the discussion with the general practitioner during the clinical encounter [52]. Therefore, it may occur that data reporting will actually be parent-report rather than child self-report, and this might introduce bias about the pain measurement, especially in longitudinal studies (i.e. children are too young to reliably self- report at the initial assessments, but they might self-report at later follow-up points) [52]. Current evidence on pain reporting suggest that children are able to self-report from the age of 8 [38], and that the agreement between child and parental report for the presence of pain

is around 50-70%, although the concordance is higher if the pain is of greater intensity and of longer duration [52]. In addition, when their child's pain is severe, parents might over-report the severity of the impacts of pain on their children as they become more concerned about potential consequences of pain [52]. Potential inaccuracies in the measurement of knee pain will be considered by means of a question about the persons responding to the follow-up questionnaire (e.g. child alone/parent alone/child together with the parent) as reported in section 2.7.2. Efforts will be done to encourage the same person to respond to all the follow-up questionnaires in order to reduce inaccuracies in pain reporting. For example, a strategy that might be adopted is to provide children with cinema tickets only if they will be the person responding to all the questionnaires.

2.8.5. Study appreciation

Information about study appreciation will be collected by asking participants questions about the acceptability of the questions, acceptability of the time needed for questionnaire completion and the most preferred frequency and method of contact. In addition, evaluation questions about information on the study, the study processes, time required to participate in the study, motivation, future participation to similar studies and potential strategies to implement the study will also be asked to the general practitioners.

2.8.6. Piloting the recruitment procedure and the prognostic tool

This project included a stage where the prognostic tool was piloted, which included a development, testing and implementation stage. Cognitive interviews were carried out after completion of the questionnaires 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 [45,48,49,53]. The aim was to improve the face, construct and content validity of the tool at this stage. This is important especially considering that a worse outcome can result if a general practitioner makes an inaccurate diagnosis of the child's knee pain or if there is a lack of communication between the general practitioner and the child with knee pain [54]. In addition, children of different age interpret the pain questions differently because of their cognitive development [39,40,54,55]. Several self-report measures for pain intensity or the impact of pain exist, with a set of appropriate pain scales for each different age range [39,40], and age-appropriate analogies or metaphors can be used in the knee pain questions in order for the children to understand the questions better [54–56]. Therefore, questions as simple as possible were developed in order for the tool to be understandable from individuals of any age [45].
After this testing and feedback stage, the prognostic tool was implemented and tested again (during a period of 2 months) in an iterative process until reaching the optimal version which will then be used in the data collection stage.

2.8.7. Stability of the prognostic tool study

A pilot study to assess the stability of the prognostic tool (test-retest reliability [45]) in children pre- and post- consultation was carried out. Children who refer to primary care for knee pain and their parents 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 parents 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.

2.9. Data management and confidentiality

The participant submitted responses will be automatically registered in a database through the Red-cap system (https://www.project-redcap.org). 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 (a request will be done to store the data for 30 years), 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.

2.10. Analysis plan

The analysis plan that will lead to the development of the final prognostic tool will include the following stages:

1. Descriptive analysis of the collected data. Results will be presented as means with SDs and as percentages.
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 [42,45,57]).
3. Estimation of 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 will inform on which factors are most related to the prognosis of knee pain and will 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 a general linear model analysis will be carried out.
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.

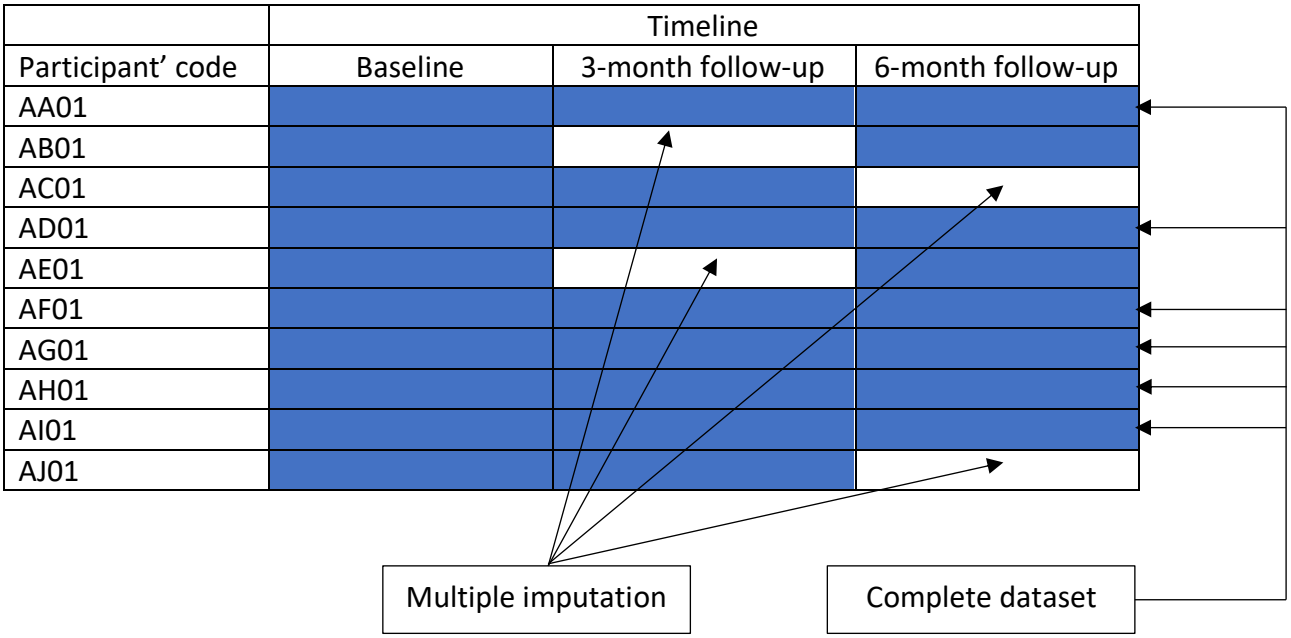
5. Creation of risk groups for the recurrence/persistence of knee pain on the basis of cut-off scores identified using the ROC curves for the overall tool score. The initial idea is to have three risk groups (low/medium/high), which have to be clinically meaningful. More importance will be given to the sensitivity of the tool over the specificity.
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 and sex.
8. Calculation of the 3-month and 6-month knee pain prognosis stratified by treatment received and baseline prognostic risk group, provided that data on the treatment given to the patients can be collected. Alternatively, instead of stratifying the analysis by treatment, analysis can be adjusted by treatment received.

   In addition, potential changes of the risk groups at 3-month follow-up depending on the treatment received might be calculated provided that the prognostic tool is delivered at the 3-month follow-up as well. In this way it might be possible to track the effectiveness of the treatment and if it resulted in a change of risk group.

2.11. Full analysis set

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. Please refer to figure 4 for a description of the full analysis set. 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 data [51]. In case of 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 for the follow-up stages (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.

Figure 4. Complete-case and multiple imputed data



2.12. Timescale

The overall planned study period is 24 months. This will include the following stages:

- Protocol development (3 months)
- General practitioners´ recruitment (4 months)
- Identification of prognostic factors (3 months)
- Selection of prognostic factors (2 months)
- Development of the prognostic tool (4 months)
- Piloting the prognostic tool (5 months)
- Piloting the recruitment procedures (5 months)
- Implementation of the recruitment procedure and prognostic tool (2 months)
- Collection of the data (12 months)
- Analysis of the data (11 months)

There will be some overlap between the different stages, which are visually described in the GANTT chart outlined in the following page.

	Year and month																							
	2018				2019												2020							
Task	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug
Protocol development																								
GPs recruitment																								
Identification of prognostic factors																								
Selection of prognostic factors																								
Development of the prognostic tool																								
Piloting the prognostic tool																								
Piloting the recruitment procedures																								
Implementation of the recruitment procedure and prognostic tool																								
Collection of the data																								
Analysis of the data																								

2.13. Consent

A unique written informed consent (including consent to take part to the study, provide personal information and being contacted at each follow-up time-point) will be obtained by the adolescents if aged 15 years old or more or from the parents if aged less than 15 years old when they will be invited to take part to the study. Participants will be reassured that they may, at any time and without any consequence (except for not receiving the cinema tickets) discontinue participation to the study.

2.14. Impact/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 and consequently provide them with the best targeted treatment. The study results will be disseminated at scientific conferences and through appropriate scientific journals. In addition, general practitioners, children and parents participating into the study will be regularly provided with feedback about the ongoing study.

Examples of papers that might be developed from this study (provisional names are provided):

1) The Adolescent Knee Pain (AK-Pain) prognostic tool: protocol for a prospective cohort study
2) Stability of prognostic factors for knee pain collected with a questionnaire in general practice
3) The development of a prognostic tool for knee pain in children and adolescents in general practice
4) Effect on the treatment delivered on the knee pain prognosis on a subsample of the participants recruited in the AK-pain project

3. Protocol amendments

Potential protocol amendments might occur during the prognostic tool piloting and development stage. Protocol amendments will be disseminated to proper scientific journals.

4. Declaration of interest

The study's investigators have no conflicts of interest to declare.

5. Access to data

The final dataset will be accessed by Alessandro Andreucci, Michael Skovdal Rathleff, Martin Bach Jensen and Sinead Holden.

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