Developing diagnostic criteria for psoriasis in children and young people: a multi-centre case control study in paediatric dermatology clinics

Draft 2.0 / Final Version 1.2
12th October 2017

Short title: Diagnostic criteria for psoriasis in children

DIPSOC

IRAS Project ID: 220116

Study Sponsor: University of Nottingham

Sponsor reference: 16109

Funding Source: NIHR DRF 2016-09-083
STUDY PERSONNEL AND CONTACT DETAILS

**Sponsor:**
University of Nottingham

**Contact name**
Head of Research Governance
Research and Graduate Services
King’s Meadow Campus
Lenton Lane
Nottingham
NG7 2NR
Phone: 0115 8467906
Email: sponsor@nottingham.ac.uk

**Chief investigator:**
Prof Kim Thomas
Prof of Applied Dermatology Research
Centre of Evidence Based Dermatology
Kings Meadow Campus
University of Nottingham
Nottingham
NG7 2NR
Phone: +44 (0) 115 84 68632
Email: kim.thomas@nottingham.ac.uk

**Medical expert:**
Dr Ruth Murphy
Consultant Adult and Paediatric Dermatologist
Department of Dermatology
Sheffield Teaching Hospitals NHS Foundation Trust
Sheffield
S10 2JF
Phone: 0114 2711832
Email: ruth.murphy@sth.nhs.net

**Co-investigators:**
Dr Esther Burden-Teh
NIHR Doctoral Research Fellow (PhD student)
Centre of Evidence Based Dermatology
Kings Meadow Campus
University of Nottingham
Nottingham
NG7 2NR
Phone: +44 (0) 115 84 68633
Email: esther.burden-teh@nottingham.ac.uk

Prof Tamar Nijsten
Prof of Dermato-Epidemiology and Dermatology
Afdelingshoofd Dermatologie
Kamernummer: GK 214
Lokatie Rochussenstraat
Erasmus MC
Burg. ’s Jacobplein 51
3015 CA Rotterdam
Study Statistician: Dr Sonia Ratib  
Centre of Evidence Based Dermatology, Division of Rheumatology, Orthopaedics and Dermatology  
Kings Meadow Campus  
University of Nottingham  
Nottingham  
NG7 2NR  
Phone: +44 (0) 115 84 32436  
Email: sonia.ratib@nottingham.ac.uk

Study Coordinating Centre: Centre of Evidence Based Dermatology, Division of Rheumatology, Orthopaedics and Dermatology  
Kings Meadow Campus  
University of Nottingham  
Nottingham  
NG7 2NR
## SYNOPSIS

<table>
<thead>
<tr>
<th>Title</th>
<th>Developing diagnostic criteria for psoriasis in children and young people: a multi-centre case control study in paediatric dermatology clinics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short title</td>
<td>Diagnostic criteria for psoriasis in children (DIPSOC)</td>
</tr>
<tr>
<td>Chief Investigator</td>
<td>Professor Kim Thomas</td>
</tr>
</tbody>
</table>
| Objectives | Primary objective: To test the diagnostic accuracy of consensus agreed diagnostic criteria for plaque psoriasis in children/young people and develop the best predictive diagnostic criteria using multivariate analysis.  
Secondary objectives:  
i) To compare the diagnostic performance of the consensus agreed and the best predictive diagnostic criteria.  
ii) To assess the inter-observer variability in the diagnostic criteria assessment.  
iii) To assess the variability in the reference standard for psoriasis.  
iv) To assess the performance of the best predictive diagnostic criteria in identifying children/young people with psoriasis currently diagnosed with indeterminate disease (nested sub-study). |
| Study Configuration | Multi-centre case-control diagnostic accuracy study with a nested sub-study. |
| Setting | Paediatric dermatology clinics in 10-15 secondary care centres. |
| Sample size estimate | The sample size calculation is based on the primary objective. To develop the best predictive criteria for diagnosing psoriasis 160 cases and 160 controls are required. This calculation is based on the TRIPOD guidance which support the current rule of thumb of 10 events per variable; there are 16 consensus agreed diagnostic criterion. 320 participants will enable will give sensitivity and specificity of 0.94 (and minimal acceptable lower 95%CI of 0.86)  
The first 40 participants 20 cases and 20 controls recruited will be included in the assessment of inter-observer variability. Clinical photographs of 20 randomly selected cases will be included in the assessment of reference standard variability. |
| Number of participants | 320 participants will be recruited for the main study. This number includes 160 cases, children/young people with a confirmed diagnosis of psoriasis by a dermatologist, and 160 controls. |
| Eligibility criteria | Inclusion criteria for cases:  
- Children/young people (0 to <18 years of age)  
- Confirmed diagnosis of plaque psoriasis by a dermatologist  
- Active disease at the time of assessment  
- Able to consent |
### Inclusion criteria for controls:
- Children/young people (0 to <18 years of age)
- Confirmed diagnosis of a scaly inflammatory rash (excluding psoriasis and indeterminate psoriasis) by a dermatologist
- Active disease at the time of assessment
- Able to consent

### Exclusion criteria
- Children/young people with pustular psoriasis
- Children/young people with erythrodermic psoriasis
- Children/young people without a dermatologist’s diagnosis

### Description of interventions
Participants will have one study visit of approximately 30 minutes.

The visit will include a diagnostic criteria assessment during which specific questions on the clinical history will be asked and a full skin examination performed. Demographic information and quality of life data will also be collected. The assessment will be undertaken by a trained research nurse or study investigator. The assessor, where possible, will be unaware of the child’s/young person’s diagnosis.

The first 40 participants (20 cases and the first 20 controls) recruited will be assessed by two different assessors consecutively to enable inter-observer variability of the diagnostic criteria to be evaluated.

At each centre an administrator will collect additional information from the medical record. These data will include the confirmed dermatologist’s diagnosis (reference standard), disease severity, duration of disease, and current skin medications.

Cases will be approached by their normal care team for optional clinical photographs as part of routine care. Data collection will otherwise be the same for both cases and controls.

### Duration of study
Planned start date September 2017 and the estimated study duration is 24 months.

### Methods of analysis
Descriptive analysis will be used to summarise the study population: age, gender, ethnicity, disease severity, disease impact (quality of life), disease duration and treatment.

The analysis will evaluate the sensitivity and specificity of the consensus agreed diagnostic criteria.

Using multivariate logistic regression the diagnostic criteria will be refined and the best predictive diagnostic criteria for plaque psoriasis in children derived.

If there is sufficient data within each strata, the effect modification of demographic and disease factors on diagnostic accuracy will be explored in the analysis.
The diagnostic ability of the consensus agreed diagnostic criteria and the best diagnostic criteria will be graphically presented and compared on Receiver Operator Characteristic (ROC) curves.

Inter-observer variability in the assessment of the diagnostic criteria will be calculated using the Kappa statistic. The Kappa statistic will also be used to calculate the level of agreement in the reference standard for psoriasis.

### Nested sub-study

**Objective:** To assess the performance of the best predictive diagnostic criteria in identifying children/young people with psoriasis currently diagnosed with indeterminate disease.

Sample size estimate: A convenience sample of children/young people with indeterminate psoriasis will be recruited. No specified sample size will be required.

**Inclusion criteria:**
- Children/young people (0 to <18 years of age)
- Diagnosis of indeterminate or possible psoriasis by a dermatologist
- Active disease at the time of assessment
- Able to consent and willing to receive a follow-up questionnaire after 24 months.

**Exclusion criteria:**
- Children/young people with pustular psoriasis
- Children/young people with erythrodermic psoriasis
- Children/young people without a dermatologist’s diagnosis

**Description of intervention:** The diagnostic criteria assessment will be identical to that described for the main study.

In addition, a patient/parent questionnaire will be sent 24 months after closure of the main study to participants. The questionnaire will confirm the current dermatologist’s diagnosis and whether this has changed from 24 months previously.

**Analysis:** The sensitivity and specificity of the best predictive diagnostic criteria will be calculated. The reference standard will be the patient reported dermatologist’s diagnosis.

**Funding:** Separate funding will be sought to conduct this as follow-up at 24 months will be outside the study period.
ABBREVIATIONS

CI     Chief Investigator overall
CRF    Case Report Form
GCP    Good Clinical Practice
NHS    National Health Service
P/GIS  Parent / Guardian Information Sheet
PI     Principal Investigator at a local centre
PIS    Participant Information Sheet
REC    Research Ethics Committee
R&D    Research and Development department
UoN    University of Nottingham
cDLQI  Children’s Dermatology Life Quality Index
CHU9D  The Child Health Utility 9D
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYNOPSIS</td>
<td>4</td>
</tr>
<tr>
<td>ABBREVIATIONS</td>
<td>7</td>
</tr>
<tr>
<td>STUDY BACKGROUND INFORMATION AND RATIONALE</td>
<td>10</td>
</tr>
<tr>
<td>STUDY OBJECTIVES AND PURPOSE</td>
<td>11</td>
</tr>
<tr>
<td>PURPOSE</td>
<td>11</td>
</tr>
<tr>
<td>PRIMARY OBJECTIVE</td>
<td>11</td>
</tr>
<tr>
<td>SECONDARY OBJECTIVES</td>
<td>11</td>
</tr>
<tr>
<td>STUDY DESIGN</td>
<td>11</td>
</tr>
<tr>
<td>STUDY CONFIGURATION</td>
<td>11</td>
</tr>
<tr>
<td>STUDY MANAGEMENT</td>
<td>12</td>
</tr>
<tr>
<td>DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT</td>
<td>12</td>
</tr>
<tr>
<td>End of the Study</td>
<td>12</td>
</tr>
<tr>
<td>SELECTION AND WITHDRAWAL OF PARTICIPANTS</td>
<td>13</td>
</tr>
<tr>
<td>Recruitment</td>
<td>13</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>13</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>13</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>14</td>
</tr>
<tr>
<td>Expected duration of participant participation</td>
<td>14</td>
</tr>
<tr>
<td>Participant Withdrawal</td>
<td>14</td>
</tr>
<tr>
<td>Informed consent</td>
<td>14</td>
</tr>
<tr>
<td>STUDY REGIMEN</td>
<td>15</td>
</tr>
<tr>
<td>Compliance</td>
<td>17</td>
</tr>
<tr>
<td>Criteria for terminating the study</td>
<td>17</td>
</tr>
<tr>
<td>ANALYSES</td>
<td>17</td>
</tr>
<tr>
<td>Methods</td>
<td>17</td>
</tr>
<tr>
<td>Sample size and justification</td>
<td>18</td>
</tr>
<tr>
<td>ADVERSE EVENTS</td>
<td>18</td>
</tr>
<tr>
<td>ETHICAL AND REGULATORY ASPECTS</td>
<td>18</td>
</tr>
<tr>
<td>ETHICS COMMITTEE AND REGULATORY APPROVALS</td>
<td>19</td>
</tr>
<tr>
<td>INFORMED CONSENT AND PARTICIPANT INFORMATION</td>
<td>19</td>
</tr>
<tr>
<td>RECORDS</td>
<td>19</td>
</tr>
<tr>
<td>Case Report Forms</td>
<td>19</td>
</tr>
<tr>
<td>Source documents</td>
<td>20</td>
</tr>
<tr>
<td>Direct access to source data / documents</td>
<td>20</td>
</tr>
<tr>
<td>DATA PROTECTION</td>
<td>20</td>
</tr>
<tr>
<td>QUALITY ASSURANCE &amp; AUDIT</td>
<td>21</td>
</tr>
<tr>
<td>INSURANCE AND INDEMNITY</td>
<td>21</td>
</tr>
<tr>
<td>STUDY CONDUCT</td>
<td>21</td>
</tr>
<tr>
<td>STUDY DATA</td>
<td>21</td>
</tr>
<tr>
<td>RECORD RETENTION AND ARCHIVING</td>
<td>22</td>
</tr>
<tr>
<td>DISCONTINUATION OF THE STUDY BY THE SPONSOR</td>
<td>22</td>
</tr>
<tr>
<td>STATEMENT OF CONFIDENTIALITY</td>
<td>22</td>
</tr>
</tbody>
</table>

This protocol is confidential and the property of the University of Nottingham. No part of it may be transmitted, reproduced, published, or used by others persons without prior written authorisation from the University of Nottingham.
STUDY BACKGROUND INFORMATION AND RATIONALE

Psoriasis is a common chronic inflammatory disease typified in adults by red, scaly, elevated plaques occurring on any site of body including the face, palms and genitals. Psoriasis is estimated to affect 0.91% to 8.5% of adults and up to 2.1% of children (Parisi, Symmons et al. 2013). However, large population-based studies on the incidence and prevalence of psoriasis in children are lacking (Burden-Teh, Thomas et al. 2016).

In children the presentation of psoriasis is often subtle. Up to 90% of psoriasis in children is plaque psoriasis (Burden-Teh E 2016). The impact of psoriasis on quality of life in childhood has been shown to be equal or higher than cystic fibrosis, asthma and epilepsy (Beattie and Lewis-Jones 2006). Psoriasis in children is also associated with an increased risk of developing juvenile psoriatic arthritis; a cause of disability and permanent joint damage (Hamilton, Gladman et al. 1990, Foster, Eltringham et al. 2007, Flato, Lien et al. 2009). Recent studies have highlighted obesity and metabolic syndrome as potential comorbidities (Kimball, Wu et al. 2012, Augustin, Radtke et al. 2015, Mahe, Beauchet et al. 2015). Figures are not available for paediatric psoriasis alone, but the cost of psoriasis is estimated to be $112 (£77) billion in the United States (Brezinski, Dhillon et al. 2015) and for lost work days/productivity alone over £1 billion in the UK (Bajorek Z 2016).

Approximately one third of adults with psoriasis first developed their condition in childhood (Farber and Nall 1974, Raychaudhuri and Gross 2000). Limited population-based epidemiological data has shown that the incidence of psoriasis increases throughout childhood and the average age of onset reported varies between 2.1 months to 10.6 years (Burden-Teh E 2016). In view of the likely chronic nature and associated comorbidities of child-onset psoriasis it is important that psoriasis is diagnosed early and accurately.

Psoriasis is a clinical diagnosis and the reference (gold) standard is a dermatologist’s diagnosis, supported by histopathology from a skin biopsy if required. No validated clinical examination-based diagnostic criteria are available for psoriasis in adults or children. The protocol for our systematic review is registered at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015032311; manuscript in preparation. In adults a diagnosis is made based on the presence of characteristic signs such as elevated scaly plaques on the extensor surfaces. In children the clinical signs are under-recognised by non-dermatologists, often morphologically different to those seen in adults, occur in covered body sites and are often misdiagnosed as common childhood skin rashes such as eczema and fungal skin infections. Kapila et al, 2012 found that only 9.4% of children with psoriasis were correctly diagnosed by their referring doctors. In contrast to eczema where there was nearly a 90% diagnostic concordance (Kapila, Hong et al. 2012). Therefore, there is a need for clinical diagnostic criteria for psoriasis in children.

The benefit of developing diagnostic criteria for psoriasis in children will be to improve diagnosis by non-dermatologists such as GPs and paediatric rheumatologists. This will ensure children are referred to secondary care, receive psoriasis specific treatment and undergo monitoring for associated diseases (eg juvenile psoriatic arthritis) as per national guidelines (NICE 2012). Diagnostic criteria will also standardise disease definitions in studies; improving quality and permitting meta-analysis. This study will also investigate the performance of the diagnostic criteria in indeterminate psoriasis; providing preliminary information on whether the diagnostic criteria can help predict psoriasis in those with possible psoriasis.

Prior to this case-control diagnostic accuracy study an eDelphi consensus study was undertaken with the International Psoriasis Council to agree a list of clinical features to be included in a list of diagnostic criteria. The consensus study identified 16 features that experts
agree are important for the diagnosis of plaque psoriasis in children (Appendix 1). The diagnostic accuracy of these features will be tested in this case-control study.

**STUDY OBJECTIVES AND PURPOSE**

**PURPOSE**
To develop diagnostic criteria for plaque psoriasis in children and young people (<18 years)

**PRIMARY OBJECTIVE**
To test the diagnostic accuracy of consensus agreed diagnostic criteria for plaque psoriasis in children/young people and develop the best predictive diagnostic criteria using multivariate analysis.

Hypothesis: The best predictive diagnostic criteria can be developed from the consensus agreed diagnostic criteria using a multivariate model and will achieve a sensitivity and specificity of >70% with the fewest number of essential items.

**SECONDARY OBJECTIVES**

1. To compare the diagnostic performance of the consensus agreed diagnostic criteria and the best predictive criteria for plaque psoriasis.
2. To assess the inter-observer variability in the diagnostic criteria assessment.
3. To assess the variability in the reference standard for psoriasis.
4. To assess the performance of the best predictive diagnostic criteria to identify psoriasis in children/young people currently diagnosed with indeterminate disease (sub-study).

**STUDY DESIGN**

**STUDY CONFIGURATION**

This study is a multi-centre case-control diagnostic accuracy study. The study will test the diagnostic accuracy and develop the best predictive diagnostic criteria for plaque psoriasis in children and young people. The diagnostic criteria are comprised of clinical features to be elicited on history and physical examination. The study will include a sub-study to investigate the diagnostic performance of the criteria in indeterminate psoriasis.

The recruiting centres will be paediatric dermatology departments (estimated 10-15) that routinely review children/young people with psoriasis. Recruiting centres will be approached through existing contacts (previous participation in research on childhood psoriasis) as well as membership of the British Society of Paediatric Dermatology and the UK Dermatology Clinical Trials Network.
Additional recruiting centres will be identified depending on the recruitment needs of the study.

**STUDY MANAGEMENT**

The Chief Investigator has overall responsibility for the study and shall oversee all study management.

The data custodian will be the Chief Investigator.

The study will be managed from the Centre of Evidence Based Dermatology, University of Nottingham. The project will be managed by Dr. Esther Burden-Teh, Dermatology Registrar and Clinical Research Fellow, who is undertaking this study as part of her PhD and NIHR Doctoral Research Fellowship. She will be responsible for the daily running of the study, maintaining good communication between members of the research team and recruiting centres, data management and conducting the analysis.

Dr Esther Burden-Teh will be supervised by Prof. Kim Thomas (CI), Dr. Ruth Murphy (Medical Expert) and Dr. Sonia Ratib (Study Statistician).

The study will be supported by a research advisory group who will provide specific expertise on aspects of the project. The group will function as a virtual group; contacted via email, teleconference and in person to review aspects of protocols, patient information sheets, procedures manual, training material, analysis plan, results and manuscript. Their role will be to provide expert guidance and ensure a high quality and transparent study. The advisory group comprises of:

- Prof. Tamar Nijsten, Prof of Dermato-Epidemiology and Dermatology, Erasmus University Rotterdam
- Test Evaluation Research Group based at the University of Birmingham lead by Prof. Jon Deeks
- 2 adult patient advisors (Carolyn Hughes and Lisa Sharples)

**DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT**

**Study Duration:**

Enrolment will begin when HRA and REC approval is granted and local NHS checks for capacity and capability have been completed at the recruiting centre. It is anticipated that sites will open in a stepwise manner. The estimated total duration of the study will be 24 months, but may be extended if recruitment is slow.

**Participant Duration:**

Participants will be involved from the point they are consented for the study until the completion of the diagnostic criteria assessment. Participant involvement in the study only requires one study visit and no follow-up visit. The study does not involve an intervention. It is estimated that individual participant duration will be approximately 30 minutes.

**End of the Study**
The end of the study will be the last study visit of the last participant.

**SELECTION AND WITHDRAWAL OF PARTICIPANTS**

**Recruitment**

Participants will be recruited from paediatric dermatology clinics. Recruitment from a secondary care setting will ensure that children/young people will have a reference standard; a confirmed diagnosis of their skin disease made by a dermatologist. Potential participants will be approached by their usual care team, either by letter or in person in clinic.

The investigator or their nominee, e.g. a member of the research team or the participant’s usual care team, will inform the participant or their nominated representative (other individual or other body with appropriate jurisdiction), of all aspects pertaining to participation in the study.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the study, the participant information sheets, and consent forms, but the consent forms and information sheets will not be printed in other languages.

It will be explained to the potential participant that entry into the study is entirely voluntary and that their treatment and care will not be affected by their decision.

**Eligibility criteria**

**Inclusion criteria**

**Inclusion criteria for cases:**
- Children and young people (0 to <18 years of age at the point of consent).
- Confirmed diagnosis of plaque psoriasis by a dermatologist. Plaque psoriasis will include all subtypes and presentations of psoriasis where plaques are the main feature and this definition includes but is not limited to chronic plaque psoriasis, guttate psoriasis, flexural psoriasis and scalp psoriasis. The dermatologist’s diagnosis is a clinical diagnosis, which may include but does not require a skin biopsy. New and follow-up patients will be eligible for recruitment.
- Active disease at the time of assessment.
- Able to consent/has a parent/guardian willing to give consent.

**Inclusion criteria for controls:**
- Children and young people (0 to <18 years of age).
- Confirmed diagnosis of a scaly inflammatory rash (excluding psoriasis or indeterminate psoriasis) by a dermatologist*. The dermatologist’s diagnosis is a clinical diagnosis, which may include but does not require a skin biopsy. New and follow-up patients will be eligible for recruitment.
- Active disease at the time of assessment.
- Able to consent/has a parent/guardian willing to give consent.
Exclusion criteria

Exclusion criteria for cases and controls:

- Children/young people with pustular psoriasis.
- Children/young people with erythrodermic psoriasis.
- Children/young people without a dermatologist’s diagnosis.

* Controls are children/young people with a scaly inflammatory rash excluding psoriasis or indeterminate psoriasis. This definition for controls has been chosen as children/young people with psoriasis are part of the scaly inflammatory skin disease population (ie the same source population). Other skin diseases within the scaly inflammatory group are the conditions that psoriasis may be mis-diagnosed for, therefore provide a clinically important group to compare the performance of the diagnostic criteria with. A list of example of diseases that can be included under the scaly inflammatory rash description will be provided; these include eczema, pityriasis rubra pilaris, pityriasis rosea, Gianotti-Crosti syndrome, mycosis fungoides, tinea corporis.

Expected duration of participant participation

Participant involvement will last for approximately 30 minutes in duration

Participant Withdrawal

Participants may be withdrawn from the study either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Participant data will be collected at the time of diagnostic criteria assessment and following this from the medical record. If the participant decides to withdrawal all data up to that point will be recorded on the CRF along with the reason for withdrawal. Attempts to contact participants will not be required as involvement is limited to one study visit.

Informed consent

All participants will provide written informed consent. For participants over the age of 16 years, the Informed Consent Form will be signed and dated by the participant before they enter the study. The Investigator will explain the details of the study and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

Where the Participant is a child under age 16 years an appropriate age range Participant Information Sheet will be provided. Parental or legal guardian consent will be obtained and the child, should they wish, will be able to provide assent on the same consent form. In the event
of any conflict between the parent and the children then the child will not be entered into the study.

Informed consent will be collected from each participant before they undergo the diagnostic criteria assessment. One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient’s hospital records.

Should there be any subsequent amendment to the final protocol, which might affect a participant’s participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

**STUDY REGIMEN**

Participants will be recruited as cases (children/young people with psoriasis) or controls (children/young people with a scaly inflammatory rash excluding psoriasis/indeterminate psoriasis). Below is a schedule of steps for each participant:

- Written consent will be taken from the participant by a research nurse or study investigator.
- All participants recruited will undergo a diagnostic criteria assessment at their study visit by a trained research nurse or study investigator. The assessor, where possible, will be unaware of the dermatologist’s diagnosis (reference standard).
- The diagnostic criteria assessment will involve a physical examination and specific questions relating to the participant’s clinical history; these will be directed to the patient or the parent/guardian depending on the age of the participant. The assessment will assess the presence or absence of each of the diagnostic features that were agreed as important in the consensus study. The assessment will take approximately 10 minutes. Demographic details and quality of life data will also be collected at this point. The assessment will be undertaken either alongside the participant’s routine clinic appointment (in a separate clinic space) or a specific research clinic. The diagnostic criteria assessment is outside the participant’s routine care.
- Cases will be approached by their usual care team for optional clinical photographs as per standard care. Data collection will otherwise be the same for both cases and controls.
- Additional clinical details will be extracted from the medical record by someone who is not responsible for undertaking the diagnostic criteria assessment (eg. the centre administrator). These data include: reference standard (dermatologist’s diagnosis) duration of skin disease, severity of skin disease and current skin-related medications. These data will be collected separately to avoid the assessor becoming aware of the child’s diagnosis. Participants will continue with their routine care and treatments.
- No follow-up visits are required for this study.
- All children will receive a voucher and a certificate/sticker recognising their involvement and to say thank you.

**Validity and quality assurance**
The study regimen includes a number of important points to ensure and check the consistency of the diagnostic criteria assessment and check the consistency of the reference standard for psoriasis.

- Training for research nurses and study investigators to undertake the diagnostic criteria assessment will be provided in the format of a PowerPoint presentation and training booklet. Following completion of the training, assessors will undertake a short questionnaire to check their understanding of the training.

- The first 40 participants, 20 cases and the first 20 controls recruited, where two assessors are available, will be included in an assessment of inter-observer variability of the diagnostic criteria. At their study visit each of the forty participants will be assessed twice by two different research nurses/study investigators consecutively. The assessment of inter-observer variability is planned as an interim analysis. If agreement is found to be low then an amendment will be made to the training programme for assessors.

- The clinical photographs (taken as part of routine care by their normal care team) of 20 randomly selected cases will be included in an assessment of reference standard variability for psoriasis. Anonymised photographs of these 20 cases and a short clinical summary based on data collected in the CRF will be distributed to the PIs of each of the recruiting centres. The PIs will be asked to make a clinical judgement as to whether the images support a diagnosis of psoriasis, possible psoriasis or are not supportive of psoriasis.

### Nested sub-study for indeterminate psoriasis

**Objective:** To assess the performance of the best predictive diagnostic criteria in identifying children with psoriasis currently diagnosed with indeterminate disease.

**Participant duration:** Participants will be involved from the point they are consented for the study until they/their GP has completed a follow-up questionnaire.

**Inclusion criteria:**
- Children and young people (0 to <18 years of age)
- Diagnosis of indeterminate or possible psoriasis by a dermatologist**. The dermatologist’s diagnosis is a clinical diagnosis, which may include but does not require a skin biopsy. New and follow-up patients will be eligible for recruitment.
- Active disease at the time of assessment
- Able to consent/has a parent/guardian willing to give consent and willing to receive a follow-up questionnaire after 24 months.

**Exclusion criteria:**
- Children/young people with pustular psoriasis
- Children/young people with erythrodermic psoriasis
- Children/young people without a dermatologist’s diagnosis

**Children/young people with indeterminate or possible psoriasis are those for whom a definitive diagnosis of psoriasis has not been made. This group includes children/young people diagnosed with psoriasis-eczema, eczematous psoriasis or psoriasis-eczema overlap.**

PROTOCOL Diagnostic criteria for psoriasis in children 12.10.2017 Final v1.2.docx  Page 16 of 26

This protocol is confidential and the property of the University of Nottingham. No part of it may be transmitted, reproduced, published, or used by others persons without prior written authorisation from the University of Nottingham.
Study regimen: The study regimen will be identical to that described for the main study. In addition, a patient/parent questionnaire will be sent 24 months after closure of the main study to participants. The questionnaire will confirm the current dermatologist’s diagnosis and whether this has changed from 24 months previously.

Analysis: The sensitivity and specificity of the best predictive diagnostic criteria in this sub-study population will be assessed. The reference standard will be the patient reported dermatologist’s diagnosis.

Sample size: A convenience sample of children/young people diagnosed with possible psoriasis will be recruited. As this is a sub-study providing preliminary data the study has not been powered to detect a minimum diagnostic accuracy.

Funding: Separate funding will be sought to conduct this as follow-up at 24 months will be outside the study period.

Compliance

Assessment of compliance is not applicable as the study does not involve an intervention.

Criteria for terminating the study

There are no criteria for terminating the study. Unused study materials should be returned to the coordinating centre, the Centre of Evidence Based Dermatology.

ANALYSES

Methods

Dr. Burden-Teh under the supervision of Dr. Ratib (Study Statistician) will undertake the analysis using Stata software.

First, descriptive statistics will be used to explore and describe the study population. Percentages, means (standard deviations) or medians, (interquartile range) will be used to describe the demographics, disease severity, disease impact (quality of life), disease duration, current skin medications of the study population. Distributions of these variables will be explored and appropriate tests (for example the Chi-shared test and T-test) will be conducted to determine differences between cases and controls. These results will provide a summary of the study population characteristics.

The analysis will evaluate the sensitivity and specificity of the consensus agreed diagnostic criteria. Sensitivity will be calculated as the proportion of people with psoriasis who were identified by the consensus agreed diagnostic criteria with psoriasis. Specificity will be calculated as the proportion of people without psoriasis who were excluded from a diagnosis of psoriasis by the consensus agreed diagnostic criteria.

Using multivariate logistic regression the diagnostic criteria will be refined and from this the best predictive diagnostic criteria for plaque psoriasis in children/young people determined. The decision to include individual criteria in the model will be based on the likelihood ratio.
If there is sufficient data within each strata, variation of the diagnostic accuracy by co-variates (demographic and disease factors) will be explored for both the consensus agreed criteria and the best predictive criteria using stratification (assessment of effect-modification).

A sensitivity analysis of the effect of new or follow-up status on the diagnostic accuracy of the criteria will be performed.

Inter-observer variability in the assessment of the diagnostic criteria will be calculated using the Kappa statistic. The Kappa statistic will also be used to calculate the variability of the reference standard for psoriasis.

The diagnostic ability of the consensus agreed diagnostic criteria and the best predictive diagnostic criteria will be graphically presented and compared on Receiver Operator Characteristic (ROC) curves.

Further details will be provided in the statistical analysis plan, which will be finalised before data lock.

**Sample size and justification**

The sample size calculation is based on the primary objective. To develop the best predictive criteria for diagnosing psoriasis 160 cases and 160 controls are required. This calculation is based on the TRIPOD guidance which support the current rule of thumb of 10 events per variable; there are 16 consensus agreed diagnostic criterion (Moons, Altman et al. 2015). A sample size of 320 participants will give sensitivity and specificity of 0.94 (and minimal acceptable lower 95%CI of 0.86) (Flahault, Cadilhac et al. 2005).

Twenty cases and 20 controls will be included in the assessment of inter-observer variability. There is no defined method of performing a sample size calculation for assessing inter-observer variability, but experts at the Test Evaluation Research Group (University of Birmingham) support 20 participants as a sufficient number for this analysis.

The clinical photographs of 20 cases will be included in the assessment of reference standard variability. Twenty is a pragmatic sample size (>10% of cases), especially as inclusion of clinical photographs taken as part of routine care is optional for participants.

**ADVERSE EVENTS**

The occurrence of an adverse event as a result of participation within this study is not expected and no adverse event data will be collected.

**ETHICAL AND REGULATORY ASPECTS**

Ethical issues are focused around the recruitment of children and young people (<18 years). It is necessary to recruit children as this is a study on childhood psoriasis. Patients under the age of 16 years are unable to consent for themselves and consent is required from a parent/guardian.
ETHICS COMMITTEE AND REGULATORY APPROVALS

The study will not be initiated before the protocol, consent forms and participant information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent or assent and parent / guardian informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or other legally authorised representative shall both sign and date the Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Study records. A second copy will be filed in the participant’s medical notes and a signed and dated note made in the notes that informed consent was obtained for the study. A third copy of the consent will be transferred to the coordinating centre for central monitoring purposes.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No study-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

Each participant will be assigned a study identity code number, for use on CRFs, other study documents and the electronic database. The documents and database will also use the site number, patient recruitment number at that site and their initials (of first and last names). This
will be a 6 figure code. If agreed to on the consent, contact details of participant will be collected to allow the results of the study to be shared with them, to contact them about the current state of their skin disease in the future and to contact them about future studies.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant’s name, date of birth, local hospital number or NHS number, and Participant Study Number, to permit identification of all participants enrolled in the study. CRFs shall be restricted to those personnel approved by the Chief or local Investigator and recorded as such in the study records.

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated. The recruiting research nurse or recruiting study investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

The following will be documented for each participant:

<table>
<thead>
<tr>
<th>Consent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data (age, sex, ethnicity, socioeconomic group)</td>
</tr>
<tr>
<td>New or follow-up status of the patient</td>
</tr>
<tr>
<td>Presence or absence of each of the diagnostic criteria</td>
</tr>
<tr>
<td>Skin disease duration</td>
</tr>
<tr>
<td>Disease severity</td>
</tr>
<tr>
<td>Presence or absence of psoriatic arthritis</td>
</tr>
<tr>
<td>Quality of life score (4-17 years)</td>
</tr>
<tr>
<td>Current skin medications</td>
</tr>
<tr>
<td>Whether the diagnostic criteria assessor is unaware of the participant’s diagnosis</td>
</tr>
<tr>
<td>Reference standard (dermatologist’s diagnosis)</td>
</tr>
<tr>
<td>Clinical photographs (cases only)</td>
</tr>
</tbody>
</table>

Source documents

Source documents shall be filed at the investigator’s site and may include but are not limited to consent forms and study records. A CRF may also completely serve as its own source data. Only study staff listed on the delegation log shall have access to study documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents shall made be available at all times for review by the Chief Investigator, Sponsor’s designee and inspection by relevant regulatory authorities.

DATA PROTECTION

All study staff and investigators will endeavour to protect the rights of the study’s participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the study. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the study staff and investigators and any relevant regulatory authorities (see above). Computer held data including the study database will be held securely and patient identifiable data will be password protected. All data will be stored on a secure dedicated web
A copy of each CRF will be transferred from the recruiting site to the coordinating centre (Centre of Evidence Based Dermatology) for central monitoring, data entry and analysis. If agreed on the consent, collected contact details will be transferred securely, separately to the CRF, to the coordinating centre. A copy of the consent form will be transferred to the coordinating centre, separately to the CRF, to enable central monitoring of informed consent. If agreed on the consent, clinical photographs will be transferred securely as per individual trust policy to the coordinating centre.

Information about the study in the participant’s medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Information collected about participants will be used to support other research in the future and may be shared anonymously with other researchers.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for clinical study participants and study staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but study participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

STUDY CONDUCT

Study conduct may be subject to systems audit for inclusion of essential documents; permissions to conduct the study; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, timeliness of visits); accountability of study materials and equipment calibration logs.

STUDY DATA

Monitoring of study data shall include confirmation of informed consent; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases.

The Study Coordinator/Academic Supervisor, or where required, a nominated designee of the Sponsor, shall carry out central monitoring of study data as an ongoing activity.

This protocol is confidential and the property of the University of Nottingham. No part of it may be transmitted, reproduced, published, or used by others persons without prior written authorisation from the University of Nottingham.
The CRF may serve as the source document in addition to consent form and the study record. The subsequent capture of the data on the study database will be checked against the CRF. Where corrections to the database are required these will carry a full audit trail and justification.

Study data and evidence of monitoring and systems audits will be made available for inspection by the REC as required.

**RECORD RETENTION AND ARCHIVING**

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The study documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include study databases and associated meta-data encryption codes.

**DISCONTINUATION OF THE STUDY BY THE SPONSOR**

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice as appropriate in making this decision.

**STATEMENT OF CONFIDENTIALITY**

Individual participant medical or personal information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant’s medical team and all appropriate medical personnel responsible for the participant’s welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this study will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

**PUBLICATION AND DISSEMINATION POLICY**

The study will be published in a high impact peer-reviewed dermatology journal and also submitted for presentation at an international dermatology meeting. Participants will not be identified in any publications. The results of the study will also be shared through the Centre of Evidence Based Dermatology website and social media accounts.
The study will also be a chapter of Dr Burden-Teh’s PhD thesis.

**USER AND PUBLIC INVOLVEMENT**

Two patient advisors (Carolyn Hughes and Lisa Sharples) are part of the research advisory group. They have been involved in the study development and will continue to be part of the research advisory group. In particular they have emphasised the importance of the research question and have been directly involved with developing the Participant Information Sheets.

The Nottingham Young Persons Advisory Group for research and 10 parents/patients in the paediatric dermatology clinics have advised on the study design, in particular participant recruitment. The Young Persons Advisory Group have also informed the development and provided detailed feedback on the Participant Information Sheets.

**STUDY FINANCES**

**Funding source**

This study is funded by an NIHR Doctoral Research Fellowship NIHR DRF 2016-09-083.

**Participant stipends and payments**

Participants will not be paid to participate in the study.

All participants will receive a gift voucher and a certificate/sticker to say thank you and in recognition of their involvement.
SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)__________________________

Signature:_____________________________________

Date: ___________
REFERENCES


