IMPROVING OUR UNDERSTANDING OF CHILDHOOD PSORIASIS:

Identifying opportunities for early intervention for the prevention of long-term harm

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Abstract

1.1 Introduction

Psoriasis is an immune-mediated chronic inflammatory disease affecting the skin and joints of adults and children. This PhD focused on psoriasis in children because it is especially for this age group that both a research need and an opportunity to improve long-term health outcomes exist. There is a deficiency of paediatric specific research to guide optimal management and, for many individuals, the persistence of psoriasis into adulthood has a negative cumulative effect over their lifetime. Difficulties can arise because of the physical, psychological, and social burden of psoriasis, including the development of psoriatic arthritis.

1.2 Research aim

The aim of this research was to identify opportunities to intervene early in the disease course of children with psoriasis and juvenile psoriatic arthritis, in order to prevent long-term harm from these conditions.

Specifically the research aims of each study were:

1. To determine current clinical practice in the assessment and management of childhood psoriasis.
2. To understand current clinical practice in the assessment of juvenile psoriatic arthritis and psoriasis.
3. To map the evidence and identify research gaps in the epidemiology of childhood psoriasis.
4. To identify studies which have developed or validated diagnostic criteria for psoriasis.
5. To derive expert agreed diagnostic criteria for plaque psoriasis in children.
6. To design a diagnostic accuracy study to develop DIagnostic criteria for PSOriasis in Children (DIPSOC Study)

1.3 Methods

The initial studies focused on identifying deficiencies in current practice and exploring barriers in the detection of psoriasis and juvenile psoriatic arthritis. This research was undertaken as a multi-centre audit and case-note review, and qualitative descriptive interviews with paediatric rheumatologists and dermatologists. Framework and thematic content analysis were used to ascertain and explore the approach clinicians' take to assess skin and joint disease. The subsequent studies have mapped the volume, nature, and characteristics of epidemiological studies and appraised the literature to inform the development of diagnostic criteria for psoriasis in children. This research was undertaken as a scoping review on the epidemiology of childhood psoriasis and a systematic review on diagnostic criteria for psoriasis. The studies in the systematic review were appraised for risk of bias using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool. The final studies focused on developing diagnostic criteria for psoriasis in children. An electronic Delphi (eDelphi) consensus study with the International Psoriasis Council (IPC) used sequential online questionnaires and scoring to reach agreement on a list of expert-derived criteria. These five studies informed the design of a multi-centre case-control diagnostic accuracy study (DIPSOC study) to test the consensus agreed criteria and develop the best predictive criteria.

1.4 Results

The audit of the care of 285 children with psoriasis showed that compliance with national guidelines was variable. Only half of children were assessed annually for juvenile psoriatic arthritis and a third of children with psoriasis were potentially misdiagnosed with having other skin diseases in primary care. Exploring this further, paediatric rheumatologists' and dermatologists' current approach for assessing skin and joint disease, respectively, may not detect psoriasis and juvenile psoriatic arthritis. Reviewing the evidence base, most epidemiological data originates from case-series and cross-sectional studies, and there were few case-control and cohort studies investigating risk factors for disease onset, comorbidities, and long-term

health outcomes in paediatric psoriasis. This work highlighted a need to improve the recognition of psoriasis in children and for new studies using standardised methodologies and definitions. Currently, no clinical examination-based diagnostic criteria for psoriasis have been developed, tested, or validated. To address this evidence gap, experts collectively agreed on 16 diagnostic features, divided into three major and thirteen minor criteria, which are important for the clinical diagnosis of plaque psoriasis in children. These consensus agreed criteria will be tested in the DIPSOC study. The design of DIPSOC aims to minimise bias in the four key domains proposed by the QUADAS-2 tool, but uses a case-control design to ensure the recruitment target is feasible within the resources available.

1.5 Discussion

The research in this PhD makes an important contribution to the field of paediatric psoriasis and culminates in the design of the DIPSOC study to test and refine a list of diagnostic criteria for psoriasis in children. The criteria are intended to improve the recognition and early diagnosis of psoriasis in children, as well as offer a standardised disease definition for clinical trials and observational research. Improved diagnostic accuracy and increasing the quality of evidence from research studies will provide opportunities for early intervention to prevent long-term harm in children with psoriasis.

Publications and presentations arising from this research

Multi-centre audit and case-note review	Lam ML*, Burden-Teh E*, Taibjee SM *et al*. A United Kingdom (UK) multi-centre audit of the assessment and management of psoriasis in children. Br J Dermatol. 2015 Mar;172(3):789-92. doi: 10.1111/bjd.13471. Epub 2015 Feb 8. *joint first authors Burden-Teh E*, Lam ML*, Taibjee SM *et al*. How are we using systemic drugs to treat psoriasis in children? An insight into current clinical UK practice. Br J Dermatol. 2015 Aug;173(2):614-8. doi: 10.1111/bjd.13671. Epub 2015 Jun 21. *joint first authors Oral presentation - A United Kingdom (UK) multi-centre audit of the assessment and management of psoriasis in children. British Association of Dermatologists Annual Meeting, July 2015
Interviews with paediatric dermatologists and rheumatologists	Burden-Teh E, Thomas KS, Rangaraj S, Cranwell J, Murphy R. Early recognition and detection of juvenile psoriatic arthritis: a call for a standardised approach to screening. Clin Exp Dermatol. 2017 Mar;42(2):153-160. doi: 10.1111/ced.13010. Epub 2017 Jan 2.

	Burden-Teh E, Thomas KS, Rangaraj S, Murphy R. Interviews with paediatric rheumatologists about psoriasis and psoriatic arthritis in children: How can specialties learn from each other? Br J Dermatol. 2017 Jul;177(1):316-318. doi: 10.1111/bjd.15090. Epub 2017 Jun 11. Poster presentation - Could early detection of juvenile psoriatic arthritis be improved by a better recognition of how psoriasis presents in children? British Association of Dermatologists Annual Meeting, July 2015. Best poster in the British Society of Paediatric Dermatology category. Oral presentation - Improving the diagnosis of juvenile psoriatic arthritis: how can specialties learn from each other? Royal College of Paediatrics and Child Health Annual Conference, April 2016. Highest scoring poster abstract and invited for oral presentation.
Scoping review on the epidemiology of childhood psoriasis	Burden-Teh E, KS Thomas, Ratib S, Grindlay D, Adaji E, Murphy R. The epidemiology of childhood psoriasis: a scoping review. Br J Dermatol. 2016 Jun;174(6):1242-57. doi: 10.1111/bjd.14507. Epub 2016 May 22. Awarded best trainee scientific paper at the Midlands Dermatology Society meeting 2016. Poster presentation - Scoping the evidence of the epidemiology of childhood psoriasis. British Association of Dermatologists Annual Meeting, July 2016

Systematic review on diagnostic criteria for psoriasis	Burden-Teh E, Phillips RC, Thomas KS, Ratib S, Grindlay D, Murphy R. A systematic review of diagnostic criteria for psoriasis in adults and children: Evidence from studies with a primary aim to develop or validate diagnostic criteria. Br J Dermatol. 2018 May;178(5):1035-1043. doi: 10.1111/bjd.16104. Epub 2018 Mar 6.
eDelphi study to develop diagnostic criteria for plaque psoriasis	Burden-Teh E, Thomas KS, Gran S, Murphy R. Development of clinical diagnostic criteria for plaque psoriasis in children: an electronic Delphi consensus study with the International Psoriasis Council. Br J Dermatol. 2019 Oct;181(4):856-857. doi: 10.1111/bjd.17994. Epub 2019 Jun 28 Oral presentation - Consensus agreed diagnostic criteria for psoriasis in children: an eDelphi study with the International Psoriasis Council British Association of Dermatologists Annual Meeting, July 2018
The design of a multi-centre diagnostic accuracy study (DIPSOC)	Burden-Teh E, Murphy R, Gran S, Nijsten T, Hughes C, Thomas KS. Protocol for a case-control diagnostic accuracy study to develop diagnostic criteria for psoriasis in children (DIPSOC study): a multicentre study recruiting in UK paediatric dermatology clinics. BMJ Open. 2019 Aug 27;9(8):e028689. doi: 10.1136/bmjopen-2018-028689. Poster presentation - Developing DIagnostic criteria for PSOriasis in Children (The DIPSOC study): a protocol for a multicentre diagnostic accuracy study designed with the Young Person's Advisory Group for research. British Association of Dermatologists Annual Meeting, July 2018

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I aspire to be a strong role model for my daughters and for all girls hoping to forge their own path in science and medicine.

"When you do the things that you can do, you will find a way." A. A. Milne

List of contents

List of figures

List of tables

List of appendices

List of abbreviations

ANA	Antinuclear antibody
anti-TNF	Anti-tumour necrosis factor
BAD	British Association of Dermatologists
BADBIR	British Association of Dermatologists Biologics and Immunomodulator Register
BSPAR	British Society of Paediatric and Adolescent Rheumatology
BSPD	British Society of Paediatric Dermatology
CDLQI	Children's Dermatology Life Quality Index
CH	Ms Carolyn Hughes
CHU-9D	Child Health Utility 9D
CRF	Case report form
CRP	C-reactive protein
CTIMP	Clinical trial of an investigational medicinal product
CXR	Chest X-ray
DG	Dr Douglas Grindlay
DIPSOC	developing DIagnostic criteria for PSOriasis in Children
DLQI	Dermatology Life Quality Index
EA	Mr Emmanuel Adaji
EBT	Dr Esther Burden-Teh
eDelphi	Electronic Delphi
ERAP1	Endoplasmic reticulum aminopeptidase type 1
EMA	European Medicine Agency
ESR	Erythrocyte sedimentation rate
FBC	Full blood count
GCP	Good clinical practice
GP	General practitioner
GPA	Global Psoriasis Atlas
GWAS	Genome wide association studies
HEP	Hepatitis screening
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HRA	Health Regulatory Authority
IFPA	International Federation of Psoriasis Associations
IGRA	Interferon gamma release assay
IL-12	Interleukin-12
IL-17	Interleukin-17
IL-22	Interleukin-22
IL-23	Interleukin-23
ILAR	International League of Associations for Rheumatology

ILDS	International League of Dermatological Societies
IPC	International Psoriasis Council
ISRCTN	International Standard Randomised Controlled Trials Number
JIA	Juvenile idiopathic arthritis
KT	Prof Kim Thomas
LFT	Liver function tests
MED	Minimal erythema dose
ML	Dr Minh Lam
NHS REC	National Health Service research ethics committee
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PAPAA	Psoriasis and Psoriatic Arthritis Alliance
PASI	Psoriasis assessment severity index
PedsQL	Pediatric Quality of Life Inventory
PEST	Psoriasis Epidemiological Screening Tool
PGA	Physician Global Assessment
pGALS	Paediatric Gait, Arms, Legs, Spine Screening Tool
PIIINP	Type III procollagen peptide
PPI	Patient and public involvement
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-analyses
PSP	Priority setting partnership
PUVA	Psoralen-ultraviolet A photochemotherapy
QUADAS-2	Quality of Diagnostic Accuracy Studies 2
RCM	Reflective confocal microscopy
RM	Dr Ruth Murphy
ROC	(S)Receiver operator characteristic (ROC)
RP	Dr Rebecca Phillips
SG	Dr Sonia Gran
SNP	Single nucleotide polymorphism
SR	Dr Satyapal Rangaraj
STARD	Statement for Reporting Diagnostic Accuracy Studies
TNF-α	Tumor necrosis factor alpha
TRIPOD	Transparent Reporting of multivariable prediction model for Individual Prognosis Or Diagnosis
UE	Urea and electrolytes
VZV	Varicella zoster virus
WHO	World Health Organisation
YPAG	Young Persons' Advisory Group for research

Chapter 1 Introduction

1.1 Rationale for investigating psoriasis in children

The World Health Organisation (WHO) recognises that psoriasis is a common and serious non-communicable disease that affects both adults and children (WHO, 2016). The WHO's 2014 paper highlighted that many people suffer needlessly from psoriasis due to incorrect or delayed diagnosis, inadequate treatment options, insufficient access to care and the effects of social stigmatization (WHO, 2014). These problems are potentially greater for children and young people, because there is a deficiency of paediatric focused research to guide clinical practice and inform our understanding (NICE, 2012, Menter et al., 2020). To bridge this problem, conclusions from adult psoriasis studies are often extrapolated to children and young people. Therefore, there is significant scope to improve the experience and care of children and young people with psoriasis through specific paediatric research.

Epidemiological data is limited, but it is estimated that worldwide psoriasis affects over 60 million individuals of all ages (GPA, 2020) and up to one third of adults first develop signs of psoriasis in childhood (Raychaudhuri and Gross, 2000). These figures suggest that the number of children and young people who are and continue to be affected by persistent psoriasis in adulthood is considerable. There is also growing support for the concept of a cumulative life course impairment in psoriasis, which describes how decisions and experiences at multiple points in an individual's life can be affected by psoriasis (Kimball et al., 2010). This cumulative disability potentially starts in childhood for up to a third of people with psoriasis and is a consequence of both the physical and psychological burden of the disease. Due to the multi-systemic nature of psoriasis, children and young people are at risk of inflammatory juvenile psoriatic arthritis and possibly metabolic comorbidities such as hypertension and insulin resistance (Osier et al., 2017). Therefore, it is important to investigate

opportunities for early intervention in children with psoriasis for the prevention of long-term harm.

1.2 Guide to this thesis

In my PhD I have taken the critical steps to understand current practice and appraise the literature, before identifying a solution to test (Chalmers et al., 2014). The starting point for this research is a genuine belief that children and young people with psoriasis are not receiving the best available treatment and management, that preventative interventions are as important as treatment, and opportunities for action are being missed.

My PhD documents an evolving project, where each study builds on new research questions posed from the previous chapter. These relationships between the chapters are shown in the conceptual map in Figure 1:1. The aim of the final two studies was to develop diagnostic criteria for psoriasis in children. In the background section, I will provide contextual information about psoriasis, psoriasis in children, juvenile psoriatic arthritis and the wider psoriasis landscape. I will then address the following questions in each chapter.

1.2.1 Research questions

1. How does current practice in the assessment and management of psoriasis in children compare against national guidelines? (Chapter 3)

2. How do paediatric dermatologists and paediatric rheumatologists assess for juvenile psoriatic arthritis and psoriasis? (Chapter 4)

3. What is the volume, nature, characteristics and content of studies reporting data on the epidemiology of psoriasis in children? (Chapter 5)

4. What is the sensitivity and specificity of diagnostic criteria developed or validated for psoriasis in adults and children? (Chapter 6)

5. Which diagnostic features do experts agree are important for the diagnosis of plaque psoriasis in children? (Chapter 7)

6. What are the important design considerations in a study to test the diagnostic accuracy of criteria for psoriasis in children? (Protocol) (Chapter 8)

1.2.2 Conceptual map linking chapters

The diagram below (Figure 1:1) shows how each chapter links to one or more successive projects in the PhD.

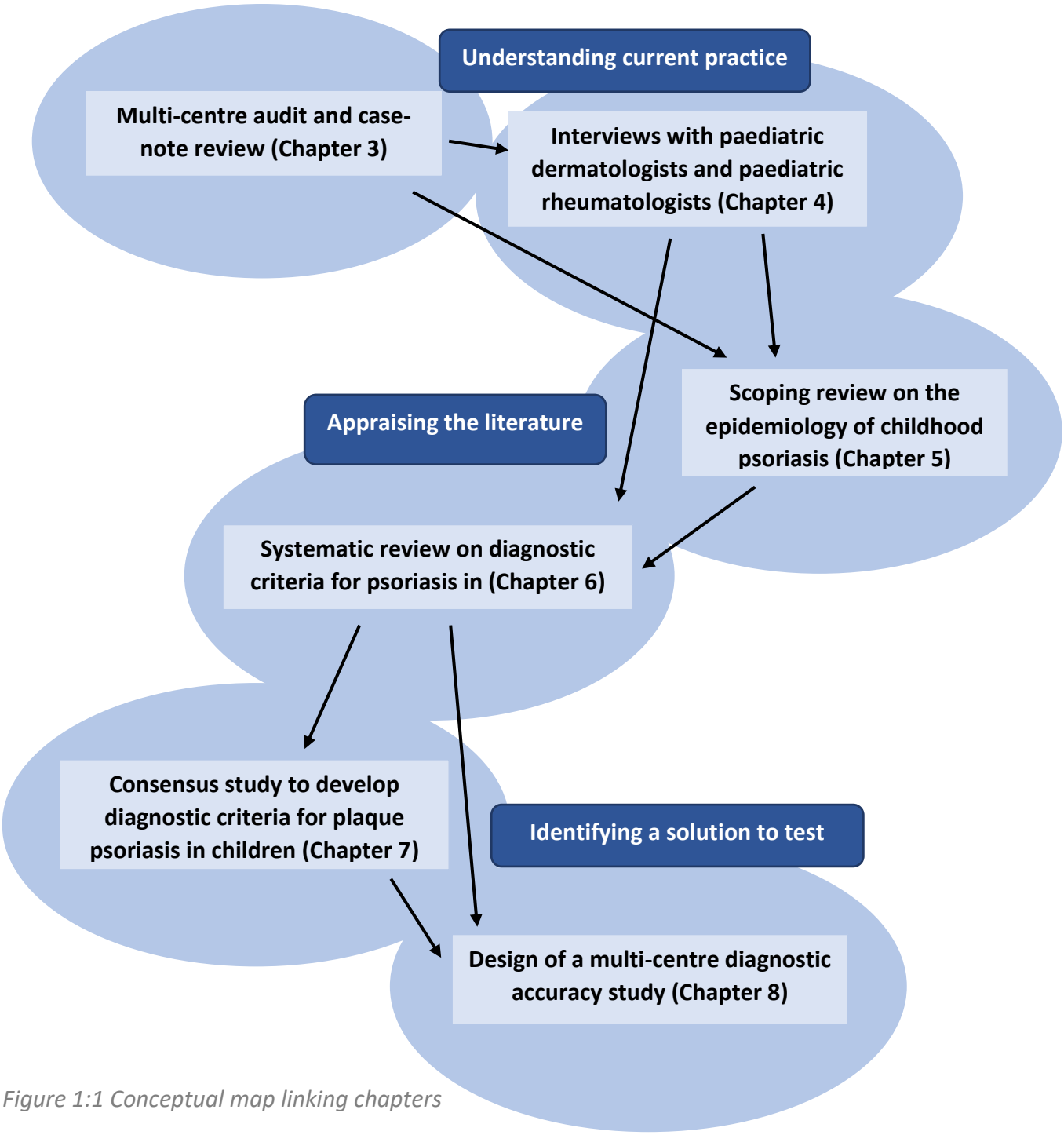

Figure 1:1 Conceptual map linking chapters

1.2.3 Aims, objectives and study design

Table 1:1 below sets out the aims and objectives for each Chapter in this thesis and the study design chosen to answer them.

Chapter	Aims	Objectives	Study design
3	**To determine current clinical practice in the assessment and management of childhood psoriasis**	1. To compare current clinical practice in the assessment and management of psoriasis in children against the NICE CG153 2012 guideline and the BAD 2009 guideline on biologic therapy. 2. To identify key areas for improvement in the provision of care for children with psoriasis. 3. To identify knowledge gaps between current practice and the available guidance in the assessment and management of psoriasis in children.	Multi-centre audit and case-note review

4	**To understand current clinical practice in the assessment of juvenile psoriatic arthritis and psoriasis in children**	1. To ascertain current clinical practice in the assessment of juvenile psoriatic arthritis and psoriasis in children. 2. To understand the impact a diagnosis of juvenile psoriatic arthritis has on the management of joint and skin disease. 3. To identify strategies for improving the detection of juvenile psoriatic arthritis and psoriasis in children.	Qualitative descriptive interviews
5	**To map the evidence and identifying research gaps in the epidemiology of childhood psoriasis**	1. To map the volume, nature and characteristics of research on the epidemiology of childhood psoriasis. 2. To summarise the available evidence answering these four questions: I. What is the prevalence, incidence and clinical presentation of childhood psoriasis? II. What are the genetic and environmental factors associated with the onset of psoriasis in childhood?	Scoping review

		III. What other conditions are associated with psoriasis in children? IV. What are the long-term outcomes for patients with child-onset psoriasis?	
6	**To identify studies which have developed or validated diagnostic criteria for psoriasis**	1. What is the sensitivity and specificity of diagnostic criteria developed or validated for psoriasis? 2. What data is provided in studies meeting the eligibility criteria on: a. Recommendations on how to diagnose psoriasis. b. Applicability of the diagnostic criteria to a paediatric population. c. Study design and study population.	Systematic review
7	**To derive expert agreed diagnostic criteria for plaque psoriasis in children**	1. To agree a list of discriminatory diagnostic features important for the diagnosis of psoriasis in children. 2. To agree a scoring algorithm to use with the diagnostic criteria.	eDelphi consensus study

8	**To design a diagnostic accuracy study to develop DIagnostic criteria for PSOriasis in Children (DIPSOC study)**	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 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.	Protocol for a case-control diagnostic accuracy study

Table 1:1 Outline of aims, objectives and study design for each chapter

1.2.4 Contributions

My interest in paediatric psoriasis was initiated and furthered by my supervisor and clinical mentor Dr Ruth Murphy. Through time spent with her in clinical practice, Ruth opened my eyes to the important differences seen in children, common misunderstandings and inadequacies in available research. It was our discussions in clinic that prompted the idea for the starting point of this PhD, a multi-centre audit and case-note review. Evaluating the strengths and inadequacies of current practice is a good place to start when deciding how to improve the health and care of children with psoriasis.

Ruth provided the light-bulb moment, but under the guidance of my supervisors I have pursued the avenues of enquiry that make up the chapters in this PhD. As each study was completed, my independence in proposing the research question, developing the study design, understanding the strengths and limitations, conducting the research, analysing the data and drawing conclusions has grown. After the first three studies were underway, it was Ruth who suggested developing diagnostic criteria for psoriasis in children. I took this idea and designed and conducted the research to create the criteria.

The research has been partly funded through a personal National Institute for Health Research (NIHR) fellowship. The funding application was peer-reviewed by clinical and methodological experts. To support my training within the fellowship and the validity of the research I formed an expert advisory group. The group is comprised of different stakeholders and methodologists, who are integral to understanding the value and application of diagnostic criteria for psoriasis in children. The group has functioned as a virtual panel and I have sought advice by email or in person on specific questions. The advice received has benefited both my training and the research studies, but I researched the methodology, designed the studies and made informed decisions. I am extremely grateful to the external support I have received and all those who have provided advice are listed at the end of this contributions section.

Under the headings of each Chapter I have detailed my contribution.

Multi-centre audit and case-series (Chapter 3)

The idea was conceived, and the project developed, by Dr Ruth Murphy (RM), myself and Dr Minh Lam (ML). I co-ordinated the project. I developed the proforma with ML. Data was collected by clinicians at each audit site. I and ML analysed the data. The project manuscripts were written by myself, ML, RM and the other co-authors.

Interviews with paediatric rheumatologists and dermatologists (Chapter 4)

The research idea was collaboratively formed by RM, EBT, Prof Kim Thomas (KT) and Dr Satyapal Rangaraj (SR). I decided on the study objectives, designed the interview guide, sought external methodological advice, interviewed the participants and transcribed the audio-recordings. I analysed all the data and for the dermatology interviews the analysis was guided by Dr Joanne Cranwell (qualitative researcher). The coding themes were discussed with RM, KT and SR and the manuscripts were reviewed by all co-authors.

Scoping review on the epidemiology of childhood psoriasis (Chapter 5)

I proposed the review topic, decided on the objectives and wrote the protocol. I designed the search strategy with training, guidance and final review from Dr Douglas Grindlay (DG). I trained and co-ordinated the role of the second reviewer (Mr Emmanuel Adaji (EA)). I analysed the data, wrote the synthesis and interpreted the findings. The manuscript was reviewed by all co-authors.

Systematic review on diagnostic criteria for psoriasis (Chapter 6)

I created the review question, decided on the objectives, wrote and registered the protocol. I designed the search strategy with training, guidance and final review from DG. I trained and co-ordinated the role of the second reviewer (Dr Rebecca Phillips (RP)). I led the critical appraisal, analysed the data, wrote the synthesis and interpreted the findings. The manuscript was reviewed by all co-authors.

Consensus study to develop diagnostic criteria (Chapter 7)

The initial idea to develop diagnostic criteria was suggested by RM. It was through RM that the International Psoriasis Council (IPC) was contacted and involved. I wrote the protocol, designed the questionnaires and analysed the data. All participant material and the analysis to inform the subsequent questionnaires was reviewed by RM. I wrote the manuscript and this was reviewed by all co-authors including the IPC.

Design of a multi-centre diagnostic accuracy study (Chapter 8)

I proposed the study idea, decided on the objectives, wrote the protocol and registered the study. I conducted the patient and public involvement work and wrote the study documents. I wrote the ethics application and presented the study at the ethics committee. I received feedback on the study design from the Test Evaluation Research Group and Prof Tamar Nijsten. I designed the statistical plan with support from Dr Sonia Gran (SG) and will be coordinating the study. The DIPSOC logo was created by Dr Natasha Rogers.

Contributors, co-investigators and the expert advisory panel

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Chapter 2 Background

2.1 Overview

Psoriasis is an immune-mediated chronic inflammatory disease affecting the skin and joints. There are different clinical subtypes and this thesis focuses on the most common phenotype, plaque psoriasis. The onset of psoriasis is due to a complex interplay of environmental triggers and genetic susceptibility, resulting in an immune mediated response. The presentation of psoriasis varies depending on the extent of disease, subtype of psoriasis and age of the individual. Psoriasis in children often has a different distribution and appearance. These and other differences with adults need to be recognised and adapted for in the clinical consultation. Psoriasis is not curable, therefore management focuses on the treatment of skin disease and monitoring for comorbidities. Personalised, stratified medicine and preventative strategies are both progressive areas for current psoriasis practice and research.

2.2 Part 1: Psoriasis

Part 1 introduces key concepts in psoriasis that are applicable to both adults and children. Where there is separate information available about children, this is provided within in each topic area.

2.2.1 Clinical subtypes

Psoriasis is not a homogenous disease and there are different clinical variants. In 2005, the IPC proposed a clearer classification system for psoriasis subtypes based on their clinical appearance (Griffiths et al., 2007). Clinical images and descriptions of these subtypes are presented in Table 2:1. Four main subtypes were defined: plaque psoriasis (psoriasis vulgaris), guttate psoriasis, pustular psoriasis and erythrodermic psoriasis. Nail psoriasis may occur within the four subtypes, or as an isolated type of psoriasis. The purpose of creating consensus-agreed psoriasis phenotypes was to

support detailed investigation into the genetics, pathogenesis and epidemiology of these groups. The benefits of disease stratification are being realised. Studies have shown different genetic and immunology profiles for plaque, guttate and pustular psoriasis (Sugiura, 2014, Holm et al., 2005, Yan et al., 2010). Clinically, the classification of psoriasis subtypes can be challenging. Within one subtype the features of psoriasis can differ depending on the anatomical site, for example plaque psoriasis on the scalp is often hyperkeratotic (thick scale) compared to the thin erythematous lesions seen in flexural psoriasis. Another challenge is that the presentation of psoriasis can change between subtypes. Psoriasis can initially present as guttate disease and then develop into plaque psoriasis, or it is possible to develop a guttate flare of plaque psoriasis (Chalmers, 2001). Similarly, plaque psoriasis can become unstable and change into generalised pustular psoriasis.

Psoriasis in children is also classified using these subtypes. In this thesis the term psoriasis refers to plaque psoriasis unless otherwise specified. Plaque psoriasis is the most common subtype in both adults and children, observed in up to 90% of people with psoriasis (Boehncke and Schon, 2015). Guttate psoriasis is an acute form of psoriasis and is more common in children compared to adults, which may be a consequence of frequent streptococcal infection, a known trigger, in children (Maruani et al., 2019). Both subtypes include plaques as the dominant feature, and therefore in later chapters of this thesis they have been grouped together under the single term of plaque psoriasis.

Psoriasis subtypes	
Plaque psoriasis	
	In plaque psoriasis the lesions are well-demarcated raised erythematous discoid plaques with silver scale. There is clear separation between the psoriasis plaque and normal skin. Lesions vary in size from 0.5 cm in diameter to large confluent areas. The following sub categories are included under plaque psoriasis (Griffiths et al., 2007). Flexural or inverse psoriasis affects areas of the body such as the groin, axilla, natal cleft and submammary (the crease under the breasts). The lesions are well-demarcated, erythematous and thin, with minimal scale. Seborrheic psoriasis or sebopsoriasis is similar in appearance to flexural psoriasis where the lesions are well-demarcated, erythematous and thin, with variable amounts of scale.

	Scalp psoriasis can vary from discrete plaques to complete scalp involvement, diffuse change to thick adherent scale. Frequently affected sites include the hairline, post-auricular and the occiput. Scalp psoriasis can lead to non-scarring alopecia (hair loss). Psoriasis affecting the palms and soles (acral psoriasis) can present as confluent erythema and scale, discrete plaques or ill-defined scaly/fissured areas.
Guttate psoriasis	
	Guttate psoriasis is described as an acute eruption of small (< 1 cm) papules of psoriasis (Chalmers et al., 2001). Guttate disease most commonly occurs on the trunk but can involve the limbs and face. The word guttate originates from the Latin word gutta, meaning drop, and guttate psoriasis is often referred to as having a raindrop appearance.
Pustular psoriasis	
	Pustular psoriasis can be either localised or generalised (Burden AD, 2016). Localised forms involve the acral surfaces as palmoplantar pustulosis or Acrodermatitis continua of Hallopeau (periungual skin and nail dystrophy). Generalised pustular psoriasis may be the first clinical presentation, or develop when plaque psoriasis becomes unstable.

Erythrodermic	
	Erythrodermic psoriasis describes confluent disease involving more than 90% of the body surface area. Erythrodermic psoriasis can develop de novo or represent a severe exacerbation of existing diseases. Erythroderma is a dermatological emergency because of effect on thermo-regulation, intravascular volume, cardiovascular output, protein loss and risk of infection.
Nail psoriasis	
	In psoriatic nail disease four main nail signs may be seen: nail pitting (small indentations in the nail plate) onycholysis (lifting of the nail plate from the nail bed), oil drops (light brown translucent patches under the nail plate) and subungual hyperkeratosis (thickening of the nail plate and bed).

Table 2:1 Classification of psoriasis subtypes with clinical images and descriptions

2.2.2 History of psoriasis

Psoriasis is an ancient disease. The long history of psoriasis has contributed to the heterogeneity of the term and complexity in classifying subtypes. Historically, classifications have been based purely on descriptive terms, and the term psoriasis includes a broad spectrum of clinical presentations. Future classifications may need to include, or be based on, the immunological and/or genetic profile of psoriasis, rather than purely clinical and epidemiological features.

The origins of psoriasis may lie in the biblical description of tzaraat, swelling and whitish-red spots on the torso, which has also been translated from Hebrew as leprosy (Grzybowski and Nita, 2016). Hippocrates used the word psora for an itchy condition of the genitals and eyelids, for which tar and climate were used as treatment (Gruber, 2012). Benjamin Franklin is credited with giving one of the earliest detailed description of psoriasis "The Scurf appears to be compos'd of extreamly thin Scales one upon another, which are white, and when rubb'd off dry, are light as Bran. When the Skin is clear'd in the Bath, it looks red, and seems a little elevated above the sound Skin that is around the Place" (Huth, 2007). However, it is Robert Willan, founder of modern dermatology, who identified psoriasis as a medical entity. Willan alongside Thomas Bateman proposed a classification of skin disease in the book 'On Cutaneous Disease' (Willan, 1808). The term psoriasis was used for papulosquamous disease, encompassing forms of psoriasis such as guttata, diffusa, gyrata, palmaria, unguium, inveterate (Figure 2:1).

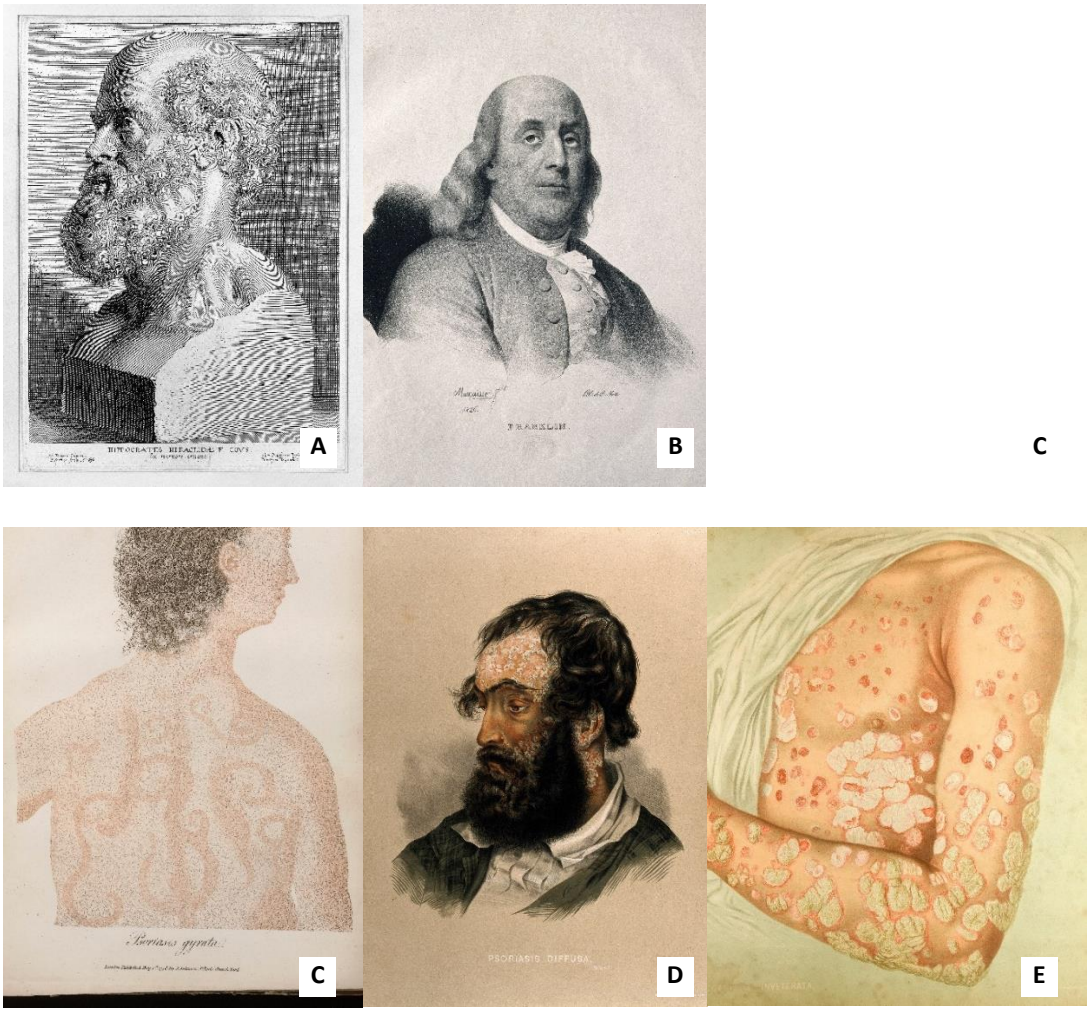


Figure 2:1 Psoriasis in history

A. *Engraving of Hippocrates. Wellcome Collection. CC BY.*
B. *Lithograph of Benjamin Franklin. Wellcome Collection. CC BY.*
C. *Oil on canvas of Robert Willan. Royal College of Physicians London.*
D. *Colour plate showing psoriasis gyrate in Willan's textbook. Wellcome Collection. CC BY.*
E. *Chromolithograph of psoriasis diffusa. Wellcome Collection. CC BY.*
F. *Chromolithograph of psoriasis vulgaris inveterate. Wellcome Collection. CC BY.*

2.2.3 Immunopathogenesis

Psoriasis is an immune-mediated disease. Psoriatic skin lesions develop due to dysregulated and amplified interactions between the innate and adaptive immune system (Boehncke and Schon, 2015, Kim and Krueger, 2015, Gooderham et al., 2018) (Figure 1.5). The innate immune system, regarded as 'inborn immunity', recognises and responds to pathogens. The adaptive immune system provides an enhanced response to pathogens through immunological memory and is considered 'acquired immunity' (Coico, 2015). Across the two systems dendritic cells, keratinocytes, T cells and immune mediators such as tumour necrosis factor (TNF)-α, Interleukin (IL)-12, IL-23, IL-17 are important contributors in psoriasis pathogenesis, and are therefore also important therapeutic targets.

Dendritic cells are an important part of the innate immune system. Activation of these antigen presenting cells leads to the production of inflammatory mediators, such as IL-12 and IL-23, that in turn promote activation and differentiation of T cells (Kim and Krueger, 2015). The exact nature of the antigens are unknown, but autoantigens such as epidermis produced antimicrobial peptide LL-37 (cathelicidin) may play a role (Lande et al., 2014, Hawkes et al., 2017). Positive feedback between dendritic cells (innate), keratinocytes and T cells (adaptive) involves transcriptions of inflammatory mediators and drives an escalating inflammatory response. It is the activation of TNF-α pathway and IL-23/TH17 axis pathway that causes dysregulation of almost all cutaneous cells seen in psoriasis (Teng et al., 2015, Lowes et al., 2014).

TNF-α is a pro-inflammatory cytokine produced by many cell types and has a multifaceted role in psoriasis (Kim and Krueger, 2015). In particular, production by dendritic cells stimulates T cell activation and directly causes keratinocyte proliferation (Zaba et al., 2007, Summers deLuca and Gommerman, 2012). IL-23 leads to dysregulated production of IL-17A, IL-17F and IL-22 (Chan et al., 2006). More recently, IL-17 has been found to be the pivotal cytokine in psoriasis pathogenesis and IL-17 blockade results in near complete resolution of psoriasis in the majority of patients (Thaci et al., 2015) . Keratinocytes are the main cells expressing IL-17 receptors and IL-17 triggers epidermal gene expression and keratinocyte

proliferation (Lowes et al., 2014, Lowes et al., 2008). A schematic diagram of the immunopathogenesis of psoriasis is shown in Figure 2:2. Greater understanding of the immunopathogenesis of psoriasis has led to the development of specific targeted treatments referred to as biologics therapies that block TNF-α, IL12/23 and IL-17.

The immunopathogenesis of psoriasis in children is understudied. In one small study of 10 children with psoriasis, the immune cell profile of psoriatic plaques were compared to age matched controls and adults with psoriasis. The findings indicate a difference between paediatric and adult disease, with a normal CD4:CD8 T cell ratio, lower levels of IL-17 producing T cells, higher levels of IL-22 producing T cells and no increases in regulatory T cells observed in children with psoriasis (Cordoro et al., 2017). Another study solely looked at the immune profile in the peripheral blood of 21 children with psoriasis and 15 healthy controls, but found regulatory T cells to be raised alongside IL-17 (Zhang et al., 2016).

Both these studies included small numbers of patients and are cross-sectional in design. Therefore, replication in larger studies and studies investigating immune profiles at different stages of psoriasis development are needed. However, if a difference in the immunopathogenesis of psoriasis between adults and children is confirmed, this would potentially support the use and development of different targeted therapies for each age group.

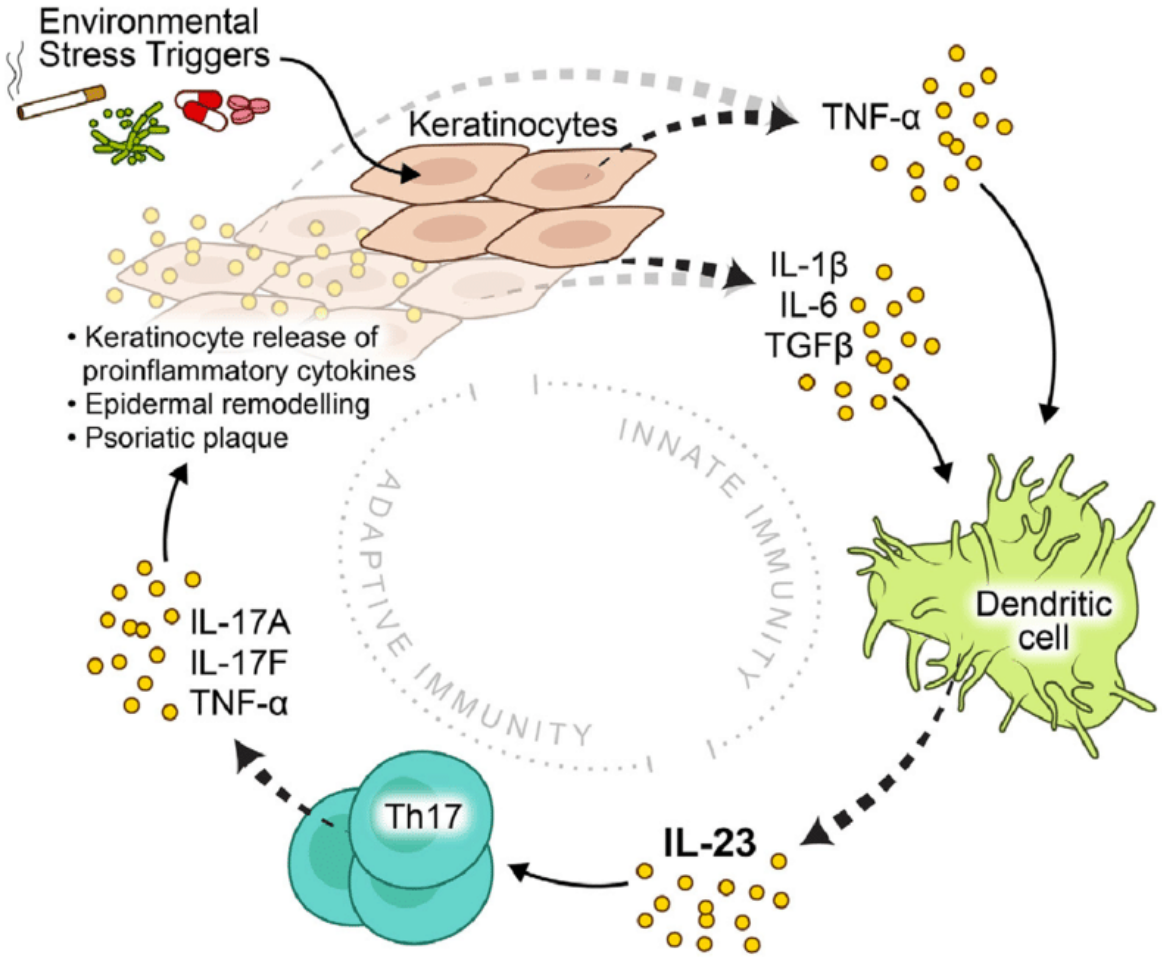


Figure 2:2 Schematic diagram of the immunopathogenesis of psoriasis (Gooderham et al., 2015)
This diagram shows the interaction between the innate and adaptive immune system. Environmental stress and triggers lead to keratinocyte damage, release of cytokines and activation of dendritic cells. Interleukin (IL)-17, IL-23 and tumour necrosis factor (TNF)-α are all central in the immunopathogenesis of psoriasis.

2.2.4 Genetics

Psoriasis is more likely in those with known genetic risk factors. Early epidemiological studies demonstrated that psoriasis clusters in families. Lomholt studied one third of the population of the Faroe Isles, a total of 10,984 inhabitants, and reported that a familial occurrence was found in 91% of cases. When both parents had psoriasis the incidence of psoriasis amongst their children was 64% (Lomholt, 1963). Farber and Nall's study of 5,600 patients reported 36% had a family member affected by psoriasis (Farber and Nall, 1974). Further evidence of the genetic basis of psoriasis comes from twin studies. Data from Denmark, Norway, the United States and Australia have shown higher concordance between monozygotic than dizygotic twins (Brandrup et al., 1978, Grjibovski et al., 2007, Duffy et al., 1993, Farber et al., 1974).

Mendelian patterns of inheritance do not explain the hereditary pattern observed in psoriasis. It is recognised that psoriasis is a complex genetic disease involving multiple alleles (Elder et al., 2001). Early genetic studies used linkage analysis to trace the pattern of clinical phenotypes to specific genomic regions; these methods identified replicable genetic loci PSOR1, 2 and 4. PSOR1 conveys the greatest risk (25-50% heritability) and is the region in which the gene for human leucocyte antigen (HLA) C is located (Mahil et al., 2015). Genome-wide association studies (GWAS) are a powerful tool, for looking at significant differences in allele frequency between cases and controls. Meta-analysis of GWAS and immunochip datasets has identified over 40 psoriasis loci (Tsoi et al., 2012, Tsoi et al., 2015).

Specific HLA associations with psoriasis were discovered over 40 years ago (Russell et al., 1972). HLA-Cw6 allele is most strongly associated with psoriasis in different populations, especially Caucasian, and onset of psoriasis under the age of 40 years (Gudjonsson and Elder, 2007, Henseler and Christophers, 1985). However, only about two thirds of people with psoriasis carry HLA-Cw6 and only 10% of HLA-Cw6 positive people have psoriasis (Elder et al., 2001).

The search to explain the genetic basis of psoriasis has furthered current understanding of psoriasis pathogenesis. Genetic associations with the adaptive immune system, skin barrier function and innate immunity have been identified

(Mahil et al., 2015). These genetic association include Endoplasmic reticulum aminopeptidase type 1 (ERAP1), IL23B/R, LCE3B/C and NF-κB (Cargill et al., 2007, Genetic Analysis of Psoriasis Consortium & the Wellcome Trust Case Control Consortium et al., 2010, Nair et al., 2009, de Cid et al., 2009).

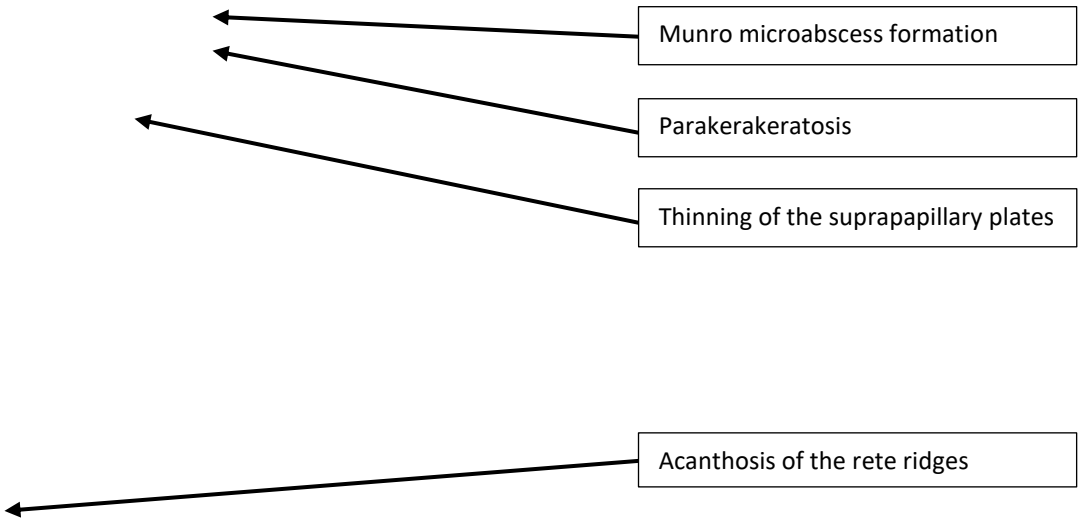
The genetic basis of psoriasis in children may be different to that seen in adults. Studies have shown that certain polymorphisms may only have an association with specific age groups. For example, the ERAP1 single-nucleotide polymorphism (SNP) is associated with child-onset disease, possibly only in cases with an onset between 10-20 years of age (Lysell et al., 2013b, Bergboer et al., 2012). Similarly to the immunopathogenesis of psoriasis, identifying and understanding a different genetic basis for children may help identify specific environmental triggers and inform targeted treatments.

2.2.5 Histopathology

The diagnosis of psoriasis is normally based solely on a clinical assessment. Skin biopsies are not routinely taken from psoriatic plaques as part of the diagnostic work-up, but may be indicated if there is diagnostic uncertainty. If biopsied, the histological changes seen vary according to the maturation of the plaque (De Rosa and Mignogna, 2007, Murphy et al., 2007, Johnson and Armstrong, 2013). Separate reports comparing or documenting the histological changes in paediatric psoriasis are not available. In clinical practice biopsies are infrequently taken from children because a biopsy can be a distressing procedure and may require sedation.

In early psoriatic skin lesions there are dilated dermal vessels with oedema and perivascular lymphocytic infiltrate. Following this, epidermal acanthosis (thickening) develops with loss of the granular layer. Mounds of parakeratosis appear, thought to relate to the shortened cell turnover seen in psoriasis (7 days) (Goodwin and Fry, 1974). Rapid keratinocyte proliferation and incomplete maturation leads to a poorly developed stratum corneum and the characteristic psoriasis scales.

In later stage lesions there is thickening and widening of the rete ridges and thinning of the suprapapillary plates, bringing dilated capillaries closer to the skin surface. More specific changes for psoriasis include collections of neutrophils in the parakeratotic scale, called microabscess of Munro, and deeper epidermal collections called spongiform pustule of Kojog (De Rosa and Mignogna, 2007, Johnson and Armstrong, 2013) (**Error! Reference source not found.**). Morphologically these h istologic changes are seen as elevated erythematous scaly plaques.



2.3 Part 2: Psoriasis in children

Part 2 introduces key concepts about psoriasis in children, highlighting differences and similarities between psoriasis in adults and children.

2.3.1 Clinical presentation

Dermatological diseases are described according to their distribution, configuration and morphology (Rimoin et al., 2015). Psoriasis is typically symmetrical; similar to other endogenous skin conditions (Cox, 2009). It can affect all squamous skin from the scalp, face, trunk and limbs, to acral, genital and mucosal surfaces. Psoriasis can also affect the nail matrix leading to the distinctive nail changes of pitting, onycholysis (lifting of the nail) and hyperkeratosis. The configuration of skin lesions can vary and includes linear koebnerised skin (trauma-induced, such as a scratch) and an annular (ring-like) pattern with central clearing. As previously mentioned in the main section on psoriasis, plaque psoriasis and guttate psoriasis are the two most common subtypes seen in children and adults. Both subtypes have psoriasis plaques as the dominant feature; in guttate disease this is an acute eruption of small lesions. The plaques in psoriasis are typically described as well-defined, elevated and erythematous, with adherent silvery scale (Boehncke and Schon, 2015). However, the clinical presentation of psoriasis can vary significantly between individuals depending on the area of the body affected, extent of disease, psoriasis subtype and the age of the patient (Raychaudhuri et al., 2014).

In children, the distribution and morphology of psoriasis often differs from adults. These differences may be the consequence of a shorter disease duration or underlying genetic and pathophysiological differences between child and adult-onset diseases. Facial and flexural psoriasis is seen more often in children, where scale may be minimal and maceration can occur in moist areas (Bronckers et al., 2015, Romiti et al., 2009, Eichenfield et al., 2018). Plaques on the trunk and limbs are often thinner and hyperkeratosis less prominent (Bronckers et al., 2015, Thomas and Parimalam, 2016, Eichenfield et al., 2018). Figure 2:3 presents photographs of

children with psoriasis demonstrating the typically thinner, less scaly plaques and facial involvement.

Previously, psoriasis has been considered non-pruritic and itch has been used as an important distinguishing feature from eczema. However, there is growing recognition of the importance of itch in paediatric psoriasis (Shahwan and Kimball, 2017) and treatments reducing itch were found to have the largest positive impact on quality of life (Oostveen et al., 2012).

With the aim to better predict severe psoriasis and offer early intervention, the relationship between body area involved and disease severity has been investigated. Two studies using a prospective cohort of children with psoriasis have identified scalp psoriasis and nail psoriasis as predictors of severe disease (Bronckers et al., 2019).

Increasing understanding and educating health professionals about the different clinical presentation of psoriasis in adults and children are important for ensuring psoriasis in children is accurately recognised. Psoriasis in children may be missed if clinicians approach diagnosis with an image of adult psoriasis in their minds, expecting to see prominent erythematous hyperkeratotic plaques on extensor surfaces.

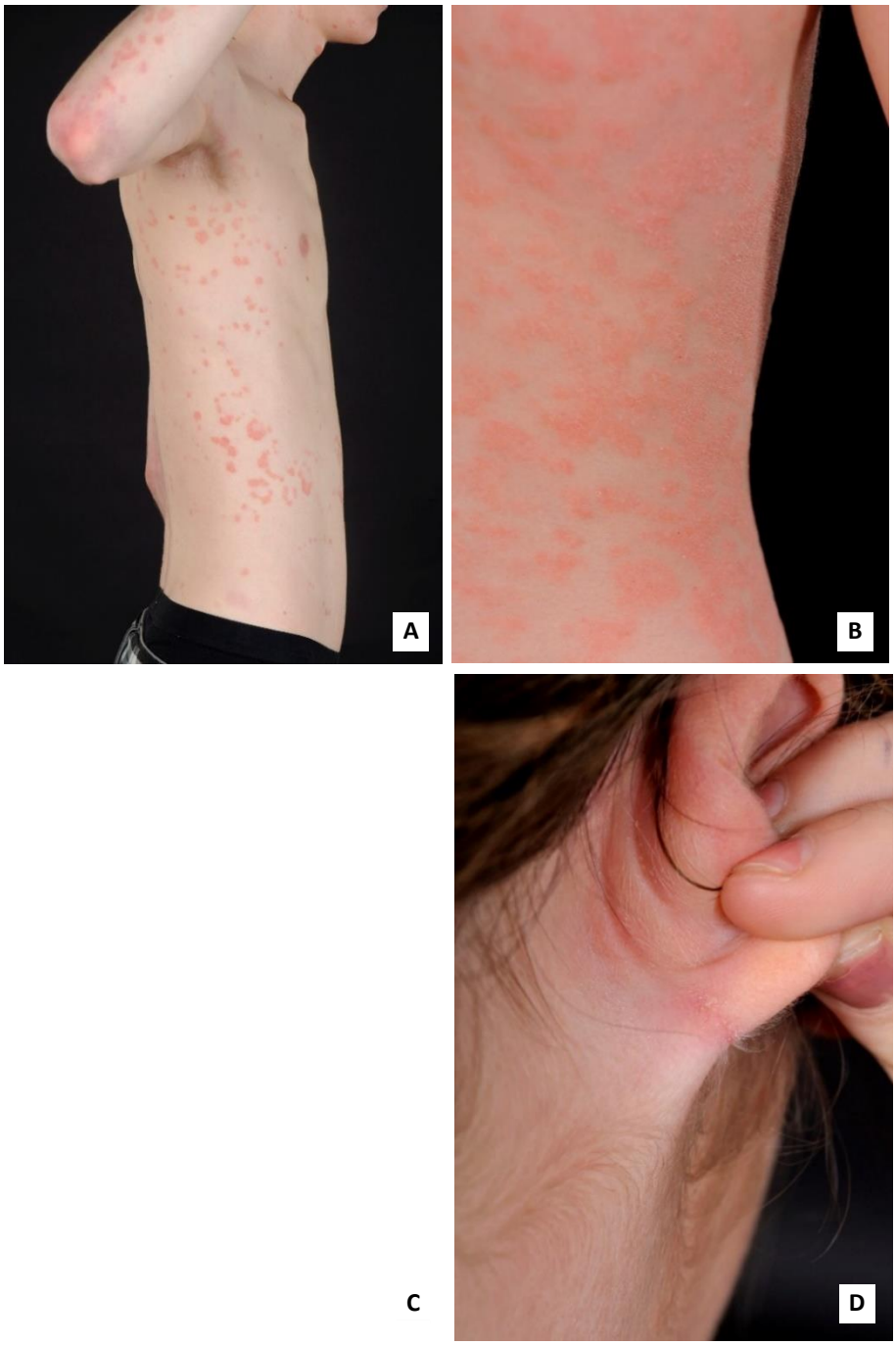


Figure 2:3 Clinical presentation of psoriasis in children.
Images consented for research and teaching at Nottingham University Hospitals NHS Trust, courtesy of Dr Ruth Murphy

A. *Plaque psoriasis on the trunk and arm with thin well-defined plaques of varying sizes*
B. *Plaque psoriasis on the trunk with minimal scale and confluent areas*
C. *Plaque psoriasis on the face with varying amounts of scale*
D. *Psoriasis affecting the crease between the ear lobe and neck*

2.3.2 Epidemiology

The data available on the epidemiology of psoriasis in children is limited. Parisi *et al*. conducted a systematic review on the prevalence and incidence of psoriasis using population-based studies published before July 2011 (Parisi et al., 2013). European studies have estimated the prevalence of psoriasis in children to be up to 2.15%, and nearly absent in Asia (Parisi et al., 2013). Only one eligible study reported the incidence of psoriasis in children. This study used healthcare database records in one region of Minnesota, United States, and calculated the dermatologist confirmed incidence of psoriasis to be 33.2 per 100,000 (95%CI: 29.3, 37) (Tollefson et al., 2010). The study showed the annual incidence of psoriasis over a 30 year time period to be increasing. However, these findings should be interpreted in the context of an individual study using a small incidence cohort of 357 children. In comparison, the prevalence and incidence of psoriasis are both estimated to be higher in adults. Seventeen studies reported a prevalence in adults between 0.91% and 8.5% and three studies reported an incidence rate between 73.2 and 207 per 100,000 person-years (Parisi et al., 2013).

Traditionally, psoriasis has been divided into Type I and Type II, separated by a bimodal age of onset (Langley et al., 2005). The first peak for mean age of onset is in late adolescence (16-22 years) and the second peak is later in life between 57-60 years of age. Type I (<40 years) is estimated to account for 75% of psoriasis, and individuals in this group are more likely to have a family history of psoriasis, develop generalised disease and be associated with HLA-Cw6 (Henseler and Christophers, 1985). More recently, psoriasis has been divided into paediatric-onset and adult-onset. In a questionnaire based cross-sectional study of 707 adult psoriasis patients, a third were completed by adults who first developed psoriasis under the age of 16 years (Raychaudhuri and Gross, 2000). However, it is not clear whether paediatric-onset individuals are accurately captured within population prevalence studies, or whether it is only on reflection that adults recall skin signs they now attribute to psoriasis.

2.3.3 Risk factors for disease onset

Psoriasis is the consequence of a complex interaction between genetic and environmental triggers. Environmental factors may initiate the immune cascade and help to explain the variable genetic expression of psoriasis seen by imperfect concordance in monozygotic twins (Gudjonsson and Elder, 2007, Kim and Krueger, 2015). Identifying triggers for disease onset in paediatric psoriasis may help to inform preventative interventions in at risk children.

Infection, trauma or injury, medications and psychological stress are all recognised as triggers for psoriasis onset, and triggering factors may be more frequently identified in children compared to adults (Raychaudhuri and Gross, 2000, Fry and Baker, 2007). Group A streptococci (*S. pyogenes*) throat infection in particular is associated with precipitating the onset of guttate psoriasis, a common presentation in children (Telfer et al., 1992). The development of psoriasis in areas of skin injury (koebnerisation) is also a common presentation in children. Koebnerisation is thought to have a key role in the development of psoriasis in the nappy area of infants from repeated mild trauma and exposure to irritants. Paradoxically, the introduction of anti-TNF therapies for autoimmune diseases such as inflammatory bowel disease and inflammatory arthritis has triggered the onset of psoriasis in a small number of children (Eickstaedt et al., 2017).

2.3.4 Comorbidities

Over the past 20 years evidence has emerged for the association of psoriasis and metabolic/cardiovascular comorbidities. Henseler and Christophers conducted one of the first cross-sectional studies which showed that obesity, diabetes, heart failure and hypertension occur more often in people with psoriasis than controls (Henseler and Christophers, 1995). It is hypothesised that multi-systemic inflammation increases the inflammatory burden leading to insulin resistance, endothelial dysfunction and atherosclerosis; referred to as the ‘Psoriatic March’ (Boehncke et al., 2011). However, whether psoriasis is an independent or causal risk factor for cardiovascular disease remains disputed in both adults and children.

A recent systematic review by Badaoui *et al*. identified 16 studies investigating the association between psoriasis and metabolic or cardiovascular comorbidities in children (Badaoui et al., 2019). The review was challenging to undertake because of large variation in disease definitions and choice of study design. Only one study included in the review was a cohort study. Overall, Badaoui *et al*. concluded that only an association between psoriasis and obesity could be supported, with obesity potentially being a trigger for the onset of psoriasis. In adults, a systematic review of cohort studies identified an increased risk of the incidence of cardiovascular disease only in those with severe psoriasis (requiring systemic treatment or hospital admission) (Dhana et al., 2019). Dhana *et al.* acknowledged that most studies did not adjust for risk factors beyond age and sex, therefore the increased risk of metabolic/cardiovascular disease observed in some studies may be the consequence of a clustering of traditional risk factors in patients with psoriasis.

In children, studies have also investigated the risk of psoriasis and other comorbidities. Anxiety and depression are more prevalent in children with psoriasis compared to controls, and psychiatric disorders can predate the onset of psoriasis, supporting the role of psychological stress as a trigger factor (Kara et al., 2019). Alongside psychiatric disease, several studies also report an association with inflammatory bowel disease (Paller et al., 2019). Therefore, there is an opportunity to minimise risk factors and monitor for comorbidities in children with psoriasis.

2.3.5 Impact on quality of life

Psoriasis is known to have a significant impact on quality of life. In adults, Findlay *et al*. found that patients with psoriasis had comparable disability to those with hypertension and diabetes (Finlay et al., 1990) Similarly, Rapp *et al.* showed that the effect of psoriasis on health related quality of life corresponds to that observed in other medical and psychiatric conditions, such as cancer, arthritis, hypertension, heart disease, diabetes, and depression. (Rapp et al., 1999). These studies were both critical evidence to change society's perceptions of psoriasis from a cosmetic disease to one exerting physical and psychological disability.

More recently, a body of research has demonstrated the negative effect psoriasis has on the quality of life of children, adolescents and their caregivers. Interviews with adolescents with psoriasis identified six themes to describe the physical, psychological and social aspects of living with psoriasis. These themes were physical symptoms, feeling different, worry about the future, increased attention, attempts to conceal skin and treatment related frustrations and worry (Randa et al., 2018). There is disagreement between studies about the effect of disease severity on quality of life (Rapp et al., 1999, Garshick and Kimball, 2015), but in these interviews adolescents with psoriasis affecting visible parts of the body reported greater impairment (Randa et al., 2018). A systematic review including 17 studies reported health related quality of life in children aged between 4 and 18 years. The average health related quality of life impairment across 15 studies using the Children's or Adult Dermatology Life Quality Index (DLQI) was moderate (mean score 7.7, 95% CI 6.67-8.73). A smaller number of studies have investigated the effect of psoriasis on the caregivers of children, and found that the domain of emotional well-being was most severely impaired (Tollefson et al., 2017, Tekin et al., 2018).

An important concept being applied in psoriasis is the cumulative life course impairment, reflecting the significant physical, social and psychological burden psoriasis can have on multiple aspects of a patient's life (Kimball et al., 2010, Warren et al., 2011). This concept aims to capture the impairment psoriasis has over an individual's lifetime, influencing the choices made and outcomes experienced, rather than assessing health related quality of life impairment at single points in time. For example, psoriasis can negatively affect relationships, work attendance and prospects, income and social activity (Kimball et al., 2010). Cumulative life course impairment supports the rationale to identify opportunities for early intervention for the prevention of long-term harm in children with psoriasis. Opportunities may exist to reduce the burden of psoriasis from an early age, enabling people to make positive decisions and fulfil their potential.

2.3.6 Assessment of disease severity and impact

Assessment of disease severity and impact is part of both new and follow-up consultations. The assessment is useful for measuring the scale of the clinical problem, documentation, informing treatment decisions and evaluating response to treatment. In children, no assessment tools have been validated for disease severity, but validated tools are available for the assessment of impact on quality of life.

The Psoriasis Assessment Severity Index (PASI) is calculated from a clinical assessment in which plaque erythema, scale, induration and body surface area in four body zones are scored (scalp, trunk, arms and legs) (Fredriksson and Pettersson, 1978). It is the most widely used severity assessment tool in specialist settings and clinical trials for both adults and children. However, it is acknowledged that PASI is poorly validated and there are specific problems with its use; for example PASI has a non-linear score, body surface area is part of the PASI assessment but is often inaccurately estimated, and PASI loses sensitivity to change when body surface area is less than 10% (NICE, 2012, Chalmers, 2015). In children, use of PASI has the additional problem that body proportions are different to adults. It has also not been determined how the thresholds of PASI relate to severity categories, but current practice often refers to severe psoriasis as a PASI score over 10. Alternative severity assessment tools used in children are the Physician Global Assessment, (PGA) rated on a 5 or 7 point scale from 'clear' to 'severe' (Chalmers, 2015), and using body surface area on its own.

The Children's Dermatology Life Quality Index (CDLQI) is validated for assessing impact on quality of life in children aged 4 to 16 years (Lewis-Jones and Finlay, 1995). The tool is a ten-item questionnaire measuring how much the skin problem has affected the individual over the past week. A cartoon version of the CDLQI has been validated against the original text questionnaire and was quicker and easier for children to complete (Holme et al., 2003). The CDLQI is the most widely used impact assessment tool in clinical practice and research. In 2012, Salek *et al.* identified 102 studies in their systematic review that had used or assessed the properties of the CDLQI. The CDLQI was found to have good internal consistency, test-retest reliability

and responsiveness to change, but other properties such as the minimally important difference have not been assessed (Salek et al., 2013). There are no disease specific quality of life measurement tools for psoriasis in children. Generic health related quality of life tools can be used and are useful when comparing psoriasis to other diseases outside of dermatology, for example the Pediatric Quality of Life Inventory (PedsQL) and the Child Health Utility-9D (Varni et al., 2001, Stevens, 2011).

2.3.7 Treatment

2.3.7.1 National guidelines

Several national guidelines have been published on the treatment of psoriasis in children. In the UK, the National Institute for Health and Care Excellence (NICE) psoriasis guidelines became available in 2012 and were updated in 2017. More recently, German and North American guidelines have been published specifically for psoriasis in children (Eisert et al., 2019, Menter et al., 2020). Treatment and management of psoriasis in all ages occurs in the knowledge that psoriasis cannot be cured. Psoriasis is a chronic condition and over time people can experience flares and remission in their disease.

The treatment approach for children is summarised below and in Figure 2:4. For many patients this follows a step-wise plan depending on whether the disease is mild, moderate or severe. Each of the separate guidelines have acknowledged that studies informing the treatment of paediatric psoriasis are lacking, and therefore data from adult studies is often extrapolated to this younger population. In the UK, only topical calcipotriol, potent steroids, acitretin and more recently certain biologic therapies are licensed for use in patients under the age of 16 years (NICE, 2012, NICE, 2017). Therefore, often treatments for psoriasis in children are used outside their licensed indication.

The NICE guideline emphasises other important considerations when managing psoriasis in children (NICE, 2012). The overarching aim for treatment is to improve health outcomes, but minimise negative long-term sequelae from both the disease

and treatment. All three stakeholders in the clinical relationship (patient, parent and clinician) need to be included in the consultation and decision-making process. In children and young people, poor health can impact on educational needs and in particular the impact in adolescence can be challenging for all stakeholders. Encouraging self-care and transitioning care between paediatric and adult services needs to be carefully planned.

Currently, psoriasis in children is usually managed within a general dermatology caseload. Most dermatologists in the UK are trained adult physicians, who have developed an interest in paediatric dermatology. Paediatric dermatology is not a standardised or centralised service, therefore the set-up of paediatric dermatology centres can differ significantly. The NICE guideline recommends that all children and young people with psoriasis are referred to a specialist at presentation.

2.3.7.2 Topical treatments

Topical (applied to the skin) treatments are the mainstay in mild disease and they can also be used in combination with other therapies for more severe disease. Topical corticosteroids and vitamin D analogues are considered first line agents. There are age restrictions for the use of both medications. Potent topical steroids can only be used over the age of one year, vitamin D analogues over the age of six years and a combination product over the age of 12 years. Historically, coal tar-based products and dithranol have been widely used, but are no longer highly recommended (Eisert et al., 2019, NICE, 2012). Only one paediatric randomised controlled trial was available to inform the Cochrane review on topical treatments for plaque psoriasis. Oranje *et al.* compared a vitamin D analogue against placebo and found a statistically significant difference between the groups for investigator overall assessment but not PASI (Oranje et al., 1997). Although the approaches for using topical therapies are similar for adults and children, there are important biological differences that prescribers should be made aware of. The body surface to body weight ratio is two to three times greater in children and the skin barrier function is not as matured (Eisert et al., 2019). Both these features increase absorption of topical treatments, potentially increasing the risk of adverse effects.

2.3.7.3 Phototherapy

If psoriasis is not controlled by topical treatment or is assessed as being extensive, causing difficulties with function or having a significant impact on well-being, then phototherapy, conventional systemic therapy or biologic therapy can be offered. Often treatment is offered as a stepwise escalation, but phototherapy may not be included depending on the area of the body affected, patient preference, availability of phototherapy appointments and concerns about long-term sequelae (skin cancer) (NICE, 2012, Eisert et al., 2019). Narrowband ultraviolet B (UVB) is the preferred type of phototherapy because it provides the best balance between clinical effectiveness and minimal adverse effects. The 2013 Cochrane review comparing narrowband UVB and psoralen-ultraviolet A photochemotherapy (PUVA) for psoriasis did not include children, because PUVA is contraindicated in this age group (Chen et al., 2013).

2.3.7.4 Conventional systemics

Conventional systemic therapies include methotrexate, ciclosporin, fumaric acid esters and acitretin. The first three drugs are classified as immunosuppressants or immunomodulators, and acitretin is a systemic retinoid. In parallel to adults, methotrexate is recommended by UK, German and North American guidelines as a first-line conventional systemic therapy for psoriasis in children (NICE, 2012, Eisert et al., 2019, Menter et al., 2020). The recommendation is based on extensive experience of using methotrexate to treat skin and joint diseases in dermatology and rheumatology. Only one randomised controlled trial (n=114 children) comparing methotrexate and a biologic therapy provides published data on the effectiveness of methotrexate in children. In this study, a modest dose of oral methotrexate (0.1-0.4mg/kg) was given to 37 children over 16 weeks and led to a 75% improvement of the PASI score in 32% of children on methotrexate (Papp et al., 2017). There is also minimal evidence to guide how methotrexate and other conventional systemic agents should be initiated and monitored. A recent Cochrane network meta-analysis on systemic pharmacological treatment for chronic plaque psoriasis did not include children (Sbidian et al., 2017).

2.3.7.5 Biologics

The development of biologic therapies has revolutionised the care of patients with psoriasis. A network meta-analysis in adults has shown biologic therapies to be significantly more effective than conventional systemics (Sbidian et al., 2017). The first available biologic therapies for psoriasis were anti-TNF agents, however developments in understanding the immunopathogenesis of psoriasis and the development of new biologic therapies have progressed simultaneously. Newer therapies focus on the IL-17, IL-12/23 and anti-TNF pathways, but currently studies are only available for adults (Niehues and Ozgur, 2019). However, studies of older biologics provide the highest quality evidence to date in the treatment of psoriasis in children (Papp et al., 2017, Paller et al., 2008). In the UK, NICE has approved the use of etanercept, adalimumab and ustekinunab for the treatment of psoriasis in children, over the ages of 6 years, 4 years and 12 years respectively (NICE, 2017).

There is ongoing concern regarding the long-term safety of biologic therapies and therefore many countries have post licensing drug registries to monitor for trends in adverse effects. In the UK, the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) collects data on adults and children on biologic therapies for psoriasis.

The mode of action of biologic therapies is to block specific immune pathways, and therefore the main adverse effects associated with their use in both adults and children are the increased risk of infection, including activation of latent tuberculosis, and cancer (Smith et al., 2017). Due to the direct effect on the immune system, live vaccines are contraindicated in patients on biologics and certain biologics need to be avoided in patients with demyelinating disease and heart failure (Smith et al., 2017).

The most concerning adverse effect when using biological therapies is the risk of serious infection. A prospective cohort study using BADBIR data from 9038 adult patients found that the most common occurring infections affected the lower respiratory tract, skin and soft tissues and urinary tract (Yiu et al., 2018). However, that compared to non-biologic therapies, no biologic showed a statistically increased

risk of severe infection (adjusted hazards ratio (HR) 0.96 (95%CI 0.73, 1.27)) (Yiu et al., 2018). This study did not compare the risk of severe infection between patients and the general population, therefore no value is provided for the absolute increase risk from baseline for patients on biologics. To date, BADBIR data has only been used to study the risk of severe infection in adults, but now paediatric data is also being collected, therefore studies in the future can also investigate this risk in children.

A new concept in the treatment of psoriasis, applied from other immune mediated inflammatory diseases, is whether early intensive systemic treatment changes the natural course of the disease. The STEPIn study is designed to compare the remission-free period after cessation of treatment with Secukinumab and narrowband UVB in adults (Iversen et al., 2018).

2.3.7.6 Monitoring for comorbidities

Alongside treatment of skin disease, the management of psoriasis also includes monitoring for comorbidities. The most recently published German and North American guidelines recommend regular screening for obesity, hypertension, hyperlipidaemia, psychiatric disorders, in particular anxiety and depression (Eisert et al., 2019, Menter et al., 2020).

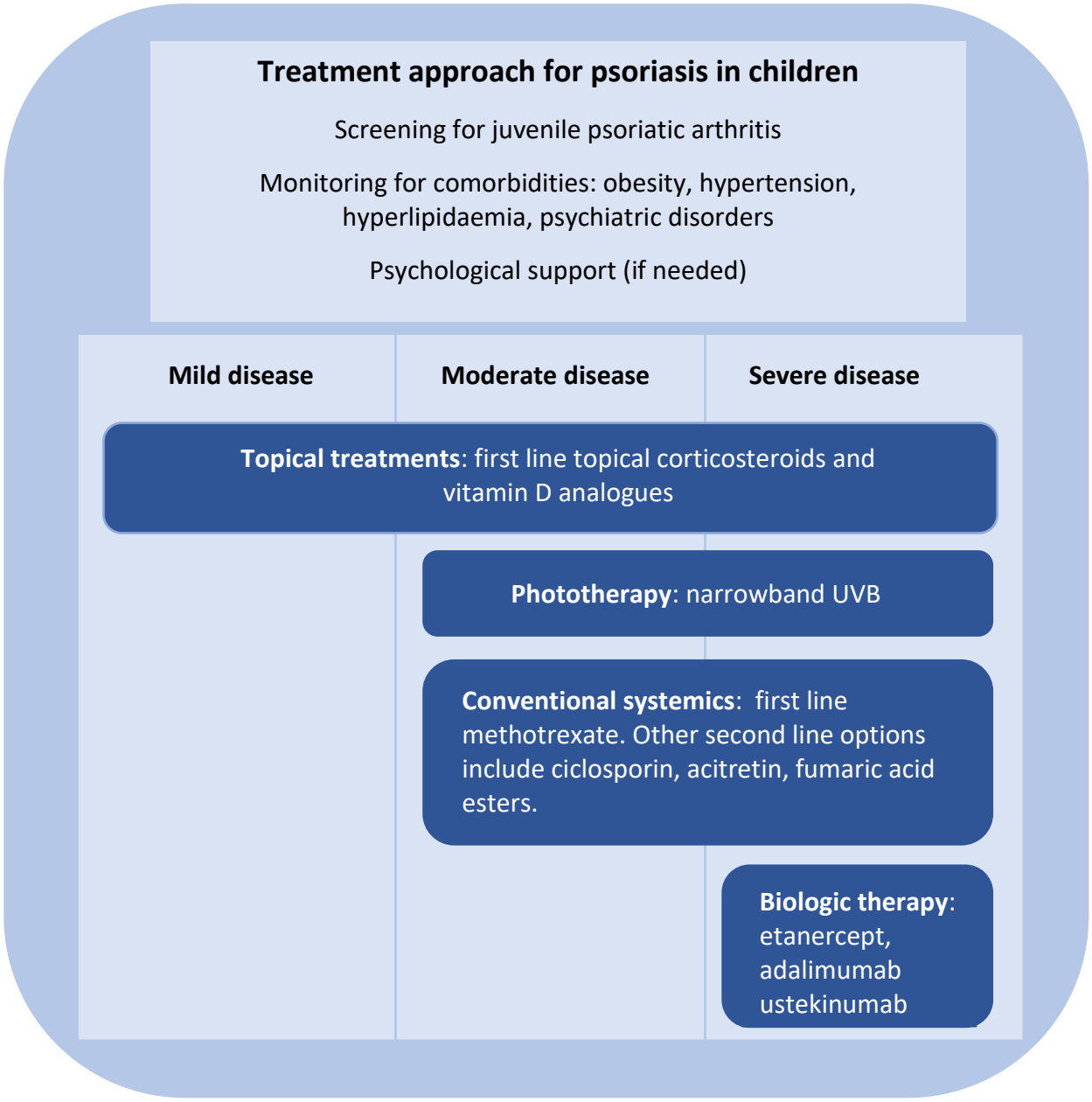


Figure 2:4 Diagram illustrating the treatment approach for psoriasis in children

2.3.8 Juvenile psoriatic arthritis

Psoriatic arthritis is an inflammatory musculoskeletal disease affecting the joints, tendon insertion points (enthesitis) or spine in adults or children (Veale and Fearon, 2018). Psoriatic arthritis is defined as juvenile psoriatic arthritis when the onset is under 16 years of age. Current disease classifications includes juvenile psoriatic arthritis as a subtype of juvenile idiopathic arthritis (JIA): an umbrella term for inflammatory arthritis in children with a spontaneous onset (Nigrovic, 2011). However previously, there has been disagreement about whether juvenile psoriatic arthritis is a separate entity from juvenile idiopathic arthritis (Stoll et al., 2011, Butbul et al., 2009). When juvenile psoriatic arthritis persists beyond 16 years, clinically it is classified as persistent juvenile psoriatic arthritis (Foster et al., 2003).

The prevalence of juvenile psoriatic arthritis is low in both children with psoriasis and children with juvenile idiopathic arthritis. A systematic review including 21 paediatric studies, mostly hospital populations, reported a pooled prevalence of 3.3% in children with psoriasis. This is similar to the prevalence calculated in a retrospective cohort study using insurance data from the United States (Brandon et al., 2018). In a UK prospective cohort study of children with juvenile idiopathic arthritis, the prevalence of juvenile psoriatic arthritis was 6% (Davies et al., 2016). There are two peaks in the age of onset of juvenile psoriatic arthritis, around 2 years of age and later childhood, and these may represent two different populations of juvenile psoriatic arthritis (Stoll et al., 2011). In the younger age group, children are more likely to be female, present with small joint disease or dactylitis and may develop polyarticular disease. Whereas older children are more like to experience enthesitis, axial disease and persist with oligoarthritis.

The International League of Associations for Rheumatology (ILAR) criteria defines juvenile psoriatic arthritis as inflammation that lasts over 6 weeks and is associated either with psoriasis or with two of the following: dactylitis (dwelling of a finger or toe), nail pitting, onycholysis or psoriasis in a first degree relative (Petty et al., 2004). Therefore, psoriasis affecting the skin and nails are critical components of the diagnosis of juvenile psoriatic arthritis. Similarly, they are also key components of the

diagnosis of psoriatic arthritis in adults (Taylor et al., 2006). However, unlike in adult disease where the chronological presentation of skin then joint diseases is widely accepted, the order of presentation is not established in children (Nigrovic, 2011).

Guidelines recommend assessment for psoriatic arthritis in both adults and children with psoriasis (NICE, 2012). The onset of psoriasis before psoriatic arthritis in up to 90% of adults has provided the opportunity for screening individuals with psoriasis for arthritis (Gelfand et al., 2005a). Consequently, screening tools have been developed for use in primary care and dermatology clinics, such as the Psoriasis Epidemiology Screening Tool (PEST) (Coates et al., 2014). Currently, no screening tools have been developed for juvenile psoriatic arthritis.

Early referral to specialist services and diagnosis is important in all types of juvenile idiopathic arthritis. Prompt review provides the opportunity to modify the natural course of the disease using drug treatments and to monitor for uveitis (Foster et al., 2007). There is no cure for juvenile psoriatic arthritis, but the aim is clinical remission (no inflammation) and no actively affected joints (Prince et al., 2010). Left untreated the inflammation can lead to joint destruction, disability and pain. It has been shown that early aggressive treatment can improve long-term outcomes, and therefore the approach is to treat all active inflammation (Foster et al., 2003). A combination of corticosteroid joint injections, disease modifying conventional systemics and disease modifying biologic therapies may be used (Prince et al., 2010). There is therapeutic cross-over with drugs used for psoriasis in children including the use of methotrexate, etanercept, adalimumab and ustekinumab.

In the UK, paediatric rheumatology services are centralised in a ‘hub and spoke’ set-up. Paediatric and adolescent rheumatologists are trained paediatricians who have undergone sub-specialty training in rheumatology. There are 12 regional paediatric rheumatology centres who coordinate new referrals and care of existing patients within their area. The British Society of Paediatric and Adolescent Rheumatology (BSPAR) recommends that all children suspected with juvenile idiopathic arthritis are referred within 6 weeks of onset and reviewed within 4 weeks (Davies et al., 2010).

2.4 Part 3: The wider psoriasis landscape

Part 3 introduces important international or national projects to improve the healthcare and research environment for psoriasis. How these projects relate to the aim of this PhD are highlighted in each section.

2.4.1 The World Health Organisation and psoriasis

In May 2014 the WHO passed a resolution recognising the large global burden of psoriasis and that many people suffer needlessly due to incorrect or delayed diagnosis, inadequate treatment options, insufficient access to care and because of social stigmatization (WHO, 2014). Responding to the resolution, in 2016 the WHO provided a detailed report on psoriasis to increase awareness and encourage policy makers to initiate practical solutions to improve the lives of people with psoriasis (WHO, 2016). Identifying psoriasis as a serious non-communicable disease helps to ensure psoriasis is not trivialised and creates a receptive environment for psoriasis research. In the recommendations for action the following points are connected with the aim of this PhD:

1. Early diagnosis and appropriate therapy gives the best chance for minimising suffering, controlling disease, and avoiding irreversible deformity and disability.
2. All health professions, especially those in primary care, should be aware of psoriasis, its management and comorbidities.
3. Consensus is needed on the classification of psoriasis and standardisation of the collection of epidemiological data.
4. There is a need for guidelines on the diagnosis of psoriasis and its treatment.

2.4.2 Priority Setting Partnership in psoriasis

The Psoriasis Association, in collaboration with the James Lind Alliance, completed a Priority Setting Partnership (PSP) in 2018. This project aimed to identify the top ten research uncertainties, written as questions, from people with psoriasis, their family and friends and healthcare professionals (Majeed-Ariss et al., 2018). The PSP covered both adults and children with psoriasis. The aim of conducting a PSP is to ensure that

future research is focused on uncertainties that are important to the stakeholders directly affected by the research findings (Chalmers et al., 2014). The psoriasis top ten research uncertainties are listed below.

1. Do lifestyle factors such as diet, dietary supplements, alcohol, smoking, weight loss and exercise play a part in treating psoriasis?
2. **Does treating psoriasis early (or proactively) reduce the severity of the disease, make it more likely to go into remission, or stop other health conditions developing?**
3. What factors predict how well psoriasis will respond to a treatment?
4. What is the best way to treat the symptoms of psoriasis: itching, burning, redness, scaling and flaking?
5. How well do psychological and educational interventions work for adults and children with psoriasis?
6. **Does treating psoriasis help improve other health conditions, such as psoriatic arthritis, cardiovascular disease, metabolic syndrome and stress?**
7. Why do psoriasis treatments stop working well against psoriasis and when they stop working well, what's the best way to regain control of the disease?
8. To what extent is psoriasis caused by a person's genes or other factors, such as stress, gut health, water quality, or change in the weather / temperature?
9. Is a person with psoriasis more likely to develop other health conditions (either as a consequence of psoriasis or due to the effect of treatments for psoriasis)? If so, which ones?
10. What's the best way to treat sudden flare ups of psoriasis?

Question 2 and 6 (highlighted in bold) relate to aims of this PhD. Both questions ask whether there is an opportunity to intervene early in psoriasis and juvenile psoriatic arthritis in order to prevent long-term harm. Thereby, providing contemporary support for this body of work.

2.4.3 Global Psoriasis Atlas

The Global Psoriasis Atlas (GPA) aims to be the leading resource on psoriasis epidemiology. It is a web-based platform (https://globalpsoriasisatlas.org/about) launched in 2019 as a collaborative venture between the IPC, International League of

Dermatological Societies (ILDS) and the International Federation of Psoriasis Associations (IFPA). The GPA has two streams of work (Griffiths et al., 2017). The first stream started in 2017 and is a series of extensive systematic reviews on psoriasis epidemiology. The second stream aims to provide a core set of methods for conducting new epidemiological studies.

The reasoning behind creating the GPA is a recognition of the significant global health challenge psoriasis poses against the background of patchy epidemiological data from different geographical regions. Although the starting point for this thesis was a clinical problem, the research in this PhD will contribute to mapping the epidemiological data for psoriasis in children and providing a standardised definition of psoriasis for new studies.

Chapter 3 Determining current clinical practice in the assessment and management of childhood psoriasis

3.1 Introduction

The first two chapters have provided the rationale for the thesis and summarised key topics about psoriasis, psoriasis in children and the wider psoriasis landscape. Within Chapter 2 are described some of the important clinical, pathological and management differences between psoriasis in children and adults. Childhood presents a unique opportunity for early intervention to prevent long-term harm from psoriasis and juvenile psoriatic arthritis. Optimising management early in the disease pathway is one strategy for early intervention. Although specific guidance for psoriasis in children is limited by the deficiency of evidence, disease management can potentially be improved by following the best available recommendations.

In 2007, the British Association of Dermatologists (BAD) in conjunction with the clinical standards unit at the Royal College of Physicians London, commissioned and conducted a national psoriasis audit. This work demonstrated variation in the resources and services available for psoriasis in adults against BAD guideline and standards. In particular, variation was recorded in access to specialist treatments (including biologics), appropriate drug monitoring, specialist nurse support and psychological services. In 2012, NICE published guidance for the assessment and management of psoriasis in people of all ages. A summary of the guidelines relating

to children is provided in Chapter 2 (2.3.7.1 National guidelines). The NICE guideline highlighted that a comparable audit for children was needed. In response, this Chapter presents an audit and case-note review of current clinical practice in the assessment and management of psoriasis in children against the 2012 NICE guidance. The 2007 audit of adult services concentrated on the structure of care, whereas this audit has focused on the provision of care.

An audit and case-note review provides an objective assessment of current practice, through which strengths and deficiencies can be identified. Appraising current practice is therefore a logical and necessary first step in a programme of research to improve the care of children with psoriasis. The conclusions from this Chapter are the starting point for subsequent studies in this thesis.

The work presented in Chapter 3 has been published in the British Journal of Dermatology (Lam et al., 2015, Burden-Teh et al., 2015).

Lam ML, Burden-Teh E, Taibjee SM *et al*. A U.K. multicentre audit of the assessment and management of psoriasis in children. Br J Dermatol. 2015 Mar;172(3):789-92.

Burden-The E, Lam ML, Taibjee SM *et al*. How are we using systemic drugs to treat psoriasis in children? An insight into current clinical U.K. practice. Br J Dermatol. 2015 Aug;173(2):614-8.

3.2 Objectives

1. To compare current clinical practice in the assessment and management of psoriasis in children against the NICE CG153 2012 guideline and the BAD 2009 guideline on biologic therapy.

2. To identify key areas for improvement in the provision of care for children with psoriasis.

3. To identify knowledge gaps between current practice and the available guidance in the assessment and management of psoriasis in children.

3.3 Methods

3.3.1 Study design

Multi-centre audit and consecutive patient case-note review. The audit was registered at Nottingham University Hospitals NHS Trust (project number 15-559c). No ethical approval was required for this audit and service evaluation project.

Audit is an essential part of clinical governance. According to the Health Regulatory Authority (HRA), the purpose of audit is to measure performance against a defined standard and produce data to inform the delivery of best care (HRA, 2013). At the time of the audit, the intervention is already in use, and the decision about choice of treatment is made by the clinician and patient (HRA, 2013).

Figure 3:1 depicts the five stages of clinical audit (Benjamin, 2008).

- Stage 1 is preparing for the audit: identifying the problem and local resources available
- Stage 2 is selecting the criteria: defining the outcome to be measured and the standard.

- Stage 3 is measuring performance: deciding and implementing the data collection method and comparing performance with Stage 2.
- Stage 4 is making improvements: making an action plan for recommendations.
- Stage 5 is sustaining improvements: repeating the audit.

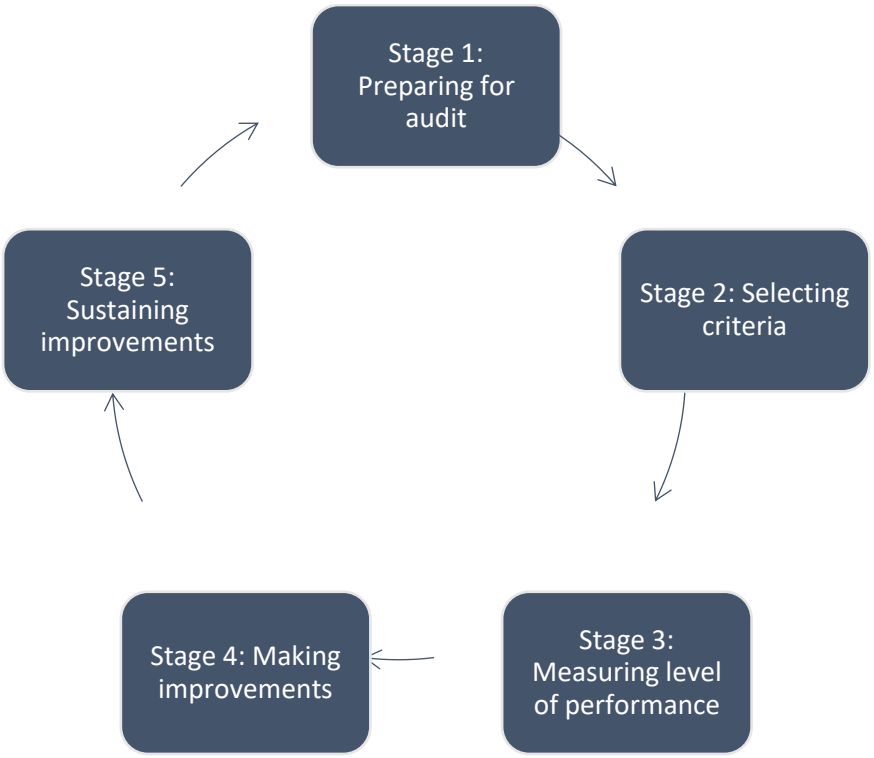


Figure 3:1 The audit cycle (Benjamin, 2008)

3.3.2 Stage 1: Preparing for the Audit

3.3.2.1 Management of the audit and case-note review

The audit and case-note review was coordinated from Nottingham University Hospitals NHS Trust. No administrative assistance was received from the hospital. Communication with sites used hospital email and proformas were sent by post. Sites which returned five or more proformas were offered authorship on any resulting publications if they contributed to the final manuscript. Sites were also offered £10 for each proforma returned and a certificate of participation. The Nottingham University Hospitals Dermatology Research Fund provided financial support of the audit and case-note review.

3.3.2.2 Site selection

Consultant members of the British Society of Paediatric Dermatology (BSPD) were emailed requesting a consultant from each paediatric dermatology department to coordinate participation in a paediatric psoriasis audit. In 2014 there were 215 consultant members in the BSPD. Due to the non-centralised set-up of paediatric dermatology in the UK, the number of paediatric dermatology departments is unknown. In total 31 dermatology consultants representing 31 paediatric dermatology departments responded. Sites self-defined the consultation setting and type.

3.3.2.3 Case-note selection

All new and follow-up patients attending outpatients aged 18 years or younger with a dermatologist's confirmed diagnosis of psoriasis were included. Data were collected over 12 consecutive weeks. At the audit site each patient was assigned an individual identity number to maintain anonymity, avoid duplication and facilitate retrieval of missing data. The inclusion of all consecutive patients over a 12 week period aimed to minimise selection bias.

3.3.3 Stage 2: Selecting criteria

Audit standards were derived from the NICE guideline CG153 (2012) key priorities for implementation and the BAD 2009 recommendations for baseline investigations and monitoring of biologic therapy (Smith, Anstey et al. 2009, NICE 2012). The agreed audit standard was 100%. The derived criteria are detailed in Figure 3:2 and covered the three domains of disease assessment, screening for comorbidities and treatment.

In specific regard to comorbidities, the guidelines for adults focus on cardiovascular risk assessment, assessment for risk factors for cardiovascular comorbidities and depression. There are no specific recommendations for children, therefore expert opinion guided the selection of known metabolic and inflammatory diseases (diabetes, inflammatory bowel disease and uveitis) and depression or psychological conditions.

3.3.4 Stage 3: Measuring level of performance

A proforma was used to standardise audit data extraction from the medical records (Appendix 1). Data extracted in addition to the audit standards included: i) demographics; ii) age at psoriasis onset; iii) family history of psoriasis and psoriatic arthritis; iv) clinical presentation of psoriasis; v) initial skin diagnosis; vi) current psoriasis control; vii) adverse effects of treatment. A draft of the proforma was circulated to all interested audit sites and minor amendments incorporated. Using a piloted standardised proforma in the audit aimed to minimise information bias.

Proformas were returned by post to Nottingham University Hospitals NHS Trust. Data were entered into a Microsoft Excel spreadsheet for analysis. Categorical responses were presented as percentages for each category. Quantitative responses were presented as a mean and range or median and inter-quartile range, depending on the distribution of the data. The level of performance was measured as the percentage of proformas which met the specified criteria. Missing data was categorised as not reported.

3.3.5 Stage 4: Making improvements and implementing change

The results of the audit and case-note review have been presented locally, at a national dermatology meeting and published in a clinically focused academic journal.

Audit domain	Audit criteria
Disease Assessment	Assessment of disease severity at diagnosis and when response to treatment is assessed. Assessment of the impact of the disease on physical, psychological and social wellbeing at diagnosis and when response to treatment is assessed.
Assessment for comorbidities	Annual assessment for psoriatic arthritis. Assessment for metabolic diseases such as diabetes and inflammatory disorders such as uveitis and inflammatory bowels disease. Assessment for depression or psychological complications.
Treatment	Topical treatment should be prescribed as per licensed indications. Topical treatment should be appropriate for site, frequency and duration. Phototherapy should be initiated if there is a clear indication. Systemic and biological treatments should be initiated if there is a clear indication, with appropriate pre-treatment investigations and ongoing monitoring.

Figure 3:2 Audit criteria for the assessment and management of psoriasis in children

3.4 Results

A total of 285 proformas were returned from the 31 departments (

Figure 3:3). Sites were asked to audit all consecutive psoriasis patients. It was not possible to calculate the proportion of audited patients. Sites returned between 2 to 37 proformas, reflecting differences in the size of departments. Twenty sites returned fewer than 10 proformas, seven sites returned 10-20 and four sites returned more than 20 proformas, (Newcastle, Liverpool, Nottingham and Glasgow).

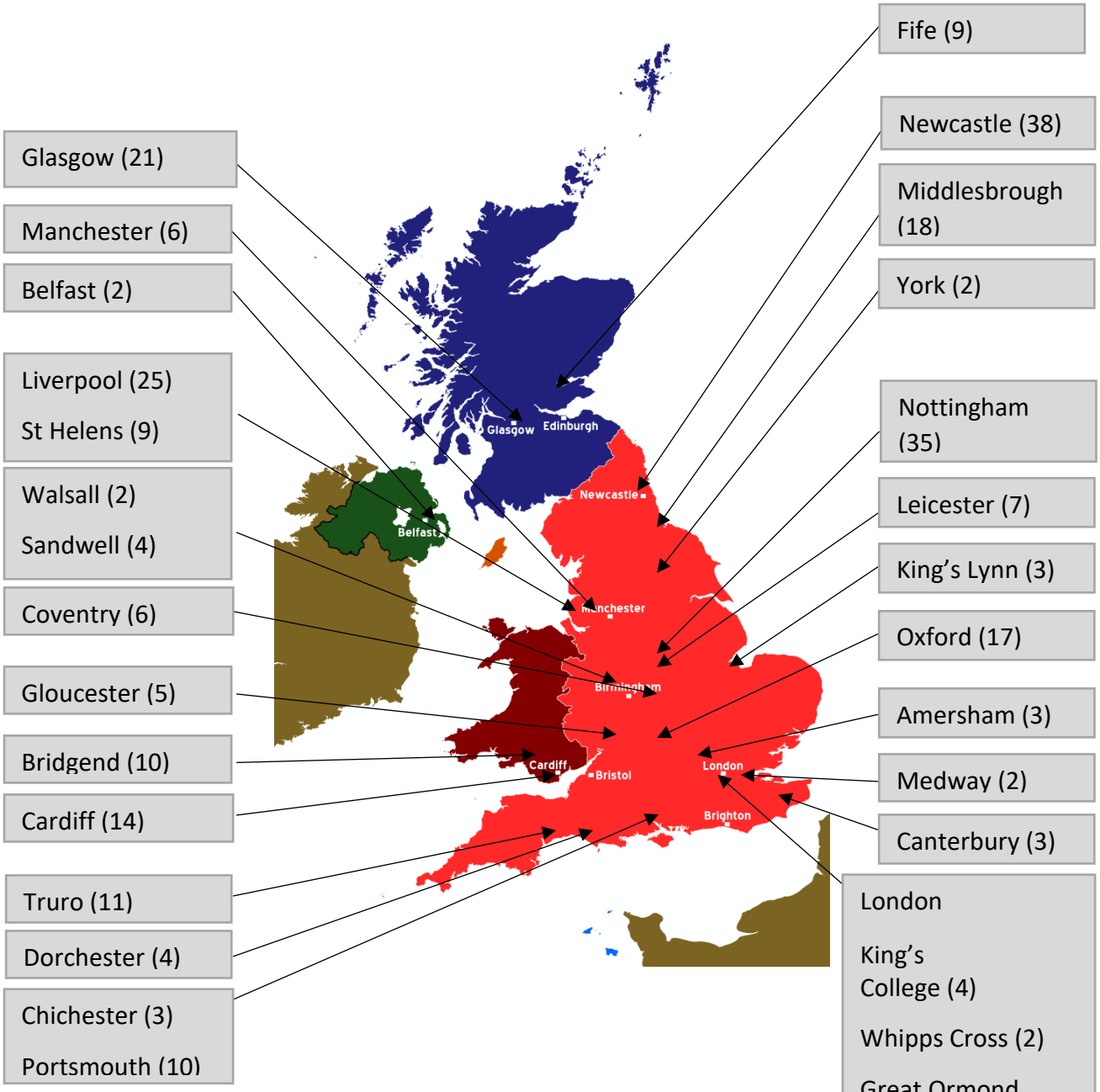


Figure 3:3 Geographical location of audit centres
The number of proformas returned from each site is provided in brackets.

3.4.1 Characteristics of the setting and consultation

Table 3:1 presents data on the setting and consultation type of patients included in the multi-centre audit and case-note review. Most consultations were secondary care referrals (89%, 255/285) and the majority of children were seen in a dedicated paediatric clinic (89%, 253/285). Three children (1%) were seen in a combined clinic with a rheumatologist, but none were seen in a combined clinic with a paediatrician. One third (33%, 93/185) of consultations were for new patients and the remaining two thirds of consultations were follow-up patients (67%, 190/285).

3.4.2 Characteristics of the audit population

Table 3:1 presents data on the characteristics of patients included in the multi-centre audit and case-note review. In the audit population there was a female predominance (61%, 174/285), the mean age of the patients at the time of data extraction was 11 years and 4 months (standard deviation 3 years and 9 months) and the majority of children were White/Caucasian (82%, 236/285).

Age of psoriasis onset ranged from the neonatal period to 16 years and 7 months. The mean age of psoriasis onset was pre-pubertal, 7 years and 6 months (standard deviation 4 years and 0 months). In nearly a quarter of patients (24%, 63/285) the age of onset was documented as under the age of 5 years. A family history of psoriasis was recorded in 57% of children (163/285), occurring in a first degree relative in 22% (62/285) and a second degree relative in 13% (37/285).

The majority of children were diagnosed with plaque psoriasis at presentation (75%, 213/285). The next most common types of psoriasis were guttate (60/285, 21%) and flexural (23/285, 8%). Seventeen children presented with nail psoriasis. Two children presented with psoriatic arthritis and in one case the arthritis preceded the skin disease. The most common sites of initial presentation were the scalp (65%, 184/285), trunk (58%, 164/285) and limbs (arms 54%, 154/285 and legs 51%, 144/285). The face was an initial site of presentation in over a third of children (35%, 99/285). Involvement of sites normally covered by clothing or hidden was also

frequently recorded. For example, behind the ears (15%, 43/285), genital/natal cleft (11%, 32/285) and flexures (axilla/inguinal 7%, 21/285).

In total 100 children (35%) were diagnosed with another skin condition before being diagnosed with psoriasis. In 22% (63/285) of children an initial diagnosis of eczema preceded the psoriasis diagnosis. In three-quarters of these children the initial diagnosis of eczema was made in primary care (76%, 48/63). Other common diagnoses were tinea infection (6%, 17/285) and seborrheic dermatitis (1.4% 4/285).

Characteristics of the consultation and audit population		Number of children n=285 (%)
Referral type	Secondary care	255 (89%)
	Tertiary care	25 (9%)
	Not recorded	5 (2%)
Clinic type	Paediatric dermatology	253 (89%)
	Adult dermatology	25 (9%)
	Combined with paediatric rheumatology	3 (1%)
	Combined with general paediatrics	0 (0%)
	Not recorded	4 (1%)
Consultation type	New patient	93 (33%)
	Follow-up	190 (67%)
	Not recorded	2 (1%)
Gender	Female	174 (61%)
	Male	105 (37%)
	Not recorded	6 (2%)
Age	Mean age at the time of data extraction (standard deviation)	11 years and 4 months (3 years and 9 months)
	Mean age of psoriasis onset (standard deviation)	7 years and 6 months (4 years and 0 months)
Ethnicity	White	236 (82%)
	Asian/Asian British	20 (7%)
	White/Asian	11 (4%)
	Black or White/Black	9 (3%)
	Other	3 (1%)
	Not recorded	6 (2%)
Family history of psoriasis	First or secondary degree relative First degree relative Second degree relative Relative not specified	163 (57%) 62 (22%) 37 (13%) 64 (22%)
	No family history psoriasis	97 (34%)
	Not recorded	25 (9%)

Family history psoriatic arthritis	Family history of psoriatic arthritis	11 (4%)
	No family history of psoriatic arthritis	151 (53%)
	Not recorded	123 (43%)
Subtype at presentation*	Plaque (small or large)	213 (75%)
	Guttate	60 (21%)
	Flexural	23 (8%)
	Nail	17 (6%)
	Palmar plantar	4 (1%)
	Psoriatic arthritis	2 (1%)
	Pustular	1 (<1%)
	Not recorded	16 (6%)
Initial site of involvement*	Scalp	184 (65%)
	Trunk	164 (58%)
	Upper limbs	154 (54%)
	Lower limbs	144 (51%)
	Face	99 (35%)
	Behind the ears	43 (15%)
	Genital/Natal cleft	32 (11%)
	Flexures (axilla/inguinal)	21 (7%)
	Nails	15 (5%)
	Joints	1 (<1%)
	Not recorded	6 (2%)
Initial diagnosis of eczema	Yes	63 (22%)
	No	220 (77%)
	Not recorded	2 (1%)
Initial diagnosis of another skin disease (excluding eczema)	Yes	37 (13%)
	No	244 (86%)
	Not recorded	4 (1%)

Table 3:1 Characteristics of the dermatology consultation and the audit population
**More than one category could be indicated.*

3.4.3 Assessment of disease severity and disease impact

The NICE guideline recommends that for all people with any type of psoriasis an assessment of disease severity and disease impact is made at diagnosis, at each referral point and when response to treatment is assessed (NICE, 2012). The assessment of disease impact should record the impact of psoriasis on physical, psychological and social wellbeing.

In the specialist setting NICE recommends the use of an objective tool for the assessment of both severity and impact, such the PASI score and CDLQI (Fredriksson and Pettersson, 1978, Lewis-Jones and Finlay, 1995). Chapter 2 (2.3.6 Assessment of disease severity and impact) provides a summary about PASI and CDLQI including strengths and limitations of their use.

New patient consultations were defined as 'at diagnosis' in the patient journey. Table 3:2 presents the number of new and follow-up consultations. In the audit and case-note review there were 93 new consultations and an objective assessment of disease severity was documented in 35% (33/93) and disease impact in 34% (32/93). Table 3:2 also presents the frequency different assessment tools were used. PASI and the CDLQI/DLQI were the preferred tools (76%, 25/33 and 91%, 29/32 respectively). At diagnosis, just over half of children only had a description of disease severity (61%, 57/93) and nearly half of children had no assessment of disease impact (46%, 43/93).

Evaluating response to prescribed treatments is part of a follow-up consultation. In the audit and case-note review there were 190 follow-up consultations and an objective assessment of disease severity was documented in 38% (72/190) and disease impact in 29% (53/190). Similar to new consultations, PASI and CDLQI/DLQI were the preferred assessment tools (24%, 46/190 and 27%, 51/190 respectively) used during follow-up consultations. Another similarity with new consultations was that over half of children at follow-up had disease severity recorded as a description only (57%, 108/190) and no assessment of disease impact (58% (101/190)).

3.4.4 Assessment for comorbidities

3.4.4.1 Assessment for juvenile psoriatic arthritis

The NICE guideline recommends that annual assessment for psoriatic arthritis should be offered to all people with any type of psoriasis (NICE, 2012). The guideline recommends that a validated tool is used in both the specialist and primary care setting, such as the PEST screening tool (Coates et al., 2013). An introduction to juvenile psoriatic arthritis is provided in Chapter 2 (2.3.8 Juvenile psoriatic arthritis). Unlike in adults, no assessment tools for juvenile psoriatic arthritis have been developed or validated for use in children (NICE, 2012).

Table 3:2 shows that almost half of children (45%, 128/285) were assessed annually for psoriatic arthritis, the majority (83%, 107/128) of these were assessed by a dermatologist asking questions. An assessment tool was used in eight out of 128 children (6%). The PEST tool was used in 2% (2/128). Other documented tools were the 'Fife Rheumatology Disease Unit Screening Questionnaire' (2/128), and 'Paediatric Rheumatology Assessment Core Set Outcomes' (1/128).

3.4.4.2 Assessment for metabolic, inflammatory and psychological diseases

The NICE guideline recommends assessment for the presence of comorbidities (NICE, 2012). Table 3:2 shows that assessment for comorbidities was recorded in less than a quarter of children for the following diseases: depression 23% (65/285); inflammatory bowel disease 15% (44/285); uveitis 15% (43/285) and diabetes 14% (39/285). However, the background prevalence of these diseases was low: depression 2% (7/285); inflammatory bowel disease <1% (1/285), uveitis 1% (2/285) and diabetes 1% (2/285).

Assessment of disease severity, disease impact and comorbidities		
New Patients		n=93 (%)
Severity Assessment	PASI	22 (24%)
	PGA	8 (9%)
	Both PASI and PGA	3 (3%)
	Description only	57 (61%)
	Not recorded	3 (3%)
Impact Assessment	DLQI/CDLQI	29 (31%)
	HAQ	3 (3%)
	Description only	18 (19%)
	Not recorded	43 (46%)
Follow up Patients		n=190 (%)
Severity Assessment	PASI	40 (21%)
	PGA	26 (14%)
	Both PASI and PGA	6 (3%)
	Description only	108 (57%)
	Not recorded	10 (5%)
Impact Assessment	DLQI/CDLQI	51 (27%)
	HAQ	5 (3%)
	Description only	24 (13%)
	Not recorded	110 (58%)
All patients		n = 285 (%)
Annual screening for juvenile psoriatic arthritis	Yes	128 (45%)
		8/128 (6%) used a formal assessment tool
	No	78 (27%)
	Unclear/Not documented	79 (28%)
Comorbidity screening documented	Depression	65 (23%)
	Inflammatory bowel disease	44 (15%)
	Uveitis	43 (15%)
	Diabetes	39 (14%)

Table 3:2 Assessment of disease severity, disease impact and comorbidities
PASI – Psoriasis Area Severity Index, PGA – Physician Global Assessment, DLQI – Dermatology Life Quality Index, CDLQI – Children's Life Quality Index, HAQ - Health Assessment Questionnaire

3.4.5 Treatment of psoriasis

3.4.5.1 Topical treatment

Topical treatments were prescribed in nearly all children, either alone (56%, 161/285) or in combination with phototherapy or systemic treatments (93%, 264/285). Table 3:3 presents the frequency that different types of topical treatments were used to treat psoriasis of the scalp, face, flexures, genitals and trunk and limbs. Overall, application frequency and treatment duration of topical therapies were poorly documented (40% and 29% respectively). The choice of topical treatments used varied between dermatology departments, for example some audit sites had a preference to use calcineurin inhibitors, combination treatments or tar products.

3.4.5.2 Scalp treatment

The NICE guideline recommends the use of a potent topical steroid in most children with scalp psoriasis. The addition of other agents, such as salicyclic acid or coal tar, can be added as required. In milder disease a vitamin D analogue or coal tar shampoo can be considered (NICE, 2012).

Scalp psoriasis was treated with topical treatments in 51% (145/285) of children. Of these, 39% (56/145) complied with the recommendation of using a potent topical steroid, often as a combination preparation such as Diprosalic™ (10/145) or Dovobet™ (18/145).

Although only recommended for adults with psoriasis, a super potent topical steroid was used in six children. In 9% (13/145), a tar shampoo alone was used; in half of these children the psoriasis was documented as well controlled (7/13).

3.4.5.3 Face, flexures and genital treatment

The NICE guideline recommends the use of a mild or moderate potency steroid once or twice daily for up to 2 weeks at sensitive sites (NICE, 2012). Sensitive sites include the face, flexures and genital skin, which are at higher risk of steroid atrophy.

Facial psoriasis was treated with topical treatments in 38% (107/285) of children. Nearly two thirds of these children (63%, 67/107) complied with guidance regarding choice of agent; for 20 children this was prescribed as a combination preparation with an antifungal component. Pimecrolimus (Elidel™) or tacrolimus (Protopic™) were prescribed in 34% of children (37/107), nearly always as a solitary topical agent (29%, 31/107). Both of these drugs are unlicensed for the treatment of psoriasis in children and adults. Nearly half of those treated (41% (15/37)) with calcineurin inhibitors were between 3 and 12 years, but no children younger than 2 years were treated with these therapies. Contrary to recommendations, 5% (5/107) of children were prescribed a potent topical steroid for the face.

Flexural psoriasis and genital psoriasis were treated with topical treatments in 10% (28/285) of children. The majority of children complied with the guidance for treating flexural (96%, 27/28) and genital (89%, 25/28) psoriasis. In three children, one child with flexural disease, one child with genital psoriasis and one child with both, pimecrolimus (Elidel™) or tacrolimus (Protopic™) were used alone or with a topical steroid. Only one patient was prescribed a potent steroid (once daily for a week) for genital disease and none for flexural psoriasis.

3.4.5.4 Trunk and limb treatment

The NICE guideline recommends for children with trunk and limbs psoriasis the use of either calcipotriol or a potent topical steroid applied once daily (NICE, 2012). In adults this is recommended to be applied for up to four weeks, in children topical treatments are advised to be reviewed after two weeks.

Seventy-one percent (202/285) of children were treated with a topical agent for limb and/or trunk psoriasis. In 61% (124/202) of these, a vitamin D analogue, potent topical steroid or combination of both was used. Dovobet™ was the most commonly prescribed topical agent for the trunk and limbs (38%, 76/202). However, Dovobet™ was prescribed to 32 children under the age of 12 years, outside its licenced indication. In 3% (7/202) a vitamin D analogue was used alone. A vitamin D analogue

was only prescribed to one child under the age of 6 years, outside its licenced indication.

Body site treated with topical agent n= 285 (%)	Topical steroid preparation characterized according to potency, n (%) *a = topical steroid of specified potency in combination with an antifungal/antibacterial agent, eg Daktacort™, Trimovate™* *b = potent topical steroid combined with salicylic acid, eg Diprosalic™*				**Topical vitamin D analogue given as a single or combination therapy, n (%)**		**Topical calcineurin inhibitors subdivided according to type and potency, n (%)**				**Topical tar preparations subtyped according to preparation, n (%)**				**Short contact dithranol/ Dithro-cream™ n (%)**	**Topical salicylic acid in varying percentages n (%)**
	Mild	Moderate	Potent	Very potent	Alone eg Dovonex™ Silkis™	With a potent topical steroid eg Dovobet™	Pimecrolimus (Elidel™)	Tacrolimus (Protopic™) 0.03%	Tacrolimus (Protopic™) 0.1%	Tacrolimus (Protopic™) potency not specified	Sebco™/ cocois™/ capasal™	Tar shampoo only	Weak tar preparation e.g. Exorex™	Strong tar preparation e.g. tar pomade		
Scalp (n=145, 51%)	1(<1%) a =1 (<1%)	2 (1%) a=0	28 (19%) b=10 (7%)	6 (4%)	6 (4%)	18 (12%)	0	0	0	0	77 (53%)	13 (9%)	1 (<1%)	9 (6%)	2 (1%)	10 (7%)
Face (n=107, 38%)	6 (6%) a=18 (17%)	43 (40%) a=2 (2%)	5 (5%) b=1 (<1%)	0	3 (3%)	0	3 (3%)	15 (14%)	10 (9%)	9 (8%)	0	0	2 (2%)	0	0	0
Flexures (n = 28, 10%)	0 a=3 (10%)	13 (46%) a=11 (39%)	0 b=0	0	1 (3%)	0	1 (3%)	0	2 (7%)	0	0	0	0	0	0	0
Genitals (n = 28, 10%)	0 a=7 (25%)	13 (46%) a=6 (21%)	1 (3%) b=0	0	4 (14%)	0	0	0	1 (3%)	2 (7%)	0	0	1 (3%)	0	0	0
Limb & Trunk (n = 202, 71%)	4 (2%) a=1 (<1%)	47 (23%) a=1 (<1%)	29 (14%) b=6 (3%)	1 (<1%)	29 (14%)	76 (38%)	0	1 (<1%)	0	1 (<1%)	3 (1%)	0	61 (30%)	15 (7%)	9 (4%)	3 (1%)

Table 3:3 Topical treatments used to treat psoriasis in children according to body site

*more than one topical agent may have been used per site

3.4.5.5 Phototherapy

The NICE guideline recommends offering narrowband UVB phototherapy to patients with psoriasis that cannot be controlled with topical treatment alone (NICE, 2012).

Nearly one third of children, 29% (83/285) had planned, ongoing or recently completed phototherapy. Of these, 39% (32/83) of children had guttate psoriasis. As shown in Table 3:4, the majority (86%, 71/83) of children were assigned to narrowband UVB. In 95% (79/83) of children there was a clear treatment indication, the most frequent indication given was extensive disease (71%, 59/83). No children had been prescribed oral PUVA, but three children (4%, 3/83) all over the age of 12 years were prescribed bath or hand and foot PUVA phototherapy. NICE guidance advises caution and to consider other treatment options over PUVA in young people with psoriasis.

3.4.5.6 Conventional systemic therapies

The NICE guideline recommends offering systemic non-biological therapy to patients with any type of psoriasis if the skin disease cannot be controlled with topical treatment alone and it has a significant impact on physical, psychological and social well-being (NICE, 2012).

Additionally, the psoriasis is required to be extensive or localised with significant functional impairment and phototherapy has been ineffective/ contraindicated According to the guidelines methotrexate is the first choice systemic agent for patients that fulfil the above criteria. The guidance recommends that patients using systemic treatment should be monitored in accordance with national and local drug guidelines and policy.

The planned or current use of conventional systemic treatments was documented in 19% (53/285) of children, with three quarters of children (74%, 39/53) stabilised on treatment. As presented in Table 3:4 methotrexate was the most frequently prescribed systemic treatment (47%, 25/53), followed by acitretin (28%, 15/53), ciclosporin (23%,12/53) and dapsone (2%, 1/53). Of the 25 children prescribed

methotrexate, seven children were receiving a subcutaneous or intramuscular preparation, in one child this was for psoriatic arthritis. The guidelines recommend the use of acitretin in children and young people only in exceptional cases. In this audit population, acitretin was the second most frequently prescribed systemic agent. None of the children were classified as pustular psoriasis, for which acitretin may be uniquely helpful (Posso-De Los Rios et al., 2014). In 94% (50/53) of children prescribed a systemic therapy a clear treatment indication was given, the most frequent indication was failure of previous treatment (77%, 41/53).

Pre-treatment investigations, monitoring during treatment and adverse event data are presented in Table 3:5. The majority (91%, 48/53) of children had documented pre-treatment routine blood test investigations in line with the British National Formulary (BNF) recommendations for adults (BNF, 2013). In contrast to the summaries of Product Characteristics recommendation for methotrexate in adults, most children did not have a baseline chest X-ray (84%, 21/25). However, all children on ciclosporin had at least one documented blood pressure reading prior to commencing treatment. All children on systemic drugs had routine blood test monitoring once stable on therapy, the frequency of which varied according to agent. An adverse effect was recorded in the notes for 24% (14/53) of patients on a systemic treatment. Nausea and abnormal liver function tests (LFTs) were the most common abnormalities reported with methotrexate treatment. In two patients on methotrexate and etanercept, methotrexate could only be prescribed at a low dose (eg 5mg weekly) due to abnormal LFTs at higher doses.

Type of treatment given	Number of children n=285 (%)	Indication for commencing treatment, n (%) (More than one indication could be specified)					MED performed if required in those who are on or recently had treatment n= 46(%)	Assessment of severity and impact either prior to treatment (P) or to evaluate response after treatment (R), n (%) (More than one method could be specified)		
		Failed previous treatment	Extensive disease	Significant impact on wellbeing	Other	No indication given		Description only	PASI, PGA	DLQI, CDLQI, HAQ
Phototherapy	83(29%)*	45 (54%)	59 (71%)	18 (22%)	2 (2%)	4 (5%)	26 (56%)	22/40 (55%) (R)	13/40 (32%) (R)	7/40 (17%) (R)
Narrowband UVB	71(25%)									
Broadband UVB	7 (2%)									
Oral PUVA	0									
Hand & foot or bath PUVA	3 (1%)									
Not specified	2 (1%)									
Systemic drug	53 (19%)*	41 (77%)	29 (55%)	22 (41%)	9 (17%)	3 (6%)	NA	12/39 (30%) (R)	19/39 (48%) (R)	9/39 (23%) (R)
Acitretin	15 (5%)									
Methotrexate **Oral** **Subcutaneous** **Intramuscular**	 18 (6%) 6 (2%) 1(<1%)									
Ciclosporin	12 (4%)									
Dapsone	1 (1%)									
Biologic drug	10 (4%)*	8 (80%)	5 (50%)	5 (50%)	3(30%)	0 (0%)	NA	0/10(0%) (P)	10/10 (100%) (P)	10/10 (100%) (P)
Etanercept	8 (3%)									
Adalimumab	1 (<1%)									
Ustekinumab	1 (<1%)									

Table 3:4 Indication and assessment of children with psoriasis prior to or during treatment with phototherapy, systemic or biologic therapies
**n = about to commence treatment, midway or stable on treatment. UVB – ultraviolet light B, PUVA – psoralen ultraviolet light A, MED – Minimal Erythema Dose, PASI – Psoriasis Area Severity Index, PGA – Physician Global Assessment, DLQI – Dermatology Life Quality Index, CDLQI – Children's Life Quality Index, HAQ – Health Assessment Questionnaire*

Systemic Treatment (n=53)	**Age range of children treated (years, months)**	**Treatment duration (months)**	**Pre-treatment screening investigations undertaken prior to commencing systemic treatment**					**Frequency of routine blood tests during systemic treatment for children stable on therapy**			**Adverse effects ****
			Routine blood tests (FBC/UE/LFT) n, %	Lipids n, %	PIIINP* n, %	CXR n, %	Other	<=monthly n, %	>monthly to <=3 monthly n, %	>3 monthly n, %	
Methotrexate n=25 **Oral n=18** **SC n = 6** **IM n=1**	6 yrs 11 mths to 17 yrs 4 mths	3 to 49 Median = 6	23/25, 92%	NA	4/25, 16%,	4/25, 16%,	VZV = 3/25 HEP= 2/25 ESR/CRP = 1/25	8/15, 53%,	7/15, 46%,	0/15, 0%	Nausea (n=4) Abnormal LFTs (n=2)
Acitretin n=15	4 yrs 1 mths to 17 yrs	5 to 49 Median = 12	14/15, 93%	4/15, 26%,	NA	NA	VZV = 2/15 HEP = 1/15 ESR/CRP = 1/15	4/12, 33%	6/12, 50%,	2/12, 16%	Xerosis/chelitis (n=1)
Ciclosporin n=12	7 yrs 4 mths to 16 yrs 9 mths	2.5 to 13 Median = 4	10/12, 83%	NA	NA	NA	BP = 12/12 Urine dip = 7/15	8/11, 72%	3/11, 27%,	0/11,0%	Gum hypertrophy (n=1) Headache (n=1) Weight gain (n=1) Hypertrichosis (n=1) Bacterial infection (n=1)
Dapsone n=1	16 yrs	10 Median = 10	1/1, 100%	NA	NA	NA	None	0/1, 0%,	1/1, 100%,	0/1, 0%	

Table 3:5 Pre-treatment investigations, monitoring and adverse effects for children prescribed conventional systemic therapies
SC - subcutaneous injection, IM - intramuscular injection, FBC – full blood count, UE – urea and electrolytes, LFT – liver function tests, VZV - varicella zoster virus serology, CXR – chest X-ray, HEP - hepatitis B & C serology, ESR/CRP - erythrocyte sedimentation rate / C-reactive protein Pro-collagen 3 N-terminal propeptide (PIIINP) is recommended for the monitoring of adult patients with psoriasis on methotrexate but this is not recommended in children. **One patient had a documented side effect of nausea, but had been on both methotrexate and ciclosporin, therefore it was not possible to determine which agent was responsible.*

3.4.5.7 Biologic systemic therapy

The NICE guideline follow the recommendations from each of the Health Technology Appraisals for etanercept, adalimumab ustekinumab and infliximab (NICE, 2012). At the time of the guideline development only etanercept was licenced for the treatment of psoriasis in young people aged 12 years and older. The recommendations for baseline investigations and monitoring were derived from the BAD guideline for biologic interventions for psoriasis 2009 (Smith et al., 2009).

Three children were about to commence, and seven children were already established on, biologic therapy (4%, 10/285). As presented in Table 3:4, etanercept was the most frequently prescribed biologic therapy (80%, 8/10). Adalimumab and ustekinumab were only prescribed to one child each, both children had previously failed treatment on etanercept. An indication for biologic treatment was given in 100% (10/10) of children. In three children the documented indication for use of etanercept was arthritis. Six children had received at least two previous systemic agents and four had also been treated with phototherapy.

Table 3:6 presents the pre-treatment investigations, monitoring and adverse effect data for biologic therapies. None of the 10 children on the biologic therapies had a complete set of the recommended baseline investigations. Of the seven children stable on a biologic therapy, five were undergoing regular blood monitoring, but none had skin checks or lymph node examinations for skin cancer.

Biologic treatment	Age range of children treated (years, months)	Pre-treatment screening investigations undertaken prior to commencing systemic treatment n, %							Frequency of routine blood tests during systemic treatment for patient stable on therapy			Lymph node check during the last 12 months	Skin cancer check during the last 12 months	Adverse effects n, %
		Routine blood tests (FBC/UE/LFT)	ANA	HEP	VZV	IGRA	HIV	CXR	<=monthly n, %	>monthly to <=3 monthly n, %	>3 monthly n, %	n, %	n, %	
All biologics (n=10, 7 stable on treatment)		7/10, 70%	6/10, 60%	7/10, 70%	6/10, 60%	2/10, 20%	2/10, 20%	7/10, 70%	1/7	3/7, 43%	1/7, 14%	0/7, 0%	0/7, 0%	None
Etanercept, (n=8, 5 children stable on treatment)	12 years 10 months to 15 years and 10 months	5/8, 62%	4/8, 50%	5/8, 62%	5/8, 62%	2/8, 25%	2/8, 25%	5/8, 62%	-	3/5, 60%	-	0/5, 0%	0/5., 0%	None
Adalimumab (n=1, stable on treatment)	4 years 1 month	1/1, 100%	1/1, 100%	1/1, 100%	0/1, 0%	0/1, 0%	0/1, 0%	1/1, 100%	1/1, 100%	-	-	0/1, 0%	0/1, 0%	None
Ustekinumab (n=1, stable on treatment)	14 years 7 months	1/1, 100%	1/1, 100%	1/1, 100%	0/1, 0%	0/1, 0%	0/1, 0%	1/1, 100%	-	-	1/1, 100%	0/1, 0%	0/1, 0%	None

Table 3:6 Pre-treatment investigations, monitoring and adverse effects for children prescribed biologic therapies
FBC – full blood count, UE – urea and electrolytes, LFT – liver function tests, ANA – antinuclear antibodies, HEP - hepatitis B & C serology, IGRA – interferon gamma release assay, HIV – human immunodeficiency virus, CXR – chest X-ray

3.4.6 Compliance with audit criteria

A summary of compliance with the audit criteria is presented in Table 3:7. Compliance with recommendations for assessment of disease severity, disease impact and comorbidities was poor. Topical treatments were often prescribed outside their licensed indications and appropriateness for body site varied. There was good compliance with the recommendation to provide a clear indication when starting phototherapy, conventional systemics or biologic therapy. Compliance with pre-treatment and monitoring routine blood tests was reasonable, but therapy specific investigations and monitoring was much poorer.

	NICE audit standard	Comparison with criteria, % of children
Disease Assessment	Assessment of disease severity at diagnosis and when response to treatment is assessed. Assessment of the impact of the disease on physical, psychological and social wellbeing at diagnosis and when response to treatment is assessed.	Assessment of disease severity using PASI of PGA undertaken in 35% (33/93) of new patients and 38% (72/190) of follow-up patients. Assessment of disease impact using DLQI, CDLQI or HAQ undertaken in 34% (32/93) of new patients and 29% (56/190) of follow-up patients.
Screening	Annual assessment for psoriatic arthritis. Screening for metabolic associations such as diabetes and inflammatory disorders such as uveitis and inflammatory bowels disease Screening for depression or psychological complications	Screening questions for joint symptoms in the last 12 months in 45% (128/285). Screening questions for diabetes in 14% (39/285), uveitis 15% (43/285) and inflammatory bowel disease 15% (44/285). Screening questions for depression/psychological complications in 23% (65/285)

Treatment	Topical treatment should be prescribed as per licensed indications	Topical treatments were prescribed outside their licensed indications. Calcineurin inhibitors (not licensed for psoriasis in children) were frequently prescribed for use in sensitive sites, most commonly the face (34%, 37/107)
	Topical treatment should be appropriate for site, frequency and duration.	Topical treatment prescribed appropriately for anatomical site as follows: scalp 39% (56/145), face 63% (67/107), flexural 96% (27/28), genital 89%, (25/28), trunk/limb 61% (124/202).
	Phototherapy should be initiated if there is a clear indication	Clear indication for treatment in 95% (79/83) commencing or treated with phototherapy
	Systemic and biological treatments should be initiated if there is a clear indication, with appropriate pre-treatment investigations and ongoing monitoring	Clear indication for treatment in 94% (50/53) and 100% (10/10) of patients commencing or stable on systemic and biologic therapy respectively. Pre-treatment routine blood tests completed in 89% of children prescribed conventional systemics and 70% of children prescribed biologic treatment. Other recommended investigations were often missing. All children prescribed conventional systemics and 70% of children on biologic treatments had routine blood test monitoring. No children on biologic treatment had regular lymph node or skin cancer checks.

Table 3:7 Summarised evidence for compliance with each audit criteria
PASI – Psoriasis Area Severity Index, PGA – Physician Global Assessment, DLQI – Dermatology Life Quality Index, CDLQI – Children's Life Quality Index, HAQ - Health Assessment Questionnaire

3.5 Discussion

3.5.1 Main findings

The demographic and clinical characteristics of the paediatric psoriasis population were similar to other secondary care case-series; a mean age of disease onset of seven years old, a greater proportion of girls were affected and the most common subtype was plaque psoriasis (Nanda et al., 1990, Kumar et al., 2004, Seyhan et al., 2006). In nearly a quarter of patients the age of onset was documented as under the age of 5 years, supporting the notion that psoriasis is a disease that commonly affects younger children as well as adolescents. The scalp was the most common site of initial presentation, but facial and flexural/genital (ie hidden site psoriasis) were also frequently documented.

Compliance with NICE guidance on the assessment of disease severity and impact was low. It is important to remember that PASI has not been validated in children, infants or primary care, and its applicability is limited to plaque psoriasis (NICE, 2012). However, PASI is routinely used in paediatric clinical practice and the 2017 Health Technology Appraisal guidance for adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people used PASI to define treatment eligibility and adequate response to treatment (NICE, 2017).

Annual assessment for juvenile psoriatic arthritis occurred in nearly half of patients, which indicates an improvement in clinical practice since a 2012 BSPD members' survey (Burden-Teh et al., 2013). Nearly all assessments were undertaken through direct questioning, but this method may be less accurate than using a validated tool or a referral to a rheumatologist (Laws et al., 2010). The PEST tool was used to assess for juvenile psoriatic arthritis in 2% of children, however this tool has not been validated for use in children (Coates et al., 2013). Assessment for other inflammatory, metabolic and psychological conditions occurred in less than 25% of children. However, because of insufficient evidence, the NICE guideline was unable to recommend a structured approach for assessing comorbidities and juvenile psoriatic arthritis in children.

Compliance with recommendations on topical therapies was variable. Drugs were often prescribed outside their licensed indication, for example calcineurin inhibitors were prescribed for over one third of children with facial psoriasis. Prescribing drugs outside their licenced indication is a common occurrence in dermatology. There are over 2000 dermatological conditions and licensing is often restricted by insufficient studies. A deficiency of evidence is a greater problem in paediatric dermatology, demonstrated by the NICE guideline extrapolating data from adult studies for most paediatric recommendations. The European Medicines Agency (EMA) recognises that there is a need for an increase in the number of paediatric studies to support authorisation of medicines in children, and have introduced measures to support this (EMA, 2015).

Conventional systemic therapies were used in nearly a fifth of children with psoriasis, despite not being licensed for this indication. At the time of the audit, biologic treatments were prescribed to only a small proportion of the paediatric psoriasis population. NICE was unable to provide specific guidance for dosing, pre-treatment investigations and monitoring in children. Therefore, variability in the completeness of pre-treatment investigations and frequency of monitoring is a likely consequence of the lack of specific guidance for children. Since the completion of this multi-centre audit and case-note review, children on conventional systemic therapies and biologic treatments are now included in BADBIR. BADBIR is a national drug registry for psoriasis and aims to investigate the long-term safety of these drugs. In the future, results from BADBIR will help inform future guidance about their use and effectiveness.

A third of children with psoriasis had initially been diagnosed with eczema or other skin diseases, mostly in primary care. Eczema is a very common skin condition in children, clinicians are more likely to suspect this diagnosis. Skin signs can evolve with time, but it is likely that a significant proportion of children with psoriasis were misdiagnosed before being referred to a dermatologist. The clinical presentation of psoriasis in children is described in Chapter 2 (2.3.1 Clinical presentation). There are some important differences with psoriasis in adults, and these can make recognition and diagnosis of psoriasis in children more challenging.

3.5.2 Context of existing literature

The 2007 BAD and Royal College of Physicians audit collected data from all regions of the UK over a one-year period. Similarly to this audit, the questionnaire was developed with experts and piloted. The audit achieved a good response rate and included 65% of dermatology units. The audit was completed before the introduction of the NICE guideline, but in 2007 recording of objective assessments of disease severity and impact was very poor. PASI and DLQI were inadequately or never recorded in outpatient consultations in 81% and 82% of patients respectively (Eedy et al., 2009). Therefore, this 2014 audit of children demonstrates an improvement in the proportion of objective assessments. The BAD conducted a more recent audit of psoriasis assessment and management in 2017. The audit included 194 dermatology units representing 1270 patients, but only 2% (25 patients) were children or young people. The 2017 audit demonstrated a further improvement in the recording of disease severity and impact; disease severity was assessed with a validated tool in 98.1% and disease impact was recorded using a validated patient-reported outcome measure in 87.5% (BAD, 2018). A higher percentage of patients also had an annual assessment for psoriatic arthritis (69.4 %). These findings suggest that NICE recommendations are becoming embedded within routine clinical practice.

Until recently few national or international guidelines have been specifically written for psoriasis in children. At a similar time to the NICE guideline, a European expert group consensus agreement on juvenile psoriasis and its clinical management was developed (Stahle et al., 2010). The study used Delphi methodology followed by a pharmaceutical sponsored nominal group meeting. The conclusions of the study focused on aligning recommendations against what is commonly practised clinically. Experts suggested that PASI was the most commonly used severity assessment measure, but specific scales for assessing children were needed. Impact on the family should also be assessed alongside assessing the impact on the child or young person. Similarly to the NICE guideline, vitamin D analogues, corticosteroids and calcineurin inhibitors were commonly used and PUVA was not recommended. The expert group also emphasised that the absence of clinical data had led to a lack of licensed treatments for psoriasis in children. The

European experts also concluded that psoriasis in children can be difficult to diagnose clinically and misdiagnosis may be common (Stahle et al., 2010).

Although no other audits of psoriasis management in children have been published, national surveys are another method of canvassing routine clinical practice. In 2017, Mahe *et al*. conducted a national survey on the management of childhood psoriasis in France (Mahe et al., 2018). The survey was sponsored by a pharmaceutical company and was sent to 19,150 general practitioners, paediatricians and dermatologists by a strategic data company. Although expected, the response rate was low. Of the 16.8% who opened the email, the survey was completed by 4.7% of GPs, 15.8% of paediatricians and 40.6% of dermatologists. Similarly to this audit, the survey found that clinician-reported severity scores were not used for the majority of patients (only used by 23.7% of dermatologists), combination treatments with topical steroids and vitamin D analogues were widely used (69.9% of dermatologists) and acitretin is still a popular treatment choice (30.6% of dermatologists). The conclusions of the survey also highlighted the challenges of licensing restrictions and the lack of data on the efficacy and safety of systemic treatments in children.

3.5.3 Strengths and limitations

This was a large multi-centre audit and case-note review involving 285 children with psoriasis from 31 paediatric dermatology departments with a wide geographical distribution. Audit standards were derived from evidence based national guidelines. To reduce selection bias, sites were asked to recruit all consecutive new and follow-up patients over a three month period. Patients were required to have a diagnosis of psoriasis made in secondary care, therefore the risk of misclassification bias is likely to be low.

Due to the set-up of paediatric dermatology services in the UK, the total number of paediatric departments is not known, and it was not possible to calculate a response rate. The composition of paediatric departments in terms of staff and resources is also unknown, therefore it is unclear whether the 31 departments provide a representative sample of all departments across the UK.

A limitation common to all case-note reviews and audits was that only documented compliance could be assessed. Actual clinical practice may have performed better. To ensure the proforma was easy to use, a draft version was circulated to all sites prior to the start of the audit. This preview may have altered clinical practice and led to an improved compliance with the guideline.

The aim of the project was to compare current clinical practice to national guidelines and identify areas for improvement. The case-note review did not aim to investigate risk factors or outcomes for psoriasis in children, therefore no comparative group was included.

3.5.4 Implications for clinical practice

This multi-centre audit and case-note review has identified variation, strengths and deficiencies in clinical practice across the UK. There is a need to improve regular assessment and recording of disease severity and patient-reported impact with validated tools. Dermatologists should be aware of these need and be supported to assess for juvenile psoriatic arthritis annually and comorbidities.

The implications for the treatment of psoriasis in children are more challenging, because of the lack of evidence, and many therapies are being used outside their licenced indications. However, it is important that clinicians provide clear documentation of the treatment indication, the explanation given to patients, the treatment regimen and the counselling provided for adverse effects.

3.5.5 Implications for this research project

Chapter 3 has investigated current practice in the assessment and management of psoriasis in children. Three important gaps in our knowledge and evidence base have been identified and will be taken forward in this thesis.

1. **How best can dermatologists assess for psoriatic arthritis in children and young people?** There is a need to explore in detail how dermatologists assess for juvenile psoriatic arthritis, the difficulties they experience and their suggestions for how assessment in dermatology clinics could be improved. Whilst there are no validated screening tools for juvenile psoriatic arthritis, there is a need to provide clinicians with clear guidance and initiate research to develop a paediatric specific tool. This question is taken forward in Chapter 4.

2. **Excluding treatments, what is our current evidence base for psoriasis in children?** The NICE guideline has appraised the literature on the assessment and management of psoriasis in children, highlighting important deficits. However, many other topics about psoriasis were out of scope of the guidelines. Chapters 5 and 6 systematically search the literature to collate available data on the epidemiology and diagnosis of psoriasis in children.

3. **How can psoriasis in children be better recognised and diagnosed by clinicians who review children with rashes?** This chapter has shown that children with psoriasis are often initially diagnosed with eczema and other skin condition. As per NICE guidance, early and accurate diagnosis is the first step to ensure children are referred to a specialist, receive psoriasis specific treatment, and are screened for comorbidities including juvenile psoriatic arthritis. Therefore, there is a need to improve the recognition and diagnosis of psoriasis in children. This question is taken forward in Chapters 4, 6, 7 and 8.

Chapter 4 Understanding current clinical practice in the assessment of juvenile psoriatic arthritis in children

4.1 Introduction

The multi-centre audit and case-note review reported in Chapter 3 identified two important questions. Firstly, how best can dermatologists assess for juvenile psoriatic arthritis in children and young people? Secondly, how can psoriasis be better recognised and diagnosed by clinicians who review children with rashes? This chapter explores the current diagnostic skills of paediatric dermatologists and rheumatologists in their recognition of juvenile psoriatic arthritis and psoriasis.

Chapter 2 (2.3.8 Juvenile psoriatic arthritis) introduced the relationship between juvenile psoriatic arthritis and psoriasis in children. Juvenile psoriatic arthritis is defined as an inflammatory arthritis diagnosed in a child under 16 years in the presence of psoriasis or two or more of the following criteria: family history of psoriasis in a first degree relative, nail pitting, onycholysis, dactylitis (Petty et al., 2004) (Figure 4:1). The recognition and accurate diagnosis of psoriasis is therefore a critical part of making a diagnosis juvenile psoriatic arthritis. As previously detailed in Chapters 2 and 3, the NICE guideline for the assessment and management of psoriasis recommends annual assessment for psoriatic arthritis in all people with psoriasis. However, a validated assessment tool or recommended approach to assessment is not available for children. Early recognition of juvenile psoriatic arthritis is important because a delay to diagnosis in all childhood inflammatory arthropathies can result in poorer long-term outcomes and disability (Foster et al., 2007).

Chapter 4 presents two qualitative studies which aimed to explore and understand paediatric dermatologists' and rheumatologists' clinical assessment of joint and skin disease.

The studies sought to provide recommendations to improve the recognition of juvenile psoriatic arthritis and psoriasis in children; exemplifying how specialties can learn from each other. Thus, adoption of these recommendations aimed to provide an early intervention for the prevention of long-term harm.

This work has been published in Clinical and Experimental Dermatology (Burden-Teh et al., 2017a) and the British Journal of Dermatology (Burden-Teh et al., 2017b)

> Burden-Teh E, Thomas KS, Rangaraj S, Cranwell J, Murphy R. Early recognition and detection of juvenile psoriatic arthritis: a call for a standardized approach to screening. Clin Exp Dermatol. 2017 Mar;42(2):153-160.
>
> Burden-Teh E, Thomas KS, Rangaraj S, Murphy R. Interviews with paediatric rheumatologists about psoriasis and psoriatic arthritis in children: how can specialties learn from each other? Br J Dermatol. 2017 Jul;177(1):316-318

Age at onset is under 16 years, disease duration is 6 weeks or greater, and other known conditions are excluded

AND psoriasis

OR two of the following dactylitis, nail pitting, onycholysis, and/or family history of psoriasis (in a first-degree relative)

EXCLUDING

Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, acute anterior uveitis

Figure 4:1 A summary of the International League for Associations of Rheumatology (ILAR) diagnostic criteria for juvenile psoriatic arthritis (Petty et al., 2004)

4.2 Objectives

1. To ascertain current clinical practice in the assessment of juvenile psoriatic arthritis and psoriasis in children.

2. To understand the impact a diagnosis of juvenile psoriatic arthritis has on the management of joint and skin disease

3. To identify strategies for improving the detection of juvenile psoriatic arthritis and psoriasis in children.

4.3 Methods

4.3.1 Study design

Two separate, but related, qualitative studies were undertaken with paediatric dermatologists and paediatric rheumatologists.

The studies used a qualitative descriptive study design. This approach aims to provide a rich and comprehensive summary of the clinician's experiences in the language of the respondents, staying close to the data and keeping inferences low (Sandelowski, 2000). A qualitative descriptive study design was appropriate for the objectives of these studies, which aimed to ascertain, understand and identify experiences and the rationale behind current practice, rather than developing a theory or intensive interpretation (Neergaard et al., 2009, Kim et al., 2017). Qualitative descriptive studies also allow for quantitative analysis (eg frequency counts) and encourage research outputs that present the findings in a way that best fits the data (Sandelowski, 2000, Neergaard et al., 2009). Appropriately for the objectives of the study, qualitative descriptive studies do not follow a particular theoretical or epistemological approach (Sandelowski, 2000).

The method employed was structured telephone interviews. These have been defined as elite interviews (Green, 2014). The term elite has no universal definition, but a common requirement is that the individual has significant decision-making influence and is in a position of seniority (Harvey, 2011). Consultant paediatric dermatologists and rheumatologists are opinion leaders in their field and therefore fulfil the description of elite practitioners. Typically, elite interviews are structured, consist of open and closed questions, are conducted over the telephone and are shorter in duration (Harvey, 2011). The reasons behind designing a qualitative descriptive study over a questionnaire survey to address the study objectives were to increase complete and detailed answers to questions and to enable further probing into the thought-processes behind current practice. All consultants contributed to the interviews in their role as a health professional.

4.3.2 Sampling strategy

Consultant members of the BSPD and the British Society of Paediatric and Adolescent Rheumatology (BSPAR) were interviewed. These participants were chosen because of their relevant clinical experience.

An email invitation was sent through each society to the membership list of the BSPD and BSPAR. The email invitation explained the format, purpose and intended audio recording of the interview. Purposeful sampling aimed to interview a paediatric dermatologist or rheumatologist at each centre. No incentive was offered for participation in the interviews. A telephone appointment was made with those who responded. All participants who agreed to take part in the telephone interviews provided verbal consent at the beginning of the recording. Only the participant and the interviewer were present during the telephone interview. To ensure anonymity, all participants were assigned a unique identifier in place of their real name and were reassured of the confidentiality of their responses. All consultants who responded to the email invitation were included in the study.

Chapter 2 (2.3.7 Treatment and 2.3.8 Juvenile psoriatic arthritis) describes the set-up of paediatric dermatology and rheumatology services in the UK. Due the centralised set-up

of paediatric rheumatology services it was possible to calculate a centre response rate, however this was not possible for paediatric dermatology.

4.3.3 Data collection

All interviews were conducted by EBT between October and November 2014 (paediatric rheumatology interviews) and March and July 2015 (paediatric dermatology interviews). The interviews took between 15 and 40 minutes each and were audio-recorded on a digital hand-held device. The interviews followed a structured interview guide and no changes were made to the questions over the duration of the study. EBT attended qualitative research training at the University of Nottingham. Naturally, the interview technique developed and the experience of EBT grew over the course of the interviews; providing greater opportunity to probe and wait for responses from participants. No field notes were taken.

4.3.4 Interview guide

The interview guide for paediatric rheumatologists included questions on: i) paediatric rheumatologists' current practice for assessing psoriasis in children with juvenile idiopathic arthritis; ii) reasons why detecting psoriasis in children may be difficult and suggestions for what would improve detection; iii) impact a diagnosis of juvenile psoriatic arthritis has on the management of inflammatory arthritis; iv) clinical presentation of skin and joint disease in juvenile psoriatic arthritis; v) recommendations for how non-rheumatologists can look for inflammatory arthritis in children.

The interview guide for paediatric dermatologists included questions on: i) dermatologists' current practice for assessing joint disease in children with psoriasis; ii) reasons why detecting juvenile psoriatic arthritis may be difficult and suggestions for what would improve detection; iii) impact a diagnosis of juvenile psoriatic arthritis has on the management of psoriasis; iv) clinical presentation of skin and joint disease in juvenile psoriatic arthritis; v) recommendations for how non-dermatologists can look for psoriasis In children. The interview guides are available in Appendix 2 and Appendix 3.

4.3.5 Data processing and analysis

The audio-recordings of the interviews were transcribed as intelligent verbatim by EBT. The transcripts were anonymised by assigning a unique identifier and recordings deleted from the audio device. Analysis was conducted using Microsoft Excel 2010.

4.3.5.1 Quantitative Analysis

Quantitative data was analysed using basic descriptive statistics. The responses to questions were categorised and the proportion of each category of response was calculated. A mean average Likert scale response was calculated for paediatric rheumatologists' confidence when assessing for psoriasis and paediatric dermatologists' confidence when assessing for joint disease. The Likert scale ranged from 1 (not at all confident) to 10 (very confident). There were no missing data.

4.3.5.2 Thematic analysis

The interviews with paediatric rheumatologists and paediatric dermatologists were analysed using framework analysis. Framework analysis is frequently used in the analysis of structured and semi-structured interviews, because themes are retained within each question or an individual's account (Gale et al., 2013). During the analysis the following seven stages were followed: transcription, familiarisation with the interview, coding, developing a framework, applying the framework, charting data into the framework and interpreting the data. The framework focused on five questions in each set of interviews and used both an inductive and deductive approach. The deductive codes were pre-identified challenges in the recognition of psoriasis, such as hidden site involvement, and psoriatic arthritis.

An additional technique was used for analysing the interviews with paediatric dermatologists. The depth and content of the responses prompted the decision to undertake thematic content analysis in addition to the planned framework analysis. This responsive decision is in keeping with the ethos of qualitative research, which encourages an iterative approach to the analysis. Thematic content analysis was applied

to the paediatric dermatologists' transcripts as a whole to identify common themes across the interviews. This is an established methodology for eliciting rich data and provided deeper understanding of the uncertainties, challenges and reasoning behind paediatric dermatologists' clinical practice (Braun, 2006). The following five-steps described by Braun and Clark were followed; familiarisation, generating initial codes, searching for themes, reviewing themes, and defining and naming themes. An inductive approach was used and therefore all codes originated from the data. The transcripts were thematically analysed until achieving saturation of themes. Saturation was defined as no new emergent themes in three consecutive transcripts.

All coding was conducted by EBT, but the themes were discussed with Dr Ruth Murphy (RM), Dr Satyapal Rangaraj (SR) and Prof Kim Thomas (KT). The participants did not comment on the transcripts but were able to provide feedback on the final published manuscripts.

4.3.6 Researcher characteristics and contributions

The studies were led and conducted by EBT, who is a dermatology registrar and clinical researcher. EBT has a long-term interest in psoriasis and psoriatic arthritis. Previous clinical and research experience has informed EBT's and the project's clinical supervisor (RM) viewpoint that both psoriasis and psoriatic arthritis are under-recognised in children, which can lead to sub-optimal care and long-term harm. This viewpoint will have influenced the interview guide and probing questions in the interviews. In EBT's role as a clinician and researcher, she had previously met participants and they are aware of her interest in the field of paediatric psoriasis. This relationship will have helped build rapport during the interviews. EBT received training in qualitative research through the University of Nottingham and the analysis of the dermatology interviews were guided by Dr Joanne Cranwell, qualitative researcher.

4.4 Results

4.4.1 Interviews with paediatric rheumatologists

Structured interviews were undertaken with paediatric rheumatologists at ten regional centres representing 83% of paediatric rheumatology expertise in the UK. The two non-participating centres were unable to be contacted by telephone or email. England (8), Scotland (1) and Northern Ireland (1) were all represented in the interviews. Six (60%) paediatric rheumatologists were female and seven (70%) were the lead for paediatric rheumatology at their centre. All participating clinicians confirmed that they had children with inflammatory arthritis under their care.

4.4.1.1 Assessment of skin disease in children with inflammatory arthritis

The frequency of responses and framework analysis for questions on the assessment of skin disease in children with inflammatory arthritis are presented in

Table 4:1. All paediatric rheumatologists ask about skin disease and specifically psoriasis or a family history of psoriasis when assessing children with inflammatory arthritis. Six paediatric rheumatologists (60%) commented that during an inflammatory arthritis consultation the skin would be examined during the joint examination, but 20% do not ask further questions or examine the skin if the patient/family responded 'no' to questioning about the presence of a rash. Four paediatric rheumatologists (40%) describe the skin changes associated with psoriasis to the patient/family if they do not understand the term psoriasis. Only three (30%) paediatric rheumatologists ask about and five (50%) examine for psoriasis in hidden sites. Hidden sites were defined as behind the ears, umbilicus, flexures, groin and natal cleft.

Paediatric rheumatologists rely on a characteristic appearance and distribution of the rash to diagnose psoriasis, acknowledging that it can be difficult to differentiate psoriasis from eczema and other skin rashes. To the question 'How would you diagnose psoriasis', the most dominant theme from the responses was to 'refer to dermatology' for confirmation of the diagnosis.

"if in any doubt would ask a dermatologist …. always keen to make 100% sure it is psoriasis …. anything looks like psoriasis and not seen one I would ask a dermatologist to look" [PR6] (Theme: 'refer to dermatology')

"low threshold to refer ….this has been useful as sometimes the diagnosis has been eczema or something else" [PR10] (Theme: 'refer to dermatology')

Reasons given by paediatric rheumatologists as to why a diagnosis of psoriasis can be difficult to make were divided into five themes. 'Atypical appearance' and 'minimal amounts of skin disease' were the two most important themes. On average, paediatric rheumatologists rated their confidence in diagnosing psoriasis as 6.4 (1 being not at all confident and 10 being very confident).

"less typical rash especially distribution and scaliness" [PR5] (Theme: 'atypical appearance')

"not very scaly in the scalp…difficult if the GP has already started treatment. You aren't seeing the true clinical picture" [PR8] (Theme: 'atypical appearance')

"history of guttate but gone at the time of the consultation…. one to two patches only" [PR4] (Theme: 'minimal amounts of skin disease')

"when the presentation is mild sometimes the family can dismiss or not notice the changes…a small patch in the scalp may be missed without a very thorough scalp examination" [PR10] (Theme: 'minimal amounts of skin disease')

When asked about suggestions to help improve paediatric rheumatologists' detection of psoriasis 'a close working relationship between dermatology and rheumatology' and 'experiential training' were the two dominant themes. Development of 'diagnostic criteria' was also a suggested method. Only one clinician (10%) felt improving rheumatologists' recognition and diagnosis of psoriasis was not needed, because either

the respondent felt the presentation was obvious or they refer the patient to dermatology for a diagnosis.

“we have a combined clinic monthly” [PR3] (Theme: ‘a close working relationship’)

“review by a dermatologist who has experience around children and understands the importance around making an accurate diagnosis” [PR5] (Theme: ‘a close working relationship’)

“education… experiential learning” [PR7] (Theme: ‘experiential training’)

“clinical training… other resources possible but no substitute for clinical training” [PR9] (Theme: ‘a close working relationship’)

Interview Question	Responses by paediatric rheumatologists n=10, (%)			
When assessing children with inflammatory arthritis, do you routinely ask any questions about skin disorders?	Yes - 10/10, (100%) Directly ask about psoriasis – 7/10, (70%)			
When assessing children with inflammatory arthritis, do you routinely ask about family history of skin disorders	Yes – 10/10, (100%) Directly ask about psoriasis – 10/10, (100%)			
When assessing children with inflammatory arthritis, are there any specific areas of the body where you ask about changes to the skin?	Scalp – 7/10 (70%), behind the ears – 1/10 (10%), face – 0/10 (0%), trunk – 0/10 (0%), umbilicus – 3/10 (30%), limbs – 3/10 (30%), acral – 0/10 (0%), nails – 4/10 (40%), flexures – 0/10 (0%), groin – 2/10 (20%), natal cleft – 3/10 (30%). 'Hidden sites'* asked about – 3/10 (30%)			
When assessing children with inflammatory arthritis, are there any specific areas of the body where you examine for skin changes?	Scalp – 9/10 (90%), behind the ears – 3/10 (30%), face – 2/10 (20%), trunk – 3/10 (30%), umbilicus – 3/10 (30%), limbs – 5/10 (50%), acral 1/10 (10%), nails – 5/10 (50%), flexures – 2/10 (20%), groin – 2/10 (20%), natal cleft – 1/10 (10%) 'Hidden sites'* examined – 5/10 (50%)			
How would you diagnose psoriasis?	Refer to dermatology – 10/10 (100%) *if in doubt ask a dermatologist [PR1]* *refer if unsure…. tend to be cautious [PR2]* *have joint clinics with paediatric trained dermatologist [PR3]* *ask a dermatologist if unsure [PR4]* *if unsure ask a dermatologist …. Can be hard to distinguish from eczema [PR5)* *if in any doubt would ask a dermatologist …. always keen to make 100% sure it is psoriasis …. anything looks like psoriasis and not seen one I would ask a dermatologist to look [PR6]* *if unsure refer to derm [PR7]* *refer to derm [PR8]* *if unsure refer to dermatology [PR9]* *low threshold to refer ….this has been useful as sometimes the diagnosis has been eczema or something else [PR10]*	Distribution – 7/10, (70%) *extensor surfaces [PR2)* *pattern of distribution …. looking in hidden sites [PR3]* *distribution …. extensors…. Can be difficult to distinguish from eczema apart from the distribution [PR5]* *arms, abdomen and legs [PR6]* *distribution of the rash [PR7]* *scalp and extensor*	Appearance - 6/10, (60%) *features …elevated scaly plaque [PR1]* *if barn door easy …. red scaly [PR2]* *scalyness…. itchy scalp….typical patches [PR3]* *scaly appearance …. salmon pink … post inflammatory hyper or hypopigmentation [PR5]* *characteristic plaques …. scaly scalp …. nail changes [PR6]* *classic rash …. scaling …. nail*	Family history of psoriasis – 1/10 (10%) *Sometimes the parents have psoriasis [PR4]*

			surfaces [PR8] *pattern recognition [PR10]*	*involvement [PR8]*	
How confident do you feel about diagnosing psoriasis on a scale of 1 to 10, 1 being not at all confident to 10 being very confident?	4 – 1/10 (10%), 5 – 2/10 (20%), 7 – 6/10 (60%), 8 – 1/10 (10%) Mean average score – 6.4				
In your experience, are there any reasons why making a diagnosis of psoriasis can be difficult?	Atypical appearance – 8/10 (80%) *modified by medications [PR1]* *atypical rash [PR2]* *if not in the normal distribution [PR3]* *less typical rash especially distribution and scaliness [PR5]* *appearance is not characteristic [PR6]* *it can look different at different ages [PR7]* *not very scaly in the scalp…difficult if the GP has already started treatment. You aren't seeing the true clinical picture [PR8]* *if not typical for example no scalp or nail involvement [PR9]*	Minimal amounts of skin disease – 6/8 (75%) *small areas, can vary from time to time [PR1]* *history of guttate but gone at the time of the consultation…. one to two patches only [PR4]* *the rash has not been going on a very long time [PR6]* *only a small patch of sore red skin [PR8]* *small patches [PR9]* *when the presentation is mild sometimes the family can dismiss or not notice the changes…a small patch in the scalp may be missed without a very thorough scalp examination [PR10]*	Anatomical area of the body involved – 5/8 (63%) *sites which are moist [PR1]* *palmar plantar involvement [PR2]* *young children especially nappies and other excoriated areas [PR3]* *young children with scaly scalps [PR4]* *palmar plantar involvement [PR9]*	Similarity in appearance to other skin disease – 5/8 (63%) *with the nails fungal needs to be excluded [PR1]* *difficult if also has eczema….if trunk possibly fungal [PR3]* *children also get other rashes ….transient, related to infection [PR5]* *psoriasis crossovers [PR7]* *rashes can be difficult to diagnose to a non-dermatologist, can appear very similar [PR10]*	No family history – 2/8 (25%) *no family history [PR4]* *no family history of psoriasis [PR6]*
Can you make any suggestions about what would help you diagnose psoriasis and therefore psoriatic arthritis?	Close working relationship between rheumatology and dermatology – 6/10 (60%) *we have a combined clinic monthly [PR3]* *review by a*	Experiential training/clinical education – 4/10 (40%) *experience [PR2]* *education… experiential learning [PR7]* *clinical training…*	Diagnostic criteria – 3/10 (30%) *more guidance on dermatological criteria [PR5]* *a list of criteria for diagnosing psoriasis [PR6]*	Diagnostic test – 1/8 (10%) *any imaging ….skin ultrasound [PR1]*	Not a problem that needs to be addressed – 1/10 (10%) *not a big problem …either*

	dermatologist who has experience around children and understands the importance around making an accurate diagnosis [PR5] *usually involve a dermatologist…easy to get hold of [PR6}* *ideal would be to have a dermatologist in a nearby clinic …. photos before treatment which could be reviewed by a dermatologist [PR8]* *sitting in psoriasis clinic [PR9]* *close working relationship with a specialist colleague [PR10]*	*other resources possible but no substitute for clinical training [PR9]* *active learning from colleagues… courses… clinical experience [PR10]*	*more formal diagnostic criteria [PR7]*	*obvious or refer [PR4]*

Table 4:1 Interviews with paediatric rheumatologists: Assessment of skin for psoriasis
**'Hidden sites' refer to behind the ears, umbilicus, flexures, groin and natal cleft.*

4.4.1.2 Impact of a diagnosis of juvenile psoriatic arthritis on clinical care

The frequency of responses and the framework analysis for the impact of a diagnosis of juvenile psoriatic arthritis on clinical care are presented in Table 4:2. Most paediatric rheumatologists (80%) thought there was a difference between juvenile psoriatic arthritis and other subtypes of juvenile idiopathic arthritis, with specific rheumatological features elicited in juvenile psoriatic arthritis. In particular, dactylitis (50%) and involvement of the small joints of the hand/distal interphalangeal joints (40%).

For the majority of paediatric rheumatologists, a diagnosis of juvenile psoriatic arthritis, compared to other juvenile idiopathic subtypes, affected the explanation given to patients/families (70%), the treatment plan (80%) and long-term outcomes (70%). In terms of the explanation given to patients/families the dominant theme was 'persistent disease and risk of joint damage', which is similar to the dominant theme for long-term outcomes of 'persistent disease'. The dominant theme for the effect on treatment plan was 'lowers the threshold for treatment escalation'.

"discuss prognosis…it can extend into adulthood" [PR3] (Theme: 'persistent disease and risk of joint damage')

"prolonged …. can be more damaging" [PR6] (Theme: 'persistent disease and risk of joint damage')

"it does give more weight to methotrexate…more likely to start methotrexate earlier" [PR2] (Theme: 'lowers threshold for treatment escalation')

"lower threshold for starting a DMARD, methotrexate in patients with involvement of less than 5 joints" [PR5] (Theme: 'lowers threshold for treatment escalation')

Although the diagnosis of juvenile psoriatic arthritis lowered the threshold for treatment escalation for half of clinicians, nine out of ten (90%) explained that the treatment pathway for all subtypes of juvenile idiopathic arthritis is the same and 4/10 (40%) emphasised that in all subtypes it is important that any active inflammation is treated.

“the plan in all types of childhood arthritis is to get on top of it quickly and completely” [PR3]

“in all types of JIA there is a zero tolerance of inflammation” [PR10]

Three paediatric rheumatologists (30%) felt that the pattern of joint involvement (e.g. mid/hindfoot, wrist, polyarticular, extended oligoarthritis) is more concerning for long-term outcomes than the juvenile idiopathic arthritis subtype and further research on long-term outcomes is required.

Interview Question	Response by paediatric rheumatologists n = 10, (%)				
From your expertise, do you consider there to be a difference between juvenile idiopathic arthritis and juvenile psoriatic arthritis?	Yes – 8/10 (80%) No – 2/10 (20%) Specific rheumatological features – 7/10 (70%) which include: dactylitis 5/10 (50%), enthesitis – 1/10 (10%), small joints of the hand/DIP -4/10 (40%), minimal swelling/drier synovitis/subtle -3/10 (30%), more aggressive -1/10 (10%), systemic inflammation – 1/10 (10%) Each subtype is a different disease – 1/10 (10%)				
Does a diagnosis of juvenile psoriatic arthritis instead of juvenile idiopathic arthritis influence what you explain to children and their parents?	Yes – 7/10 (70%) No – 3/10 (30%)				
	Persistent disease and risk of joint damage – 6/7 (86%) *discuss prognosis…it can extend into adulthood [PR3]* *less likely to happen (go into remission) [PR5]* *prolonged …. can be more damaging [PR6]* *less reassuring regarding spontaneous remission* [PR7] *might not go away, remits and relapses [PR9]* *less likely to grow out of it [PR10]*	Treatment strategy – 4/7(57%) *early intervention can be very effective… slightly different approach [PR3]* *pattern of disease means that it is important to get on top of it [PR5]* *intermittent lifelong immunosuppression [PR6]* *more likely to need lifelong treatment [PR10]*	Helps disease explanation (skin and joints) – 2/7 (29%) *starting point for explaining autoimmune disease …helps explain treatment as you can use methotrexate for skin and joints [PR2]* *explain link to psoriasis [PR4]*	Comorbidities – 2/10 (29%) *development of uveitis [PR1]* *need to monitor eyes for uveitis [PR3]*	Cautious explanation of genetics - 2/10 (29%) *Try to stay away from the blame of genetics [PR2]* *need to careful when discussing inheritance as strong relationship [PR3]*
Does a diagnosis of juvenile psoriatic arthritis instead of juvenile idiopathic arthritis influence your treatment plan?	Yes – 8/10 (80%) No – 2/10 (20%)				
	Lowers the threshold for treatment escalation - 5/8 (63%) *if wrist or hindfoot disease are more likely to start methotrexate or biologic earlier [PR1]*		Choice of biologic therapy – 2/8 (25%) *more likes to choose Humira*	Combined approach for skin/uveitis and joints – 2/8 (25%) *if uveitis and skin involvement may alter treatment used [PR6]* *If the skin is bad it may prompt moving onto the next*	

	it does give more weight to methotrexate…more likely to start methotrexate earlier [PR2] *do have a low threshold, like all polyarticulars, of getting them on biologics early [PR3]* *lower threshold for starting a DMARD, methotrexate in patients with involvement of less than 5 joints [PR5]* *inclined to start systemic earlier… lower threshold to escalate treatment {PR7}*	*over Enbrel [PR1]* *low threshold for Enbrel in the you, Humira if older [PR3]*	*treatment sooner [PR9]*
In your experience, are long-term outcomes different in children with psoriatic arthritis compared to juvenile idiopathic arthritis?	Yes – 7/10 (70%) No – 3/10 (30%)		
	Persistent disease – 5/7 (71%) *can have ongoing disease into adulthood [PR2]* *persists into adults [PR3]* *less likely to go into remission [PR5]* *less likely to burn out than oligo [PR6]* *less likely to grown out of it [PR10]*	Risk of long-term joint damage and comorbidity – 4/7 (57%) *hindfoot/foot disease and wrist can be difficult to treat and very bad prognosis prior to biologics [PR1]* *adults have been found to have damage from undertreated psoriatic JIA [PR2]* *increased incidence of uveitis [PR5]* *appears to be more aggressive and erosive but we don't have that information yet [PR8]*	Increased need for aggressive treatment – 2/7 (29%) *tend to start methotrexate and biologic earlier in these patients [PR1]* *need earlier aggressive treatment [PR2]*

Table 4:2 Interviews with paediatric rheumatologists: Impact a diagnosis of juvenile psoriatic arthritis has on clinical care

4.4.1.3 Presentation of skin and joint disease in juvenile psoriatic arthritis

In their experience, four paediatric rheumatologists (40%) thought that joint signs presented before psoriasis in juvenile psoriatic arthritis, and two commented that this may be a result of referral bias. There were varied opinions on whether skin or joints presented first. Two clinicians (20%) thought skin presented first, three (30%) thought it could be either and one (10%) thought a simultaneous presentation was most likely. The majority of paediatric rheumatologists (80%) found it very difficult to estimate the percentage of children presenting with skin, joint or simultaneous disease and of these 40% of paediatric rheumatologists thought it was unclear and 30% suggested equally divided.

The most common presenting skin feature was thought to be scalp involvement (30%), although four paediatric rheumatologists (40%) felt there was no clear skin pattern in juvenile psoriatic arthritis. The most frequent joint patterns clinicians observed in juvenile psoriatic arthritis were small joint involvement of the hand/distal interphalangeal (60%), large joints (50%), dactylitis (40%), oligoarthritis/asymmetric (40%), mid/hindfoot (30%), sacroiliitis (20%), polyarticular (20%), minimal swelling (10%) and no clear pattern (10%). Two paediatric rheumatologists (20%) thought the pattern of joint involvement varied with the age of the child/young person, with digit involvement and dactylitis seen in younger children and large joint and spinal involvement seen in older children.

4.4.1.4 Recommendation on how paediatric dermatologists could look for inflammatory arthritis in children

Nine paediatric rheumatologists (90%) recommended that paediatric dermatologists reviewing children with psoriasis could use the Paediatric Gait Arms Legs Spine (pGALS) screening tool. A third of paediatric rheumatologists (30%) emphasised that it is important that paediatric dermatologists practice the pGALS examination regularly.

“pGALS, fairly quick and easy” [PR2]

"pGALS, there is an educational package to support this freely online. Good screening tool for all inflammatory arthritis so long as the person knows how to use it". [PR5]

"pGALS, dermatologists should practice performing it regularly to know what a normal joint looks like. Suitable for screening for PsA, can be performed in 1-2 minutes and as a screening tool it has been shown to be sensitive". [PR10]

4.4.2 Interviews with paediatric dermatologists

A total of 23 consultant paediatric dermatologists were interviewed. The consultants represented a good geographical distribution across the UK: England (18), Wales (2), Scotland (2) and Northern Ireland (1). Seventeen dermatologists (74%) were female. Sixteen dermatologists (70%) were the clinical lead for paediatric dermatology at their centre. Twelve (52%) worked in a secondary referral centre, two (9%) in a tertiary referral centre, and nine (39%) in both. The average number of children seen by each dermatologist with psoriasis per month was four (range 1 to 10). Nine dermatologists had children with psoriasis and psoriatic arthritis under their care at the time of the interview.

4.4.2.1 Assessment of joint disease in children with psoriasis

The frequency of responses and framework analysis for questions on the assessment of joint disease in children with psoriasis are presented in

Table 4:3. In total 18 (78%) paediatric dermatologists routinely ask children with psoriasis about joint disease. The proportion of clinicians who routinely ask about joint diseases was higher in those working in tertiary care or tertiary and secondary care (n=11, 100%) than those working in secondary care alone (n=7, 58%). The clinicians who ask about joint disease focus on new patients (13/18, 72%) and four (4/18, 22%) always ask about joint disease at every visit. About half of paediatric dermatologists (12/23, 52%) ask about a family history of psoriatic arthritis.

To the question 'how would you ask a child or their parents, about joint disease?' the dominant theme was 'ask about symptoms', and all paediatric dermatologists who ask

about symptoms focus on pain and soreness. A smaller proportion ask about swelling and stiffness.

"I just ask them if they are sore" [PD15] (Theme: 'ask about symptoms')

"have they noticed any joint symptoms, any swelling, or stiffness, any pain, any effect on movement" [PD6[(Theme: 'ask about symptoms')

I usually ask them about getting out of bed in the morning …, because you don't want to lead them, and if they've got early morning stiffness they will usually mention it" [PD23] (Theme: 'ask about symptoms')

"inflammation in the tendons such as any pain or swelling at the back of the heel" [PD9] (Theme: 'ask about symptoms')

Six clinicians (26%) have used or know of a screening/assessment tool for juvenile psoriatic arthritis, of those four mentioned PEST and one cited a locally modified PEST to cover for axial disease. Only a small number of paediatric dermatologists examine for arthritis (3/23, 13%) and described their assessment as 'move and feel' with particular focus on the small joints; however no systematic approach was described.

"There is that tool I use for adults, the PEST score, I do sometimes give that to children, but I don't know if it is validated in children" [PD9]

"I do a quick ball-park examination, to see if there is anything gross, and if there was anything significant I would refer for a paediatric rheumatology opinion" [PD6]

"I'm not a rheumatologist, I'll do my best and see whether they look swollen" [PD2]

'Inexperience and lack of training in musculoskeletal examination' were identified as the main reason why paediatric dermatologists may find detecting arthritis difficult. Addressing this barrier with an 'assessment tool or guideline' and 'clinical training or

experience', were the two dominant themes in responses to the question 'what would help you detect joint disease in children with psoriasis?'.

"We aren't trained in joint assessment in general are we in dermatology" [PD19] (Theme: 'inexperience and lack of training')

"I'm not a rheumatologist, I'm not trying to be a joint expert …I wouldn't have the confidence" [PD18] (Theme: 'inexperience and lack of training')

"Just lack of experience" [PD10] (Theme: 'inexperience and lack of training')

"a dedicated psoriatic screening tool for children that could be something to use" [PD4] (Theme: 'assessment tool or guideline')

"if there were some easy to ask key questions that were sensitive and specific that would be quite helpful" [PD14] (Theme: 'assessment tool or guideline')

"more training, I suppose, don't know if there has been and I am not aware …. online training is very unlikely that dermatologists would find time to do it so I think it would be mainly in sessions" [PD11] (Theme: 'clinical training or experience')

"then we could always go and work with our rheumatology colleagues and talk to them and perhaps see a few patients with arthritis with them" [PD8] (Theme: 'clinical training or experience')

On average paediatric dermatologists rated their confidence in assessing joint disease in children at 3 (1 being not at all confident and 10 being very confident).

"I'm a paediatrician by background, I did paediatric rheumatology as a specialism in my paediatric training, so not that I focus on it as much nowadays but probably about a 7" [PD19]
"I don't feel very confident about it at all" [PD14]

Interview question	Response by paediatric dermatologist	Number of responses, n=23, (%)
When you see children with psoriasis, do you routinely ask about joint disease? **If yes, how often do you ask?***	Yes No First consultation When prompted by symptoms or signs Every visit Twice a year Annually	18 (78%) 5 (22%) 13/18 (72%) 6/18 (33%) 4/18 (22%) 2/18 (11%) 1/18 (6%)
When you see children with psoriasis, do you ask about a family history of psoriatic arthritis?	Yes No	12 (52%) 11 (48%)
How would you ask a child or their parents, about joint disease?*	Ask about symptoms: • Pain or soreness • Swelling • Redness • Stiffness • Morning stiffness • Specific sites of symptoms eg hands, heel *"I just ask them if they are sore" [PD15]* *"Have they noticed any joint symptoms, any swelling, or stiffness, any pain, any effect on movement" [PD6]* *I usually ask them about getting out of bed in the morning …, because you don't want to lead them, and if they've got early morning stiffness they will usually mention it" [PD23]* *"inflammation in the tendons such as any pain or swelling at the back of the heel" [PD9]*	19 (83%) 19 (83%) 9 (39%) 4 (17%) 3 (13%) 1 (4%) 5 (22%)
	Limitations on activity *"or had they had any discomfort in their joints that had stopped them from doing things they had really wanted to do" [PD14]* *"but normally in children I would ask about what things they cannot do, if they have ever missed a PE session or are limited in any way with their activities" [PD11]*	7 (30%)
	Not meeting expectations *"are they functioning as fully as they would expect" [PD1]* *"if there is anything that kind of has inhibited their day to day activities at school or games" [PD10]*	6 (26%)
	Open question 'any problems'? *"I would ask really has anyone had any joint problems" [PD18]*	2 (9%)
In your experience are there any reasons why you may find detecting psoriatic arthritis in children with psoriasis difficult?	Lack of experience or training in joint assessment *"We aren't trained in joint assessment in general are we in dermatology" [PD19]* *"I'm not a rheumatologist, I'm not trying to be a joint expert …I wouldn't have the confidence" [PD18]*	11 (48%)

	"Just lack of experience" [PD10]	
	Physical signs may be subtle or difficult to detect in children "*I suppose they are young so maybe doing the examination would be harder so that is why I would have a very low threshold for referring" [PD22]* *"they are so much smaller …. you may not see inflammation as easily particularly if they are chubby, little tiny ones" [PD6]*	6 (26%)
	Lack of awareness of the association between psoriasis and juvenile psoriatic arthritis by family and clinicians *"I think it is just thinking to ask about it and to be aware of it" [PD5]* *"parents might not be expecting it so they may have discounted all these growing pains and all these sort of things, so you might need to be able to dig a little bit behind all of that" [PD7]*	4 (17%)
	More difficult communication with children *"children won't necessarily localise pain or be able to describe joint pain in the same way as an adult" [PD4]* *"present or complain of something different to the words an adult might use" [PD7]*	4 (17%)
	Alternative diagnoses for joint symptoms *"I think it is difficult anyway because children often have growing pains, which they relate to joint pains" [PD17]*	4 (17%)
	Other: eg rely on rheumatology, time limited in clinic, limited investigations *"It is because I always get the rheumatologists to do it I think, because we work so closely" [PD1]* *"The thing is I wouldn't have time" [PD11]* *"we don't have access to ultrasound" [PD14]*	5 (22%)
	No difficulties experienced *"Well the children I have looked after who have had psoriatic arthritis have been very obviously in difficulty" [PD12]*	2 (9%)
Can you make any suggestions about what would help you detect joint disease in children with psoriasis?	Assessment tool/guideline *"a dedicated psoriatic screening tool for children that could be something to use" [PD4]* *"if there were some easy to ask key questions that were sensitive and specific that would be quite helpful" [PD14]*	14 (61%)
	Clinical training or experience *"more training, I suppose, don't know if there has been and I am not aware …. online training is very unlikely that dermatologists would find time to do it so I think it would be mainly in sessions" [PD11]*	8 (35%)

	"then we could always go and work with our rheumatology colleagues and talk to them and perhaps see a few patients with arthritis with them" [PD8]	
	Other: eg education through national meetings, simple investigations, improved identification of at risk children *"If we had any simple investigations, for instance I know that our rheumatology department here are routinely scanning for enthesitis …. more research data on which children may be more/most susceptible to joint psoriasis" [PD6]* *"more embedded in meetings that the dermatologists attend" [PD11]*	5 (22%)
	No suggestion given *"I would have to say that our paediatric rheumatologists are fantastic, we don't really need to advise them" [PD1]*	1 (4%)

Table 4:3 Interviews with paediatric dermatologists: Assessment of joint disease in children with psoriasis

4.4.2.2 Impact of a diagnosis of juvenile psoriatic arthritis on clinical care

The frequency of responses and framework analysis for questions on the impact a diagnosis of juvenile psoriatic arthritis has on the clinical care of children with psoriasis are presented in Table 4:4. The majority (20/23, 87%) of paediatric dermatologists said that the presence of juvenile psoriatic arthritis would influence their management of psoriasis. The two main ways management would be influenced were 'choice of agent' and by adopting a 'more aggressive approach'.

"much more likely to use methotrexate for instance if you had evidence of any comorbidities or psoriatic arthritis, or even biologics" [PD5] (Theme: 'choice of agent')

"I'm much more likely to go to methotrexate early if they have arthritis rather than phototherapy" [PD2] (Theme: 'choice of agent')

"I would push them forwards very quickly" – [PD23] (Theme: 'more aggressive approach')

"I would probably go sooner to disease modifying drugs" [PD20] (Theme: 'more aggressive approach')

A high proportion of paediatric dermatologists (15/23, (65%)) were unsure about the long-term health outcomes for children with psoriasis and psoriatic arthritis and felt unable to base their answers in evidence or direct experience.

"honestly I don't know, I have a hunch that it is probably not so good" [PD23]

"haven't a clue" [PD3]

"I don't really have the experience to know" [PD8]

4.4.2.3 Presentation of skin and joint disease in juvenile psoriatic arthritis

The frequency of responses for questions on the order or pattern of presentation of skin and joint disease in juvenile psoriatic arthritis are presented in Table 4:4. Most paediatric dermatologists (16/23, 70%) thought that psoriasis presents before arthritis, but many commented that their perception might reflect referral bias, since dermatologists were more likely to be referred patients with skin disease. Overall, participants were often unsure or felt no particular pattern was associated with the presentation of skin (8/23 (35%)) or joint disease (12/23 (52%)).

Interview question	Response by paediatric dermatologist	Number of responses, n =23, (%)
In your experience, do you feel skin signs or joint signs develop first in children with psoriatic arthritis?	Psoriasis first	16 (70%)
	Unsure about order of presentation	5 (22%)
	Joints first	1 (4%)
	Simultaneous presentation	1 (4%)
In your experience do you feel there are any particular skin patterns in children with psoriatic arthritis?*	Unsure or no pattern associated	8 (35%)
	Acral	3 (13%)
	Nail	3 (13%)
	Severe psoriasis	3 (13%)
	Chronic plaque	2 (9%)
	Scalp	2 (9%)
	Less likely to occur with guttate psoriasis	2 (9%)
	Other: localised, flexural, correlation between sites of psoriasis and arthritis	3 (13%)
In your experience do you feel there are any particular joint patterns in children with psoriatic arthritis?*	Unsure or no pattern associated	12 (52%)
	Small joint disease	5 (22%)
	Monoarthritis	3 (13%)
	Enthesitis	3 (13%)
	Knee	2 (9%)
	Other: Elbow, ankles, dactylitis, widespread, mutilating	5 (22%)
In your experience, does the presence of psoriatic arthritis influence your management plan?*	Yes No	20 (87%) 3 (13%)
	Choice of treatment *"much more likely to use methotrexate for instance if you had evidence of any comorbidities or psoriatic arthritis, or even biologics" [PD5]* *"I'm much more likely to go to methotrexate early if they have arthritis rather than phototherapy" [PD3]*	9/20 (45%)
	More aggressive approach "*I would push them forwards very quickly" [PD23]* *" I would probably go sooner to disease modifying drugs" [PD20]*	8 (40%)
	Single treatment for skin and joints *"we would work out what would do well for both the skin and the joints" [PD14]* *"if it was severe enough to warrant a systemic then you could try and treat both aspects with one drug, that would be beneficial for the child" [PD10]*	5 (25%)
	Easier to treat skin *"It may make it easier to treat the skin because we've not got NICE approval" [PD19]*	2 (10%)

In your experience, what are the long-term outcomes in children with psoriasis and psoriatic arthritis?*	Unsure *"honestly I don't know, I have a hunch that it is probably not so good" [PD23]* *"haven't a clue" [PD3]* *"I don't really have the experience to know" [PD8]*	12 (52%)
	More likely to have severe and persistent psoriasis *"I would say they are more disease resistant at times, they are going to have difficult treatment, difficult disease to get under control" [PD22]* *"I have followed children up into their 30s and those children with difficult psoriasis in childhood have disease in adulthood" [PD12]*	11 (48%)
	Poorer compared to children with psoriasis alone *"I would feel that if they've got multi-system disease it is more likely to be more aggressive and therefore the prognosis is worse I imagine" [PD18]* *"I always worry that they are going to have a poor outcome" [PD17]*	6 (26%)
	Increased concern about comorbidities *"quality of life, self-esteem, and possibility comorbidity" [PD4]* *"we are all worried all of the time about comorbidities in psoriasis …. chronic inflammatory burden of psoriasis and psoriatic arthropathy will feed into that" [PD14]*	4 (17%)
	Psoriasis is likely to do well on rheumatological drugs *"if they do have to go on a systemic for their joints then their skin tends to do rather well and in the long-term their skin does better than children who are not treated early with a systemic" [PD1]*	4 (17%)
	Other: increased need for aggressive treatment, joint disease can be disabling, poorer quality of life *"I have seen some horrible permanent joint deformity with very very significant impact on function in those with really bad psoriatic arthritis ….. so that is a massive impact on quality of life, function" [PD6]*	6 (26%)

Table 4:4 Interviews with paediatric dermatologists: Impact a diagnosis of juvenile psoriatic arthritis has on clinical care and the presentation of skin and joint disease
**More than one response possible*

4.4.2.4 Recommendation on how paediatric rheumatologists could look for psoriasis in children

Thirteen (57%) paediatric dermatologists recommended a full examination of the skin, ensuring that hidden sites are examined (8/23, 35%). Eight (35%) recommended paediatric rheumatologists referred children with a juvenile idiopathic arthritis and a rash to dermatology for a diagnosis. Four (17%) paediatric dermatologists commented that the pattern of psoriasis in children is different to adults and misdiagnosis is common. Whereas three (13%) clinicians felt that paediatric rheumatologists' approach and recognition of skin disease was good. No specific tool was recommended by paediatric dermatologists for the recognition of psoriasis.

"I would suggest they look at the scalp, and behind the ears, belly button, under the arms, gluteal cleft, check their nails. I think quite often you can see something in the nails fairly early …. No, more a question of actually looking rather than specific tools really, I think it is getting to remember to look" [PD1]

"describe psoriasis looks like when it is classical but also to describe more subtle lesions that might be available, obviously the distribution and that's not the same in children as adults" [PD8]

"Well I mean, as we struggle with joints they struggle with skin and they can sometimes mistake different types of rashes for psoriasis" [PD5]

4.4.2.5 Thematic content analysis

The thematic content analysis generated four main themes: i) identity and attitudes; ii) knowledge; iii) barriers to action; iv) age specific differences in managing children compared to adults with psoriasis. The themes are presented in Table 4:5. Respondent quotations are used to substantiate each theme and subtheme. Saturation of themes was achieved when no new themes emerged in three consecutive transcripts. In specific regard to theme 3, subtheme 'set up of paediatric services', currently none of the dermatologists interviewed offer a combined paediatric dermatology/rheumatology clinic at their centre, but many share care between the two specialties for children with skin and joint disease. The contact between consultants varied between referral by letter and direct contact.

Theme	Subtheme	Quotations from paediatric dermatologists
Identity and attitude	**Confidence** Low confidence due to limited training and guidance.	*'I'm not that confident' [PD3]* *'I don't think I would ever be confident examining joints or be confident clinically' [PD9]* *'I don't regard myself as doing a proper musculoskeletal examination' PD1]*
	Awareness Opinions on ease of detecting juvenile psoriatic arthritis varied but the need for vigilance by clinicians and families for juvenile psoriatic arthritis is recognised	*'I think we would be able to tell if there is a serious inflammatory joint problem' [PD4]* *'you may not see inflammation as easily [PD6]* *'I do highlight to parents at the first visit that there can be a link and it is important if they develop any joint symptoms or signs to check it' [PD6].*
	Division of roles Joint assessment and examination was strongly associated with paediatric rheumatology	*'if there is evidence of arthritis I hand them off to the rheumatologists' [PD3]* *'because we work so closely I've never really taken it on board (assessment of joints)' [PD1]*
Knowledge	**Uncertainty** Unsure about the clinical presentation and long-term health outcomes	*'I don't know, I haven't seen enough to give a valid answer for that' [PD17]* *'I don't think I can answer that because I am not involved enough in follow-up' [PD1]* *'what information about psoriatic arthritis starting in children and how is the natural history of this condition progressing on to adulthood, I don't think there is hardly any data' [PD3].*
	Treatment Choice of treatment is influenced by knowledge and understanding of the disease	*'much more likely to go to methotrexate early if they have arthritis rather than phototherapy' [PD2]* *'in the long-term their skin does better than children who are not treated early with a systemic' [PD1]*
	Disease impact Disability and challenging management	*'I have seen some horrible permanent joint deformity with very, very, significant impact on function' [PD6]* *'you know these are going to be difficult cases for life' [PD22].*
Barriers to action	**Signs and symptoms** Reliance on a history of joint symptoms to prompt examination	*'if they've had any joints that are sore, swollen or red' [P9]* *'if the specifically said one joint was troublesome then I would look more carefully at that' [PD7]*
	Set-up of paediatric services Variation in the working relationship between specialties and opportunity for training	*'we do a joint paediatric rheumatology-dermatology clinic every three months' [PD6]* *'they aren't geographically particularly close . . . I know the name of the paediatric rheumatologist but I've never met them' [PD8].*

Age specific differences	Differences in consultation requirements and presentation of disease	*'children won't necessarily localise pain or be able to describe joint pain in the same way as an adult' [PD4]* *'I think often the parental anxiety and involvement can be really difficult' [PD5]* *'you may not see inflammation as easily particularly if they are chubby, little tiny ones' [PD6]*

Table 4:5 Interviews with paediatric dermatologists: Main themes and subthemes from thematic content analysis

4.5 Discussion

4.5.1 Main findings

These interviews are the first two studies to detail and compare the experiences of paediatric rheumatologists', assessing for psoriasis in children with juvenile idiopathic arthritis, and paediatric dermatologists', assessing for juvenile psoriatic arthritis in children with psoriasis. Paediatric rheumatologists routinely ask about a personal and family history of psoriasis during their consultation, however only half of paediatric rheumatologists ask about or examine hidden sites, and a smaller number examine the groin (20%), genitals (10%) and natal cleft (10%). Most paediatric dermatologists ask about joint disease, but their assessment focuses on new patients, asking about joint pain and relies on symptoms to prompt an examination. Neither group of clinicians described a structured or consistent approach to assessing the skin and joints.

Paediatric rheumatologists and dermatologists differed in rating their self-confidence in assessing skin and joint disease. Paediatric rheumatologists rated their confidence in diagnosing psoriasis as moderate (likert average 6.4), whereas paediatric dermatologists rated their confidence in diagnosing juvenile psoriatic arthritis as low (likert average 3). Low confidence was also an important subtheme in the thematic content analysis of the dermatologists' interviews.

Both groups of clinicians rely on characteristic clinical features to recognise psoriasis and juvenile psoriatic arthritis. For paediatric rheumatologists, these are a classical appearance and distribution of the rash, whereas paediatric dermatologists rely on asking about pain. However, these are not the critical core features that specialists would recommend in order to detect psoriasis and juvenile psoriatic arthritis. An 'atypical appearance' and 'minimal amounts of skin disease' were two dominant themes as to why psoriasis may be difficult to diagnose by paediatric rheumatologists. Whereas paediatric dermatologists gave a 'lack of experience or training' and 'subtle signs' as the main reasons why detecting juvenile psoriatic arthritis may be difficult. Both paediatric rheumatologists and dermatologists suggested that clinical experience and training

would help their assessment. Paediatric rheumatologists also suggested a 'close working relationship' between the specialities and dermatologists suggested an 'assessment tool or guideline'. These suggestions support the need for combined clinics between paediatric rheumatology and dermatology, where widening the clinical experience of both specialties is an integral part of the clinic. There is evidence to support the benefit of combined rheumatology and dermatology clinics in adult medicine (Haberman et al., 2018).

Most paediatric dermatologists thought skin signs presented first in juvenile psoriatic arthritis, whereas paediatric rheumatologists were unsure about the order of presentation. Both groups recognised that their opinions were likely to be influenced by referral bias. Overall, for both paediatric rheumatologists and dermatologists, a diagnosis of juvenile psoriatic arthritis would change their management of skin and joint disease and they commented that further research was needed into long-term outcomes.

4.5.2 Strengths and limitations

The interviews were undertaken with a geographically diverse and institutionally varied group of paediatric rheumatologists and paediatric dermatologists, who are experts in their field, suggesting that their views and practices are likely to be representative of UK clinicians. Purposeful sampling of paediatric rheumatologists ensured 83% of UK regional centres were included in the interviews. The set-up of paediatric dermatology is not regionalised, but interviews with 23 participants provided a rich and detailed dataset and saturation of themes was achieved; this sample size is acceptable for elite interview qualitative research (Harvey, 2011). No specific data was collected on paediatric dermatologist non-responders, but geographical distribution and gender (74% vs 67%) representation was similar between paediatric dermatologists who took part in the interviews and those who did not respond to the email invitation.

It is likely that those who participated in the interviews were more likely to have a specialist interest in juvenile psoriatic arthritis and childhood psoriasis, and therefore implement best practice. The effect of this selection bias would be to minimise rather

than augment the conclusions of these interviews. It is also recognised that clinical assessment of psoriatic arthritis is not without its limitations and there is growing appreciation of the role ultrasound may play in the detection of subclinical enthesitis (Bandinelli et al., 2013).

The quality of the interviews was strengthened by the involvement of a qualitative researcher (Dr Joanne Cranwell), who provided methodological expertise on the analysis of the paediatric dermatology interviews. However, the interviews, familiarisation and coding of the data were conducted by one researcher (EBT). The themes, and supporting codes, were discussed with RM, SR and KT, providing an opportunity for interpretation of the data from multiple perspectives.

4.5.3 Implications for clinical practice

Opportunities exist for paediatric dermatologists and paediatric rheumatologists to learn from each other. Juvenile psoriatic arthritis may be missed by paediatric rheumatologists if psoriasis occurring in 'hidden sites' are not asked about and examined. It is important to examine these 'hidden sites' as there is sometimes discordance between patients' awareness of psoriasis and changes detected on examination. Dermatologists are best placed to develop paediatric psoriasis training material and diagnostic guidance for their rheumatology colleagues.

Paediatric dermatologists commonly associate inflammatory arthritis with pain or soreness; however these may not be the most important differentiating symptoms in detecting inflammatory arthritis in children. Joint swelling or loss of function may be more indicative of the presence of joint inflammation. Clinicians would therefore benefit from clearer guidance about core questions to ask when assessing for inflammatory arthritis in the history. The absence of specific screening tools for juvenile psoriatic arthritis was introduced in Chapter 2 (2.3.8 Juvenile psoriatic arthritis). An important finding from these interviews was that paediatric rheumatologists recommend the use of pGALS to screen for all types of joint disease in children (Foster et al., 2006). Due to dermatologists' lack of awareness of an examination-based tool and low confidence in

assessing joint disease, successful implementation of pGALS would benefit from a national strategy for dissemination and education amongst paediatric dermatologists.

4.5.4 Implications for this research project

Chapter 4 has explored current practice amongst paediatric rheumatologists and paediatric dermatologists in the assessment of skin and joint disease in psoriasis and juvenile psoriatic arthritis. The chapter builds and is congruent with the findings of Chapter 3, and the following questions will be taken forward in this thesis.

1. **How can psoriasis in children be better recognised and diagnosed by clinicians who review children with rashes?** This chapter has shown that non-dermatologists are not looking for psoriasis in 'hidden sites' and there is a lack of awareness that the presentation and distribution can be different in a paediatric population. The development of diagnostic criteria for psoriasis in children and an accompanying educational package may provide clinicians with this guidance. It is not known whether research towards developing diagnostic criteria has been initiated and what methodology has been employed. This question is taken forward in Chapters 6 and 7.

2. **Excluding treatment, what is our current evidence base for psoriasis in children?** Clinician's opinions differ on the chronological onset of skin and joint disease in juvenile psoriatic arthritis. Paediatric dermatologists are unsure about the clinical presentation and long-term outcomes for children with psoriasis and psoriatic arthritis. Greater understanding of the timing of onset will inform which screening setting for juvenile psoriatic arthritis would be most useful: paediatric dermatology, paediatric rheumatology and/or primary care. This question is taken forward in Chapter 5.

Chapter 5 Mapping the evidence and identifying research gaps in the epidemiology of childhood psoriasis: A scoping review

5.1 Introduction

Chapters 3 and 4 have reviewed and explored current practice in the assessment and management of psoriasis and juvenile psoriatic arthritis. They have identified improving early detection of psoriasis and therefore juvenile psoriatic arthritis as opportunities for early intervention, which may help to prevent long-term harm. The NICE guideline (audit standard for Chapter 3) collated and appraised the evidence for the treatment of psoriasis in children, but the diagnosis and epidemiology of psoriasis was out of scope of the guideline development. Improved understanding of the natural history of psoriasis in children and the relationship with juvenile psoriatic arthritis would help inform screening for juvenile psoriatic arthritis, as well as identifying other opportunities for early intervention. Epidemiological studies not only contribute to understanding distribution and determinants of disease, but also inform the development of primary and secondary prevention measures, including therapeutic interventions (Haynes et al., 2004).

Chalmers *et al*. in a series for the Lancet explained that an important part of reducing research wastage is to make a systematic assessment of what is already known or being researched. This approach ensures there is no unnecessary duplication and that new research can address deficiencies in previous studies (Chalmers et al.,

2014). Therefore, the next step before proposing a primary research study was to systematically search for and map the existing literature on the natural history of psoriasis in children.

I proposed a scoping review on the epidemiology of psoriasis in children in order to provide an overview of the epidemiological studies and data available. Scoping reviews aim to map the existing literature in a field of interest in terms of the volume, nature and characteristics of the primary research (Pham et al., 2014). A scoping review can therefore identify gaps in the available evidence. The subject topic of the epidemiology of childhood psoriasis was too broad for an individual systematic review, but a scoping review can be the starting point for identifying a focused research question.

The aim of this Chapter was to catalogue the number, type, population and timeline of studies providing data on the epidemiology of psoriasis in children. This information provides a picture of where research activity is concentrated. The scoping review also aimed to provide a comprehensive clinically useful summary about the frequency, clinical presentation, risk factors, comorbidities and long-term outcomes for children with psoriasis.

This work was published in the British Journal of Dermatology (Burden-Teh et al., 2016).

Burden-Teh E, Thomas KS, Ratib S, Grindlay D, Adaji E, Murphy R. The epidemiology of childhood psoriasis: a scoping review. Br J Dermatol. 2016 Jun;174(6):1242-57.

5.2 Objectives

1. To map the volume, nature and characteristics of research on the epidemiology of childhood psoriasis

2. To summarise the available evidence answering these four questions:
   I. What is the prevalence, incidence and clinical presentation of childhood psoriasis?
   II. What are the genetic and environmental factors associated with the onset of psoriasis in childhood?
   III. What other conditions are associated with psoriasis in children?
   IV. What are the long-term outcomes for patients with child-onset psoriasis?

5.3 Methods

5.3.1 Study design

Scoping review

5.3.2 Search strategy

The search strategy was designed with an information specialist (DG) (Appendix 4). The strategy was designed around three core concepts 'child' AND 'psoriasis' AND 'epidemiology'. It utilised both MeSH headings and free text search terms. The aim was to create a sensitive search, which would capture all articles related to these concepts. OVID MEDLINE In-Process & Non-Indexed Citations and OVID MEDLINE 1948 to present, and OVID Embase were searched on 27th May 2015. The reference lists of studies included in the review and non-systematic review articles were hand searched until saturation was reached and no further additional studies were identified. Google Scholar was searched using the terms 'epidemiology of psoriasis in children' and 'epidemiology of paediatric psoriasis' and the first 100 citations were reviewed on 15th September 2015.

5.3.3 Eligibility criteria

Articles were included if they were observational studies about child-onset psoriasis, or studies with separated data for this group, that provided primary epidemiological data on one of the four core questions. Children were defined as those with a disease onset under the age of 18 years, although flexibility was shown for studies with grouped data including patients up to the age of 20 years. Systematic reviews of observational studies were included. Therapeutic intervention studies were excluded. Single case reports were also excluded, because they did not provide group level data about psoriasis in children. Non-English studies (n=8) and conference abstracts (n=16) were included as part of mapping the research characteristics, but the results data were not extracted. Non-English studies and conference abstracts were excluded because of insufficient resources for translation and incomplete data contained within the abstracts.

5.3.4 Data management

Titles, abstracts and where available full-text articles were screened by two authors (EBT and EA). The full-text of studies which met the inclusion criteria were independently assessed for eligibility by two authors (EBT and RM). Data extraction was undertaken by one author (EBT) using a structured form (Appendix 5). The accuracy of data extracted from 10% of included studies was checked by a second author (RM). Studies were categorised for mapping according to definitions and description of methods provided in the published articles. Where there was uncertainty regarding the classification this was discussed between two authors (EBT and SR).

5.3.5 Data synthesis

Critical appraisal of individual studies and meta-analysis was not performed, because this is outside the purpose of a scoping review. By nature, the breadth of the review question and heterogeneity of the studies required a narrative synthesis.

5.4 Results

Figure 5:1 presents a flow diagram showing the inclusion and exclusion of studies from identification to synthesis. The search strategy yielded 2490 potential citations. After removal of duplicates, initial screening, and review for eligibility, 112 articles remained. A further 19 articles were identified through hand-searching and Google Scholar. In total 131 articles were mapped. After removal of non-English studies and conference abstracts, 107 articles were included in the results summary.

5.4.1 Mapping of studies

The characteristics of included studies are presented in Table 5:1. There has been a linear increase in the number of observational studies on child-onset psoriasis over the past 20 years (1996-2000 n=8, 2011-2015 n=50) Figure 5:2. Most studies were based in Europe (65/131), in particular the UK (10/131), Sweden (9/131), Germany (7/131) and Turkey (6/131).

Cross-sectional studies (75/131) and case-series (30/131) were most frequent study types. The majority of studies were based in secondary/hospital care (95/131), and a smaller number collected data from the general population (18/131) or used routinely collected health data (17/131). No studies were based in primary care. Observational studies conducted up to 2015 have concentrated on the prevalence or incidence of psoriasis (47/131), age of onset/gender/family history of people with psoriasis (69/131) and clinical presentation of psoriasis (63/131).

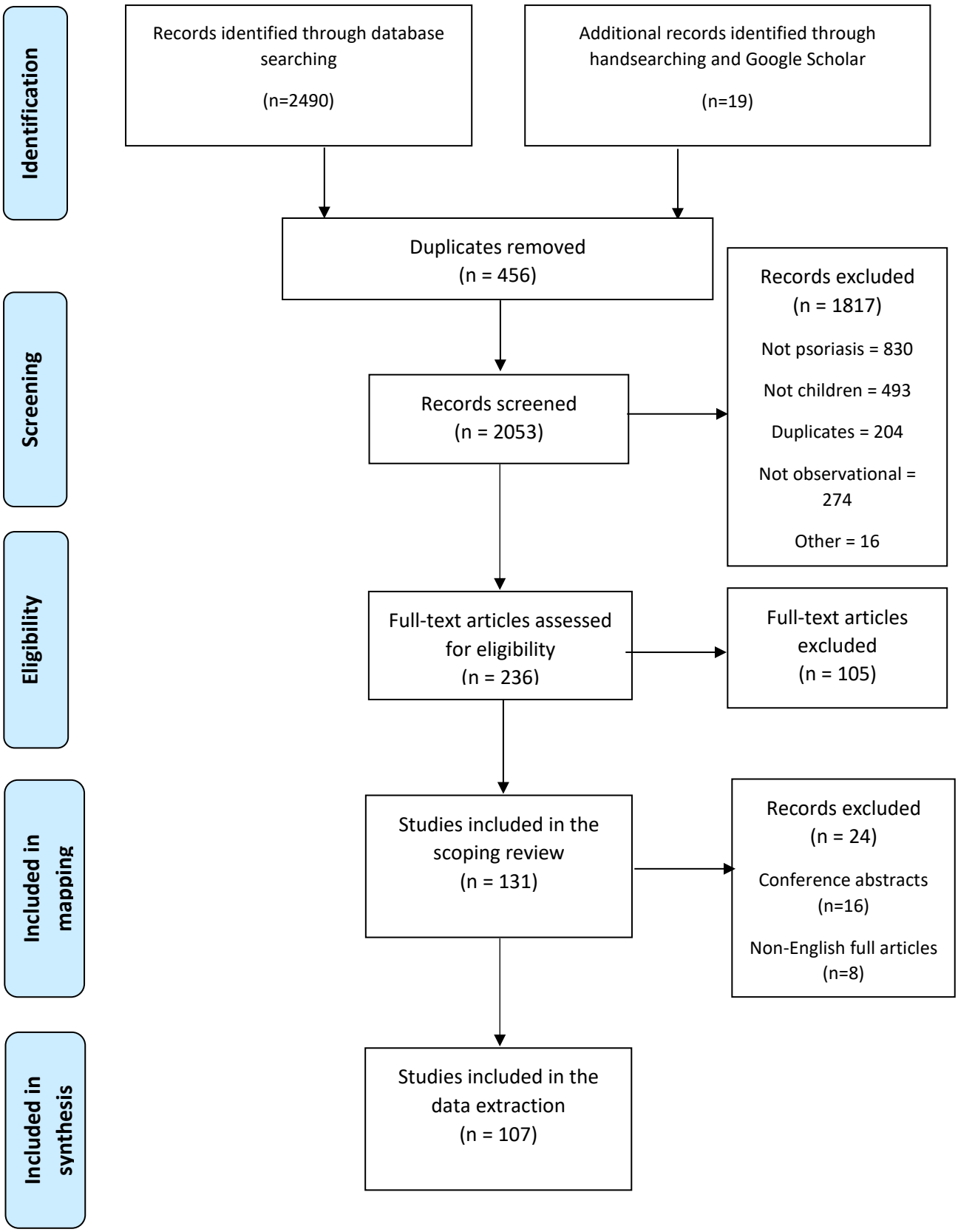


Figure 5:1 Flow diagram showing the inclusion and exclusion of studies from identification to synthesis

Study Characteristic		Number of studies, n=131, (%)
Publication year	<1995	18 (14)
	1996-2000	8 (6)
	2001-2005	15 (11)
	2006-2010	40 (30)
	2011-May 2015	50 (39)
Study location	Europe	65 (49)
	Asia	26 (20)
	North America	22 (17)
	Africa	10 (8)
	South America	3 (2)
	Australasia	3 (2)
	Study locations in ≥2 continents	2 (1)
Publication type	Full journal article	107 (82)
	Conference abstract	16 (12)
	English abstract only	8 (6)
Study type	Systematic review	1 (<1)
	Prospective cohort	3 (2)
	Retrospective cohort	12 (9)
	Case-control	10 (8)
	Cross-sectional	75 (58)
	Case-series	30 (23)
Study population	Primary care	0
	Secondary/hospital care	95
	Routinely collected health data	17
	General population	18
	Unspecified	1
Epidemiological data*	Prevalence and incidence	47
	Age of onset, gender, family history	69
	Clinical presentation	63
	Risk factors for disease onset	27
	Genetics	8
	Associated disease/comorbidities	24
	Juvenile psoriatic arthritis	21
	Long-term outcomes	22

Table 5:1 Mapping of study characteristics of full articles, conference abstracts and abstracts from non-English papers included in the scoping review
**Studies often contained more than one category of epidemiological data*

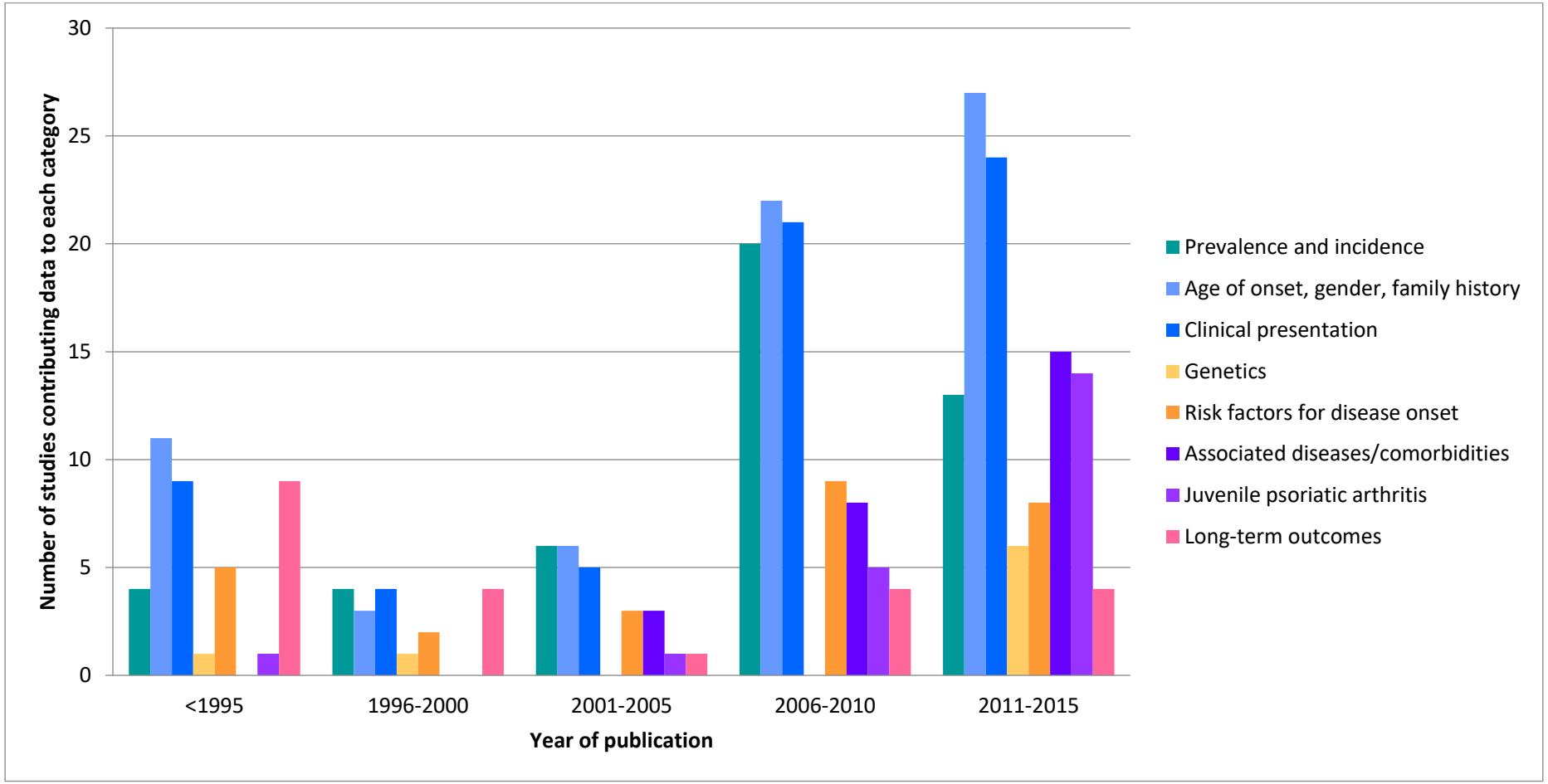


Figure 5:2 Graph presenting number of studies contributing data to each epidemiological category according to year of publication

5.4.2 What is the prevalence, incidence and clinical presentation of childhood psoriasis?

5.4.2.1 Incidence and prevalence

Overall, there were two incidence studies, 37 prevalence studies and one systematic review (Parisi et al., 2013). Seventeen prevalence studies were population-based (Augustin et al., 2010, Augustin et al., 2012, Augustin et al., 2015, Braathen et al., 1989, Chen et al., 2008, Ferrandiz et al., 2001, Gelfand et al., 2005b, Koebnick et al., 2011, Larsson and Liden, 1980, Matusiewicz et al., 2014, Naldi et al., 2009, Popescu et al., 1999, Seminara et al., 2011, Shapiro et al., 2007, Wu et al., 2011, Yamamah et al., 2012, Yang et al., 2007). Twenty studies were secondary/hospital care prevalence studies (Al-Dhalimi, 2007, Al-Hoqail, 2013, Alakloby, 2005, Bilgili et al., 2013, Child et al., 1999, El Euch et al., 2003, El-Khateeb, 2011, Fischer, 2010, Goh and Akarapanth, 1994, Gul et al., 2008, Kapila et al., 2012, Katsarou et al., 2012, Kawada et al., 2003, Leclerc-Mercier et al., 2010, Leow and Giam, 1994, Nanda et al., 1999, Seyhan et al., 2006, Stefanaki et al., 2011, Sinniah et al., 2010, Storan et al., 2013).

The prevalence of childhood psoriasis varied depending on the study population included. Estimates reported from population-based studies ranged from 0% to 2.1%, the highest values were from European studies, Italy (2.1%, n=3179 (Naldi et al., 2009)), Germany (1.3%, n=192,014 (Augustin et al., 2012)) and UK (1.3% (95%CI 134.84-139.93) for 10-19 year olds (Gelfand et al., 2005b)) compared to a low prevalence reported in Taiwan (0%, n=4076 and n= 3273 (Yang et al., 2007, Chen et al., 2008)) and Egypt (0.05%, n=2194 (Yamamah et al., 2012)). Studies which stratified prevalence according to age reported psoriasis to be more common after puberty, 0.6% to 1.3%, than before puberty, 0.1% to 0.5%. Psoriasis was a fairly common presentation in paediatric dermatology clinics with a reported secondary care/hospital prevalence of 0.7% to 6.2%.

With regard to incidence studies, a health survey of self-reported psoriasis in Norwegian twins showed that incidence of psoriasis increased with age throughout childhood (0-3 years to 16-19 years) from 0.5 to 2.9 (95%CI 0.27-0.93, 2.20-3.83) and

0.3 to 2.0 (95%CI 0.11-0.80, 1.36-2.94) per 1000 person years in girls and boys respectively (Olsen et al., 2005). Tollefson *et al.* showed that the number of children diagnosed with psoriasis had increased over a 30 year period in the United States from 29.6 to 62.7 (95%CI 20.9-38.3, 50.4-65.0) per 100 000 patient years. Proposed reasons for this increase included changes in risk factors such as psychosocial stress, infection and obesity, but an increase in incidence could also be result of improved reporting of psoriasis. (Tollefson et al., 2010).

Studies varied in how cases of psoriasis were ascertained (self-reported, diagnostic codes in health records, physician examination) and potentially how psoriasis was defined; most studies required a 'clinical diagnosis' of psoriasis with no pre-defined criteria.

5.4.2.2 Gender

Forty-two studies provided data on the gender distribution in childhood psoriasis. Thirty-three studies provided data on the percentage of the study population which were male (Andersen and Thomsen, 1971, Al-Hamdi, 2008, Al-Mutairi et al., 2007, Alsuwaidan, 2011, Becker et al., 2014, Bellet et al., 2009, Boccardi et al., 2009, Chandran et al., 2012, de Jager et al., 2010, De Jager et al., 2011, de Oliveira et al., 2010, Fan et al., 2007, Farber and Nall, 1974, Kapila et al., 2012, Kumar et al., 2004, Kwon et al., 2012, Lam et al., 2015, Lysell et al., 2015, Mahe et al., 2013, Masood et al., 2011, Morris et al., 2001, Moustou et al., 2014, Nanda et al., 1990, Nanda et al., 2000, Nyfors and Lemholt, 1975, Oostveen et al., 2014, Raychaudhuri and Gross, 2000, Seyhan et al., 2006, Stefanaki et al., 2011, Vogel et al., 2012, Winge et al., 2013, Wu et al., 2011, Zelickson and Muller, 1991).

Twenty five of these 33 studies found that less than half of children with psoriasis were boys (range 35.9-49%).The male to female ratio was provided in 16 studies and varied from 1.14:1 to 1:2.33 (Al-Hamdi, 2008, Al-Mutairi et al., 2007, Chiam et al., 2011, Kim et al., 2010, Kumar et al., 2004, Kwon et al., 2012, Leow and Giam, 1994, Mercy et al., 2013, Nanda et al., 1990, Nanda et al., 2000, Ozden et al., 2011, Popadic and Nikolic, 2014, Seyhan et al., 2006, Stefanaki et al., 2011, Tollefson et al., 2010,

Wu et al., 2010). Matusiewicz *et al.* (n=1, 200,000) reported that the prevalence of psoriasis in children was lower in boys than girls, 0.35% (95%CI 0.33-0.36) compared to 0.44% (95%CI 0.43-0.46) (Matusiewicz et al., 2014), and Farber *et al's* survey of 5600 psoriasis patients found that childhood onset in boys was less common than girls (Farber and Nall, 1974). This female predominance in the prevalence of childhood psoriasis is the opposite of what is commonly observed in adults (Hagg et al., 2013).

5.4.2.3 Age of onset

Age of onset of psoriasis was reported by 30 studies. The range of age of onset was reported by 17 studies and included from birth to 18 years (Bellet et al., 2009, Boje Rasmussen et al., 1986, Chandran et al., 2012, Chiam et al., 2011, de Oliveira et al., 2010, Fan et al., 2007, Farber et al., 1986, Kumar et al., 2004, Lam et al., 2015, Liao et al., 2002, Morris et al., 2001, Nanda et al., 1990, Nanda et al., 2000, Popadic and Nikolic, 2014, Seyhan et al., 2006, Stefanaki et al., 2011, Zelickson and Muller, 1991). The average age of onset was reported by 22 studies and varied from 2.1 months to 10.6 years (Andersen and Thomsen, 1971, Becker et al., 2014, Bellet et al., 2009, Chandran et al., 2012, Chiam et al., 2011, Fan et al., 2007, Kapila et al., 2012, Kwon et al., 2012, Lam et al., 2015, Leow and Giam, 1994, Mahe et al., 2013, Nanda et al., 1990, Nanda et al., 2000, Neville and Finn, 1975, Nyfors and Lemholt, 1975, Oostveen et al., 2014, Ozden et al., 2011, Popadic and Nikolic, 2014, Stefanaki et al., 2011, Tollefson et al., 2010, Winge et al., 2013, Wu et al., 2010).

Age of onset may vary with psoriasis subtype. An earlier age of onset was reported for pustular psoriasis (Bellet et al., 2009, Popadic and Nikolic, 2014). Popadic *et al.* (n=20) described the 20 year experience of childhood pustular psoriasis at their centre and found that 50% of children presented before 1 year old (Popadic and Nikolic, 2014). The average age of onset in plaque psoriasis is less clear. This variation may reflect differences in subtype definition, for example, inclusion of scalp, flexural or napkin psoriasis in the term plaque psoriasis. Leow and Giam reported a case-series of 112 children; 91.9% had plaque psoriasis and 37.5% developed psoriasis under 1 year old (Leow and Giam, 1994). However, four studies

including children with predominantly plaque psoriasis reported an average age of onset around 10 years (Fan et al., 2007, Katsarou et al., 2012, Kwon et al., 2012, Wu et al., 2010). Only one study of 245 children with mostly guttate psoriasis (44%) found a clear peak in age of onset for girls, at eight years, but possibly three peaks for boys, at 5, 10 and 13 years (Nyfors and Lemholt, 1975).

Reliance on medical documentation and patient/parent recall, as well as inconsistencies in subtype definition, all contribute to difficulties in accurately understanding age of onset in childhood psoriasis.

5.4.2.4 Family history

Thirty-eight studies provided data on family history (Al-Hamdi, 2008, Alsuwaidan, 2011, Andersen and Thomsen, 1971, Becker et al., 2014, Bellet et al., 2009, Boccardi et al., 2009, Boje Rasmussen et al., 1986, Chandran et al., 2012, Chiam et al., 2011, de Jager et al., 2010, de Oliveira et al., 2010, Fan et al., 2007, Farber et al., 1986, Ganemo et al., 2011, Kapila et al., 2012, Kim et al., 2010, Kumar et al., 2004, Kwon et al., 2012, Leow and Giam, 1994, Lysell et al., 2015, Mahe et al., 2013, Mahe et al., 2015, Masood et al., 2011, Mercy et al., 2013, Morris et al., 2001, Moustou et al., 2014, Neville and Finn, 1975, Nanda et al., 1990, Nanda et al., 2000, Nyfors and Lemholt, 1975, Oostveen et al., 2014, Ozden et al., 2011, Popadic and Nikolic, 2014, Raychaudhuri and Gross, 2000, Seyhan et al., 2006, Stefanaki et al., 2011, Zelickson and Muller, 1991, Wu et al., 2010).

The percentages of children with a positive history in a first degree relative varied from 6.2% to 54.7% and a positive family history in any family member from 4.5% to 88%. Farber *et al.* (n=645) found that adolescents with psoriasis (10-19 years) were most likely to have a family member with psoriasis (33%), compared to other age groups (Farber and Nall, 1974). The large variation reported in family history of psoriasis may in part be due to genetic differences between ethnic populations. For example, a study comparing Asian and European children (n=207) found only 13.6% of Singaporean children had a first or second degree relative affected by psoriasis compared with 73.3% of Dutch children (Chiam et al., 2011). This supports child-

onset psoriasis as a genetically heterogeneous condition and further research is needed into gene-environment interactions in different populations.

5.4.2.5 Clinical presentation

Eleven studies reported the initial body site of presentation in child-onset psoriasis (Chandran et al., 2012, Fan et al., 2007, Kim et al., 2010, Kumar et al., 2004, Leow and Giam, 1994, Mahe et al., 2013, Nanda et al., 2000, Ozden et al., 2011, Raychaudhuri and Gross, 2000, Seyhan et al., 2006, Wu et al., 2010). Collectively they included nearly 3000 children. The scalp, limbs and trunk were the most common body sites affected (17.9% to 64.8%, 9.5% to 90%, and 7.8% to 93.3% respectively). The face was a common site of presentation, 3.5% to 56.7%, and facial involvement may be an important clinical sign when differentiating psoriasis from eczema in children (Kapila et al., 2012). Napkin skin changes were present in most infants with psoriasis and therefore this feature needs to be considered an important presenting sign in this age group (Farber et al., 1986).

Twenty-three studies presented data on the frequency of different subtypes in childhood psoriasis (Al-Hamdi, 2008, Becker et al., 2014, Chandran et al., 2012, Chiam et al., 2011, de Jager et al., 2010, Fan et al., 2007, Ganemo et al., 2011, Kapila et al., 2012, Kim et al., 2010, Kumar et al., 2004, Kwon et al., 2012, Leow and Giam, 1994, Lysell et al., 2015, Mahe et al., 2015, Morris et al., 2001, Masood et al., 2011, Moustou et al., 2014, Nanda et al., 1990, Nanda et al., 2000, Seyhan et al., 2006, Stefanaki et al., 2011, Tollefson et al., 2010, Wu et al., 2010). Similar to the adult population, the most common subtype was chronic plaque. The percentage of children of children with specific subtypes were: plaque psoriasis 9% to 91.9%, guttate psoriasis 1.6% to 48.2%, pustular 0% to 13.1%, erythrodermic 0.1% to 5.8%, palmoplantar 0.9% to 12.8%. Nail psoriasis was also a common subtype or current site of involvement, between 2% and 39.3%, and one study of 419 children found it to be the sole presenting feature in 2.3% of patients (Kumar et al., 2004).

A few studies have compared the clinical presentation of childhood psoriasis according to ethnicity, gender and age. No clear conclusions can be drawn about the

effect of ethnicity (Chandran et al., 2012, Chiam et al., 2011). The clinical presentation may vary according to gender. A multicentre cross-sectional study of 181 children from the United States found that nail psoriasis was found more frequently (odds ratio (OR) 3.01 (95%CI 1.62-5.6)) and scalp psoriasis less frequently (OR) 0.40 (95%CI 0.19-0.84)) in boys compared to girls (Mercy et al., 2013). The authors suggested that this may be a result of the Kobener phenomenon, because boys may be more physical with their hands and girls may brush their hair more often.

Age appears to be an important factor influencing presentation. Kwon *et al.* (n=382) reported that guttate and generalised pustular psoriasis were significantly more common in children under the age of 12 years (27.6% vs 13.5% and 11.6% vs 4.8% respectively) (Kwon et al., 2012). Flexural involvement was found to be more common in pre-pubertal children (adjusted OR 2.8, 95%CI 1.1-7.1, $p<0.05$), especially boys (adjusted OR 2.5, 95%CI 1.1-6.1, $p<0.05$) (Lysell et al., 2015). In a study of 30 adults and 30 children, Kim *et al.* found involvement of the face to be a more frequent presentation in children compared to adults (56.7% vs 26.7%) (Kim et al., 2010).

Percentages for the frequency of initial site of presentation and subtype of psoriasis varied widely. Possible explanations include differences in clinic populations studied as well as the definition, assessment and documentation of subtypes and sites of presentation.

5.4.3 What are the genetic and environmental factors associated with the onset of psoriasis in childhood?

5.4.3.1 Genetic factors

Eight studies reported genetic findings on paediatric-onset psoriasis (Table 5:2) (Bergboer et al., 2012, Brenner et al., 1978, Lysell et al., 2013a, Lysell et al., 2015, Nanda et al., 2000, Nikamo et al., 2014, Oostveen et al., 2014, Winge et al., 2013).

The studies suggest a difference in the genetics of pre- and post-pubertal onset psoriasis. Lysell *et al.* (2013) found that endoplasmic reticulum aminopeptidase type 1 (ERAP1) was only associated with onset of psoriasis between the ages of 10 and 20 years (Lysell et al., 2013a). In 2015, Lysell *et al.* that the found the proportion of HLA-C*06 positive patients was higher amongst those with post-pubertal onset (Lysell et al., 2015). Conversely, the IL-22 promotor and IL12B were only associated with onset of psoriasis under the age of 10 years (Nikamo et al., 2014, Oostveen et al., 2014).

Nanda *et al.* found no association between psoriasis and HLA-C*06 in Kuwaiti children, unlike similar studies in mostly Caucasian children (Nanda et al., 2000). This study highlights the need for genetic studies in more diverse populations.

Two studies specifically looked at the genotype-phenotype correlation. HLA-C*06 was associated with guttate psoriasis (OR 3.4, 95%CI 1.1-10.7, $p<0.5$) and facial lesions (OR 3.8, 95%CI 1.5-9.7, $P<0.01$), after controlling for demographic variables (Lysell et al., 2015), but HLA-C*06 negative patients were found to have greater nail involvement (OR 0.32, 95%CI 0.14-0.76) (Oostveen et al., 2014). Whilst there are some data, it is evident that further genotype-phenotype correlations in childhood psoriasis are needed.

Genetic factors in childhood psoriasis					
Author, year	Country	Study design	Type of psoriasis	Sample size (pre-pubertal)	Main genetic findings
Bergboer *et al*, 2012	Netherlands	Case-control. 217 patients stratified by age of onset and 450 healthy controls	Psoriasis vulgaris excluding solitary scalp or napkin psoriasis	80	IL23R, ERAP1, LCE3C_LCE3B deletion and HLA-C*06 significantly associated with paediatric-onset psoriasis.
Brenner *et al*, 1978	Austria	Cross-sectional. 77 patients stratified by age of onset.	Psoriasis vulgaris excluding pustular psoriasis and psoriatic arthritis	57	Higher prevalence of HLA-Cw6 in patients with an age of onset between 10-20 years compared to 35-45 years.
Lysell *et al*, 2013	Sweden	Case-control. 954 patients stratified by age of onset and 1748 controls	Plaque or guttate psoriasis excluding solitary scalp or napkin psoriasis	322 (119)	Strongest association for HLA-C*06:02 and a significant association with ERAP1 in patients with an age of onset between 10 and 20 years. ERAP1 was not associated with onset of psoriasis under the age of 10 years.
Lysell *et al*, 2015	Sweden	Cross-sectional. 109 patients recruited stratified for pre-pubertal and post-pubertal onset	All psoriasis types except solitary scalp of napkin psoriasis	109 (63)	HLA-C*06 associated with age of onset controlling for family history, guttate phenotype and facial lesions controlling for demographic variables. Higher proportion of HLA-C*06 positive patients in post-pubertal children.
Nanda *et al*, 2000	Kuwait	Cross-sectional. 50 patients recruited under the age of 12 years and 120 controls	Not specified	50	Significant association with HLA-A3, HLA-Cw1 and HLA-DR7. No association found with HLA-Cw6
Nikamo *et al*, 2014	Sweden	Case-control. 1069 patients recruited stratified for age of onset and 1529 controls	Not stated. Solitary scalp or napkin psoriasis excluded	603 (207)	IL22 promotor association confined to onset before the age of 10 years
Oostveen *et al*, 2014	Netherlands	Case-control. 151 patients recruited stratified for age of onset before or after the age of 10 years, and 450 controls	Plaque-type psoriasis	151 (86)	IL23R, ERAP1, HLA-C806, LCE3C_LCE3B deletion and HLA-C*06 significantly associated with paediatric-onset psoriasis. IL12B significantly associated with age of onset <10 years
Winge *et al*, 2013	Sweden	Case-control. 241 patients recruited under the age of 15 years and 314 controls	Not specified	241	No association with FLG mutations (prevalent or novel) in early onset psoriasis

Table 5:2 Studies reporting genetic factors in childhood psoriasis

5.4.3.2 Environmental factors: Infection, emotional stress, trauma and obesity

Trigger factors for the onset of psoriasis were reported in 20 studies but often the study design employed did not allow the time relationship between exposure and the onset of psoriasis to be assessed. The data from these 20 studies are presented in Table 5:3 (Al-Hamdi, 2008, Becker et al., 2014, Boccardi et al., 2009, Chiam et al., 2011, de Oliveira et al., 2010, Fabrizi et al., 2001, Kim et al., 2010, Kumar et al., 2004, Leow and Giam, 1994, Mercy et al., 2013, Nanda et al., 1990, Nanda et al., 2000, Nyfors and Lemholt, 1975, Oostveen et al., 2014, Ozden et al., 2011, Raychaudhuri and Gross, 2000, Seyhan et al., 2006, Wu et al., 2010, Zelickson and Muller, 1991, Koebnick et al., 2011). Only one paper, Ozden *et al.*, specifically investigated environmental risk factors for the onset of childhood psoriasis in a case control study (Ozden et al., 2011).

Infection was identified as a potential trigger factor in up to 43.4% of children. The most commonly described infection was an upper respiratory tract infection. Two studies specifically reported streptococcal infection, occurring in 22.1% (n=181) to 21.3% (n=61) of children (Mercy et al., 2013, Seyhan et al., 2006), and Nyfors and Lemholt (n=245) found elevated antistreptococcal titres in 60% of children with psoriasis (Nyfors and Lemholt, 1975). Other types of infectious triggers were urinary tract infections, chicken pox and otitis media.

Stress was identified as a potential trigger factor in 1% to 66.7% of children; this was mostly defined as emotional or psychological stress. Ozden *et al.* (n=1048) found that a stressful life event was a risk factor for the onset of psoriasis (OR 2.94, 95%CI 2.28-3.79) (Ozden et al., 2011).

A history of trauma was identified as a potential trigger factor in 1 to 11.5% of children. Koebnerisation was reported in 20.4% to 49.6% of children but further details about the timing in relation to disease onset were not always reported.

Obesity may be an important risk factor for the onset of psoriasis. Ozden *et al.* (n=1048) found that that a BMI >26kg/m^2 was a risk factor for psoriasis in children

(OR 2.52, 95%CI 1.42-4.49). A small retrospective cohort study of 27 children with psoriasis found a diagnosis of obesity or being overweight preceded psoriasis in 93% of children (Becker et al., 2014). Boccardi *et al.* (n=96) reported that the OR of being obese at first diagnosis of psoriasis was 2.55 (95%CI 1.31-4.96) (Boccardi et al., 2009).

There is a need for studies to differentiate between risk factors for disease onset and aggravating factors for a disease flare. Details on identification and measurement of potential risk factors are often minimal, making evaluation of their clinical relevance difficult.

Environmental risk factors in childhood psoriasis							
Author, year, country	Participants	Type of psoriasis	Sample size	Infection	Stress	Trauma	Other
Retrospective cohort studies							
Becker *et al*, 2014, USA	5-17 years,	Psoriasis type not specified	27 (no controls)				Overweight or obesity (BMI >85th and >95th percentile) preceded psoriasis by >2 years in 93%
Case-control studies							
Oostveen *et al*, 2014, Netherlands	<18 years at onset	Plaque	151 (450 controls)			Koebner positive 30.9%	
Ozden *et al*, 2011, Turkey	<18 years at onset	All types of psoriasis	537 (511 controls)		Stressful life event adjusted OR^{A} 2.94 (95%CI 2.28-3.79) ^{A}adjusted for age, sex, calendar year and other unspecified covariates		Tobacco smoke at home adjusted OR^{A} 2.9 (95%CI 2.27-3.78)* BMI >26kg/m^2 adjusted OR^{A} 2.52 (95%CI 1.42-4.49)*
Cross-sectional studies							
Boccardi *et al*, 2009, Italy	<15 years	Not specified	96 (100 controls)				BMI >110%: adjusted OR^{B} 2.55 (95%CI 1.31-4.96) ^{B}adjusted for age and sex
Chiam *et al*, 2011, Netherlands and Singapore	<18 years	All types of psoriasis	207 (no controls)	Infection not specified Netherlands 20% Singapore 25%	Stress Netherlands 66.7% Singapore 50%		

Fabrizi *et al*, 2001, Italy	5 to 19 years	Not specified	20 (29 controls)	10% of psoriasis patients vs 17% of controls had a positive C-urea breath test for H. Pylori			
Kim *et al*, 2010, Korea	<15 years	All types of psoriasis	30 (30 adult patients)	Upper respiratory tract infection 43.4% vs 26.7%	Psychological stress 3.3% vs 6.7%		Atopic dermatitis 6.7% vs 0% Other 23.3%
Koebnick *et al*, 2011, USA	2 to 19 years	Not specified	1350 (707, 599 controls)				Underweight OR[C] 0.68 (95%CI 0.44-1.06) Overweight OR[C] 1.31 (95%CI 1.13-1.63) Obese (BMI≥30kg/m2) OR[C] 1.39 (95%CI 1.19–1.63) Extremely obese (BMI ≥35kg/m2) OR 1.78[C] (95%CI 1.49-2.14) [C]adjusted for age, sex, ethnicity, medical centre size, insurance status
Mercy *et al*, 2013, USA	5 to 17 years	Plaque	181 (no controls)	Streptococcal infection 22.1%			
Nanda *et al*, 2000, Kuwait **	<12 years	Not specified	305 (no controls)	Upper respiratory tract infection 3%	Stress 1%	Trauma 1%	Winter season 14% Summer season 9%
Raychaudhuri *et al*, 2000, USA	Questionnaires completed by adult psoriasis patients, data stratified for age of onset before and after 16 years	Psoriasis type not specified	223 (484 adult onset)	Sore throat 11.6% vs 7.9%		Onset at the site of trauma 11.5% vs 9.8% Koebnerisation 49.6% vs 38.9%	

Case-series							
Al-Hamdi *et al*, 2008, Iraq	Infancy to 11 years	All types of psoriasis	104	Infections and fever 27.9%	Emotional stress 15.2%		Environmental factors 4.8% Teething 2.9% No cause found 49.1%
de Oliveira *et al*, 2010, Brazil	≤12 years	Pustular	7	Tonsillitis 14.2%	Emotional stress 14.2%		Winter 14.2% Withdrawal of systemic corticosteroids 14.2%
Kumar *et al*, 2004, India	<14 years	All types of psoriasis	419	Throat infection 2.3%	Emotional factors 0.7%	Trauma 3.3% Koebnerisation 27.9%	Drugs for fever 0.2%
Leow *et al*, 1994, Singapore	<12 years	All types of psoriasis	112	Upper respiratory tract infection 7.1% Chicken pox 2.7% Urinary tract infection 0.9%			Cosmetic product 0.9%
Nanda *et al*, 1990, India	<14 years	All types of psoriasis	112	Throat infection 15.2%	Emotional factors 1.8%	Injury 3.6% Koebnerisation 30.3%	Drugs 0.9% Vaccination 0.9%
Nyfors *et al*, 1975, Denmark	Children	All types of psoriasis	245	Infection, particularly sore throats 16.7% Elevated antistreptococcal titres 60%			
Seyhan *et al*, 2006, Turkey	<18 years	All types of psoriasis	61	Upper respiratory tract infections 14.8% Positive throat culture for group A β haemolytic streptococcus 21.3%, Otitis media 9.8%	Psychological stress 54% Psychiatric morbidity 9.8%		Atopic dermatitis 3.3% thyroid dysfunction 4.9% Drugs (systemic corticosteroids, anti-inflammatory, antibiotics) 9.8%
Wu *et al*, 2010, China	<14 years	All types of psoriasis	137	Upper respiratory tract infection 28.5%	Psychological stress 5.1%	Trauma 2.9% Koebnerisation 20.4%	

Zelickson *et al*, 1991, USA	<18 years	Pustular	13	Infections (otitis, streptococcal, staphylococcal, urinary tract infection) 38%	Stress 15%	Sun 38% Tar 30% Winter 15%

Table 5:3 Studies reporting potential environmental triggers or risk factors for the onset of psoriasis in childhood
**Case-control study but data on environmental risk factors cross-sectional at baseline ** Cross-sectional study providing data on risk factors with nested case control genetics study.*

5.4.4 What other conditions are associated with psoriasis in children?

5.4.4.1 Hypertension, obesity and metabolic disease

Studies investigating diseases associated with psoriasis varied in methodology and only three used a study design which allowed a causal relationship to be assessed (Kaye et al., 2008, Kimball et al., 2012, Mallbris et al., 2004). Eighteen studies reported data on associated diseases (Table 5:4) (Augustin et al., 2010, Augustin et al., 2015, Cohen et al., 2008, Goldminz et al., 2013, Jensen et al., 2014, Kaye et al., 2008, Kimball et al., 2012, Lysell et al., 2015, Mahe et al., 2013, Mahe et al., 2015, Mallbris et al., 2004, Matusiewicz et al., 2014, Paller et al., 2013, Pietrzak et al., 2004, Shapiro et al., 2007, Torres et al., 2014, Wu et al., 2010, Remrod et al., 2013). Nineteen studies reported data on juvenile psoriatic arthritis, and these papers are summarised below.

Eleven studies have provided data on cardiovascular disease and hypertension. Childhood psoriasis may increase the risk of hypertension. In two retrospective cohort studies hypertension was found in 1% of children with psoriasis compared to 0.7% of controls (p=0.0005) (n=7404) (Kimball et al., 2012) and up to 0.5% of children following a diagnosis of psoriasis (n=6945) (Kaye et al., 2008). A significant association with cardiovascular disease has not been shown.

Obesity data were presented in eleven studies, many of which support a significant association between psoriasis and obesity. Kimball *et al.* (n=7404) reported the prevalence of obesity following a diagnosis of psoriasis to be 1.8% of children with psoriasis compared to 1.3% of controls (p=0.0007) (Kimball et al., 2012), much lower than large cross-sectional studies such as Mahe *et al.* 2015 (n=545), Lysell *et al.* (n=109) and Paller *et al.* (n=614), 10% (p=0.001), 15% and 20.2% (p<0.001) respectively (Lysell et al., 2015, Mahe et al., 2015, Paller et al., 2013). This may imply that obesity was coexistent at the onset of psoriasis, as reported by Becker *et al.* (Becker et al., 2014).

Twelve studies have presented data on metabolic disease. A retrospective cohort study (n=7404) found children were at higher risk of diabetes (1% vs 0.7%, p=0.0037) and hyperlipidaemia (2% vs 1.3%, p<0.001) following a diagnosis of psoriasis (Kimball et al., 2012).

5.4.4.2 Psychological disease

Four studies reported findings on psychological disorders and childhood psoriasis. Kimball *et al.* (n=7404) investigated the onset of a psychological disorder following a diagnosis of psoriasis. The hazards ratio was significantly raised for any psychiatric disorder (HR 1.25(95%CI 1.11-1.4)) (Kimball et al., 2012)

5.4.4.3 Juvenile Psoriatic arthritis

Nineteen studies reported data on juvenile psoriatic arthritis in a paediatric psoriasis population (Augustin et al., 2015, Becker et al., 2014, Chiam et al., 2011, de Jager et al., 2010, de Oliveira et al., 2010, Fan et al., 2007, Ganemo et al., 2011, Jensen et al., 2014, Kimball et al., 2012, Kumar et al., 2004, Lysell et al., 2015, Mahe et al., 2015, Mercy et al., 2013, Moustou et al., 2014, Nanda et al., 1990, Ozden et al., 2011, Paller et al., 2013, Stefanaki et al., 2011, Wu et al., 2010).

In a predominantly plaque or guttate psoriasis population, the prevalence of psoriatic arthritis was reported between 0.7% and 10.5%. In a case-series of seven children with pustular psoriasis, two children were found to have psoriatic arthritis (de Oliveira et al., 2010). The highest percentage (10.5%) was reported by Mercy *et al* in a secondary/hospital multicentre study of 545 children with plaque psoriasis aged 5 to 17 years (Mercy et al., 2013). No studies provided data on the order of presentation of psoriasis and juvenile psoriatic arthritis.

Associated diseases in childhood psoriasis								
Author, year, country	Data source	Sample size	Type of psoriasis	Cardiovascular disease and hypertension	Obesity	Metabolic disease	Psychological	Other
Retrospective cohort studies								
Kaye *et al*, 2008, UK	General practice database	6945 (34, 666 controls)	Not specified	Hypertension: <10 years: 0% vs0% 10-19 years: 0.5% vs 0.6% Myocardial infarction: <10 years: 0% vs 0% 10-19 years: 0.2% vs 0.1%	BMI >30kg/m^2 : <10 years: 0.6% vs 0.7% 10-19 years: 8.2% vs 7.5%	Diabetes: <10 years old: 0.3% vs 0.3% 10-19 years: 0.6% vs 0.6^ Hyperlipidaemia: <10 years: 0% vs 0% 10-19 years: 0.1% vs 0.2%		
Kimball *et al*, 2012, USA	Insurance database	7404 (37, 020 controls)	Not specified	Cardiovascular disease: 0.3% vs 0.2% (p=0.367)* Hypertension: 1% vs 0.7% (p=0.0005)*	Obesity NOS: 1.8% vs 1.3%(p=0.0007)*	Diabetes: 1% vs 0.7% (p=0.0037)* Hyperlipidaemia: 2% vs 1.3%(p=<0.0001)*	Any psychiatric disorder: adjusted HR^A 1.25 (95%CI 1.11-1.40) Depression: adjusted HR^A 1.23 (95%CI 1.06-1.43) Anxiety: adjusted HR^A 1.32 (95%CI 1.09-1.61) Bipolar: adjusted HR^A 1.55 (95%CI 1-2.42)	Peripheral vascular disease: 0.2% vs 0.1%(p=0.0984)*

							[A] adjusted for age, sex, obesity, Charlston comorbidity index, region, type of healthcare plan
Mallbris *et al*, 2003, Sweden	National inpatient registry and the Swedish Psoriasis Association	1685 (no controls)	Not specified	Cardiovascular death: Inpatient standardised mortality ratio 0 (95%CI 0.00-3.74) Outpatient standardised mortality ratio 0 (95%CI 0.00-20.3)			
Case-control studies							
Jensen *et al*, 2014, Denmark	Secondary/hospital care	30 (30 controls)	Plaque	Systolic blood pressure: 105 mmHg, difference in means 6mmHg (95%CI 1-11, p=0.023)* Diastolic BP: 66 mmHg, difference in means 2mmHg, (95%CI -2-6, p=0.354)*	BMI: 20.3 kg/m^2, difference 17kg/m^2 (95%CI 0.1-3.2, p = 0.036)* Abdominal circumference: 72cm, difference 6cm (95%CI 2-10, p=0.004)*	Glucose: 5.3 mmol/L, difference 0.04 mmol/L (95%CI 0.01-0.9, p=0.043)* Glycated haemoglobin: 5.25%, difference 0.06% (95%CI -0.17- 0.29, p=0.596)* Total cholesterol: 3.8 mmol/L, difference -0.1 mmol/L (95%CI -0.5-0.3, p=0.702)*	

						Triglycerides: 0.96 mmol/L, difference 0.02, 95%CI -0.24-0.28, p=0.876*		
Mahe *et al*, 2015, France	Secondary/hospital care	261 (261 age and sex matched controls)	Plaque	Hypertension: 0.8% vs 0% (p=0.15)*	Overweight (BMI>97th percentile) with abdominal obesity: 8.4% vs 7.3% (p=0.009)* Obese (BMI>30): 10% vs 3.1% (p=0.001)*	Diabetes: 0% vs 0% (p=1) Dyslipidaemia: 3% vs 0.8% (p=0.08)*		
Cross-sectional studies								
Augustin *et al*, 2010, Germany	Insurance database	2549 (331, 758 controls)	Not specified	Ischaemic heart disease: PR 1.52(95%CI 0.97-2.38) Arterial hypertension: PR 1.89 (95%CI 1.47-2.67)	Obesity NOS: PR 1.70 (95%CI 1.49-1.93)	Hyperlipidaemia: PR 2.15 (95%CI 1.65-2.8) Diabetes: PR 2.01 (95%CI 1.32-3.04)		Crohn's disease: PR 3.69 (95%CI 2.15-6.35) Rheumatoid arthritis: 5.21 (95%CI 1.4-19.44) Ulcerative colitis: PR 1.13 (95%CI 0.38-3.35)
Augustin *et al*, 2015, Germany	Insurance database	1313 (291, 868 controls)	Not specified	Arterial hypertension: PR 2.09 (95%CI 1.18-3.69, p<0.05) Ischaemic heart disease: PR 1.27 (95%CI 0.18-9.07, p>0.05)	Obesity NOS: PR 1.89 (95%CI 1.53-2.34, p<0.05)	Hyperlipidaemia: PR 1.79 (95%CI 1.08-2.99, p<0.05) Diabetes: PR 1.97 (95%CI 0.98-2.34, p>0.05)	Depression: PR 1.69 (95%CI 1.05-2.73, p<0.05)	Iridocyclitis: PR 9.55[B] (95%CI 3.9-23.42) Alopecia areata: PR 3.82[B] (95%CI 1.7-8.58) Nail disorders: PR 3.17[B] (95%CI 2.29-4.39) Atopic dermatitis: PR 2.83[B] (95%CI 2.5-3.21) Impetigo: PR 2.32[A] (95%CI 1.72-3.14) Contact dermatitis: PR 2.16[B] (95%CI 1.61-2.88)

							Viral warts: PR 1.75[B] (95%CI 1.48-2.01) Allergic rhinitis: PR 1.66[B] (95%CI 1.43-1.93) Bronchial asthma: PR 1.34[B] (95%CI 1.14-1.59) Crohn's disease: PR 0[C] Ulcerative colitis: PR 3.05[C] (95%CI 0.75-12.32) [B](p<0.05) [C](p>0.05)
Cohen *et al*, 2008, Israel	Health provider database	585 (19,697 controls)	Not specified			Diabetes: adjusted OR[D] 2.10 (p>0.05) [D]adjusted for age and sex	
Goldmin z *et al*, 2013, USA	Secondary/ho spital care	20 (20 age and sex matched controls)	Not specified	Systolic blood pressure: 111.7mmHg +/- 8.5 vs 110.2mmHg +/- 9.5 (p=0.64) Diastolic blood pressure: 70.9mmHg +/- 8.5 vs 69mmHg +/- 5.6 (p=0.65)	BMI: 22.7 kg/m2 +/- 5.4 vs 22.7 kg/m2 +/- 5.7 (p=0.89) Waist circumference: 81.1cm +/- 16.0 vs 77.6cm +/- 13.2 (p=0.42)	Metabolic syndrome: 30% vs 5% (p=0.04) Fasting blood glucose: 91.1 g/dL +/-7.4 vs 82.9 g/dL +/- 10.3 (p=0.01)	
Lysell *et al*, 2015, Sweden	Secondary/ho spital care	109 (no controls)	All types of psoriasis		Overweight/obese NOS: 15%		

Mahe *et al*, 2013, France	Secondary/hospital care	545 adults with child onset psoriasis (1636 adults with adult-onset psoriasis	Majority plaque	Hypertension: 12.5% vs 30.5%[E] Major adverse cardiovascular event: 2.6%vs 7.8%[E] [E] Reduced compared to adult onset (p<0.0001)	BMI 25.8kg/m^2 +/- 5.8 vs 27.4kg/m^2 +/- 5.7 [E] Waist circumference: 91.5cm +/- 15.7 vs 97.3cm +/- 15.9[E]	Diabetes: 4.6% vs 12.9%[E] Dyslipidaemia: 16.4% vs 31.1%[E] Metabolic syndrome: 7.6% vs 17.8%[E]		
Matusiewicz *et al*, 2014, Germany	Insurance database	4499 (138, 338 controls)	Not specified	Heart valve and rheumatic heart disease: 0.6% vs 0.4%[F] [F]controlled for age and sex		Serious endocrine and metabolic disease: 0.4% vs 0.2%[F]	Delirium/psychosis/psychotic and dissociative disorder: 1.1% vs 0.4%[F] Depressive episodes: 0.7% vs 0.2%[F]	
Paller *et al*, 2013, USA/Italy/Netherlands	Secondary/hospital care	409 (205 age and sex matched controls)	Plaque		Excess adiposity (BMI>85th percentile): 37.8% vs 20.5% (p<0.001)/ OR 2.65 (95%CI 1.7-4.15) Obese (BMI>95th percentile): 20.2% vs 7.3%(P<0.001)/ OR 4.29 (95%CI 1.96-9.39)			
Pietrzak *et al*, 2002, Poland	Secondary/hospital care	70 (43 controls)	Psoriasis vulgaris					No difference in liver measurements and parenchymal echogenicity between

							psoriatic and healthy children.
Remrod *et al*, 2013, Sweden	Secondary/hospital care	48 adults with child onset psoriasis (53 adults with adult-onset psoriasis)	Plaque				Higher anxiety score Higher depression score Higher scores of four personality traits: embitterment, irritability, mistrust, verbal
Shapiro *et al*, 2006, Israel	Insurance database	4658 (481, 666 controls)	Psoriasis type not specified			Diabetes: 0-5 years: OR 12.45 (p>0.05) 5-15 years: OR 1.98 (P>0.05)	
Torres *et al*, 2014, Portugal	Secondary/hospital care	20 (27 controls)	Plaque	Systolic/diastolic blood pressures>90th percentile: 30% vs 3.7% (p=0.032)	BMI >90th percentile:25% vs 3.7% (p=0.03), adjusted OR 9.4 (95%CI 1-90.4)^{F} Waist circumference >75th percentile: 75% vs 29.6% (p=0.002), adjusted OR 7.4 (95%CI 2-27.7)^{F} ^{F}adjusted for age and sex	Diabetes: 0% Dyslipidaemia: 15% vs 7.4% (p=0.68) Metabolic syndrome: 25% vs 3.7% (p=0.07)	

Case-series				
Wu *et al*, 2010, China	Secondary/hospital care	137	All types of psoriasis	Allergic contact dermatitis 22.6% Eczema: 4.3% Vitiligo: 3.6% Alopecia areata: 2.2% Systemic lupus erythematosus: 0.7% Asthma: 0.7% Hepatitis: 0.7%

Table 5:4 Studies reporting associated diseases in childhood psoriasis
*The main findings from each study are presented. All figures presented represent an increased risk of a disease association or comorbidity unless stated otherwise. PR = prevalence ratio, OR = odds ratio, HR = hazards ratio, NOS = not otherwise specified, BMI = body mass index. *cross-sectional data at baseline*

5.4.5 What are the long-term outcomes for patients with child-onset psoriasis?

Twenty-two studies provided data on the natural history and long-term outcomes of child-onset psoriasis (Andersen and Thomsen, 1971, Boje Rasmussen et al., 1986, de Jager et al., 2010, De Jager et al., 2011, Farber et al., 1986, Farber and Nall, 1974, Finzi and Benelli, 1998, Kim et al., 2015, Leow and Giam, 1994, Liao et al., 2002, Lomholt, 1963, Mahe et al., 2013, Meeuwis et al., 2010, Nanda et al., 1990, Neville and Finn, 1975, Nyfors and Lemholt, 1975, Ohkawara et al., 1996, Papp et al., 2010, Popadic and Nikolic, 2014, Raychaudhuri and Gross, 2000, Swanbeck et al., 1995, Warren et al., 2011).

Ten studies reported the percentage of adult psoriasis patients with child-onset disease; this was found to be between 12% and 37.1% and much lower in a study solely on genital psoriasis (5%) (Meeuwis et al., 2010). Four studies, either prospectively or retrospectively, followed up infants with psoriasiform napkin disease. In a small cohort of nine infants, seven had recurrent psoriasis (Farber et al., 1986), whereas the proportion in larger studies was much lower. Neville and Finn found that 16.9% of 71 infants with psoriasiform changes developed psoriasis in childhood (Neville and Finn, 1975), while Andersen and Thomsen found that this occurred in only 3% of 67 infants (Andersen and Thomsen, 1971). Continuous disease throughout childhood occurred in 5.4%, 29% and 56% of children (n=112, n=245, n=18 respectively) (Nanda et al., 1990, Nyfors and Lemholt, 1975, Popadic and Nikolic, 2014).

In terms of long-term severity of child-onset disease, Lomholt reported that 35% of psoriatics (n=312) with child-onset disease had significant disease and flares compared with 18% of those with onset over the age of 20 years (Lomholt, 1963). Two studies investigated quality of life in child-onset psoriasis. De Jager *et al.* (n=1762) found that intra-patient rating of quality of life was lower in childhood compared to adulthood in those with persistent disease (De Jager et al., 2011). Kim *et al.* (n=114) found lifetime quality of life scores were lower for those with child-onset compared to adult-onset disease (Kim et al., 2015). This impact on quality of

life supports the theory of a cumulative life-course impairment described by Warren *et al.* (n=4) (Warren et al., 2011).

Cohort studies on the natural history of child-onset psoriasis have to date have focused on napkin psoriasis and therefore information on outcomes even within childhood is extremely limited. Data on child-onset psoriasis is often obtained from adults with persistent disease, which introduces the risk of recall bias and misses those whose psoriasis resolves

5.5 Discussion

5.5.1 Summary of findings

Over the past 25 years there has been a dramatic increase in the volume of published studies in the field of childhood psoriasis epidemiology; the majority of which have been case-series and cross-sectional studies concentrated in Europe, Asia and North America. However, there is an evidence gap for high quality studies to answer all four questions the scoping review posed.

The prevalence of childhood psoriasis was found to be higher in European countries, older children and females. Nearly half of children had a positive family history of psoriasis in a first degree relative. The most frequent subtype was plaque psoriasis and the most common initial sites of presentation were scalp, limbs and trunk. Specific genetic differences have been found between child-onset and adult-onset populations. There were few case-control studies and cohort studies investigating risk factors for psoriasis onset, comorbidities and long-term health outcomes.

5.5.2 Strengths and limitations

This scoping review is the first study to map and summarise epidemiological data on child-onset psoriasis. The search strategy was designed to be extensive and the protocol designed to reduce selection bias in the stages of screening and eligibility assessment of papers. Reference lists were hand-searched until saturation of additional studies was reached. Cross checking the accuracy of extracted data occurred for 10% of studies, but minimal discrepancies were found in this sample and any errors are likely to have an unpredictable effect on the results.

A narrative synthesis within a scoping review summarises the available literature in a broad topic, providing an overview which is not possible with more traditional systematic reviews. Through exploring the scope of the literature, the feasibility and design considerations of future focused systematic reviews can be understood. A

limitation of this review is the absence of structured critical appraisal of individual studies, however a scoping review is a starting point for such work.

5.5.3 Current literature

Since the search date of this scoping review (May 2015), two further systematic reviews have been published that provide data towards answering one of the four core questions. Michelek *et al*. completed a systemic review on the incidence and prevalence of psoriasis in adults and children (Michalek et al., 2017). The systematic review was conducted to inform the WHO Global Report on Psoriasis and searched 15 electronic medical databases. The eligibility criteria were decided a priori as per best practice, and the review excluded studies unlikely to be representative of the general population (eg hospital-based studies). The review identified one new study reporting the incidence of psoriasis in children from Italy. In 2006 the incidence of psoriasis was 60 per 100,000 and in 2012 57 per 100,000 based on a primary health physician diagnosis (Cantarutti et al., 2015). The review included 12 prevalence studies, with similar findings to this review (prevalence ranged from 0% to 1.37%), but a study with a higher prevalence by Naldi *et al.* was not included. Badaoui *et al*. conducted a systematic review into metabolic and cardiovascular comorbidities (Badaoui et al., 2019). The review only included case-control and cohort studies. No meta-analysis was possible because of the large variation in the methods and definitions included in the studies. Overall, the review found support for an association between psoriasis in children and obesity, but not with hypertension, dyslipidaemia, diabetes, metabolic syndrome and cardiovascular disease.

5.5.4 Implications for research

This scoping review has identified gaps in our evidence base about childhood psoriasis relating to all four core questions this review set out to address. Although over 100 studies contain epidemiological data, the choice of study design and heterogeneity in methodology limit the validity and generalisability of the information, consistency of the results and comparability of the studies.

A clear definition of psoriasis and psoriasis subtypes would ensure included participants in studies are confirmed to have the same disease and subtype frequencies could be accurately recorded. Clear definition of potential risk factors and associated diseases, as well as uniformity of parameters measured, would help the clinical applicability of the findings and allow a meta-analysis of results. Work towards standardisation of disease definition, exposure and outcomes should follow the methodology of ongoing projects to develop core outcome sets for clinical trials.

Population-based prevalence and particularly incidence studies are needed to understand the burden of disease globally. These studies should explore the impact of variables such as geographic location, socioeconomic class and ethnicity on frequency data. Studies using routinely collected healthcare records, existing birth cohort studies as well as purposely designed community-based research projects should all be considered. Prospective multi-centre cohort studies in secondary care would provide the opportunity to obtain accurate data on the clinical presentation of psoriasis in childhood (eg subtypes, sites of involvement, severity) and explore the impact of variables such as puberty and ethnicity on the genotype-phenotype presentation. Prospective cohort studies will also enable long-term health outcomes to be investigated in a hospital population. Individual centre case-series and cross-sectional studies are not as valuable as a coordinated effort of prospectively collected data, because they are unable to investigate the chronology events and there is a higher risk of selection bias.

There are very few specifically designed case-control and cohort studies that have investigated risk factors for disease onset and associated diseases. Meta-analysis of all available data in these areas will be challenging due to heterogeneity in how risk factors and comorbidities are defined and measured, as well as heterogeneity in study design and population. There is an indication that infection, trauma, stress and obesity are important triggers, but because much of the data is from cross-sectional studies and case-series it is not clear whether the results are valid. There is also an indication that psoriasis is associated with several comorbidities, but this conclusion needs to be substantiated and the level of risk assessed. Multi-centre case-control

studies, recruiting from both the community and secondary care, and cohort studies using population-based data with nested case-control studies would help answer these questions and investigate long-term outcomes for children with psoriasis.

5.5.5 Implications for this research project

Chapter 5 has scoped and summarised the epidemiological literature about child-onset psoriasis and contributes to answering the question set out in Chapters 3 and 4 'What do we know about psoriasis in children?' The following question will be taken forward in this thesis:

I. **Can a clear definition of psoriasis in children be developed to support epidemiological research?** This chapter has shown that high quality studies are needed to help answer all four of the core questions that this scoping review set out to answer. A lack of clear definition of diseases and outcomes was a major weakness across all topics covered in the review, including studies providing basic epidemiological data such as prevalence and incidence (Chapter 4, section 4.4.2.1 Incidence and prevalence). Therefore, the provision of a clear definition and diagnosis of psoriasis, critical to ensure accurate case ascertainment, is a fundamental starting point for new higher quality studies into the epidemiology of psoriasis in children. The development of diagnostic criteria for psoriasis in children would also help address the question **'How can psoriasis in children be better recognised and diagnosed by clinicians who review children with rashes?'**: an area of research need identified in chapters 3 and 4.

Chapter 6 Identifying studies which have developed or validated diagnostic criteria for psoriasis: A systematic review

6.1 Introduction

Chapters 3 and 4 identified early detection of psoriasis and juvenile psoriatic arthritis as opportunities for early intervention. The case-note review in Chapter 3 showed that a third of children with psoriasis were previously diagnosed with a different skin disease, mostly eczema in primary care. Accurate recognition of psoriasis is important to ensure children are referred to a specialist as per NICE guidance, where psoriasis specific treatment and monitoring can be started. The interviews in Chapter 4 showed that through poor recognition of psoriasis in children, paediatric rheumatologists were potentially missing an opportunity to differentiate juvenile idiopathic arthritis into juvenile psoriatic arthritis. In particular, many were not aware that psoriasis in children many have a different distribution compared to adult disease and often involves 'hidden' sites. Chapter 5 summarised the available literature on the epidemiology of childhood psoriasis. Assimilating information in the scoping review was challenging because different disease, exposure and outcome definitions were used. This variation was also seen in how psoriasis was defined and is an obstacle in future systematic reviews and epidemiological research.

In routine dermatology practice, a diagnosis of psoriasis is made based on pattern recognition of clinical features, including the distribution, configuration and morphology of skin changes (Rimoin et al., 2015, Naldi and Gambini, 2007, Cox, 2009). The gold or reference standard is conventionally accepted to be a clinical diagnosis made by a qualified dermatologist, which may be supported, when required, by a skin biopsy. Unlike in other conditions such as Behçets disease and atopic dermatitis, where diagnostic criteria are used to aid clinical assessment or in clinical research, diagnostic criteria are not widely used in the assessment of psoriasis (Williams et al., 1994, Brenninkmeijer et al., 2008, Davatchi, 2012). However, the earlier studies in this PhD have shown that diagnostic criteria would be useful to both improve the recognition of psoriasis and provide a standardised disease definition in clinical research.

Similar to the rationale behind Chapter 4, following identification of a problem the next step is to systematically search and critically appraise the available literature. Therefore, the aim of this systematic review was to identify and critically appraise studies which had a primary aim to develop or validate diagnostic criteria for psoriasis in adults or children.

This systematic review has been published in the British Journal of Dermatology (Burden-Teh et al., 2018)

> Burden-Teh E, Phillips RC, Thomas KS, Ratib S, Grindlay D, Murphy R. A systematic review of diagnostic criteria for psoriasis in adults and children: evidence from studies with a primary aim to develop or validate diagnostic criteria. Br J Dermatol 2018 May;178(5):1035-1043. doi: 10.1111/bjd.16104. Epub 2018 Mar 6.

6.2 Objectives

1. What is the sensitivity and specificity of diagnostic criteria developed or validated for psoriasis.

2. What data is provided in studies meeting the eligibility criteria on:

    a. Recommendations on how to diagnose psoriasis
    b. Applicability of the diagnostic criteria to a paediatric population
    c. Study design and study population used in studies to develop diagnostic criteria

6.3 Methods

6.3.1 Study design

Systematic review

The protocol was registered on PROSPERO (www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015032311). PROSPERO was developed by the Centre of Reviews and Dissemination in York and funded by the National Institute for Health Research. It is an international database of prospectively registered systematic review protocols in health and other topics where there is a health-related outcome. By maintaining an accessible and permanent record of protocols, PROSPERO aims to help reduce duplication and reporting bias in the completed review.

The systematic review has been reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) check list (Moher et al., 2009). PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.

6.3.2 Search strategy

A search strategy was developed with an information specialist (DG) using MeSH headings and free text search terms around the keywords 'diagnosis' AND 'criteria' AND 'psoriasis' (Appendix 6). The search was conducted in October 2016 in Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) 1946 to Present, and Ovid Embase 1974 to 2015. Reference citations from included studies were hand-searched for additional relevant papers.

6.3.3 Eligibility criteria

Studies were included where the primary aim was to develop or validate diagnostic criteria for psoriasis. The term 'diagnostic criteria' was defined as diagnostic features which were applied as a group to support a diagnosis of psoriasis. No exclusions were made based on study type, age of participants, language, type of psoriasis or type of diagnostic criteria developed. This systematic review included both adult and paediatric studies, because in the potential absence of studies focusing on children it was important to learn from any progress made towards developing diagnostic criteria for psoriasis in adults. Included studies were not required to have a comparator group or test diagnostic accuracy. Review articles and studies developing diagnostic criteria for psoriatic arthritis were excluded. Conference abstracts were also excluded. This exclusion was a change from the protocol because conference abstracts were found to contain insufficient information for critical appraisal.

6.3.4 Data management

Titles and abstracts of identified studies were independently screened by two authors against the inclusion and exclusion criteria (EBT and either RP, SR or DG). Full text papers were obtained for studies meeting these criteria. Two authors (EBT and RP) independently assessed the eligibility of full text papers. Study authors were contacted to clarify missing data from potentially eligible studies. Any disagreements on study eligibility were resolved through discussion and involvement of a third author (KT).

Data were independently extracted by two authors (EBT and RP) using a standardised proforma (Appendix 7). The proforma was piloted on three studies and refined before independent extraction was initiated. Discrepancies between the two sets of data extraction were discussed and checked against the original manuscript. For those studies not reported in English, data was extracted by an associate proficient in that language.

6.3.5 Critical appraisal

Diagnostic accuracy studies were individually critically appraised for risk of bias by two authors (EBT and RP) using the QUality Assessment of studies of Diagnostic Accuracy included in Systematic reviews 2 tool (QUADAS-2) (Whiting et al., 2011). Any disagreements on study quality were resolved through discussion and involvement of a third author (KT or SR).

The QUADAS-2 tool was chosen because it was specifically designed to assess the risk of bias in primary diagnostic accuracy studies. The original QUADAS tool was developed using a structured approach to quality assessment tool development (Whiting et al., 2003). The QUADAS tool was updated in response to a systematic review of QUADAS usage, reviewers' feedback, new evidence on sources of bias in diagnostic accuracy studies and conclusions from studies which have evaluated QUADAS. An adapted version of QUADAS is used in Cochrane Diagnostic Test Accuracy reviews and is recommended by NICE for use in their guideline development.

The QUADAS-2 tool instructs researchers to assess risk of bias across four domains. For each domain, researchers are guided by prompt questions and asked to grade the risk of bias as low/high/unclear (Whiting et al., 2011).

- Domain 1 is patient selection: the prompt questions ask about recruitment of consecutive or a random sample, avoidance of a case-control design and avoidance of inappropriate exclusions.

- Domain 2 is the index test (diagnostic criteria): the prompt questions ask about whether the results were interpreted without knowledge of the reference standard and use of a pre-specified threshold.
- Domain 3 is the reference standard (gold standard): the prompt questions ask about whether the results were interpreted without knowledge of the index test and whether the reference standard was likely to correctly classify psoriasis.
- Domain 4 is the flow of patients in the study: the prompt questions ask about the interval between the index test and reference standard, complete verification and inclusion of all patients in the analysis.

In this systematic review, only diagnostic accuracy studies were able to be appraised using the QUADAS-2 tool. All studies, regardless of quality in each of the domains, were included in the data synthesis. The critical appraisal was used to highlight important areas of bias and studies with high risk of bias across multiple domains were interpreted with caution.

6.3.6 Analysis

In the protocol, paired forest plots and summary receiver operator characteristic (SROC) curves were planned for the analysis of the primary outcome, for studies which were clinically similar and suitable for meta-analysis. Paired forest plots are used to display sensitivity and specificity data separately for each study. In a systematic review, forest plots are a standard method to present individual and pooled data. However, unlike in a trial, each study in a diagnostic accuracy systematic review generates two or more statistics. Paired forest plots are unable to demonstrate the trade-off (co-variation) between sensitivity and specificity (Leeflang et al., 2008). Therefore, SROC are the preferred method of presenting data when the thresholds determining sensitivity and specificity of the same test vary (Leeflang et al., 2008). A narrative synthesis was planned for secondary outcomes.

At the time of analysis it was decided that meta-analysis was not possible due to heterogeneity of the diagnostic criteria in terms of different study populations, experimental and reference tests (Deeks, 2001). A narrative synthesis was undertaken for all outcomes and a scatterplot of the paired results for sensitivity and specificity (available for diagnostic accuracy studies only) were plotted as points in a ROC space (Leeflang et al., 2008).

6.4 Results

The search strategy identified 11,702 citations. Studies were excluded because they were duplicates (n=4374), did not focus on psoriasis (n=4266), did not mention diagnostic criteria for psoriasis (n=2950), did not develop or validate diagnostic criteria (n=34) or were review articles (n=55). A PRISMA flow diagram of included and excluded studies is presented in Figure 6:1

No clinical examination based diagnostic criteria for psoriasis in adults or children were found within the 11,702 citations. Only 23 studies met the inclusion criteria and presented a broad range of diagnostic criteria including genetic, molecular, dermoscopy, confocal microscopy, histopathology, questionnaire-based, computer aided and traditional Chinese medicine criteria. (Alonso et al., 2016, Chen et al., 2011, Guo et al., 2014, Inkeles et al., 2015, Kamsteeg et al., 2010, Maejima et al., 2014, Sundarrajan and Arumugam, 2016, Yin et al., 2015, Boone et al., 2013, Koller et al., 2009, Lallas et al., 2012, Liu et al., 2015, Pan et al., 2008, Rossi et al., 2011, Zhong et al., 2012, Braegelmann et al., 2016, Braun-Falcon et al., 1979, Hanno et al., 1986, Park et al., 2016, Shrivastava et al., 2016, West and West, 2000, Dominguez et al., 2009, Yang et al., 2013). The characteristics of included studies are presented in Table 6:1. Sixteen studies were of a case-control design, five studies were case-series, one study was cross-sectional and one study was a Delphi consensus study. No studies developed diagnostic criteria specifically for children or validated diagnostic criteria in a paediatric population.

The diagnostic criteria have been summarised, including consideration of their utility, and study quality has been reported using the QUADAS-2 tool. The results of the critical appraisal using QUADAS-2 are presented in Figure 6:3.

With regards to the systematic review primary outcome, sensitivity and specificity of the diagnostic criteria, only 16 of the included studies were diagnostic accuracy studies (Alonso et al., 2016, Chen et al., 2011, Guo et al., 2014, Inkeles et al., 2015, Maejima et al., 2014, Sundarrajan and Arumugam, 2016, Yin et al., 2015, Koller et al.,

2009, Lallas et al., 2012, Liu et al., 2015, Pan et al., 2008, Zhong et al., 2012, Park et al., 2016, Shrivastava et al., 2016, West and West, 2000, Dominguez et al., 2009). Out of these 16 diagnostic accuracy studies only 13 provided data on sensitivity and specificity (Chen et al., 2011, Inkeles et al., 2015, Sundarrajan and Arumugam, 2016, Yin et al., 2015, Koller et al., 2009, Lallas et al., 2012, Liu et al., 2015, Pan et al., 2008, Zhong et al., 2012, Park et al., 2016, Shrivastava et al., 2016, Dominguez et al., 2009, Maejima et al., 2014). In the paper by Chen *et al*. this data was only available after a request was made to the author (Chen et al., 2011). Figure 6:2 shows a scatterplot of the available sensitivity and specificity results for these 13 studies.

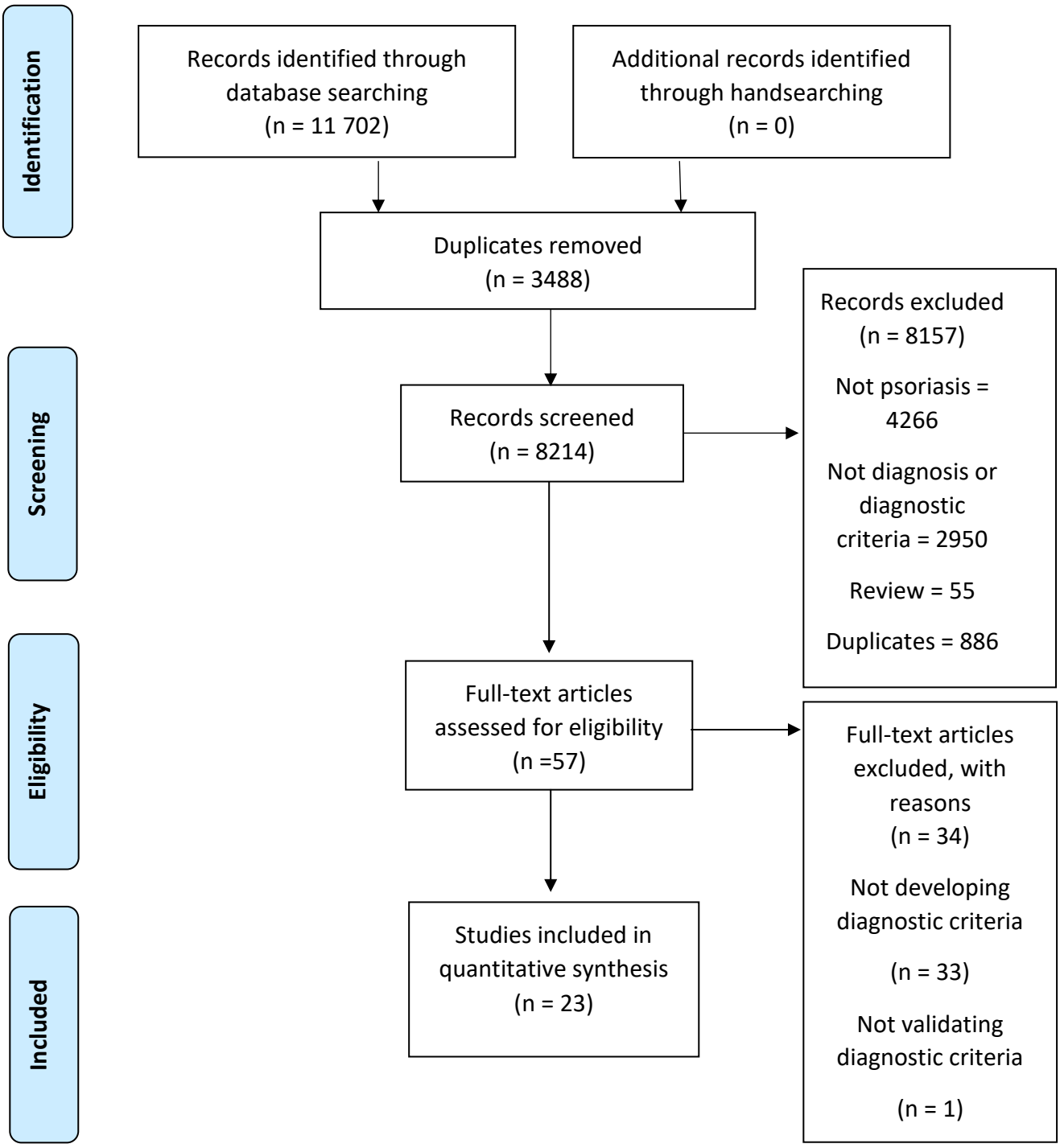


Figure 6:1 Flow diagram showing inclusion and exclusion of studies from identification through to synthesis

Characteristics of studies that have developed or validated diagnostic criteria for psoriasis						
Author, year, country	Study aim	Study type	Study population and sample size	Reference standard for psoriasis	Diagnostic criteria	Key findings
Genetic and molecular diagnostic criteria						
Alonso *et al*, 2016	To identify new biomarkers associated with disease diagnosis and disease activity	Case-control	Secondary care Adults Caucasian Psoriasis type not stated Discovery cohort: 1210 immune mediated inflammatory diseases, including 187 psoriasis, and 100 controls Validation: 1200 immune mediated inflammatory diseases, including 200 psoriasis, and 200 controls	Not stated	Urine metabolome classifier	28 significant associations for immune mediated inflammatory diseases Validation cohort psoriasis classifier: AUC 0.7 (95%CI 0.64-0.75)
Chen *et al*, 2011, USA	To examine the discriminatory and predictive ability of a psoriasis genetic risk score	Case-control	Adults and children European ancestry Plaque and guttate psoriasis Setting not stated 731 cases, 2084 controls, 281 family samples	Not stated	Genetic risk score (GRS) of 10 SNPs	AUC for GRS 66.5% (95% CI 64.2-68.8), sensitivity 65.6% and specificity 58.2% AUC for weighted GRS 72% (95%CI 69.9-74.1), sensitivity 77.7% and specificity 55.2%

Guo *et al*, 2013, China	To construct a robust disease classification model based on marker genes	Case-control	Gene Expression Omnibus database Setting, age, ethnicity and psoriasis type not stated. 91 cases, 85 controls	Not stated	Gene classification model	Ac clustering heatmap of 21 features (18 genes) 98.86% Ac binary classifier of 3 features (2 genes) 99.81%
Inkeles *et al*, 2015, USA	To identify disease specific gene expression signatures to build a multi-disease classifier	Cross-sectional	Gene Expression Omnibus database Setting, age, ethnicity and psoriasis type not stated. Training and internal validation: 311 skin samples including 91 psoriasis External validation: 143 psoriasis, 11 atopic dermatitis, 9 leprosy, 10 melanoma, 9 normal skin.	Not stated	Genetic multi-disease classifier	Classifier internal validation: sensitivity 0.98, specificity 0.99 Classifier external validation: sensitivity 0.97 and specificity 0.97
Kamsteeg *et al*, 2009, Netherlands	To analyse gene expression signatures and develop a tool for molecular diagnostics of inflammatory conditions	Case-control	Secondary care Moderate to severe plaque psoriasis Age range and ethnicity not stated Sample size not stated	Dermatologist's diagnosis	Gene expression signatures in epidermal cells	hBD-2, elafin, IL-1F9 and VNN3 specific for psoriasis in mRNA and protein expression profiles CCL17, hBD-2 and NELL2 genes were found to have 'perfect prediction' and an error rate of 12.7%
Maejima *et al*, 2014, Japan	To identify diagnostic markers for psoriasis vulgaris and psoriatic arthritis	Case-control	Adults Psoriasis vulgaris Setting and age range not stated	Not stated	Autoantigen serodiagnostic markers	11 positive proteins identified as autoantigens AUC moesin 0.747, sensitivity 71.0 and specificity 76.9

			Serum samples: 31 psoriasis, 12 psoriatic arthritis, 13 controls			AUC STIP 0.792, sensitivity 80.6 and specificity 69.2
Sundarrajan and Arumugam, 2016, India	To build a classifier of psoriasis specific hub signatures to robustly distinguish psoriasis samples	Case-control	Gene Expression Omnibus database Setting, age, ethnicity and psoriasis type not stated. Network analysis: 58 cases and 64 controls Validation: sample size unknown	Not stated	Classifier of psoriasis specific hub genes	Sensitivity 0.96 and specificity 1
Yin *et al*, 2015, China	To create a predictive model with 14 common psoriasis variants and evaluate their discriminatory performance	Case-control	Adults and children Han Chinese Setting and type of psoriasis not stated 3805 cases and 3515 controls Validation: 736 cases and 736 controls	Diagnosis by two dermatologists	Polygenic risk score (PRS)	AUC SNP HLA model 0.8583 (95%CI 0.8491-0.8675), sensitivity 84.7%, specificity 81.7% AUC validation study 0.8225 (95%CI 0.7991-0.8458) AUC eczema patients 0.51
Skin imaging diagnostic criteria						
Boone *et al*, 2013, Belgium	To correlate dermatopathologic descriptors of inflammatory skin conditions with features observed by HD-OCT	Case-control	Adults and skin types II and II Chronic plaque psoriasis Setting not stated 23 psoriasis, 93 allergic contact dermatitis, 30 atopic dermatitis, 2 erythema mulitforme, 3 discoid lupus erythematosus	Clinical and 3 diagnosed on histology	An algorithm of HD-OCT features	Main criteria: hyperkeratosis and parakeratosis Secondary criteria: regular acanthosis, swollen dermal papillae and papillomatosis, dilated blood vessels in the dermal papillae

Koller *et al*, 2009, Austria	To evaluate morphological features determined by RCM for their presence absence, diagnostic performance and reliability	Case-control	Secondary care Age range, ethnicity and psoriasis type not stated 27 psoriasis, 20 contact dermatitis, 10 mycosis fungoides, 14 subacute cutaneous lupus erythematosus, 4 cutaneous discoid lupus erythematosus, 10 health controls	Clinical diagnosis and histology	25 diagnostic reflective confocal microscopy features	Sensitivity 89.13% and 95.41% specificity Three features (increased dermal papillae, tortuous/twisted and dilated capillary loops and elongated papillae) correctly classified 82.72% of psoriasis lesions
Lallas *et al*, 2012, Greece	To determine the dermoscopic patterns associated and to assess the validity of certain dermoscopic criteria in the diagnosis of plaque psoriasis	Case-control	Secondary care Caucasian Plaque psoriasis Age range not stated 83 psoriasis, 41 dermatitis, 25 lichen planus, 20 pityriasis rosea	Clinical diagnosis and histology	Dermoscopic features	All dermoscopic variables: sensitivity 86% and specificity 96.4% Regularly distributed dotted vessels, light red background with diffuse white scales: AUC 0.935, sensitivity 84.9% and specificity 88%
Liu *et al*, 2015, China	To explore the characteristics of skin lesions and assess the effectiveness of dermoscopy in the diagnosis of psoriasis vulgaris	Case-control	Psoriasis vulgaris Setting, age range and ethnicity not stated 117 cases, 50 chronic eczema, 20 pityriasis rosea	Clinical diagnosis or histology	Dermoscopic features	Red background, dotted vessels and regular blood vessel arrangement together: sensitivity 98% and specificity 97%
Pan *et al*, 2008, Australia	To describe the most significant morphological findings seen on dermoscopy and	Case-control	Secondary care Plaque psoriasis Age range and ethnicity not stated	Clinically confirmed by 2 dermatologists or biopsy	32 consensus agreed dermoscopic features	Homogenous global vascular pattern, red dots, light-red background and an absence of arborizing vessels: diagnostic probability 99%, sensitivity 45%, specificity 99.5%

	formulate a diagnostic model		100 psoriasis plaques, 150 sBCC, 50 IEC			
Rossi *et al*, 2011, Italy	To create a VSCAPSI (Videodermoscopy Scalp Psoriasis Severity Index) for the evaluation of scalp psoriasis	Case-series	Secondary care Scalp psoriasis Age range and ethnicity not stated 900 patients 16 images reviewed by 146 dermatologists to assess reproducibility	Clinical, videodermoscopy and histology in ambiguous cases	VSCAPSI (Videodermoscopy Scalp Psoriasis Severity Index)	85 new cases of scalp psoriasis 68% of dermatologists correctly recognised ≥13 images
Zhong *et al*, 2011, China	To determine the sensitivity and specificity of Munro's microabscesses detected by reflective confocal microscopy	Case-control	Secondary care Psoriasis vulgaris Age range and ethnicity not stated 50 psoriasis, 24 eczema, 15 pityriasis rosea, 13 seborrhoeic dermatitis, 3 pityriasis rubra pilaris	Clinical findings and histology histology in 5 patients	Munro's microabscesses identified on reflective confocal microscopy	Observed in 90% of psoriasis patients: sensitivity 90% and specificity 96.4%
Histopathological diagnostic criteria						
Braegelman *et al*, 2016, Germany	To investigate the usefulness of immunohistological IL-36γ staining in the diagnosis of psoriasis based erythroderma	Case-series	Secondary care Erythrodermic psoriasis Age range and ethnicity not stated 12 psoriasis, 11 eczema, 9 drug reactions, 8 cutaneous T cell lymphoma, 1 pityriasis rubra	Retrospective review of diagnosis in patient records	IL-36γ staining of skin biopsy	Significantly enhanced expression of epidermal IL-36γ in erythrodermic psoriasis. Expression of IL-36γ in four or more cell layers only occurred in psoriasis cases.

			pilaris, 1 graft versus host disease, 4 idiopathic			
Braun-Falco *et al*, 1979, Germany	To develop strong criteria to differentiate psoriasis and seborrheic eczema of the scalp	Case-series	Psoriasis vulgaris Setting, age and ethnicity not stated 40 patients with psoriasis and seborrheic eczema	Clinical diagnosis	Histopathological criteria	Strong criteria: moderate condensed hyperkeratosis with alternating parakeratosis, PAS-reactive serum inclusions and Munro abscesses within the horny layer, spongiform pustules and neutrophilic leukocytes within the epidermis
Hanno *et al*, 1986, USA	To investigate whether nail biopsy provided useful diagnostic information and to see which histological features were most helpful in histopathologic diagnosis	Case-series	Secondary care Nail psoriasis Age range and ethnicity not stated 20 biopsies including 6 psoriasis	Not stated	Histopathologic criteria	Major criteria: neutrophils in nail bed epithelium and in adherent parakeratotic nail plate fragments Minor criteria: hyperkeratosis with parakeratosis, serum like proteinaceous exudate within the horny layer, focal hypogranulosis, psoriasiform hyperplasia of nail bed epithelium, dilated subepithelial blood vessels
Park *et al*, 2016, Korea	To evaluate the histopathological differences between seborrheic dermatitis and psoriasis of the scalp and find favourable criteria for differential diagnosis	Case-control	Secondary care Scalp psoriasis Adults and children Ethnicity not stated 15 psoriasis, 20 seborrhoeic dermatitis	Clinical examination and histology (of plaques on other areas of the body)	Histological features	Mounds of parakeratosis with neutrophils, spongiform micropustules of Kogoj, clubbed and even length rete ridges observed more frequently in the psoriasis group ($p<0.05$) ≥6 mitotic figures in 1 high power field: sensitivity 33.3%, specificity 90%

Computer-aided diagnostic criteria						
Shrivastava et al, 2015, India	To analyse the performance of computer aided diagnosis of psoriasis	Case-control	Secondary care Indian ethnicity Plaque psoriasis Age-range not stated 270 psoriasis images and 270 healthy skin images from 30 patients	Not stated	Computer aided diagnosis systems for psoriasis utilising higher order spectra features, texture features and colour features	The combination of all three feature sets (higher order spectra, texture and colour): 100% sensitivity and 100% specificity
West and West, 2000, USA	To investigate the decision accuracy of neural network models for differential diagnosis of 6 erythematous squamous diseases	Case-series	Secondary care Age range, ethnicity and psoriasis type not stated 358 erythematous squamous diseases including 111 psoriasis	Clinical examination and histology	Medical diagnostic decision support system	Base performance: average case 9.3 errors and best case 7.4 errors Two stage network: 5.7 errors
Questionnaire-based diagnostic criteria						
Dominguez *et al*, 2009, USA[38]	To provide pilot data of the Psoriasis Screening Tool	Case-control	Secondary care, adults, English speaking Psoriasis type not stated 111 cases, 111 controls	Board-certified dermatologist	Psoriasis Screening Tool: a self-administered 8 item questionnaire	Questions 1,2,3,4: sensitivity 98%, specificity 95%, PPV 95%, NPV 98%
Traditional Chinese medicine diagnostic criteria						
Yang *et al*, 2013, China	To develop a consensual checklist for psoriasis classification by TCM symptoms and signs	Delphi study	16 experts in TCM	Not applicable	Not applicable	96 items in 8 domains Intra-observer Kappa coefficient 0.96 Inter-observer Kappa coefficient 0.12-0.18

Table 6:1 Characteristics of studies that have developed or validated diagnostic criteria for psoriasis
AUC = area under the curve, CI = confidence intervals, Ac = overall accuracy, TCM = traditional Chinese medicine, sBCC = superficial basal cell carcinoma, IEC = intraepidermal carcinoma, RCM = reflective confocal microscopy, HD-OCT = high definition optical coherence tomography

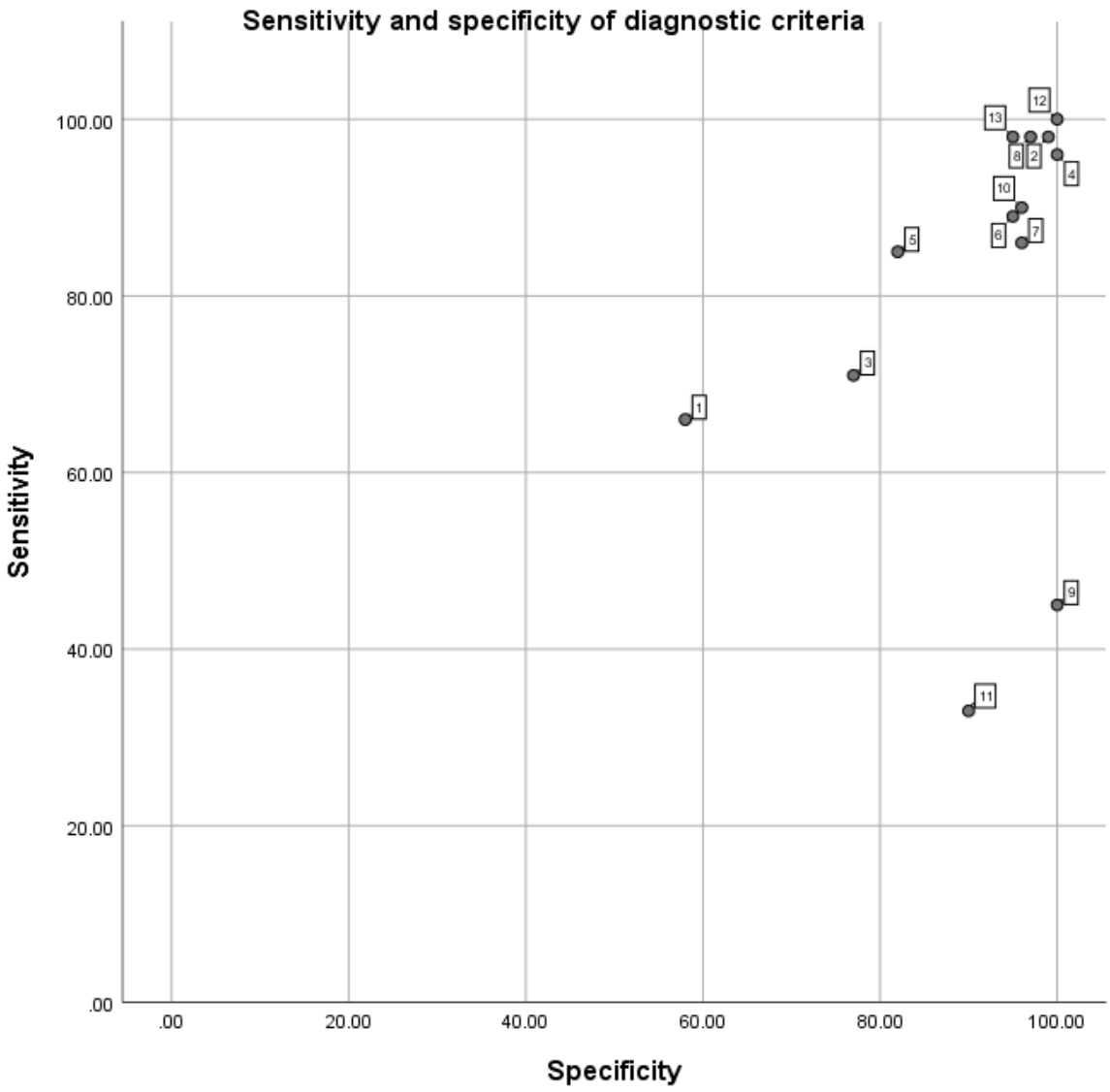


Figure 6:2 Scatterplot showing sensitivity and specificity of diagnostic criteria in diagnostic accuracy studies.

Thirteen out of the 23 studies from the review provided sensitivity and specificity data. The data labels on the scatterplot relate to the list of reference below. For Maejima et al. the moesin data are presented.

1. Chen *et al.*
2. Inkeles *et al.*
3. Maejima *et al.*
4. Sundarraj and Arumugam
5. Yin *et al.*
6. Koller *et al.*
7. Lallas *et al.*
8. Liu *et al.*
9. Pan *et al.*
10. Zhong *et al.*
11. Park *et al.*
12. Shrivastava *et al.*
13. Dominguez *et al.*

6.4.1 Genetic and molecular diagnostic criteria

Six studies reported genetic (Sundarrajan and Arumugam, 2016, Kamsteeg et al., 2010, Chen et al., 2011, Guo et al., 2014, Inkeles et al., 2015, Yin et al., 2015) and two studies reported molecular (Alonso et al., 2016, Maejima et al., 2014) diagnostic criteria (Table 6:1). These studies aimed to identify a combination of genetic or molecular markers which could best predict psoriasis. Seven studies were of a case-control design and one was a cross-sectional study. Sensitivity and specificity results of the criteria were presented or available on request for five studies; the sensitivity values ranged from 65.6% to 98% and specificity from 58.2% to 100% (Chen et al., 2011, Inkeles et al., 2015, Sundarrajan and Arumugam, 2016, Maejima et al., 2014, Yin et al., 2015). Diagnostic accuracy results were often reported as an area under the curve (AUC) and four studies reported a value of 0.7 or greater (Chen et al., 2011, Alonso et al., 2016, Maejima et al., 2014, Yin et al., 2015) . Six studies undertook validation testing of their developed criteria (Guo et al., 2014, Alonso et al., 2016, Inkeles et al., 2015, Kamsteeg et al., 2010, Sundarrajan and Arumugam, 2016, Yin et al., 2015); in two studies (Inkeles et al., 2015, Yin et al., 2015) this was conducted in a separate cohort but no studies planned a validation study in the criteria's intended population. Two studies used the Gene Expression Omnibus database as the source of the genetic samples and there was an overlap in the sample sets used (Guo et al., 2014, Inkeles et al., 2015), but each used a different statistical techniques to build classifiers for different purposes.

6.4.1.1 Risk of bias

Domain 1 (patient selection) was scored high risk of bias in six studies (Alonso et al., 2016, Chen et al., 2011, Guo et al., 2014, Maejima et al., 2014, Sundarrajan and Arumugam, 2016, Yin et al., 2015). The remaining three domains were nearly all scored low or unclear risk of bias in the seven diagnostic accuracy studies (Figure 6:3). The low scores reflect that the index test was interpreted separately from the reference standard and the flow of patients through each study minimised bias. However, the reference standard was only detailed in one study (Yin et al., 2015).

6.4.1.2 Utility of criteria

Across the eight studies, the study authors proposed a number of ways that their diagnostic criteria could be used. These applications include: improving the efficiency and/or accuracy of psoriasis diagnosis and screening individuals at high risk for psoriasis (Guo et al., 2014, Yin et al., 2015); improving disease outcomes (Alonso et al., 2016); furthering understanding of psoriasis pathogenesis (Inkeles et al., 2015, Chen et al., 2011); contributing to the development of personalised medicine (Inkeles et al., 2015, Yin et al., 2015) and new treatment for psoriasis (Sundarrajan and Arumugam, 2016). The authors of two studies proposed that these genetic criteria would, in time, translate into routine clinical practice (Inkeles et al., 2015, Sundarrajan and Arumugam, 2016).

In conclusion, the research and clinical utility of these genetic and molecular criteria for the diagnosis of psoriasis requires further exploration and new validation studies are needed. The genetic studies mostly used skin samples for genetic material and therefore the cost and skill required to take a skin biopsy and the invasiveness of the procedure are likely to be barriers to adoption. It is also unknown whether the anatomical site from which the biopsy is taken alters the diagnostic performance of the test. In the future, alternative methods to obtain genetic samples without a biopsy, such as saliva, may be found to be suitable. Currently, the adoption of criteria that require urine or serum testing are likely to be more acceptable to patients. The eight sets of genetic and molecular criteria also differ in their purpose between differentiating psoriasis from other inflammatory diseases and differentiating psoriasis from healthy controls. It is likely that those that aim to distinguish psoriasis from other inflammatory skin diseases will be most useful in clinical practice.

6.4.2 Skin imaging diagnostic criteria

Four studies reported dermoscopic or videodermoscopic diagnostic criteria (Lallas et al., 2012, Liu et al., 2015, Pan et al., 2008, Rossi et al., 2011), two studies reported reflective confocal microscopy (RCM) (Koller et al., 2009, Zhong et al., 2012) criteria and one study reported high definition optical confocal tomography criteria (HD-OCT) (Boone et al., 2013) (Table 6:1). All seven studies were of a case-control study

design and five studies (Koller et al., 2009, Lallas et al., 2012, Liu et al., 2015, Pan et al., 2008, Zhong et al., 2012) assessed the diagnostic accuracy of the proposed criteria in distinguishing psoriasis from other inflammatory skin disease and skin cancer.

The different dermoscopic criteria studies reported variable sensitivity (45% to 98%), but high specificity (88% to 99.5%) for diagnosing psoriasis (Lallas et al., 2012, Liu et al., 2015, Pan et al., 2008). Koller *et al.* reported high sensitivity (89.13%) and specificity (95.41%) for the RCM criteria tested (Koller et al., 2009), and Munro's microabscesses on RCM achieved both high sensitivity and specificity (90% and 96.4%) (Zhong et al., 2012). The Videodermoscopy Scalp Psoriasis Severity Index (VSCAPSI) criteria had poor inter-observer reproducibility; only 68% of dermatologists recognised ≥13 images (Rossi et al., 2011). None of the imaging studies included testing the diagnostic criteria in a validation cohort.

6.4.2.1 Risk of bias

The risk of bias was highly variable across the five diagnostic accuracy studies (Figure 6:3). These scores not only reflect study quality but also the quality of study reporting; for example the details reported by Liu *et al.* (Liu et al., 2015) and Zhong *et al.* (Zhong et al., 2012) were brief and therefore many of the domains were scored as unclear. Lallas *et al.* and Koller *et al.* (Lallas et al., 2012, Koller et al., 2009) achieved a low risk of bias score in three out of four domains, demonstrating careful planning to separate the index test and reference standard, pre-specification of the index test threshold, and detailed reporting.

6.4.2.2 Utility of criteria

The authors of the seven skin imaging studies proposed that the developed criteria may assist clinical diagnosis and therefore reduce the need for skin biopsy (Boone et al., 2013, Pan et al., 2008, Zhong et al., 2012), help identify an optimal site to biopsy (Koller et al., 2009), enable response to treatment and side effect monitoring (Lallas et al., 2012), and help identify patients requiring screening for psoriatic arthritis

(Rossi et al., 2011). One group of authors highlighted that the feasibility of applying imaging criteria in clinical practice requires further evaluation (Lallas et al., 2012). The authors of another study suggested that the criteria could be adopted as an outcome measurement tool in clinical trials (Rossi et al., 2011).

In conclusion, further discussion is needed about the clinical and research utility of imaging criteria in the diagnosis of psoriasis, including planned validation of their diagnostic accuracy in the proposed setting and population they will be used. Nearly all the studies developing skin imaging diagnostic criteria aimed to differentiate psoriasis from other skin conditions with a similar appearance. Therefore, intuitively these criteria have a potential clinical application. The adoption of imaging criteria is likely to be restricted to the specialist setting because this is where equipment and trained professionals are available. Dermoscopy is widely practised amongst dermatologists for the assessment of skin cancer and therefore further training could advance existing skills to assessment of inflammatory lesions. However, the availability of confocal microscopy is limited to specialist research centres. Further studies are also needed to guide lesion selection, as it is not clear whether the diagnostic accuracy of the criteria varies when plaques affecting different areas of the body are assessed.

6.4.3 Histopathological diagnostic criteria

Four studies have contributed to the development of histopathological criteria (Park et al., 2016, Braun-Falcon et al., 1979, Braegelmann et al., 2016, Hanno et al., 1986), focusing on clinical situations where diagnosing psoriasis is recognised as challenging; isolated scalp psoriasis, isolated nail psoriasis and erythroderma (Table 6:1). Three were case-series and one study was a case-control design (Park et al., 2016) and provided diagnostic accuracy data. None included a validation cohort. Park *et al.* reported poor sensitivity (33%) and good specificity (90%) of >5.75 mitotic features in one high power field for the diagnosis of psoriasis (Park et al., 2016).

6.4.3.1 Risk of bias

Minimal study details were provided and therefore the risk of bias was high or unclear across the four domains evaluated (Figure 6:3). The study was strengthened by assessment of histological samples by three independent histopathologists, but no inter-observer data was provided.

6.4.3.2 Utility of criteria

The authors of the four histopathology studies provided few details on the potential application of the proposed diagnostic criteria, except stating they would assist clinical diagnosis. The evidence supporting the accuracy of histological criteria is poor, especially considering histology was often part of the participant eligibility criteria for many studies within this review. A skin biopsy is a small but invasive procedure, incurs costs and is not widely available outside the specialist setting. These factors are likely to limit the adoption of histological criteria outside dermatology clinics and within clinical trials. Clinically, histological criteria may be of greatest benefit in those with indeterminate skin changes. At present the criteria proposed are for specific anatomical sites, and therefore it is unknown if these findings are applicable to other areas of the body.

6.4.4 Computer-aided diagnostic criteria

Two case-control studies developed computer-aided diagnostic criteria and reported high diagnostic accuracy (sensitivity and specificity 100%, 5.7 errors per 100 cases) (Shrivastava et al., 2016, West and West, 2000) (Table 6:1). Neither included a validation group, but both studies aimed to develop their machine learning models. The data used to build the models differed between the two studies. Shrivastava *et al*. used clinical images, whereas West and West used clinico-sociological and histological features.

6.4.4.1 Risk of bias

The risk of bias across the four domains varied between the two studies, reflecting the specific details reported in West and West on the reference test and index test (West and West, 2000, Shrivastava et al., 2016) (Figure 6:3).

6.4.4.2 Utility of criteria

Both sets of authors proposed that their criteria would be used in the clinical setting, although differed on whether the computer-aided tool would augment or replace current diagnostic practices. The criteria also differed in their purpose within each study; the criteria by Shrivastava *et al.* aimed to differentiate psoriasis from healthy controls, whereas the criteria by West and West aimed to differentiate psoriasis from other erythematous scaly skin diseases. The criteria used by both studies grouped features together as diagnostic criteria, but it is not easy to interpret which features are included in the best predictive models. Validation of both sets of computer-aided criteria is needed, but the increasing use of technology by individuals and health care systems means that these advances in technology-assisted diagnosis are timely. In the future, computer-aided tools may become incorporated into teledermatology services or personal health applications on mobile or tablet devices.

6.4.5 Questionnaire-based diagnostic criteria

Dominguez *et al.* developed a self-administered screening questionnaire for the diagnosis of psoriasis (Dominguez et al., 2009). In this case-control study the questionnaire achieved high diagnostic accuracy; sensitivity 98% and specificity 95% (Dominguez et al., 2009) (Table 6:1). However, the performance of the questionnaire relied heavily on question number three, 'I have been diagnosed with psoriasis by a dermatologist' (sensitivity 93%, specificity 98%). When this question was removed the sensitivity of the questionnaire fell to between 35% and 50%, but specificity remained high (Dominguez et al., 2009).

6.4.5.1 Risk of bias

The risk of bias assessment differed across the four domains. In particular, the quality of the study was limited by a lack of clarity as to whether the index test (questionnaire) was separated from the reference standard (dermatologist's diagnosis) (Figure 6:3).

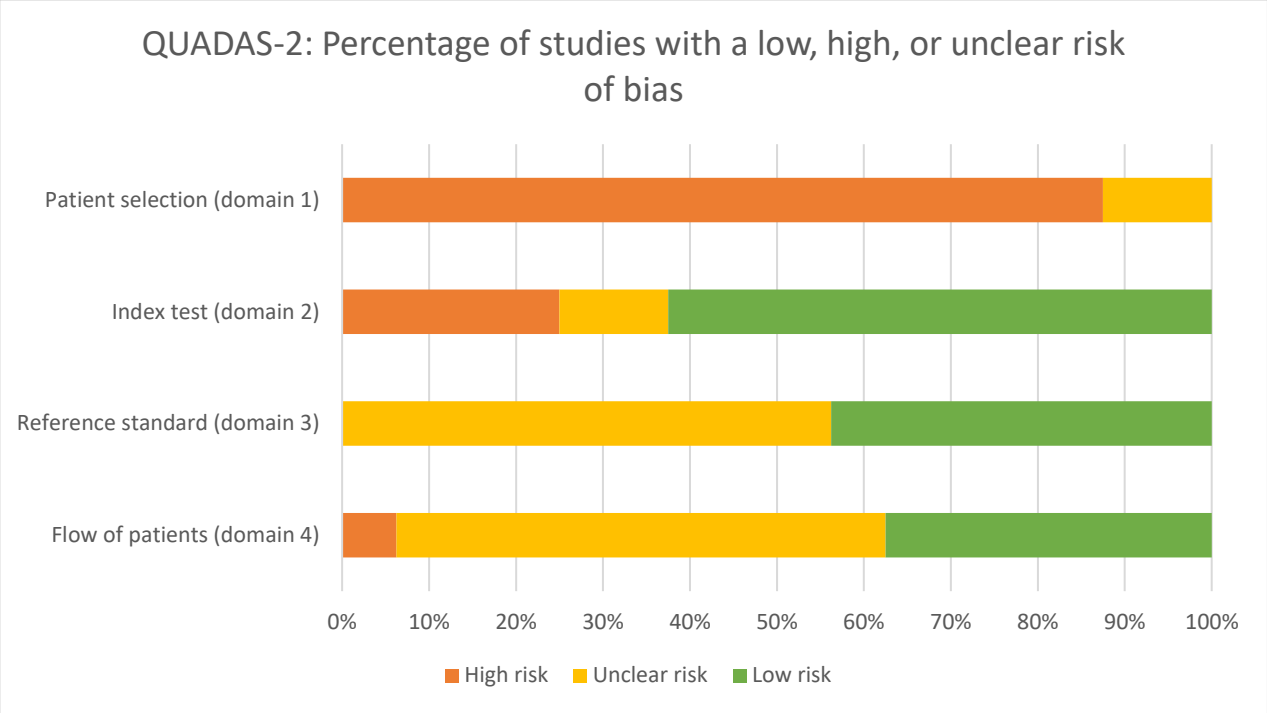
6.4.5.2 Utility of criteria

The study authors designed the questionnaire for research purposes in order to reliably ascertain psoriasis and psoriasis subtypes in remote populations (Dominguez et al., 2009). Therefore, the diagnostic accuracy of the criteria may be poor in areas with low levels of access to dermatologists, potentially limiting its usefulness in this setting. A questionnaire is a low-cost diagnostic tool which would be suitable for case ascertainment in large population-based studies. In the future, studies are needed to validate the questionnaire in a community setting and explore the impact minimal disease or psoriasis affecting only certain body sites may have on the questionnaire's diagnostic ability.

6.4.6 Traditional Chinese Medicine diagnostic criteria

A Delphi consensus study, Yang *et al.* (Yang et al., 2013) aimed to develop a checklist for traditional Chinese medicine symptoms and signs of psoriasis. The study did not assess diagnostic accuracy, but within the consensus study there was good intra-observer (Kappa statistic 0.96) but poor inter-observer agreement (Kappa statistic 0.18).

The study authors proposed that the criteria may aid the diagnosis and classification of psoriasis in clinical practice and research (Yang et al., 2013), but no further details were provided. It is likely that the usefulness of these criteria will be mostly limited to settings practising traditional Chinese medicine. Further testing of the criteria in a diagnostic accuracy study and validation study are both needed.



Study	Patient selection	Index test	Reference standard	Patient flow
Alonso *et al*	☹	☺	?	?
Chen *et al*	☹	☺	?	?
Guo *et al*	☹	☺	?	?
Inkles *et al*	?	☺	?	?
Maejima *et al*	☹	☹	?	?
Sundharrajan and Arumugam	☹	☺	?	?
Yin *et al*	☹	☺	☺	☺
Koller *et al*	☹	☺	☺	☺
Lallas *et al*	☹	☺	☺	☺
Liu *et al*	☹	?	?	?
Pan *et al*	☹	?	☺	☺
Zhong *et al*	☹	☹	?	?
Park *et al*	☹	☺	☺	☺
Dominguez *et al*	☹	☹	☺	☹
Shrivastava *et al*	☹	☹	?	?
West and West	?	☺	☺	☺

☺ = low risk of bias ? = unclear risk of bias ☹ = high risk of bias.

Figure 6:3 Risk of bias assessment using the QUADAS-2 diagnostic accuracy critical appraisal tool

a) Graph showing the percentage of studies with a low, high or unclear risk of bias for each of the four domains. b) Table showing risk of bias for each domain for individual studies. Sixteen out of 23 studies were diagnostic accuracy studies and were critically appraised using the QUADAS-2 tool.

6.5 Discussion

6.5.1 Summary of key findings

This systematic review identified 23 studies that reported diagnostic criteria for psoriasis, but it is surprising that no clinical examination-based diagnostic criteria have been developed or tested. The questionnaire-based criteria by Dominguez *et al.* were the closest in type to clinical diagnostic criteria. However, the questionnaire was designed for use as a self-report tool in epidemiological studies and the highest diagnostic performance relied on patients' confirmation of a dermatologist's diagnosis (Dominguez et al., 2009). No studies focused on developing diagnostic criteria for children, and only two genetic studies included children in their study population. Most studies that developed molecular or genetic based diagnostic criteria included validation in the study design, but no studies validated their criteria in the setting and population they were intended to be used. Due to the heterogeneity of diagnostic criteria identified it was not possible to directly compare the diagnostic accuracy in a meta-analysis. Nevertheless, high sensitivity and specificity (>90%) were reported in many studies.

There was significant variation in study reporting, with frequently high risk of bias in domains where details were limited or missing about the study population, reference standard and flow of patients in the study (Whiting et al., 2011). Most diagnostic accuracy studies were undertaken on a selected population using a case-control study design and therefore the QUADAS-2 domain 1 (patient selection) was rated high risk of bias in nearly all critically appraised studies. A case-control design has been shown to over-estimate the diagnostic accuracy of a test or tool (Lijmer et al., 1999, Rutjes et al., 2005).

Overall, study authors often provided minimal details about how the criteria would be used in clinical practice or research, and did not propose the next phase of work needed to validate and implement them. Studies focused, where detailed, on plaque

psoriasis and the diagnostic performance of the criteria in different ethnic groups, ages of patients, distribution and extent of psoriasis is not known.

6.5.2 Diagnostic criteria in dermatology

The benefits of diagnostic criteria in supporting improved clinical diagnosis, research studies and systematic reviews are widely reported (Chuh et al., 2012, Flohr, 2011, Naldi and Gambini, 2007). However, diagnostic criteria have only been developed for a small number skin diseases. The reasons for very few sets of diagnostic criteria has not been explored, but may reflect that most diagnoses in dermatology are made using clinical observations and require few investigations. Also, developing diagnostic criteria may not have previously been prioritised because mortality and end organ damage from skin diseases is rare.

Two systematic reviews have appraised diagnostic criteria for eczema and Behçet's disease. Brenninkmeijer *et al.* summarised and assessed the validity of six examination-based diagnostic criteria for eczema, developed mostly for research purposes (Brenninkmeijer et al., 2008). These criteria achieved varied diagnostic accuracy and Brenninkmeijer *et al.* commented that the methodological quality in both the conduct and reporting differed substantially between the included studies; a similar finding to this review on diagnostic criteria for psoriasis. Davatchi *et al*. appraised 17 sets of examination-based diagnostic criteria that were developed to aid clinical diagnosis of Behçet's disease (Davatchi et al., 2015). The best performing criteria for Behçet's disease were two sets developed through international collaboration. Davatchi *et al.* emphasised that further validation studies in different countries were required and it is important to recognise that the clinical presentation of a disease may change over time (Davatchi et al., 2015). These are three concepts (international collaboration, global validation and fluidity of diagnosis) that need to be considered during the process to develop diagnostic criteria for psoriasis.

Diagnostic criteria have also been proposed for a small number of other dermatological conditions, primarily those with extra-cutaneous involvement and diseases requiring multi-professional input. For example, mucous membrane pemphigoid, PHACE (Posterior fossa, Haemangioma, Arterial lesions, Cardiac abnormalities, Eye abnormalities) syndrome and erosive lichen planus (Chan et al., 2002, Metry et al., 2009, Simpson et al., 2013)

6.5.3 Strengths and limitations

This systematic review is the first to collate and appraise available studies that have developed and/or validated diagnostic criteria for psoriasis. The search strategy was designed to be comprehensive and was supported by an information specialist. Diagnostic accuracy studies were critically appraised using the robust QUADAS-2 tool.

Unlike eczema, it was anticipated that none or few studies had developed clinical diagnostic criteria for psoriasis. However, it was important to search the literature to discover if any progress towards developing diagnostic criteria had been made. Any uncovered studies could then be critically appraised, and if suitable, form the foundations for future work in this PhD. The definition of diagnostic criteria was kept broad to ensure new modalities of diagnosis could be captured. For example, biomarkers, genetic profiles, machine-learning. This decision provides a comprehensive picture of diagnostic options in psoriasis. However, meta-analysis was not possible because no two (or more) studies tested the diagnostic accuracy of the same diagnostic criteria.

6.5.4 Implications for clinical practice

Diagnostic criteria in dermatology aim to support not replace clinical diagnosis, especially in the specialist setting where the reference standard of dermatologist's diagnosis is available. In this review many of the criteria identified were 'test-based'. The usefulness of skin imaging or histopathological diagnostic criteria in isolation may be limited, because they are unlikely to be used without a clinical assessment. However, these criteria are likely to be useful adjuvants to clinical diagnosis. For

example, in cases of clinical diagnostic uncertainty dermoscopic followed by a histopathological diagnostic criteria may be applied. At present, it is more difficult to recognise how genetic or molecular diagnostic criteria would be used in routine clinical practice.

For patients, the implications of not receiving an accurate psoriasis diagnosis (false negatives) include a delay in initiating effective treatment and monitoring for comorbidities. Incorrectly identifying patients with psoriasis (false positives) may result in inappropriate treatment for their skin condition and the possible anxiety of being labelled with a potentially life-long skin condition.

The eligibility criteria for this review included studies that developed or validated diagnostic criteria for adults and/or children. Most studies in this review, where stated, included an adult secondary care population, therefore the findings would be difficult to directly translate to children or a community setting where the diagnostic challenges are different.

6.5.5 Implications for research

Only the questionnaire-based diagnostic criteria were specifically developed for research purposes (Dominguez et al., 2009). However, the diagnostic accuracy of this tool in the community setting has not yet been assessed in a validation study. Genetic and molecular diagnostic criteria may play an important role in future geno-epidemiological studies, developing biobanks and stratifying patients according to their disease profile. However, further work is needed to improve the diagnostic accuracy of such criteria and validate them.

The diagnostic criteria identified in this review are currently not suitable to standardise psoriasis disease definition in clinical trials and observational studies; confirming an important gap in the available literature.

6.5.6 Implications for this research project

Chapter 6 has systematically collated and appraised the available literature about diagnostic criteria for psoriasis in adults and children. No clinical examination-based diagnostic criteria have been identified for psoriasis to support clinical diagnosis and standardisation of disease definition in research studies. Studies have also concentrated on an adult population and no criteria have been developed specifically for children. This systematic review therefore reaffirms the gap in our evidence base of an absence of diagnostic criteria for psoriasis in children. **The next two chapters will detail the initial stages of developing diagnostic criteria for children and young people (<18 years of age).**

Chapter 7 Consensus on diagnostic criteria for plaque psoriasis in children: An eDelphi study with the International Psoriasis Council

7.1 Introduction

Chapters 1 to 6 have presented the background, rationale and evidence gap for undertaking work to develop diagnostic criteria for psoriasis in children. Chapters 3 and 4 have reviewed and explored clinical practice, and showed that the diagnosis of psoriasis may be missed in children. Chapter 5 demonstrated that the development of diagnostic criteria for psoriasis in children would be useful to standardise the disease definition in research studies. Chapter 6 systematically searched the literature for diagnostic criteria for psoriasis and identified no clinical examination-based diagnostic criteria. Specifically, no validated diagnostic criteria are available for psoriasis in children. This Chapter presents the first step in developing diagnostic criteria for psoriasis in children.

Psoriasis in children can be more challenging to diagnose compared to adult disease. An overview of childhood psoriasis and differences between psoriasis affecting these two age groups are introduced in Chapter 2. Often, psoriasis is expected to present with hyperkeratotic (thick scaly) plaques on the extensor (outer) surfaces of the elbows and knees. However, psoriasis in children can have a different and more

subtle presentation. The plaques tend to be thinner, with finer scale, can occur frequently on the face and flexures, including areas of the body usually covered by clothing. There is also reduced awareness amongst non-dermatologists that psoriasis can occur in children. Kapila *et al.* showed that in children referred with a papulosquamous rash, psoriasis was only indicated by the referring general physician for one in ten children with psoriasis. Whereas eczema was correctly recognised in eight in ten children. (Kapila et al., 2012). Under recognition of psoriasis in children may also occur because there are many common differential diagnoses, such as eczema, viral exanthems and allergic eruptions. However, when trying to differentiate psoriasis from other childhood rashes there may be specific clinical features that are helpful to identify. Kapila *et al.* suggested that infra-auricular and post-auricular rashes and splitting occurred more frequently in children with psoriasis than children with eczema (Kapila et al., 2012).

Therefore, there is a need and opportunity to develop diagnostic criteria for psoriasis in children. Before testing a set of criteria in a diagnostic accuracy study, it is first necessary to compile a list of clinical features that psoriasis experts propose are important for the diagnosis of psoriasis in children.

The aim of this Chapter was to reach consensus on a list of diagnostic criteria for plaque psoriasis in children (<18 years). The emphasis was placed on identifying a core list of diagnostic features that would distinguish psoriasis from other skin diseases in children.

This study has been published in the British Journal of Dermatology (Burden-Teh et al., 2019b).

> Burden-Teh E, Thomas KS, Gran S, Murphy R. Development of clinical diagnostic criteria for plaque psoriasis in children: an electronic Delphi consensus study with the International Psoriasis Council. Br J Dermatol. 2019 Oct;181(4):856-857. doi: 10.1111/bjd.17994. Epub 2019 Jun 28.

7.2 Objectives

To agree:

1. A list of discriminatory diagnostic features important for the diagnosis in children

2. A scoring algorithm to use with the diagnostic criteria

7.3 Methods

7.3.1 Study design

Electronic Delphi (eDelphi) consensus study

The Delphi methodology has been extensively used to develop clinical guidelines, diagnostic criteria and core outcome sets (Graham et al., 2003, Prinsen et al., 2014, Gillies et al., 2015, Simpson et al., 2013, Cox et al., 2016). An eDelphi study is conducted as a series of sequential electronic questionnaires, answered anonymously by a panel of participants with relevant expertise (Sinha et al., 2011). It is a methodology that supports seeking expert opinion in an iterative and structured manner to reach a consensus (Diamond et al., 2014). In this multi-stage process participants are provided structured anonymous feedback of collective responses from the previous round. These responses shape the content of the subsequent questionnaire. An important advantage of this type of study is to prevent dominance of the groups' opinion by an individual or individuals.

This eDelphi included three rounds followed by a feedback questionnaire and is summarised in Figure 7:1. Round 1 consisted of initial scoring of diagnostic features and the opportunity to suggest additional features. Round 2 provided feedback on Round 1, asked for suggestions for a diagnostic algorithm, re-scoring on diagnostic features and scoring on whether each feature independently supported a diagnosis

of psoriasis. Round 3 provided feedback on Round 2 and finalised scoring on a diagnostic algorithm. Typically there are between two and four rounds in a Delphi study, which is a compromise between reaching consensus and increasing attrition between rounds (McMillan et al., 2016, Keeney et al., 2001)

The conduct and reporting of this eDelphi follows the checklist provided by Sinha *et al.* (Sinha et al., 2011).

7.3.2 Participants

The IPC is a dermatology-led, voluntary non-profit organisation with representation from 24 countries. At the time of the eDelphi there were 106 councillors; invitation to join the Council is based on globally recognised expertise in psoriasis research, treatment and education (IPC, 2004). Councillors of the International Psoriasis Council were chosen as participants for the eDelphi in accordance with Delphi best practice, which recommends that participants should have the necessary expertise to participate meaningfully (Keeney et al., 2001). All Councillors received an invitation through the IPC, asking for the participation from Councillors with a clinical interest in paediatric psoriasis. This approach is an example of criterion sampling, which is typical for Delphi studies (Hasson et al., 2000).

7.3.3 Sample size

There is little agreement or specific recommendations for the number of participants in an eDelphi study (Keeney et al., 2001). This type of study does not attempt to include a representative sample of the population in order to explore statistical inferences. A relatively small number of participants, for example 20, may provide reliable outcomes if they are selected via strict inclusion criteria (Akins et al., 2005). Typically, a Delphi expert panel includes 15 experts (McMillan et al., 2016). An eDelphi design, instead of paper questionnaires, allows the research team to coordinate a larger panel. However, a larger panel can lead to greater attrition between rounds, which could risk the integrity of the study (Sinha et al., 2011).

7.3.4 Protocol

A protocol for the conduct of the eDelphi was written before starting the study but registered retrospectively on the Centre of Evidence Based Dermatology, University of Nottingham website.
(https://www.nottingham.ac.uk/research/groups/cebd/resources/protocol-registration.aspx)

7.3.5 Management of the eDelphi

The eDelphi was coordinated by EBT. The eDelphi questionnaires were designed and completed using Survey Monkey™ software. IPC Councillors were initially contacted by RM through the IPC to collect expressions of interest. The electronic link for the online questionnaire was distributed by email to IPC Councillors who had expressed an interest in the eDelphi consensus.

At the beginning of the eDelphi the aims, purpose of the diagnostic criteria, design of the study, participation details and required level of commitment were provided to Councillors. It was explained that the aim of the eDelphi was to agree a list of discriminatory features which would differentiate plaque psoriasis from other rashes in children. The importance of completing all rounds for the integrity of the consensus was emphasised at the beginning of each questionnaire. The identity and responses of participants were fully anonymised from the group, but not from the study coordinator (quasi-anonymous). The identities of the panel were known to EBT and non-responders were followed up to ensure a high participation rate in each round. No incentive was offered, and it was explained that completing the questionnaire provided agreement to participate in the eDelphi consensus. Each questionnaire remained open for two weeks and up to three reminders were sent during this time. Responders from Round 1 were invited to participate in Rounds 2 and 3. Non-responders were not invited to participate in the next round.

In each Round of the eDelphi, data were collected on the country of clinical practice, age of patients seen in usual dermatology practice (not collected in Round 1),

gender, number of years experience as dermatologist and number of years specialist interest in psoriasis.

7.3.6 Round 1

The Round 1 questionnaire presented a list of 21 potential diagnostic features for psoriasis in children. These features were compiled from two sources: i) a scoping review on the epidemiology of childhood psoriasis (Chapter 4); ii) interviews with paediatric dermatologists (Chapter 3) (Burden-Teh et al., 2016, Burden-Teh et al., 2017a). The 21 diagnostic features are listed in Appendix 8. Diagnostic features were presented randomly in the online questionnaire to each participant in order to minimise question order bias. This type of bias occurs when participants respond differently to a question depending on where it is positioned in the questionnaire (Brookes et al., 2018).

Based on their clinical experience, participants were asked to score the importance of each item for making a diagnosis of psoriasis in a child. The rating scale included five categories; 'very important', 'important', 'less important', 'not important' and 'unsure'. Participants were also asked to suggest additional diagnostic features if they felt an important distinguishing feature had been omitted. Participants were also able to provide feedback on individual items and any aspect of Round 1.

Suggestions for new diagnostic features were reviewed by EBT and RM and if sufficiently unique were included in Round 2. All 21 diagnostic features were carried forward to Round 2.

7.3.7 Round 2

The Round 2 questionnaire provided participants with collective feedback for each diagnostic feature. Feedback was provided as the percentage response of the group for each category on the rating scale. In response to feedback from Round 1, new items were added, and the wording of diagnostic features changed.

After reflecting on the feedback, participants were asked to re-score each diagnostic feature on the five-category rating scale. Features that reached consensus (see below for the definition of consensus) were carried through to Round 3. Participants were also asked whether the presence of a diagnostic feature alone could be used to support a diagnosis of psoriasis in a child. Response options were 'yes', 'no' and 'maybe'. Features with consensus agreement that the item alone could independently support a diagnosis of psoriasis were classed as a major criterion. All features that did not reach consensus as a major criterion were classed as minor criteria. Participants were asked for suggestions for a diagnostic scoring algorithm to use with the consensus agreed diagnostic features. Participants were also asked for feedback on any aspect of Round 2.

7.3.8 Round 3

The Round 3 questionnaire provided participants with a list of consensus agreed diagnostic features. Round 3 also provided collective feedback on whether each feature alone could be used to support a diagnosis of psoriasis. Feedback was provided as the percentage response of the group for 'yes', 'no' and 'maybe'.

After reflecting on the feedback, participants were asked to re-score whether an item alone could support a diagnosis of psoriasis. Participants were also asked to score the number of minor criteria needed to support a diagnosis in the absence of a major criterion. Lastly, participants were asked to clarify whether: i) two very similar items ("scaly erythematous plaques on the trunk triggered by a sore throat or other infection" and "raindrop plaques typical of guttate disease on the trunk or limbs") should be kept in the diagnostic criteria; ii) clinical features needed to be present on examination. Participants were also asked for feedback on any aspect of Round 3.

7.3.9 Feedback survey

The three rounds of eDelphi questionnaires were followed up by a feedback survey. This survey presented participants with the eDelphi consensus conclusions and a summary of additional comments provided in each round. Participants were asked

whether they felt the diagnostic criteria would distinguish psoriasis from other childhood rashes and whether they agreed with the proposed scoring algorithm. Participants were then given the opportunity to comment on the conclusions and direction of future research.

7.3.10 Definition of consensus

Consensus for inclusion was defined as ≥70% of participants agree that an item was 'very important'/'important' and ≤15% of participants agree that an item was 'not important' or 'unsure' using the five-category scale. Major criteria were defined as agreement of ≥70% that the presence of a diagnostic feature alone would allow a diagnosis of psoriasis to be made. To minimise bias, the definition of consensus should be agreed at the study outset (Gillies et al., 2015). In this study a 70% threshold for consensus was decided a priori.

There are no specific recommendations on how to define consensus because it is influenced by the purpose and topic of the study. The concept of consensus is built on the premise an item should be included if the majority agree on its critical importance and only a minority consider it unimportant (Gillies et al., 2015). A systematic review by Diamond *et al.* found that of studies using a definition based on a percentage, the median threshold was 75% (Diamond et al., 2014).

7.3.11 Analysis

Collective responses were calculated as the percentage response of the group for each category on the rating scale.

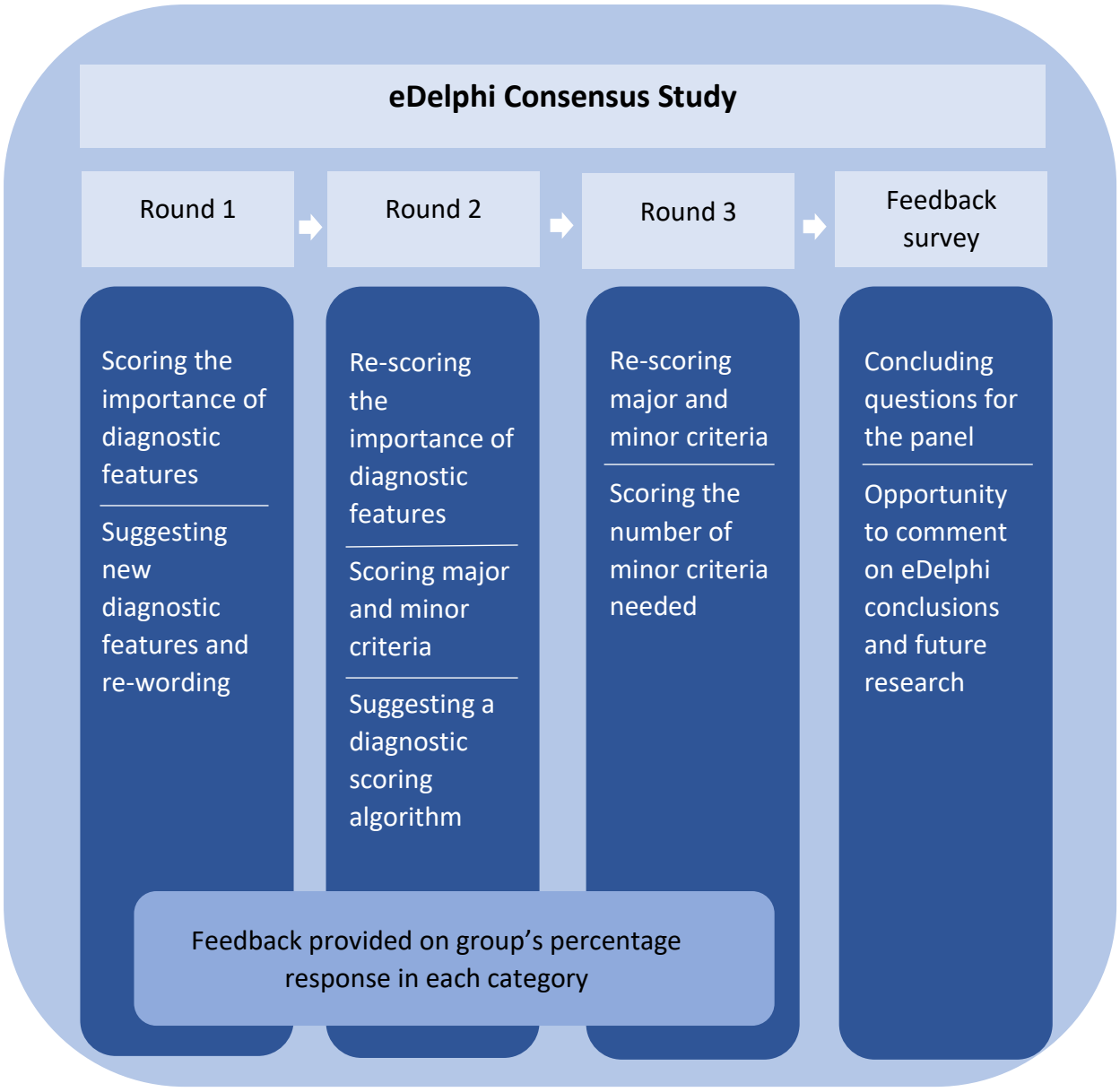


Figure 7:1 eDelphi study flow from Round 1 to the feedback survey

7.4 Results

Table 7:1, Table 7:2, Table 7:3 present the participant characteristics, participant scores from Round 2, and participant scores from Round 3 defining the major and minor criteria. Figure 7:2 presents the final eDelphi diagnostic criteria.

7.4.1 Participant characteristics

An email invitation to participate in Round 1 of the eDelphi was sent to all 106 councillors of the International Psoriasis Council on the 15th December 2015. In total 41 participants completed the first Round. Of these 34 (83%) fully completed Round 2 and 31 (76%) Round 3.

Across the three rounds, the participants represented 19 countries and most of the participants (48-54%) had 20 years or more dermatological experience. Over half of participants frequently manage children and adults as part of their routine clinical practice

Table 7:1.

Participant characteristics	Round 1 (%)	Round 2 (%)	Round 3 (%)
Number of participants	41	34	31
Number of years' experience as a dermatologist			
<5 years	1 (2.6%)	0	0
5-10 years	4 (10.3%)	3 (8.8%)	4 (12.9%)
11-15 years	9 (23.1%)	8 (23.5%)	7 (22.6%)
16-20 years	4 (10.3%)	5 (14.7%)	5 (16.1%)
>20 years	21 (54%)	18 (52.9%)	15 (48.4%)
No data	2	0	0
Number of years' specialist interest in psoriasis			
<5 years	0	0	0
5-10 years	5 (12.8%)	4 (11.8%)	5 (16.1%)
11-15 years	11 (28.2%)	9 (26.5%)	6 (19.65%)
16-20 years	5 (12.8%)	7 (20.6%)	5 (16.1%)
>20 years	18 (46.2%)	14 (41.2%)	15 (48.4%)
No data	2	0	0
Current routine practice			
Adults only	No data	1 (2.9%)	0
Mostly adults and rarely see children	collected	13 (38.2%)	10 (32.3%)
Mostly adults and frequently see children		19 (55.8%)	20 (64.5%)
Mostly children		1 (2.9%)	1 (3.2%)
Gender			
Male	29 (74.4%)	25 (73.5%)	22 (71%)
Female	10 (25.6%)	9 (26.5%)	9 (29%)
No data	2	0	0
Country of practice			
Argentina	1 (2.4%)	1 (2.9%)	1 (3.2%)
Canada	5 (12.2%)	5 (14.7%)	4 (12.9%)
Chile	2 (4.9%)	1 (2.9%)	2 (6.5%)
Columbia	1 (2.4%)	1 (2.9%)	1 (3.2%)
Denmark	3 (7.3%)	3 (8.8%)	3 (9.7%)
Egypt	1 (2.4%)	1 (2.9%)	1 (3.2%)
Germany	1 (2.4%)	1 (2.9%)	1 (3.2%)
India	1 (2.4%)	1 (2.9%)	1 (3.2%)
Iran	1 (2.4%)	1 (2.9%)	1 (3.2%)
Ireland	1 (2.4%)	1 (2.9%)	0 (0%)
Italy	4 (9.6%)	3 (8.8%)	2 (6.5%)
Japan	1 (2.4%)	1 (2.9%)	1 (3.2%)
Netherlands	3 (7.3%)	3 (8.8%)	3 (9.7%)
Singapore	2 (4.9%)	2 (5.9%)	1 (3.2%)
South Africa	1 (2.4%)	1 (2.9%)	1 (3.2%)
Spain	2 (4.9%)	2 (5.9%)	2 (6.5%)
United Kingdom	1 (2.4%)	1 (2.9%)	1 (3.2%)
United States	8 (19.5%)	5 (14.7%)	5 (16.1%)
No data	2 (4.9%)	0 (0%)	0 (0%)

Table 7:1 Participant characteristics for Rounds 1, 2 and 3 of the eDelphi consensus study

7.4.2 Round 1

Participant feedback from Round 1 was incorporated into Round 2. The following diagnostic feature was divided into two items; “retroauricular erythema and/or fissures”. Three new diagnostic features were added: “persistent well-demarcated erythematous scaly rash anywhere on the body”; “raindrop plaques typical of guttate disease on the trunk or limbs”; “scaly erythema inside the external auditory meatus”. “Scale growing down the hair shaft” and “scaly scalp in the first year of life” were amalgamated as “scaly scalp”. The wording of certain criteria were changed to include the word “persistent” and other small changes were made to improve the clarity of the wording. Participants commented on the importance of facial involvement in psoriasis in children.

7.4.3 Round 2

Sixteen diagnostic features reached consensus as being important for a diagnosis of psoriasis in children. Nine potential features did not reach consensus and therefore were dropped for Round 3 and not included in the diagnostic criteria. Participant scores from Round 2, including which features were carried forward or dropped for Round 3, are presented in Table 7:2

Diagnostic feature	Very important	Important	Less Important	Not Important	Unsure	Included in diagnostic criteria
Criteria which reached ≥70% consensus as 'very important' or 'important'						
Scale and erythema in the scalp involving the hairline	26%	71%	3%	0	0	Yes
Retro-auricular erythema (including behind the earlobes)	3%	71%	26%	0	0	Yes
Scaly erythema inside the external auditory meatus*	24%	50%	24%	0	3%	Yes
Scaly erythematous plaques on the trunk triggered by a sore throat or other infection	79%	18%	3%	0	0	Yes
Raindrop plaques typical of guttate disease on the trunk or limbs*	71%	26%	3%	0	0	Yes
Persistent well-demarcated erythematous scaly rash anywhere on the body*	44%	44%	12%	0	0	Yes
Scaly erythematous plaques on the extensor surfaces of the elbows and knees	85%	15%	0	0	0	Yes
Fine scaly patches involving the upper thighs and buttocks	0	71%	24%	6%	0	Yes
Well-demarcated erythematous rash in the napkin area involving the crural folds	0	76%	24%	0	0	Yes
Persistent erythema in the umbilicus	18%	71%	12%	0	0	Yes
Nail pitting	29%	65%	6%	0	0	Yes

Onycholysis of the nail(s)	24%	68%	6%	3%	0	Yes
Subungal hyperkertosis of the nail(s)	12%	79%	9%	0	0	Yes
Positive family history of psoriasis	35%	59%	6%	0	0	Yes
Koebner Phenomenon	3%	85%	12%	0	0	Yes
Fusiform swelling of a toe or a finger suggestive of dactylitis	40%	40%	9%	6%	0	Yes
Criteria which <u>did not</u> reach ≥70% consensus as 'very important' or 'important'						
Scaly scalp	3%	59%	38%	0	0	No
Retro-auricular skin splitting (including behind the earlobes)	12%	14%	47%	0	0	No
Persistent well-demarcated facial rash with fine or absent scale	0	59%	41%	0	0	No
Persistent erythematous periorbital rash with fine or absent scale	0	15%	62%	24%	0	No
Well-demarcated erythematous rash in the axilla(e)	6%	44%	44%	6%	0	No
Natal cleft erythema and/or skin splitting	21%	32%	44%	3%	0	No

Persistent nappy rash	0	44%	50%	6%	0	No
Sleep not disturbed by itch	0	0	41%	58%	0	No
Absence of skin xerosis	0	0	38%	62%	0	No

Table 7:2 The results from Round 2 of the eDelphi consensus study presenting the groups' percentage scores on the importance of diagnostic features in making a diagnosis of plaque psoriasis in children
** Diagnostic features suggested in the feedback from Round 1 and included in Round 2*

7.4.4 Round 3

The results of Round 3, defining major and minor criteria, are presented in Table 7:3. Participants reached consensus that either “scaly erythematous plaques on the extensor surfaces of the elbows and knees” or “scaly erythematous plaques on the trunk triggered by a sore throat or other infection” alone would allow a diagnosis of psoriasis to be made. Fifty-five percent of participants agreed to keep both “raindrop plaques typical of guttate disease on the trunk or limbs” and “scaly erythematous plaques on the trunk triggered by a sore throat or other infection”, therefore they are both are listed as a major criterion.

The 13 minor criteria listed are items that reached consensus as being important for the diagnosis of psoriasis in children, but their presence alone could not support a diagnosis. Forty-eight percent of participants felt that in the absence of at least one major criterion, three or more minor criteria would support a diagnosis of psoriasis in children. When asked whether a diagnostic criterion involving a clinical sign should be present on examination, 55% responded “yes”.

The final eDelphi diagnostic criteria are presented in Figure 7:2 and photographs exemplifying some these features are presented in Figure 7:3.

Major criteria	The presence of this feature alone would allow a diagnosis of psoriasis to be made		
	Agree	**Disagree**	**Unsure**
scaly erythematous plaques on the extensor surfaces of the elbows and knees	93%	7%	0
scaly erythematous plaques on the trunk triggered by a sore throat or other infection	71%	13%	16%
raindrop plaques typical of guttate disease on the trunk or limbs	*	*	*
Minor criteria	The presence of this feature alone would not allow a diagnosis of psoriasis to be made		
	Agree	**Disagree**	**Unsure**
scale and erythema in the scalp involving the hairline	90%	7%	3%
retro-auricular erythema (including behind the earlobes)	61%	29%	10%
scaly erythema inside the external auditory meatus	64%	26%	10%
persistent well-demarcated erythematous scaly rash anywhere on the body	91%	9%	0%
fine scaly patches involving the upper thighs and buttocks	52%	29%	19%
well-demarcated erythematous rash in the napkin area involving the crural folds	77%	16%	7%
persistent erythema in the umbilicus	60%	37%	3%
nail pitting	84%	13%	3%
onycholysis of the nail(s)	67%	20%	13%
subungal hyperkeratosis of the nail(s)	74%	20%	6%
positive family history of psoriasis	71%	26%	3%

koebner phenomenon	59%	34%	7%
fusiform swelling of a toe or a finger suggestive of dactylitis	86%	11%	3%

Table 7:3 The results from Round 3 of the eDelphi consensus study presenting the groups' percentage scores on whether the presence of a diagnostic feature alone would support a diagnosis of psoriasis.
**55% of participants agreed to keep both "raindrop plaques typical of guttate disease on the trunk or limbs" and "scaly erythematous plaques on the trunk triggered by a sore throat or other infection"*

Major criteria The presence of one major criterion supports a diagnosis of plaque psoriasis in a child
scaly erythematous plaques on the extensor surfaces of the elbows and knees
scaly erythematous plaques on the trunk triggered by a sore throat or other infection
raindrop plaques typical of guttate disease on the trunk or limbs
Minor criteria The presence of three or more minor criteria support the diagnosis of plaque psoriasis in a child
scale and erythema in the scalp involving the hairline
retro-auricular erythema (including behind the earlobes)
scaly erythema inside the external auditory meatus
persistent well-demarcated erythematous scaly rash anywhere on the body
fine scaly patches involving the upper thighs and buttocks
well-demarcated erythematous rash in the napkin area involving the crural folds
persistent erythema in the umbilicus
nail pitting
onycholysis of the nail(s)
subungal hyperkeratosis of the nail(s)
positive family history of psoriasis
koebner phenomenon
fusiform swelling of a toe or a finger suggestive of dactylitis

Figure 7:2 The eDelphi consensus study agreed diagnostic criteria for plaque psoriasis in children

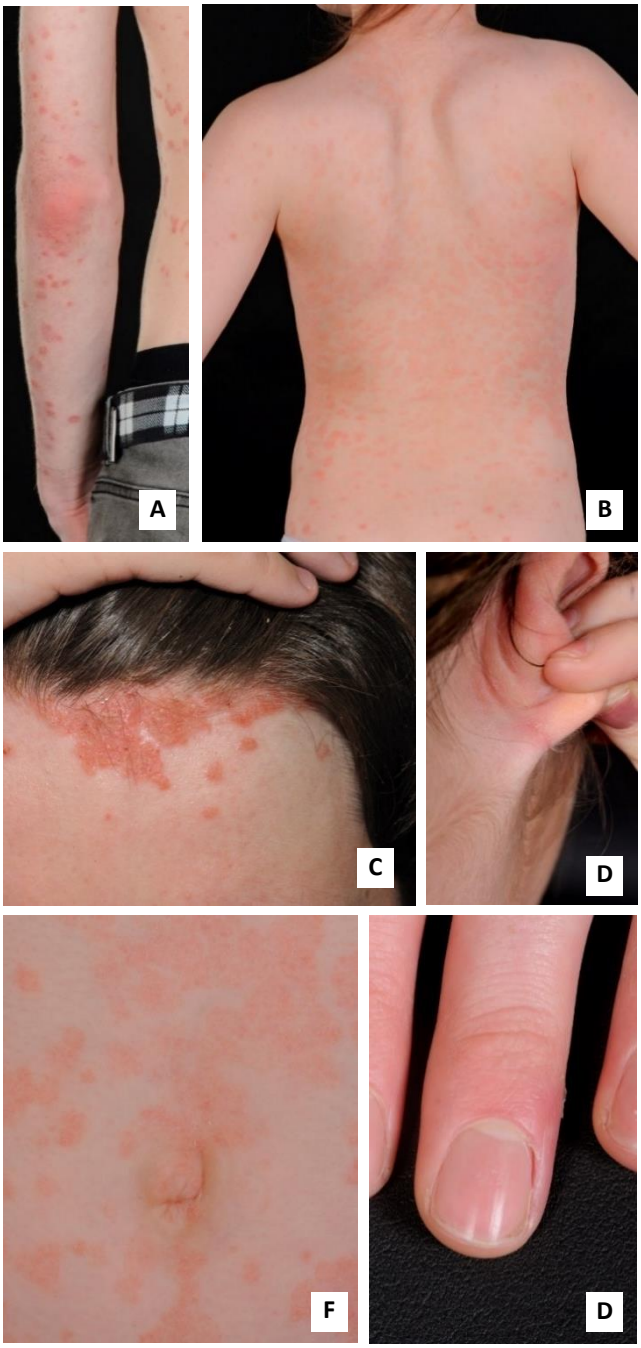


Figure 7:3 Photographs exemplifying some of the final diagnostic criteria
Images consented for research and teaching at Nottingham University Hospitals NHS Trust, courtesy of Dr Ruth Murphy

A Scaly erythematous plaques on the extensor surfaces of the elbows and knees
B Raindrop plaques typical of guttate disease on the trunk or limbs
C Scale and erythema in the scalp involving the hairline
D Retro-auricular erythema (including behind the earlobes)
E Persistent erythema in the umbilicus
F Nail pitting

7.4.5 Feedback survey

Twenty-seven (66%) participants completed the feedback survey. In the feedback round, 17 (63%) participants agreed and seven (26%) were unsure that the diagnostic criteria would be able to distinguish psoriasis from other childhood rashes. Twenty-three participants (84%) agreed that in the absence of a major criterion, three or more minor criteria would support a diagnosis of psoriasis. The eDelphi feedback outlining uncertainties and future research is summarised in Figure 7:4.

Participant feedback outlining uncertainties and future research
A need to test and validate the diagnostic criteria in different populations globally
To consider the role of diagnostic features which did not reach consensus but have repeatedly appeared in comments supporting their importance in the diagnosis of psoriasis in children. These features include natal cleft erythema/splitting/Brunstings sign, retroauricular splitting, and axillary psoriasis.
To decide whether a clinical sign needs to be present on examination or whether a historical sign can be included; recognising that clinical signs can develop over time.
To investigate the number of minor criteria required to support a diagnosis of psoriasis
To consider the implications of using the diagnostic criteria in clinical practice and for research
Rewording and combining certain diagnostic criteria, such as combining the three criteria relating to nail disease.
The use of clinical photographs to represent each item in the diagnostic criteria.
The possible role of histopathological and dermatoscopic diagnostic features

Figure 7:4 Participant feedback from the eDelphi consensus study outlining uncertainties and future research

7.5 Discussion

7.5.1 Summary of findings

The eDelphi has identified 16 diagnostic features which are important for the clinical diagnosis of plaque psoriasis in children. The consensus aimed to reach agreement based on participants' expert clinical opinion. This approach is particularly valid for a condition such as psoriasis, for which a dermatologist's diagnosis is the gold standard. The participants agreed on three major and thirteen minor diagnostic criteria, and proposed a diagnostic scoring algorithm. Feedback from participants highlighted that further work was needed to evaluate the criteria using empirical data, to possibly refine the diagnostic dataset and confirm the number of minor criteria required to support a diagnosis. The eDelphi is however an important first step in developing diagnostic criteria for psoriasis in children; providing a clinically derived list that can be tested in subsequent diagnostic accuracy studies.

7.5.2 Relevance to existing literature

A consensus approach fits naturally with developing diagnostic criteria. Informal consensus methods have been used to develop international diagnostic criteria for autoimmune urticaria and tuberous sclerosus. The European Academy of Allergy and Clinical Immunology reviewed the existing literature on the laboratory and clinical evidence for autoimmune urticaria and reached consensus at a final meeting. The output was a recommendation for a diagnostic gold standard (Konstantinou et al., 2013). No details were provided on the composition of the taskforce or the method by which consensus was reached. The International Tuberous Sclerosis Complex Consensus Conference convened to reach agreement on diagnostic and management of tuberous sclerosis (Northrup et al., 2013). A summary of the panel composition was provided, but minimal details were provided on how consensus was reached. Recommendations were presented for discussion, modified if needed, and then received final approval. The main problems with informal consensus methods is the lack of transparency about steps taken to reach consensus, reporting of excluded criteria and clarity about how consensus is defined.

An eDelphi study offers a structured, widely accepted and transparent methodology to reach consensus. An eDelphi approach has been used for developing diagnostic criteria for erosive lichen planus and ulcerative pyoderma gangrenosum. Simpson *et al*. conducted an eDelphi with 73 experts representing multiple specialties involved in the diagnosis and care of patients with erosive lichen planus (Simpson et al., 2013). The composition of the panel and method of eDelphi is well described, but it is not clear whether the definition of consensus was decided a priori. The attrition rate between the first and last round was very low (5%). Items were excluded after Round 1, which may be a source of bias. Maverakis *et al.* conducted an eDelphi to develop diagnostic criteria for ulcerative pyoderma gangrenosum and tested the diagnostic accuracy against clinical photographs (Maverakis et al., 2018). The panel were asked to rate the appropriateness of statements in the diagnosis of pyoderma gangrenosum and the average response and disagreement index were calculated statistically. Similarly, to Simpson *et al.*, it is not clear if the definition of consensus was decided a priori and there was no attrition between rounds. The diagnostic testing was conducted on unblinded images in a case-control design, with statistical manipulation using imputation for missing data. Therefore, further diagnostic testing and validation of the criteria for pyoderma gangrenosum is still required.

7.5.3 Strengths and limitations

The eDelphi was conducted in line with best practice guidance (Sinha et al., 2011). Importantly an 'a priori' decision on the definition of consensus was made. Good international representation was achieved with involvement of 19 countries. The web-based design of the study facilitated wide geographical participation and ensured quasi-anonymity of the participants. Essential for the development of expert agreed diagnostic criteria there was a high level of dermatological expertise amongst participants and participation was maintained between rounds.

However, Africa, Asia and South America were underrepresented by International Psoriasis Council Councillors who participated in the eDelphi. As a consequence, experience of psoriasis occurring in skin types IV and V, and therefore identification

of important differentiating clinical signs, may have been limited amongst participants. Although all participants were psoriasis experts, only two thirds of participants frequently reviewed children with psoriasis; potentially diluting the specificity of the criteria for psoriasis in children. The eDelphi aimed to develop diagnostic criteria for the most common psoriasis subtype, plaque psoriasis, and therefore does not assist diagnosis in rarer subtypes such as generalised and localised pustular psoriasis. Additionally, it is unknown whether there are important phenotypic divisions within plaque psoriasis which have a different natural history, aetiology and prognosis. It is important to emphasise that the eDelphi diagnostic criteria for plaque psoriasis in children are not intended to be transferable to an adult population.

There are also limitations of the Delphi process itself. Hasson *et al*. and Kenney *et al.* both provide a critique of the methodology in their review articles (Hasson et al., 2000, Keeney et al., 2001). The overarching aim of the methodology is to reach consensus, and therefore the priority to do this can force consensus and encourage participants to conform to the group opinion (Sinha et al., 2011). There is minimal opportunity for within group discussion, to explore and provide further detail on opinions. The findings may be unreliable, because a different expert panel may reach a different consensus. The last limitation can be reduced by trying to include representation from a wide range of experts with differing experiences.

7.5.4 Implications for clinical practice

In dermatological practice, diagnostic criteria for psoriasis would support, not replace, clinical diagnosis. Diagnostic criteria would also provide a structure for the assessment and documentation of skin signs in psoriasis. It is intended that the development of diagnostic criteria will help improve the recognition of psoriasis by non-dermatologists, such as primary care physicians and paediatric rheumatologists. Thereby, supporting referral to dermatology as per NICE guidance and differentiation of juvenile idiopathic arthritis into juvenile psoriatic arthritis (NICE, 2012, Burden-Teh et al., 2017a). Further steps to test and validate the criteria are needed, but in the interim the eDelphi diagnostic criteria provides clinicians with a prompt list for

clinical assessment. Increased research activity around the diagnosis of psoriasis will also raise awareness amongst health professionals about how psoriasis typically presents in children.

7.5.5 Implications for this research project

Chapter 7 has developed expert derived diagnostic criteria for plaque psoriasis in children using eDelphi methodology. The consensus has proposed 16 diagnostic features that experts feel are important for diagnosis. However, there is a need to test the diagnostic accuracy, potentially refine the criteria and then validate them in the population and setting they are intended to be used. **The next Chapter will describe the development of a multi-centre diagnostic accuracy study to test and refine the criteria using statistical methods.**

Chapter 8 Developing diagnostic criteria for psoriasis in children (DIPSOC study): The design of a multi-centre diagnostic accuracy case-control study in UK paediatric dermatology clinics

8.1 Introduction

Chapter 7 has provided a list of expert-derived diagnostic criteria for plaque psoriasis in children and builds on the research gaps identified in Chapters 1-6. This Chapter presents the design of a diagnostic accuracy case-control study to test and refine the consensus agreed diagnostic criteria. The Chapter will describe how patient and public involvement work has been integrated throughout the research cycle, the rationale behind the study design, statistical analysis plan, study set-up and site management. From conceptualisation to dissemination planning, stakeholders have had a critical role in the study. These stakeholders include dermatologists, paediatric rheumatologists, GPs, children/young people and their families and researchers. The title of the study is developing **DI**agnostic criteria for **Pso**riasis in **C**hildren, known as the DIPSOC study.

The protocol for DIPSOC has been published in BMJ Open (Burden-Teh et al., 2019a).

> Protocol for a case-control diagnostic accuracy study to develop diagnostic criteria for psoriasis in children (DIPSOC study): a multicentre study recruiting in UK paediatric dermatology clinics. Burden-Teh E, Murphy R, Gran S, Nijsten T, Hughes C, Thomas KS. BMJ Open. 2019 Aug 27;9(8):e028689

8.2 Patient and Public Involvement

The aim of patient and public involvement (PPI) work in DIPSOC was to provide a patient perspective on the importance of diagnosis, to ensure the study design was patient-centred, to inform the design of participant facing documents and check they were easy to understand, and to direct public dissemination of the results. Figure 8:1 shows how PPI has been integrated into the DIPSOC study research cycle.

A patient advisor (CH) has contributed to the funding application for this PhD and is a DIPSOC study co-investigator. In the text below CH shares her thoughts about what it is like to be a patient adviser in the project.

"I've been affected by psoriasis and psoriatic arthritis and I joined the CEBD Patient Panel to help other people. My first panel meeting inspired me to get involved with Cochrane and as a patient/consumer I've commented on several Cochrane reviews over the past 10 years. I've been involved in DIPSOC as a patient collaborator and gave feedback on the design of the study and suggestions to improve the participant information sheets.

I have enjoyed being involved in the project and feeling that I could contribute something useful to it. It was great to be named as a co-author on the published protocol. I believe that a diagnostic tool for psoriasis in children is much needed and will benefit patients and their parents. Getting a 'proper' diagnosis of psoriasis often seems quite difficult and frustrating for patients and their carers.

I think all patients can make a useful contribution to research into health conditions. The experience of 'being a patient' is not easy or pleasant, but you can put it to good use. Just commenting on the practical aspects of conducting a study, or a confusing sentence in a leaflet, makes you feel as if you're helping to make things better for others in the future."

The study is also supported by the Psoriasis and Psoriatic Arthritis Alliance (PAPAA), a UK patient association for people with psoriasis and psoriatic arthritis. In 2016, two workshops were held with the Young Persons' Advisory Group for Research (YPAG) Nottingham. The YPAG is funded by the NIHR to support the design and delivery of paediatric research in the UK. The workshops included up to 14 young people aged between 9 and 19 years of age and have provided feedback on the topic of diagnosis, the study design, participant information sheets, website ideas and dissemination. I have also met with young people and parents in paediatric dermatology clinics. A summary of changes made to the DIPSOC study in response to PPI work are outlined in Figure 8:2.

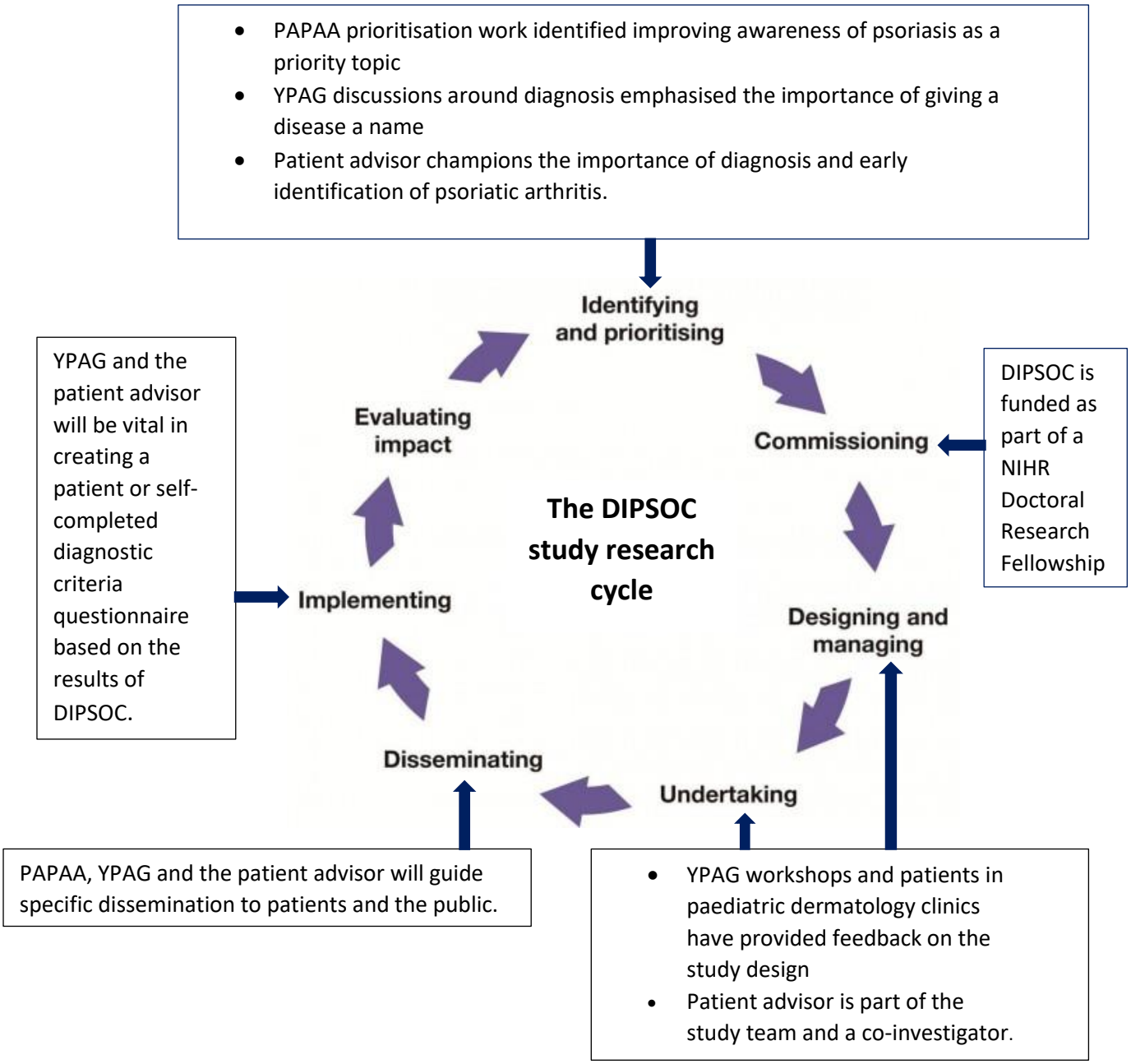


Figure 8:1 How patient and public involvement has been important in the DIPSOC study research cycle
Image from https://www.nihr.ac.uk/patients-and-public/how-to-join-in/the-research-cycle. PAPAA – Psoriasis and Psoriatic Arthritis Alliance, YPAG – Young Persons' Advisory Group for Research, NIHR – National Institute for Health Research.

Suggestions from patient and public involvement work that have informed the DIPSOC study
Study design • Include on the day recruitment and the option to attend for a separate research visit • Invite participants by letter in advance of their clinic appointment
Participant information sheets • Change the format to a leaflet or booklet • Colourful boxes around the text and different colours for different sections • Emphasise confidentiality and the assessment will take place in a private space • Include photographs of the research team • Don't include photographs of psoriasis • Provide electronic versions of the information sheets on a website
Create a distinctive logo for the study
Provide a colouring-in sheet
Give a certificate and sticker at the end of the research visit

Figure 8:2 Suggestions from patient and public involvement work that have informed the DIPSOC study

8.3 Study Objectives

8.3.1 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.

8.3.2 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

8.4 Methods

8.4.1 Study design

Multi-centre case-control diagnostic accuracy study.

The DIPSOC study is designed as a case-control diagnostic accuracy study that will recruit in paediatric dermatology clinics. This is an appropriate and feasible study design for the first study to test and refine the consensus agreed criteria, but it is likely to overestimate the diagnostic ability of the criteria (Leeflang et al., 2008). The clinic prevalence for psoriasis in children is estimated to be between 3-7%, therefore within the time and resources available it was not feasible to recruit an unselected study population (Burden-Teh et al., 2016). DIPSOC is a development study and further work will be needed to validate the diagnostic accuracy of the criteria in the primary care, secondary care and research settings where they might be used.

The protocol for the DIPSOC study was registered on the CEBD website before the first participant was recruited (www.nottingham.ac.uk/go/dipsoc). The DIPSOC study was also registered on the International Standard Randomised Controlled Trials Number (ISRCTN) website in November 2017 https://doi.org/10.1186/ISRCTN98851260.

DIPSOC has been designed and will be reported according to the Statement for Reporting Diagnostic Accuracy Studies (STARD) (Bossuyt et al., 2015).

8.4.2 Ethical approval

Health Regulatory Authority (HRA) and National Health Service Research Ethics Committee (NHS REC) approvals were granted in February 2017 (REC Ref: 17/EM/0035). The study follows the declaration of Helsinki. The four principles of biomedical ethics were considered in the study design and documentation. The purpose, aims and details of taking part in the study are explained in the participant information sheets. It is explained that taking part is voluntary and not taking part will have no effect on the patient's medical care. Informed consent is necessary before any part of the study is completed. It is also explained that taking part in the study will have no direct medical benefit for the patient, but may help the diagnosis of other children or young people in the future. The study is non-therapeutic and is not a Clinical Trial of an Investigational Medicinal Product (CTIMP). All study investigators are required to be Good Clinical Practice (GCP) trained.

8.4.3 Study documents

The following DIPSOC documents are included as appendices

- Case Report Form (CRF) - Appendix 9
- Participant information sheets - Appendices 10-13
- Training manual - Appendix 14

8.4.4 Study setting

DIPSOC will recruit in paediatric dermatology clinics. This is a suitable setting in which to recruit participants with a confirmed reference standard (dermatologist's diagnosis) and to ensure the sample size is recruited within the time and resources available.

8.4.5 Participant selection

Participant eligibility is a clinical decision to be made by the patient's dermatologist. If there is uncertainty over eligibility, then the researcher is advised to check with the clinical team.

The researcher is required to document in the case report form (CRF) that the participant meets the eligibility criteria. The inclusion and exclusion are summarised in Figure 8:3.

8.4.5.1 Inclusion criteria

Cases and controls are children and young people aged 0 to <18 years, with active skin disease (rash present) at the time of assessment and are able to consent or have a parent/guardian willing to give consent.

Including patients aged 0-17 years of age reflects the population reviewed in paediatric dermatology clinics. This is a wide age range and therefore stratification for age at assessment into pre- and post-puberty strata is planned in the analysis. The clinical presentation of psoriasis may differ between young children and adolescents, for example flexural psoriasis may be more common in younger children, and it will be important to explore the effect of age on the diagnostic accuracy and final composition of the criteria.

Active skin disease at the time of assessment requires the patient to have a skin rash present on the day of the research visit. Therefore, in line with the opinion of half of the eDelphi panel (Chapter 7), it is the presence rather than the history of skin

changes that will be assessed in the study. The clinical presentation may be altered by chronicity and treatment, therefore to explore the effect of disease duration on the diagnostic accuracy of the criteria, the analysis will be stratified for new and follow-up patients.

Definition for cases

Cases are defined by having a confirmed diagnosis of plaque psoriasis by a dermatologist. In DIPSOC, plaque psoriasis has been used as a broad term to include all subtypes and presentations of psoriasis where plaques are the main feature. For example, chronic plaque psoriasis, guttate psoriasis, scalp psoriasis and flexural psoriasis are included under the term plaque psoriasis, but purely nail psoriasis or juvenile psoriatic arthritis without skin involvement are excluded. The decision to define plaque psoriasis in this way reflects the outcome of the eDelphi consensus study (Chapter 7). Plaque followed by guttate psoriasis are the two most common subtypes (Chapter 5) and the clinical presentation can flux between the two.

Definition for controls

Controls are defined by having a confirmed diagnosis of a scaly inflammatory rash (excluding psoriasis or indeterminate psoriasis) by a dermatologist. Skin conditions that may be included in the control population are eczema (atopic dermatitis), pityriasis rubra pilaris, pityriasis rosea, ichthyosis, mycosis fungoides, Gianotti-Crosti syndrome and tinea corporis. These conditions are not an exhaustive list and the decision as to whether a participant's skin disease meets the eligibility criteria will be made by the patient's dermatologist. Figure 8:4 provides examples of skin diseases that may be included in the control population.

The definition for the control group was chosen to represent the population from which the cases were identified (i.e. patients with papulosquamous disease). In clinical practice, it is this group of papulosquamous diseases in which the diagnostic dilemma occurs; demonstrated by the pre-psoriasis diagnoses listed in the multi-centre audit and case-note review (Chapter 3). Including all children who presented to paediatric dermatology clinics would not reflect clinical practice, because many of

the presenting complaints would not be part of the differential diagnoses for psoriasis (eg individual lesions, hair disorders, pigmentary changes).

8.4.5.2 Exclusion criteria

Children or young people with pustular psoriasis, erythrodermic psoriasis or a skin disease without a confirmed dermatologist's diagnosis will be excluded. Pustular psoriasis is considered to have a different pathophysiological and genetic basis to plaque psoriasis, and therefore this subtype has been excluded from the study (Sugiura, 2014). Erythrodermic psoriasis has also been excluded because there may be diagnostic uncertainty and erythroderma is rarely encountered in the community or paediatric rheumatology clinics (Braegelmann et al., 2016).

Eligibility criteria for the DIPSOC study
Inclusion criteria
Children and young people aged 0 to <18 years
Active skin disease (rash present) at the time of assessment
Able to give informed written consent
Cases have a confirmed diagnosis of plaque psoriasis by a dermatologist
Controls have a confirmed diagnosis of a scaly inflammatory rash (excluding psoriasis or indeterminate psoriasis) by a dermatologist.
Exclusion criteria
Pustular psoriasis
Erythrodermic psoriasis
No confirmed dermatologist's diagnosis

Figure 8:3 Eligibility criteria for the DIPSOC study

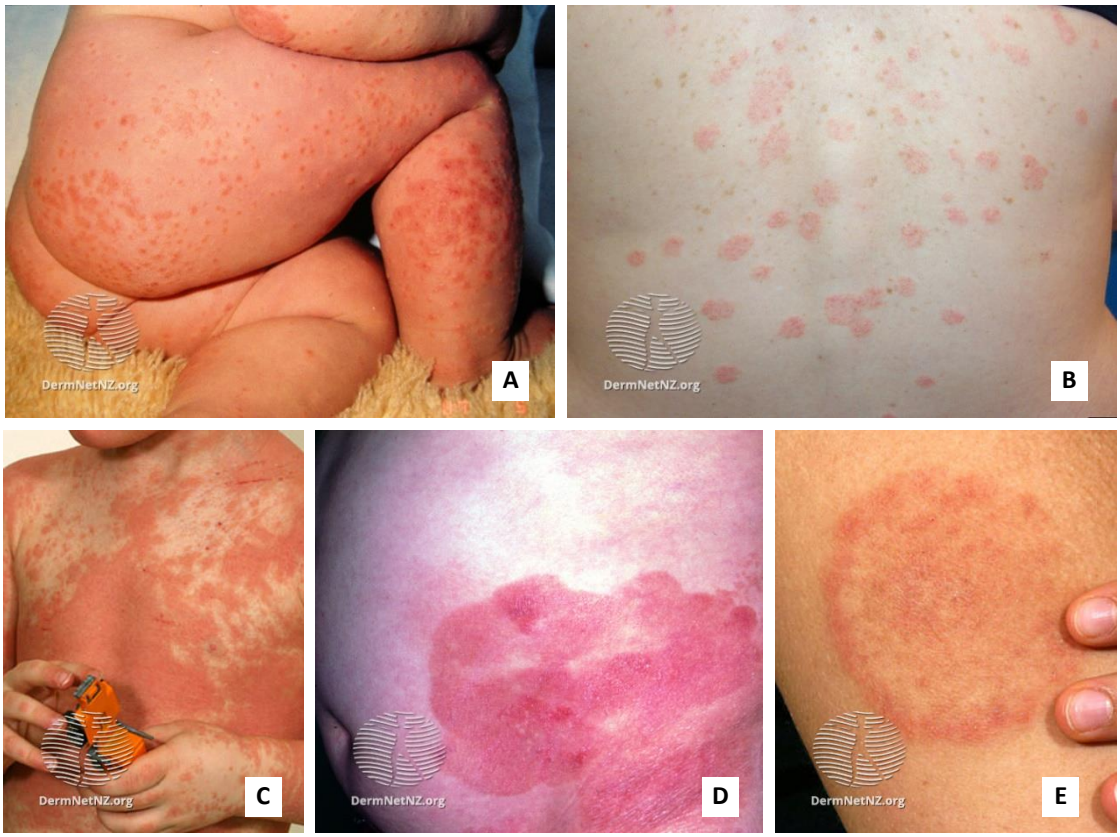


Figure 8:4 Photographic examples of skin diseases that may be included in the control population for the DIPSOC study

Dermnet NZ is the source of these images and has provided permission to share under CC BY-NC-ND 3.0 NZ license. (https://creativecommons.org/licenses/by-nc-nd/3.0/nz/)

A Gianotti-Crosti
B Pityriasis rosea
C Pitryriasis rubra pilaris
D Plaque type mycosis fungoides
E Tinea corporis

8.4.6 Index test

The index test is the investigation or intervention which is being assessed in the diagnostic accuracy study. In DIPSOC the index test is the diagnostic criteria. The criteria will be assessed in a clinical examination by a trained study investigator. During the assessment the investigator will be advised to use the assessment training manual as a reference aid. The training manual contains photographic examples and plain language explanations of the diagnostic criteria. The index test in DIPSOC is separated into two parts, because there are two parts to the primary objective.

8.4.6.1 Index test 1

The eDelphi consensus study agreed 16 diagnostic features that are important for the diagnosis of psoriasis in children and separated them into major and minor criteria. In the consensus study a scoring algorithm was proposed, where the presence of one or more major criteria or, in the absence of a major criterion, three of more minor criteria would support a diagnosis of psoriasis (Chapter 7). Together these 16 diagnostic features and the scoring algorithm form index test 1.

8.4.6.2 Index test 2

Two additional features were close to reaching consensus and were emphasised as important in the feedback from the expert panel. These two additional features with the 16 consensus-agreed diagnostic criteria will be used to create the best predictive criteria using multivariable analysis. The best predictive criteria form index test 2. Including features that are close to reaching consensus is justified because the experts in the panel highlighted these as clinically important (Diamond et al., 2014).

8.4.7 Reference test

The reference standard is the best available comparator and is informally referred to as the 'gold standard'. In DIPSOC the reference standard is the dermatologist's diagnosis as recorded in the participant's medical record. Using a dermatologist's

diagnosis best reflects current clinical practice. Psoriasis is a clinical diagnosis and therefore the diagnosis may include, but does not require, a skin biopsy.

8.4.8 Study flow

The study flow is presented in Figure 8:5. Children and young people who meet the eligibility criteria to be a case or control will be approached by their usual dermatology team. They will be invited to attend a research visit on the same day, at their next consultation or at a separate research visit. All consecutive psoriasis patients will be approached and consecutive control patients when a case is identified on the same list. Cases identified from existing medical records will be approached by letter from their usual dermatology team. At the time a patient is approached they will be given an age appropriate information sheet and a parent/guardian information sheet. The participant information sheets were designed by EBT with feedback from the YPAG (Appendix 10, Appendix 11, Appendix 12, Appendix 13)

After an investigator has taken informed consent, all participants will undergo the same structured research visit. The visit comprises of demographic questions, quality of life questionnaires (for those aged 4 to 17 years) and a diagnostic criteria assessment by a study investigator who is blinded to the participant's diagnosis (i.e. blinded to the reference standard). The two quality of life questionnaires being used in the DIPSOC study are the CDLQI and CHU-9D. The CDLQI is a dermatology specific quality of life instrument and is described in Chapter 2 (2.3.6 Assessment of disease severity and impact).

After completing the research visit, each participant will be offered a certificate, sticker and voucher to say 'thank you' for taking part. Information will then be extracted from the medical record by an investigator who did not perform the assessment (i.e. blinded to the index test). Data to be extracted includes the reference standard (skin disease diagnosis), duration of disease, disease severity and current treatments. A summary of the data variables that will be collected in the DIPSOC study are presented in Figure 8:6 and the CRF is included in Appendix 9.

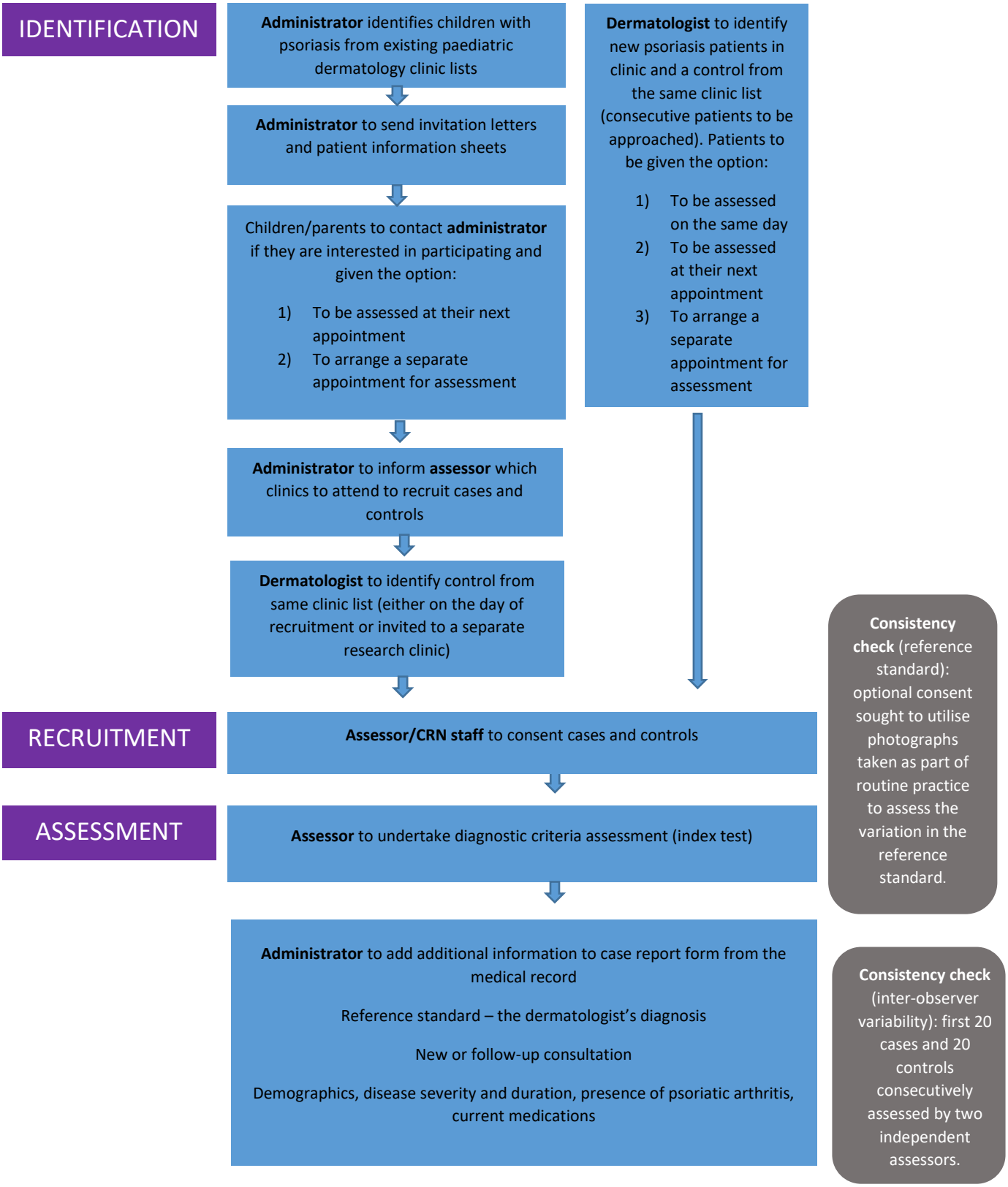


Figure 8:5 Study flow in the DIPSOC study

Data variables collected in the DIPSOC study
Research visit
Demographic information: age, sex, ethnicity, household occupation
Diagnostic criteria assessment: presence and absence of each of the 18 diagnostic features (index test)
Experience level of the diagnostic criteria assessor
Un-blinding of the diagnostic criteria assessor
Quality of life questionnaires (4-17 year olds) – CDLQI and CHU-9D*
Contact details (optional consent)
Medical record
Participant's diagnosis (reference standard)
Age at diagnosis
Age at onset of symptoms
Skin biopsy result
Disease severity
Presence of psoriatic arthritis
Current skin treatments – topical, systemic, phototherapy
Clinical photographs (optional consent)

Figure 8:6 Variables collected at the research visit and extracted from the medical record in the DIPSOC study
CDLQI - Children's Dermatology Life Quality Index, CHU-9D - Child Health Utility 9D

8.4.9 Consistency checks

To assess the inter-observer variability in the diagnostic criteria assessment, the assessment will be conducted consecutively by two independent assessors in the first 40 participants where two assessors are available. There are no recommendations for the number of observations required for assessing inter-observer variability. The decision to include 40 participants was made after discussion with the Test Evaluation Research Group.

To assess the variability in the reference standard for psoriasis, the twelve consultant dermatologist principal investigators will be asked to score clinical images as to whether they agree or disagree with a diagnosis of psoriasis. A convenience sample of clinical images taken as part of routine care will be used. Participants will have the opportunity to provide optional consent for their images to be used for the consistency check.

8.4.10 Data management

Data will be collected at the time of assessment and from the medical record. A number of steps have been planned to help ensure high quality data collection. All DIPSOC study investigators will undergo standardised training and will receive a study manual to use as a practical guide when conducting the study. The training material and study manual were written by EBT. All DIPSOC diagnostic criteria assessors will be trained face-to-face or by teleconference using a PowerPoint presentation by EBT (a clinical dermatologist with an interest in paediatric psoriasis). During the diagnostic criteria assessment, investigators will use the training manual as a reference aid to guide their assessment (Appendix 14). Diagnostic criteria assessors may come from both a dermatology and non-dermatology background. Understanding of the training material will be checked using a short assessment based on clinical photographs. All assessors will be required to achieve a minimum of 90% in the assessment. After completing the assessor training, investigators will be provided with a certificate for the site file.

The CRF includes guidance notes and has been piloted for ease and accuracy of completion; both these measures aim to reduce errors in data collection. The quality of life questionnaires being used in the DIPSOC study are both well-designed and validated. A data management process has been designed to minimise errors.

All data monitoring will take place centrally at the CEBD and will be coordinated by EBT. Returned copies of the consent forms, CRFs and quality of life questionnaires will be checked against a data checklist. Any queries will be entered into a standardised data query table, specifying action required, and emailed to recruiting sites. Sites will be requested to return data queries within one week.

Data will be entered into a purposely designed Microsoft Access 2016 database with inbuilt data validation checks. The database will be piloted will dummy data before the start of data entry and a pilot export of the data into Stata software (version 15) will be tested. The data for the primary objective (diagnostic criteria assessment and dermatologist's diagnosis) will be entered independently into two databases, and discrepancies between the two databases compared. A summary of the data management plan is presented in Figure 8:7.

A plan to minimise data errors in the collection and processing of data
DIPSOC study documents
CRF includes guidance notes and piloted for ease and accuracy of completion
Training of investigators
Face-to-face site initiation visit and investigator training with all recruiting sites
Study manual detailing a practical guide to DIPSOC provided to all investigators
PowerPoint assessor training and short assessment with EBT (dermatologist)
Diagnostic criteria training manual provided as a reference aid to be used during the assessment
Completion of investigator training documented in site file training log
Data-checking
All returned consent forms, CRFs and quality of life questionnaires checked at the coordinating centre by EBT or a trained administrator.
Standardised data checking form
Data queries and action required entered into a standardised data query table
Data query table sent to recruiting sites and a response requested within one week
Database
Database fields parallel CRF. The administrator is not required to code or calculate responses.
Training and written guidance provided to the administrator
Data type and field length limited
Drop down lists for all categorical variables
Validation rules (eg date of birth and date of research visit)
Entry into fields made mandatory
Dummy data used to pilot database and test export into statistical software

Figure 8:7 The data management process for the DIPSOC study

8.4.11 Sample size and data analysis

The full DIPSOC study statistical analysis plan is available at www.nottingham.ac.uk/go/dipsoc.

8.4.11.1 Sample size

The sample size is based on the primary objective. Reporting guidance for risk prediction models (Transparent Reporting of multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD)) have stated that there are no clear methods for calculating an adequate sample size. The guidance supports the current rule of thumb for sample size calculations of 10 events per variable (Moons et al., 2015). As there are 16 diagnostic features in the consensus agreed diagnostic criteria a sample size of 160 cases and 160 controls has been calculated. For a sample size of 320 participants, the precision to which a sensitivity and specificity of 80% could be estimated is calculated to be 73.6% to 86.4% (95%CI) (Hajian-Tilaki, 2014).

8.4.11.2 Study variables

Data on the variables below will be collected at the time of the research visit or extracted from the medical record. There are no time varying variables, because all data are collected at one time point and there are no follow-up visits.

- Age at the time of assessment (continuous) – years

Calculated as the number of days between the date of birth and date of the research visit. Date of birth collected at the research visit.

- Age at the time of first symptoms (continuous) – years

Extracted as the age in years at the time of first symptoms (eg rash) from the GP referral letter or the first dermatology consultation. If under 1 year of age then recorded as 0 years. If not recorded in the medical record, then there is an option for 'not documented' (missing data).

- Disease duration calculated from date of first diagnosis (continuous) – years

Extracted as the date first received current skin diagnosis from a dermatologist. This will often be the first consultation date as a new patient. If clearly stated in the medical history that a diagnosis from a dermatologist was given at another centre, then this date will be used.

- Sex (categorical) – male/female/other/prefer not to say

Collected at the research visit - participants/parents asked which category the child/young person identifies with.

- Ethnicity (categorical) – groups as per UK census

Collected at the research visit - participants/parents asked which category the child/young person identifies with.

- Socioeconomic group (ordered categorical) – groups as per UK census

Collected at the research visit – participants/parents asked what occupation the adults in the household hold. These data are then categorised into the five socioeconomic status groups as per the Office for National Statistics.

- New or follow-up patient (categorical) – binary

Extracted from the most recent consultation. A new patient is defined as a new presentation of skin disease and the patient is not currently undergoing dermatology follow-up (i.e. new referral has been made from primary care). A follow-up patient is defined as a patient currently undergoing dermatology follow-up.

- Disease severity (ordered categorical) – mild, moderate, severe, not documented

Extracted from the most recent consultation where this is documented.
A new variable of categorised disease severity will also be created. If severity is not documented then the free text description of severity and/or PASI score will be used, if possible, to categorise severity.

- Treatment (ordered categorical) – topical, phototherapy, systemic, biologic

Extracted from the most recent consultation (i.e. medications the participant is on at the time of assessment).

- Quality of life – CDLQI and CHU-9D (continuous)

Collected at the research visit. Quality of life impairment will then be categorised as per guidance provided by the authors of the CDLQI and CHU-9D.

- Assessor type (ordered categorical) – grouped as per CRF

Collected at the research visit. Investigators self-report their assessor type.

- Blinding of assessor (categorical) – binary

Collected at the research visit. Investigators document if they were unblinded before or during the diagnostic criteria assessment.

8.4.11.3 Stratification and sensitivity analysis

Variation of the diagnostic accuracy by the following variables will be explored. This analysis will compare the performance of the diagnostic criteria across different clinical contexts. No minimum amount of data is required in each strata, because the analysis is descriptive, but the results will be presented with confidence intervals.

- Age at the time of assessment – 1) 9 years and younger; 2) 10 years and older
  Defined as per WHO guidance for child vs adolescent (i.e. the onset of puberty).
- Sex – 1) male; 2) female; 3) other or prefer not to say
- Assessor type – 1) dermatology trained (dermatology cons, paediatric cons, dermatology registrar, dermatology nurse); 2) dermatology untrained (other doctor, non-dermatology nurse, other investigator)
- New or follow-up – 1) new; 2) follow-up

A sensitivity analysis will be performed using the following variables. This analysis will help understanding of whether the performance of the diagnostic criteria differs when a part of the study population is removed.

- Ethnicity – remove the category 'white'
- Blinding of assessor – remove unblinded 'no'
- Disease severity - remove all categories except mild

8.4.11.4 Analysis of baseline characteristics

The study population will be analysed descriptively for age, gender, ethnicity, socioeconomic group, disease severity, disease duration and treatment. Continuous data will be presented if parametric, as means and standard deviation, and if non-parametric, medians and interquartile range. Categorical data will be presented as percentages.

8.4.11.5 Analysis for the primary objective

The primary objective aims to determine the diagnostic accuracy (sensitivity and specificity) of the consensus agreed diagnostic criteria (either 1 major criterion and/or 3 minor criteria) for plaque psoriasis in children/young people and develop the best predictive criteria using multivariate analysis.

Diagnostic accuracy of the consensus agreed criteria.

The consensus agreed criteria will be applied to the study data and a new binary variable created. Sensitivity will be calculated as the proportion of people with psoriasis who were identified by the consensus agreed diagnostic criteria as having psoriasis. Specificity will be calculated as the proportion of people without psoriasis who were excluded from a diagnosis of psoriasis by the consensus diagnostic criteria. Likelihood ratios will also be calculated.

Developing the best predictive criteria.

The best predictive criteria are defined as the list of major and/or minor criteria (including determining the minimum coefficient threshold for minor criteria), that

best predict a diagnosis of psoriasis in the multivariable model. The term best prediction has been interpreted as the diagnostic accuracy of the criteria reaching a threshold of 80% sensitivity and 80% specificity. This threshold was decided upon after discussion with the expert advisory group for the DIPSOC study.

In order to develop the best predictive criteria the following steps will be taken.

1. The sensitivity and specificity of each of the major criterion will be calculated. Those criteria reaching the sensitivity and specificity threshold (80% sensitivity and 80% specificity), and therefore individually support a diagnosis of psoriasis, will be kept as major criteria. Those criteria which don't meet this threshold will be included in the analysis for minor criteria

2. The sensitivity and specificity of each of the minor criteria (and the two criteria that were close to reaching consensus) will be calculated. All minor criteria will be entered into a backward logistic regression model to develop the best predictive minor criteria. Likelihood ratios will be presented. The ROC curve will also be used to determine a coefficient threshold, above which the score supports a diagnosis of psoriasis. The minimum diagnostic accuracy threshold for the major and minor criteria is the same (80% sensitivity and 80% specificity).

3. The best predictive criteria will be applied to the study population and the sensitivity and specificity (diagnostic accuracy) determined. A receiver operator characteristic (ROC) curve will be drawn and the area under the curve will be calculated.

4. Internal validation will be undertaken using bootstrapping. This approach will quantify the over estimation of the predictive performance of the modelled criteria (Pavlou et al., 2015).

5. Prediction performance of the model will be assessed in terms of calibration and discrimination. Calibration assesses the agreement between the predicted outcome and the observed outcome. This will be assessed using the Hosmer-Lemeshow statistic. Discrimination is the ability to separate participants with and without the outcome of interest (i.e. those with and without psoriasis). Discrimination will be assessed using area under the receiver operator characteristic (ROC) curve. The adjusted R^2 will also be used as an overall measure of goodness of fit.

8.4.11.6 Analysis for the secondary objectives

1. To compare the diagnostic performance of the consensus agreed diagnostic criteria and the best predictive criteria for plaque psoriasis in children.

The consensus agreed diagnostic criteria and the best predictive criteria will be compared using receiver operator characteristic (ROC) curves.

2. To evaluate the inter-observer variability in the assessment of the consensus agreed diagnostic criteria.

The inter-observer variability will be evaluated using the Kappa statistic (95% CI)

3. To assess the variability in the reference standard for psoriasis.

The variability in the reference standard will be evaluated using the Kappa statistic (95% CI)

8.4.11.7 Missing data

Diagnostic accuracy data will be collected prospectively at the time of assessment and recorded on the case report form. A confirmed dermatologist's diagnosis is part of the eligibility criteria. Therefore, it is anticipated that the proportion of missing data for the primary objective will be low.

Data on the other variables will be collected retrospectively from the medical records and therefore the proportion of missing data may be greater, depending on the completeness of documentation.

Missing or unclear data will be checked through central monitoring and additional details requested from the recruiting site if data is identified as missing. The missing data will be reported as a percentage for each variable for cases and controls. Indeterminate results are not anticipated within the study. Multiple imputation will not be used to replace missing data.

A complete case analysis and all participant analysis will be completed and compared in a sensitivity analysis. Also, two separate all participant analyses will be performed and compared, one where all missing criteria will be coded as 'no' (worst case scenario) and one where all missing criteria are coded as 'yes' (best case scenario). This will allow the size of the effect from missing data to be assessed.

8.4.12 Minimising bias

Potential sources of bias in the DIPSOC study have been considered and minimised in the study design.

Selection bias will be minimised by asking sites to approach all eligible cases and consecutive controls. All those approached, recruited or not, will be included in a screening log to demonstrate a non-selective approach. An inclusive study has been designed by keeping exclusion criteria to a minimum. This decision helps to minimise selection bias and prevents deliberate exclusion of participants in whom the index test may perform less well at identifying true positives and true negatives.

Spectrum bias will be present because participants for DIPSOC will be recruited from paediatric dermatology clinics. Patients in secondary care are likely to have more severe skin disease compared to those in the community. The potential effect of spectrum bias may be to overestimate the diagnostic accuracy of the criteria,

because those with severe disease may be more straightforward for the index test to differentiate into case or control.

Information bias related to the index test will be minimised by ensuring the diagnostic criteria assessment will be undertaken by an investigator who is unaware of (blinded to) the dermatologist's diagnosis of the participant. In the diagnostic criteria assessment training, investigators are trained to focus on the presence or absence of each clinical feature and to refrain from making a clinical diagnosis. The effect of unblinding will be explored in a sensitivity analysis. DIPSOC will test a pre-specified scoring algorithm suggested through the eDelphi consensus study and a pre-specified diagnostic threshold decided with the expert advisory group (80% sensitivity and 80% specificity). These decisions have been taken a priori, which will help minimise bias related to the index test.

Information bias related to the reference standard will be minimised by ensuring the reference standard (dermatologist's diagnosis) is extracted from the medical record by an investigator who is blinded to the diagnostic criteria assessment. Separation of the reference standard from the index test is also strengthened by DIPSOC being a case control study and therefore participant diagnosis pre-dates the assessment. Verification bias will be reduced by using the best available reference standard, a dermatologist's diagnosis, for all participants. Differential verification bias may be introduced because different clinicians are making the diagnosis across different recruiting sites. To evaluate the possible extent of this type of bias, a secondary objective aims to compare the diagnosis of psoriasis amongst dermatologists using clinical photographs. All participants will have a reference standard, therefore there is no risk of partial verification bias.

Time-lag bias will be minimised by using same day recruitment directly from clinic, therefore the time elapsed between the reference standard and index test for most participants will very short. Result elimination bias will be reduced by including all participants in the analysis and a complete data set sensitivity analysis is planned.

8.5 Discussion

8.5.1 How will the findings of the DIPSOC study be used?

The DIPSOC study is a multi-centre diagnostic accuracy study that has the primary objective to test the diagnostic accuracy of the eDelphi consensus agreed diagnostic criteria and to develop the best predictive criteria using multivariable analysis. The study will provide sensitivity and specificity data for the consensus agreed criteria and the refined criteria list. DIPSOC is a development study, therefore the diagnostic accuracy values will not be directly transferable to clinical practice or the research setting. However, the data from DIPSOC will be a useful indicator of the diagnostic potential of the criteria. In order to provide diagnostic accuracy data for specific clinical and research settings, the best predictive criteria will need to be tested in these settings. The diagnostic accuracy data from DIPSOC will help inform the sample size calculations for these validation studies.

In the future, the intended purpose of validated diagnostic criteria for psoriasis in children will be to improve the recognition and diagnosis of psoriasis and juvenile psoriatic arthritis. Clinically, the criteria will be used in primary care and paediatrics as a triage tool to prompt referral to a dermatologist, but will also be useful for objectively defining and recording the diagnosis by dermatologists. Validated diagnostic criteria will support standardised disease definition in clinical trials and case ascertainment in observational studies. They may be used by trained researchers to determine eligibility of participants, support self or parent reported diagnosis, or structure retrospective identification of patients from medical records and clinical history. High quality clinical trials and observational studies will provide new evidence to guide treatment and management of psoriasis in children.

8.5.2 Strengths and limitations

DIPSOC has been designed with careful adherence to key quality components in a diagnostic accuracy study. The study has been designed and will be reported in accordance to STARD reporting guidelines. An important strength of the DIPSOC

study is that steps have been taken and described to minimise bias (8.4.12 Minimising bias). Additionally, DIPSOC is a multicentre study and therefore will benefit from the clinical diversity of patients. Although the reference standard will differ at different recruiting sites, the inclusion of 12 sites will provide better representation of a dermatologist's diagnosis compared to diagnosis and recruitment at a single site. Consistency assessments of the reference standard and diagnostic criteria assessments between investigators (inter-observer variability) are planned. DIPSOC has been designed with an informed sample size and precision value around the anticipated sensitivity result. The involvement of both investigators with and without dermatology training is a strength and will be compared in the stratified analysis. The final validated diagnostic criteria will be of most clinical value in settings where health professionals have had limited dermatology training.

An important limitation of DIPSOC is the choice of case-control design. Participants will be recruited when the diagnosis of their skin disease is already confirmed by a dermatologist. A case-control design has been shown to overestimate the diagnostic accuracy of the test. Lijmer *et al.* investigated the effect different study design components had on the diagnostic accuracy estimates of different tests, by extracting data from meta-analyses of diagnostic tests and comparing studies with and without specific features. The observational study estimated the diagnostic odds ratio when comparing studies that used a case control design to those using an unselected population to be 3.0 (95%CI 2.5-4.0). This finding is supported by a similar study by Rutjes *et al*., but the authors made a distinction between studies that compared severe cases against healthy controls and other case-control designs. The diagnostic odds ratio in these two circumstances were 4.9 (95%CI 0.6–37.3) and 1.1 (95%CI 0.4–3.4) respectively. In DIPSOC, controls will be recruited with a scaly inflammatory rash, because this group represents the clinical population in which the diagnostic challenge for psoriasis occurs. The decision to mimic the clinical experience will help minimise over-estimation of diagnostic accuracy.

Another limitation in DIPSOC is the retrospective data extraction from the medical records for certain participant characteristics. This approach to obtain data for

descriptive analysis and stratification will increase the risk of missing data. However, it was a compromise in the study design to ensure that the investigator leading the research visit can remain blinded to the participant's diagnosis, enabling them to be a blinded assessor for the diagnostic criteria.

8.5.3 Study progress

DIPSOC has now finished recruiting in 12 UK paediatric dermatology departments. The geographical location of the recruiting sites are shown in Figure 8:8. I successfully gained capacity and capability approvals through research and development departments at each of the recruiting sites. At each site, I undertook a face-to-face site initiation visit with the principal investigator (PI) and the research team. I provided all sites with the required study documentation (consent forms, participant information sheets, CRFs, study manual) and a site file.

I am proud of my role as the DIPSOC study coordinator, and my ability to lead the study to successful recruitment of the target sample size of 160 cases and 160 controls within 16 months. I have worked hard to maintain good communication with sites through the dedicated DIPSOC email account and over the telephone. I held trouble-shooting teleconferences with sites that were experiencing recruitment difficulties, to discuss solutions to problems they were having with identifying patients or with the study flow. My responsive management approach turned around recruitment in two sites which were struggling (Sheffield and St George's). To foster a DIPSOC community I designed and emailed bi-monthly newsletters (Appendix 15) and held bi-monthly teleconferences. These methods of communication enabled me to share recruitment data, help encourage high-quality data collection and support sites to advise each other about recruitment. I also recruited participants and completed all data extraction in Nottingham, the largest recruiting site.

The data for DIPSOC are not included within this PhD because at the time the study recruitment finished I had started thesis pending and soon afterwards maternity

leave. The included Chapters in this PhD detail my research journey and present the foundations of the DIPSOC study.

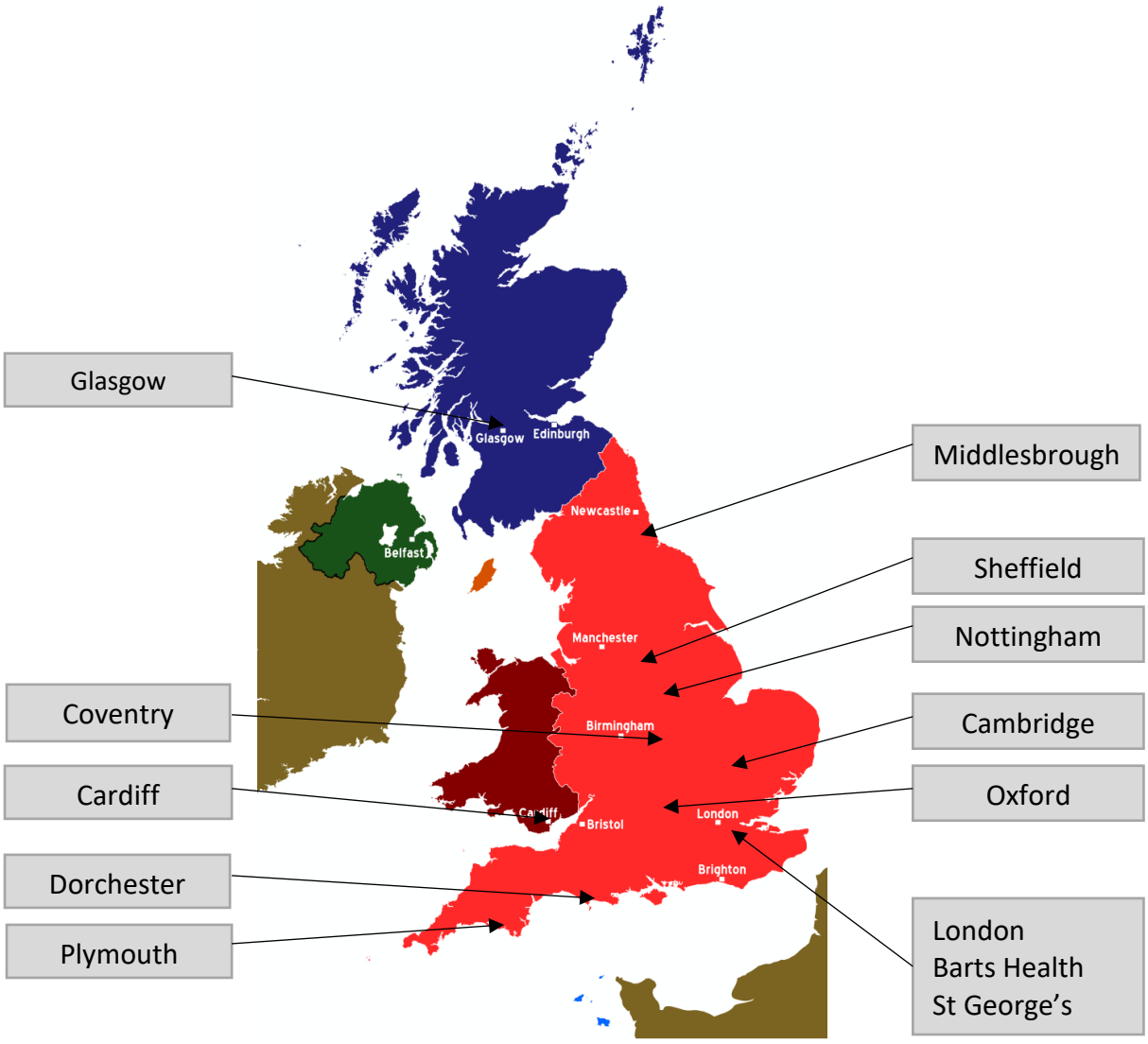


Figure 8:8 Geographical location of DIPSOC study recruiting sites

Chapter 9 Discussion and future plans

9.1 What was the aim and rationale of the research?

The aim of this PhD was to identify opportunities for early intervention for the prevention of long-term harm in children with psoriasis. This research focused on children with psoriasis because there is a deficiency of paediatric specific evidence to inform best practice and the persistence of disease into adulthood can have a life-long negative cumulative effect.

9.2 How has the research addressed this aim?

In a series of studies, I have evaluated and explored current clinical practice and searched and appraised the literature to identify opportunities for early intervention. A key opportunity identified through this research was to improve the accuracy of how psoriasis is diagnosed in children and provide a standardised disease definition for research: the solution proposed was to develop diagnostic criteria for psoriasis in children.

Improving the recognition and diagnosis of psoriasis will help to prevent long-term harm by ensuring children with psoriasis are referred to a dermatologist, given appropriate information and treatment, and monitored for juvenile psoriatic arthritis. A standardised disease definition will help to standardise case-definitions in observational research, eligibility criteria for clinical trials, and support synthesis of data in systematic reviews. These new studies will help identify opportunities for early intervention and assess the effectiveness of interventions for the prevention of long-term harm.

9.3 Interpretation and impact of the research

The multi-centre audit and case-note review (Chapter 3) has increased awareness amongst dermatologists of the specific recommendations in the national psoriasis guideline for children. The variability in clinical practice may reflect the large gaps in the evidence base for the assessment and management of psoriasis in children. When evidence is absent, a clinician's practice is more likely to be rooted in their own experience and learning, which naturally varies between individuals. Completing the work in Chapter 3 highlighted that NICE were unable to provide recommendations on how to screen children for juvenile psoriatic arthritis and there is minimal information available and synthesised about the epidemiology of psoriasis in children. Therefore, an important impact of Chapter 3 was to identify deficiencies in clinical practice and research, and prompt the other studies in this PhD.

The qualitative interviews (Chapter 4) showed that paediatric dermatologists and rheumatologists are not focusing on many of the necessary clinical features to recognise arthritis or psoriasis, respectively. Therefore, this situation presents an opportunity for specialties to learn from each other. Shared learning can be encouraged at a local level within hospitals, and at a national level through collaborative research and guidelines. Paediatric rheumatologists recommended pGALS for screening all children who are at risk of inflammatory arthritis, but this tool may need to be adapted to concentrate on the patterns of joint involvement seen in juvenile psoriatic arthritis. Alongside the introduction of an examination based screening tool, measures to increase the confidence of dermatologists in assessing for arthritis will also be needed. The interviews with dermatologists have been used by NICE to evaluate take-up of the psoriasis guideline.

The scoping review (Chapter 5) has identified that new studies are needed to answer basic questions about the epidemiology of psoriasis in children. Although formal critical appraisal was outside the remit of the scoping review, there were broad quality issues such as inappropriate choice of study design and lack of rigour in the study conduct; often 'quick' case-series or cross-sectional studies were completed in

secondary care. A key impact of the review will be to encourage new well-designed studies using standardised definitions, a case-control or cohort design if aiming to establish timing of onset, and inclusion of both community and hospital populations.

The systematic review (Chapter 6) deliberately included a broad definition of the term diagnostic criteria and therefore the types of criteria identified were extremely varied. Beyond confirming that no clinical examination-based criteria have been developed, the review revealed some of the new developments in diagnostic techniques for psoriasis and skin disease. For example, advances being made in genetic and molecular risk prediction models and dermoscopy may be useful for the assessment of inflammatory lesions as well as skin cancer. The review also reinforced that high-quality diagnostic accuracy study design is essential and this requirement has influenced the design of the DIPSOC study in Chapter 8.

The eDelphi consensus study (Chapter 7) produced a list of expert-derived diagnostic criteria for psoriasis in children, but no diagnostic accuracy data on their performance. In the interim, the agreed criteria provides clinicians with a guide on how to examine when looking for psoriasis. The DIPSOC study (Chapter 8) will be the first step in testing the diagnostic accuracy of the criteria, following which further development and validation will be needed in different setting and populations.

9.4 Future plans

After the completion of the DIPSOC study, I plan to continue to develop and validate the diagnostic criteria for specific purposes in clinical practice and research.

- Epidemiological research – I plan to work with stakeholders to modify the diagnostic criteria so they are able to be used as a self or parent completed questionnaire. When developing the questionnaire I plan to conduct cognitive interviews with patients and parents to evaluate the interpretation of the criteria and ease-of-use of the questionnaire. I will then test the questionnaire-based diagnostic criteria in a cross-sectional study in secondary care to calculate the diagnostic accuracy in this setting. This work will

contribute to developing a tool which can support case ascertainment in community-based research, where a confirmed dermatologist's diagnosis is not easily available.

- Clinical practice – I plan to develop the criteria into an educational package for use in primary care and by paediatric rheumatologists. If feasible, future validation work is needed to test the diagnostic accuracy of the criteria in these settings.

The studies in this thesis have also raised the following question:

1. How should paediatric dermatologists screen for juvenile psoriatic arthritis in children? Validated screening tools are available for adults, but no specific tools have been developed and validated for children. Paediatric rheumatologists have recommended pGALS, but the tool may need to be adapted to assess for the specific small joint signs seen in juvenile psoriatic arthritis. However, dermatologists are most familiar with the PEST questionnaire screening tool for adults, therefore could a paediatric version or alternative questionnaire be developed?

9.5 My reflections on the PhD

My PhD has been an academic and personal journey. I started my research time as a clinical research fellow whilst out of programme from my dermatology physician training. At the beginning, I had very little academic experience, but a genuine interest to improve patients' health through research.

Applying for an NIHR doctoral research fellowship taught me to consolidate, detail and understand the strengths and limitations of my research plan. The application process encouraged me to reach out to clinical and methodological experts, from whom I have learnt substantially from and am now working collaboratively with. Alongside my PhD training, the fellowship has provided the opportunity to study for an MSc in Epidemiology by distance learning. So far, the course has provided training

in basic epidemiology, medical statistics, practical aspects of designing studies and collecting data, critical appraisal and scientific writing.

Each study in the PhD has also been a unique learning opportunity, through which I have worked with different methodologists, co-authors and patients. The PhD has provided experiential training in qualitative research and the progression of analytic techniques in Chapter 4 demonstrates how my understanding in this area has developed. Through completing the systematic reviews and eDelphi study, I have also acquired important academic skills in study design, study management, leadership of a small research team and coordinating an international study. Finally, developing the DIPSOC study has taught me about diagnostic accuracy study design, the NHS ethics process, and the practical considerations of setting up and organising a multi-centre study.

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Appendices

Each patient requires a SEPARATE proforma which should only be identifiable by the CENTRE ID and PATIENT ID.

There are 33 centres participating in this Audit which covers the UK. It will run from January for 3 months.

All data for the audit will be anonymous and whilst we ask you to keep a note of the patients included to avoid duplication this can be destroyed after the audit is complete
So that we can enter data as we go, at the end of each month please place the completed proformas in an envelope with any receipts for postage and packing to:
Dr Ruth Murphy, Paediatric Dermatology Department, Queen's Medical Centre, Derby Road, Nottingham, NG7 2UH.

YOU ARE CENTRE ID 1
Please contact us if there are any problems or queries (Dr Esther Burden-Teh, Esther.Burden-Teh@nuh.nhs.uk)

GENERAL DETAILS

PATIENT ID e.g. 01	_____
Type of referral	☐ Secondary ☐ Tertiary
In which type of clinic was this patient seen?	☐ Paediatric Dermatology ☐ Joint Paediatric Rheumatology ☐ Joint Dermatology clinic with a Paediatrician ☐ Adult dermatology
New patient or follow-up?	☐ New patient ☐ Follow-up patient If this is a FU is it the 1st FU ☐ 2-5th FU ☐ 6-10th FU ☐ >11th FU
Age (years and months)	_____years_____months
Gender	☐ Male ☐ Female
Ethnicity	☐ White ☐ White/Asian ☐ White/Black Caribbean ☐ White/Black African ☐ Asian/Asian British ☐ Black / African / Caribbean / Black British ☐ Arabic ☐ Other

DISEASE HISTORY

Age of onset of psoriasis (years/months)	☐ Specify_____ ☐ Not recorded
FH of psoriasis?	☐ Yes Specify e.g father_____ ☐ No ☐ Not recorded
FH of psoriatic arthritis?	☐ Yes ☐ No ☐ Not recorded
Subtype at presentation (more than one can be indicated)	☐ Plaque small or large ☐ Flexural ☐ Guttate ☐ Palmar plantar psoriasis ☐ Nail ☐ Pustular ☐ Psoriatic arthritis ☐ Joints ☐ Not recorded
Initial site of presentation (more than one can be indicated)	☐ Scalp ☐ Face ☐ Behind ears ☐ Trunk ☐ Upper limbs ☐ Lower limbs ☐ Flexures ☐ Axilla ☐ Inguinal folds ☐ Nails ☐ Genital ☐ Natal cleft ☐ Joints ☐ Not recorded
Current site of involvement (more than one can be indicated)	☐ Scalp ☐ Face ☐ Behind ears ☐ Trunk ☐ Upper limbs ☐ Lower limbs ☐ Flexures ☐ Axilla ☐ Inguinal folds ☐ Nails ☐ Genital ☐ Natal cleft ☐ Joints ☐ Not recorded

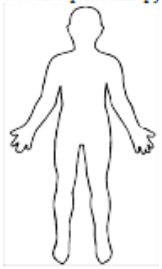
Was psoriasis initially diagnosed as eczema? **Or any other skin disorder? e.g. tinea infection**	☐ Yes ☐ No If yes in: ☐ Primary care ☐ Secondary care ☐ Yes ☐ No Specify _____ If yes in: ☐ Primary care ☐ Secondary care
Did the patient initially present with guttate psoriasis?	☐ Yes ☐ No ☐ Not known
Has this patient with psoriasis been diagnosed with any of the following disorders?	Inflammatory bowel disease (diagnosed by a gastroenterologist) ☐ Yes ☐ No ☐ Not recorded Uveitis (diagnosed by an ophthalmologist) ☐ Yes No ☐ Not recorded Diabetes ☐ Yes ☐ No ☐ Not recorded Depression/Psychosocial e.g. CAMS ☐ Yes ☐ No ☐ Not recorded Any other significant past medical history Please specify_____
Were any questions asked to screen for the following co-morbidities?	Inflammatory bowel disease ☐ Yes ☐ No ☐ Not recorded Uveitis ☐ Yes ☐ No ☐ Not recorded Diabetes ☐ Yes ☐ No ☐ Not recorded Depression/Psychosocial e.g. CAMS ☐ Yes ☐ No ☐ Not recorded
Has this patient been asked about joint symptoms in the last 12 months? **Was a specific assessment tool used to assess for arthritis?**	☐ Yes ☐ No ☐ Not recorded If yes: ☐ By a dermatologist ☐ By a rheumatologist ☐ Yes ☐ No ☐ Not applicable How was the assessment documented in the notes _____

CURRENT TREATMENT

Please fill in all the details you can about the current therapy. Not all the sections will be applicable

Please circle which therapies the patient is currently on (You may circle more than one)

None Topical Phototherapy Systemic Biologic

Is the psoriasis currently well controlled?	☐ Yes ☐ No
How was the *severity* of psoriasis assessed at this consultation? Specify tool e.g. physicians written assessment (improved/worse etc) PASI, PGA or score	☐ PASI ☐ Physician Global Assessment ☐ Description only ☐ Not recorded Other please specify _____
How was the *impact* of the psoriasis recorded at this consultation? Specify tool e.g. cDLQI/DLQI and score	☐ DLQI ☐ cDLQI ☐ Health Assessment Questionnaire ☐ Not recorded ☐ Other please specify_____
What were the follow up arrangements?	☐ GP follow up/Discharged with *clear* instructions for an assessment date in primary care. Specify how long_____ ☐ GP follow up/Discharged with *no clear* instructions for an assessment date in primary care ☐ Secondary care follow up as an open appointment ☐ Secondary care follow up as a fixed appointment; specify how long _____
Current TOPICAL THERAPY **Please indicate on the body diagram, all topical treatments indicating their FREQUENCY, DURATION of use and the SPECIFIC BODY SITE they are applied to. e.g Dovobet™ o.d to the trunk for 3 weeks** **Scalp** **Face** **Behind the ears** **umbilicus** **Flexures** **Groin** **Face** **Body** **Nails** **Hands** **Feet**	Not on topical therapy go to next section 

How was/will the response to TOPICAL therapy be assessed and documented? (more than one can be indicated)	☐ PASI ☐ Physician Global Assessment ☐ Description only ☐ DLQI ☐ cDLQI ☐ Health Assessment Questionnaire ☐ Other please specify_____ ☐ Not assessed
How long was/will the current topical treatment be prescribed before a decision regarding its efficacy is made?	_____months _____weeks ☐ Not sure
Who will assess the response to therapy?	☐ Secondary care FU ☐ GP follow up/Discharged
Additionally, list the last 3 topical therapies used for each site stating duration and frequency of use e.g scalp, Betnovate scalp application™, o.d for 2 months, Cocois™ o.d for1 month, Dovobet gel™, o.d for 3 months	
PHOTOTHERAPY	☐ No plans to commence Phototherapy (skip to next section) ☐ About to commence/just started phototherapy ☐ Mid-way through the treatment course ☐ Recently completed course
What type of phototherapy?	☐ Narrowband UVB (TLO1) ☐ Broadband UVB ☐ PUVA ☐ other
Was an MED/MPD performed first?	☐ Yes ☐ No ☐ Not applicable
Was it clear in the notes why a decision was made to commence phototherapy? (You may tick more than one)	☐ Yes: ☐ Failed topical treatment ☐ Extensive disease ☐ Significant impact on wellbeing ☐ Other - Specify_____ ☐ No

How long was phototherapy used before a therapeutic response was determined?	_____weeks OR ____ number of sessions
Who assessed the response to phototherapy?	☐ Nurse in secondary care ☐ Doctor in secondary care ☐ GP in primary care
How was the therapeutic response to PHOTOTHERAPY assessed? (more than one can be indicated)	☐ PASI ☐ Physician Global Assessment ☐ Description only ☐ DLQI ☐ cDLQI ☐ Health Assessment Questionnaire ☐ Other please specify _____ ☐ Not assessed
How long since the last course of phototherapy was prescribed?	☐ First Course ☐ Since previous course _____weeks/ _____months ☐ Not known
How many repeated courses of phototherapy were prescribed before commencing systemic therapy?	Please specify _____ ☐ No Systemic therapy planned/prescribed
CONVENTIONAL SYSTEMIC THERAPY	☐ Not on or planning a systemic agent (skip to next section) ☐ About to commence/just started systemic therapy ☐ Stable on a systemic therapy
Was it clear in the notes why a decision was made to commence systemic therapy? (You may tick more than one)	☐ Yes: ☐ Failed topical treatment ☐ Not responding to phototherapy ☐ Needing repeated courses of phototherapy ☐ Extensive disease ☐ Significant impact on wellbeing ☐ Other - Specify_____ ☐ No
Which systemic agent is being used?	☐ Acitretin ☐ Methotrexate ☐ oral ☐ subcutaneous ☐ intramuscular ☐ Ciclosporin ☐ Fumaderm ☐ Other please specify _____

How long has the patient been on the systemic treatment?	_____years _____months _____weeks
Which blood tests were performed before starting treatment?	☐ FBC ☐ U&E ☐ LFT ☐ Fasting lipids ☐ PIIINP ☐ Other_____
Was a chest X ray performed prior to treatment?	☐ Yes ☐ No ☐ Not applicable
How frequently were the blood tests performed once stable?	☐ Weekly ☐ Fortnightly ☐ Monthly ☐ 3/12 ☐ >3/12
Was urine dip result documented?	☐ Yes ☐ No ☐ Not applicable
Was blood pressure documented?	☐ Yes ☐ No ☐ Not applicable
How was the therapeutic response to SYSTEMIC therapy assessed? (more than one can be indicated)	☐ PASI ☐ Physician Global Assessment ☐ Description only ☐ DLQI ☐ cDLQI ☐ Health Assessment Questionnaire ☐ Other please specify_____ ☐ Not assessed
BIOLOGICAL THERAPY	☐ Planning to commence Biological therapy ☐ Not on a biologic agent (skip to next section) ☐ During the induction phase of therapy ☐ Stable on a biological agent
Which biologic agent is being prescribed?	☐ Etanercept ☐ Adalimumab ☐ Ustekinumab ☐ Infliximab
Has a previous biologic agent been prescribed?	☐ Yes ☐ No Please specify_____
Was it clear in the notes why a decision was made to commence Biological therapy? (You may tick more than one)	☐ Yes: ☐ Failed topical treatment ☐ Failed phototherapy ☐ Failed/intolerant systemic therapy ☐ Extensive disease ☐ Significant impact on wellbeing ☐ Other - Specify_____ ☐ No

How was the *severity* of psoriasis assessed prior to commencing biological therapy? Specify tool e.g. physicians written assessment (improved/worse etc) PASI, PGA or score	☐ PASI score____ ☐ Physician Global Assessment ☐ Description only ☐ Not recorded Other please specify _____
How was the *impact* of the psoriasis recorded prior to commencing biological therapy? Specify tool e.g. cDLQI/DLQI and score	☐ DLQI___ ☐ cDLQI ____ ☐ Health Assessment Questionnaire ☐ Not recorded ☐ Other please specify_____
Which systemic therapies had been prescribed *before* commencing a biological therapy?	☐ Acitretin ☐ Methotrexate ☐ oral ☐ subcutaneous ☐ intramuscular ☐ Ciclosporin ☐ Fumaderm ☐ Other please specify _____
Which tests were performed before commencing biological therapy?	☐ FBC ☐ U&E ☐ LFT ☐ ANA ☐ Hep B&C ☐ VZV ☐ IGRA ☐ HIV ☐ CXR
Which blood tests were routinely performed once stable?	☐ FBC ☐ U&E ☐ LFT ☐ Other_____
How frequently were the blood tests usually performed once stable?	☐ Monthly ☐ 3/12 ☐ >3/12
Was there documentation of a lymph node check carried out on the patient treated with biological therapy during the last 12 months?	☐ Yes ☐ No
Was there documentation that a skin cancer check carried out on the patient treated with a biological therapy in the last 12 months?	☐ Yes ☐ No
How many weeks/months until the next follow up	_____weeks OR _____months ☐ Not sure
How long will/was current biological treatment be prescribed before a decision regarding efficacy is/was made?	_____weeks OR _____months ☐ Not sure

SIDE EFFECTS	
Side effects (if any) of topical, systemic or biologic treatment. Please consult the index below and select the appropriate codes. State whether these apply to a topical, systemic or biological therapy (Can tick more than one) e.g. abnormal LFT's record as ☐ Systemic 28	☐ No adverse effects recorded ☐ Topical: Adverse effect code(s) _____ ☐ Phototherapy: Adverse effect code(s) _____ ☐ Systemic: Adverse effect code(s) _____ ☐ Biologic: Adverse effect code(s) _____

Coding index: Adverse effects

Cutaneous

1. Skin atrophy
2. Skin striae
3. Dyspigmentation
4. Skin/clothing staining
5. Hypertrichosis
6. Burning/stinging
7. Erythema/Burning
8. Blistering
9. Tanning
10. Hairloss
11. Xerosis/Chelitis
12. Worsening of existing skin condition
13. Development of a new skin condition e.g. eczema. Please specify

Infection

14. Secondary bacterial skin infection
15. Varicella zoster
16. Herpes Simplex
17. Reactivation of latent TB
18. Molluscum contagiosum

Systemic

19. Nausea
20. Headache
21. Flushing
22. Diarrhoea
23. Paraesthesia
24. Injection/infusion reaction
25. Demyelinating symptoms
26. Cardiac symptoms, e.g. chest pain, breathlessness, ankle swelling
27. Development of skeletal abnormalities e.g. DISH

Monitoring abnormalities

28. Abnormal FBC
29. Abnormal U&Es
30. Abnormal LFTs
31. Abnormal lipids
32. Positive ANA
33. Abnormal BP
34. Abnormal urine dip

Any additional comments:

Structured Questions for Interviews with Paediatric Rheumatologists:

Thank you for your time. I am going to ask you a series of structured questions about skin conditions in inflammatory arthritis.

Check they are happy that this will be recorded

Background:

What is your job designation?

Are you the lead for paediatric rheumatology at your centre?

How often do you see children with inflammatory arthritis?

Assessing children with inflammatory arthritis:

In children with juvenile idiopathic arthritis which skin conditions do you ask about or examine for?

Which areas of the body do you specifically ask about?

What areas of the body do you specifically examine?

How do you clinically differentiate JIA and psoriatic arthritis?

How do you diagnose psoriasis?

How confident do you feel diagnosing psoriasis on a scale of 1 to 10, 1 being not at all confident to 10 being very confident?

In your experience, are there any reasons why making a diagnosis of psoriasis can be difficult?

Can you make any suggestions about what would help you diagnose psoriasis and therefore psoriatic arthritis?

Management of inflammatory arthritis:

Does a diagnosis of juvenile psoriatic arthritis instead of JIA influence what you explain to children and their parents? (Prompt: for example how you describe prognosis)

Does a diagnosis of juvenile psoriatic arthritis instead of JIA influence your treatment plan? (Prompt: for example medications prescribed, escalation of treatment, follow-up)

In your experience, are long-term outcomes different in children with psoriatic arthritis different from JIA? (Prompt: for example disability, quality of life, complications of treatment)

Early detection of psoriatic arthritis:

In your clinical experience, do you feel skin signs or joint signs develop first in children with psoriatic arthritis?

Can you estimate the percentage who you feel develop joints first, skin first, simultaneously skin and joint disease?

In your experience do you feel there are any particular skin patterns in children with psoriatic arthritis?

In your experience do you feel there are any particular joint patterns in children with psoriatic arthritis?

How would you advise paediatric dermatologists to look for inflammatory arthritis in children?

Are there a specific assessment tool you would recommend paediatric dermatologists or GPs to use when looking for inflammatory arthritis in children?

Own experience:

Have you ever had an experience where psoriasis was found in a hidden site?

Can you think of an interesting case of a child with psoriatic arthritis where early detection of arthritis was important or where the diagnosis was delayed?

Future research:

Can you identify any areas of research need in childhood psoriasis and psoriatic arthritis?

Do you have any research questions which you feel need to be answered in this area?

Structured Questions for Interviews with Paediatric Dermatologists:

Introduce myself and thank them for their participation

Check they are happy that this will be recorded

Background

Can you tell me your job designation? Do you consider yourself a paediatric dermatologist?

Do you work at a secondary or tertiary centre, or both?

At which hospitals do you work?

Are you the lead for paediatric dermatology at your centre?

How many children with psoriasis on average do you see in one month?

Do you have children with psoriasis and psoriatic arthritis under your care? If so, how many?

All the following questions refer to when you see children with psoriasis

Please tell me a bit about your experiences of psoriasis and psoriatic arthritis in children?

In your opinion, how are psoriasis and psoriatic arthritis related in children?

Do you routinely ask children with psoriasis about joint disease?

How often would you ask a child with psoriasis about joint disease?

Do you ask about a family history of psoriatic arthritis?

How would you ask a child, or if too young their parents, about joint disease? Are there any specific questions you would ask?

Do you examine for arthritis? If so, how do you assess the joints?

Are there any specific joints you would examine?

Do you use or know of any screening/assessment tools to look for psoriatic arthritis in children?

How confident do you feel about assessing joint disease in children on a scale of 1-10 (1 being not very confident at all and 10 being very confident)?

In your experience, are there any reasons why you may find detecting psoriatic arthritis in children with psoriasis difficult?

Can you make any suggestions about what would help you detect joint disease in children with psoriasis?

All the following questions refer to the management of children with psoriasis and psoriatic arthritis

How is psoriatic arthritis in children managed at your centre?

Does the presence of psoriatic arthritis influence your management plan for the skin? If so, how?

In your experience, do you feel the long-term outcomes for skin are any different for children with or without psoriatic arthritis?

In your experience, what are about the long-term outcomes in children with psoriasis and psoriatic arthritis?

All the following questions are about the presentation of skin and joint disease in children with psoriasis and psoriatic arthritis

In your experience, do you feel skin signs or joint signs develop first in children with psoriatic arthritis?

In your experience do you feel there are any particular skin patterns in children with psoriatic arthritis?

In your experience do you feel there are any particular joint patterns in children with psoriatic arthritis? If no, do you know of any joint patterns associated with psoriatic arthritis in children?

How would you advise paediatric rheumatologists to look for psoriasis in children with inflammatory arthritis?

Are there any assessment tools you would recommend paediatric rheumatologists or GPs to use when looking for psoriasis in children?

These questions are about your own experience

Can you think of an interesting case of a child with psoriatic arthritis? A delayed diagnosis?

Can you identify any areas of research need in childhood psoriasis?

Can you identify any areas of research need in childhood psoriatic arthritis?

Is there anything extra you would like to tell me which I have not covered in this interview?

End

Thank you very much for your time. I will follow-up this interview with an email, as the last few questions may have put you on the spot. If you recall any interesting cases, fully anonymised, or research needs please email them to me.

Would you be happy to be contacted again about further research in this area?

OVID Embase

exp Infant/ or infant$.mp. or infancy.mp. or newborn$.mp. or baby$.mp. or babies.mp. or neonat$.mp. or exp Child/ or child$.mp. or kid.mp. or kids.mp. or toddler$.mp. or exp Adolescent/ or adoles$.mp. or teen$.mp. or boy$.mp. or girl$.mp. or exp Pediatrics/ or pediatric$.mp. or paediatric$.mp. or paediatric$.mp. or young people.mp.

AND

psoria$.mp. or exp Psoriasis/

AND

Epidemiology/ or epidemio$.mp. or exp case control study/ or exp cohort analysis/ or case control.mp. or (cohort adj (study or studies)).mp. or cohort analy$.mp. or (follow up adj (study or studies)).mp. or (observational adj (study or studies)).mp. or longitudinal.mp. or retrospective.mp. or cross sectional.mp. or cross-sectional study/

OVID MEDLINE

exp Infant/ or infant*.mp. or infancy.mp. or newborn*.mp. or baby*.mp. or babies.mp. or neonat*.mp. or exp Child/ or child*.mp. or kid.mp. or kids.mp. or toddler*.mp. or exp Adolescent/ or adoles*.mp. or teen*.mp. or boy*.mp. or girl*.mp. or exp Pediatrics/ or pediatric*.mp. or paediatric*.mp. or peadiatric*.mp. or young people.mp.

AND

psoria$.mp. or exp Psoriasis/

AND

Epidemiologic studies/ or epidemio*.mp. or exp case control studies/ or exp cohort studies/ or case control.mp. or (cohort adj (study or studies)).mp. or cohort analy$.mp. or (follow up adj (study or studies)).mp. or (observational adj (study or studies)).mp. or longitudinal.mp. or retrospective.mp. or cross sectional.mp. or cross-sectional studies/

Appendix 5 Data extraction form for scoping review of epidemiological studies

Title of paper

Year
First author
Study location (country)
International multicentre Y or N

Screening

			Y	N
Does this study include patients with psoriasis?				
Does this study include patients with psoriatic arthritis?				
Does this study include data only on <18 at age of onset?				
Does this study include data separated for <18 at the age of onset?				
Does this study include data on any of the seven questions?	How common is psoriasis in the population	Prevalence		
		Incidence		
		Other		
	Who gets psoriasis	Age of onset		
		Gender		
		Family history		
		Other		
	Risk factors for psoriasis	Infection		
		Psychological stress		
		Injury		
		Other		
	Genetics	Childhood		
		Other		
	Clinical presentation	Initial sites of presentation		
		Site of involvement		
		Type of psoriasis/morphology		
		Alternative diagnosis		
	Comorbidities	Cardiovascular		
		Obesity/Metabolic		
		Inflammatory bowel		
		Uveitis		
		Psychological		
		Psoriatic arthritis		
		Other		
	Long-term outcomes	Natural history (relapse/remit)		
		QOL		
		Other		

Study Type

	Yes	No
Case-series		
Cross-sectional		
Case-control		
Retrospective cohort		
Prospective cohort		
Systematic review		
Other specify		

Publication type

	Yes	No
Abstract only		
Conference abstract		
Full article		

Study population

	Yes	No
Primary care		
Secondary care		
Primary and secondary care		
Is this routinely collected data?		
If yes, insurance data?		
Other eg survey		
Additional information		

Overall sample size	
Number of patients <18 years at the age of onset	
Separate data for pre-pubertal population (<10-12 yrs)	Y or N
If Y how many pre-pubertal children	……. or 'unclear'

What are the types of psoriasis included in the study?	Yes	No
Plaque		
Guttate		
Pustular		
Erythrodermic		
Palmar plantar		
Nail		
Psoriasis NOS		
What is the main type of psoriasis included in the study? (options)		

How common is psoriasis <u>Guidance</u> *To extract data on how common psoriasis is in a specified population eg UK, insurance database. To record whether variations in prevalence have been explored.*	Prevalence estimate for study population <18 years Specify unit Prevalence estimate for specific age categories Y or N Prevalence estimate for geographic distribution within a country Y or N Prevalence estimate for socioeconomic grouping Y or N Prevalence estimates changing over time Y or N
	Incidence estimate for study population <18 years Specify unit Incidence estimates changing over time Y or N
	Other/Notes
Who gets psoriasis <u>Guidance</u> *To extract data on the age, gender and frequency of a positive family history in childhood psoriasis. This will answer the question 'In which children is psoriasis most commonly seen?'*	Range of age of onset (years) Average age of onset average (years) Average age of onset in males (years) Average age of onset in females (years)
	Proportion (%) of the psoriasis population male Female to male ratio
	Proportion (%) with a family history of psoriasis in a first degree relative Proportion (%) with a family history of psoriasis in a second degree relative Proportion (%) with a family history of psoriasis NOS
	Other/Notes
Risk factors for psoriasis (specify if %, OR, RR) <u>Guidance</u> *To extract data on events/diagnoses occurring before the onset of psoriasis. Data in studies may have been collected retrospectively and therefore causation may not be able to be*	Proportion (%)/OR/RR* with any type of infection before the onset of psoriasis [A] Specify type of infection (respiratory, GI, skin, urinary, viral, other) Proportion (%)/OR/RR with streptococcal infection before the onset of psoriasis [A] Proportion (%)/OR/RR with a throat infection before the onset of psoriasis
	Proportion (%)/OR/RR with a history of a stressful life event before the onset of psoriasis [A] Proportion (%)/OR/RR with a history of a psychological condition before the onset of psoriasis [A]

established. This will answer 'what factors may be associated with the development of psoriasis in childhood' **Odds ratio* **Relative risk* [A] Specify if increased or decreased risk and if significant	Proportion (%)/OR/RR with a history of an injury before the onset of psoriasis [A] Proportion (%)/OR/RR with documented koebnerisation as the presenting sign of psoriasis [A]
	Other/Notes
Genetics <u>Guidance</u> *To extract data on the genetic mutations specifically seen in child-onset psoriasis. This does not include early onset psoriasis (<40) unless separate data provided for <18*	Specify allele found to be associated with an onset of psoriasis under the age of 16 years Specify allele found to be associated with an onset of psoriasis before puberty
	Other
Clinical presentation of psoriasis <u>Guidance</u> *To extract data on the clinical features seen in childhood psoriasis and how psoriasis presents. This will answer the question 'what is the distribution and type of psoriasis seen in childhood and can the diagnosis be delayed/misdiagnosed?'*	Proportion (%) with specified body site involvement at presentation Scalp Face Trunk Limbs Palmar Plantar Flexural Genital/Natal cleft Nails Joints
	Proportion (%) with specified body site involvement at anytime Scalp Face Trunk Limbs Palmar Plantar Flexural Genital/Natal cleft Nails Joints

	Proportion (%) with specified type of psoriasis Plaque Guttate Pustular Erythrodermic Palmar plantar Nail
	Proportion (%) who have received a different skin diagnosis before psoriasis If yes what proportion (%) of children previously received a diagnosis of eczema
	Other
Comorbidities (specify if %, OR, RR, PR) <u>Guidance</u> *To extract data on diseases which may be associated with childhood psoriasis – maybe presented as risk. To answer the question 'What diseases can be associated with childhood psoriasis?'* *Odds ratio Relative risk Prevalence ratio [A] Specify if increased or decreased risk and if significant	Proportion (%)/OR/RR/PR* with MACE <18 years [A]
	Proportion (%)/OR/RR/PR with central obesity<18 years [A] Proportion (%)/OR/RR/PR with obesity defined by BMI <18 years [A] Proportion (%)/OR/RR/PR with obesity NOS <18 years [A] Proportion (%)/OR/RR/PR with diabetes <18 years [A] Proportion (%)/OR/RR/PR with hypertension <18 years [A] Proportion (%)/OR/RR/PR with high cholesterol <18 years [A]
	Proportion (%)/OR/RR/PR with Crohns disease <18 years [A] Proportion (%)/OR/RR/PR with Ulcerative colitis disease <18 years [A]
	Proportion (%)/OR/RR/PR with uveitis <18 years [A]
	Proportion (%)/OR/RR/PR with psychological disease <18 years [A] Specify type of psychological disease
	Proportion (%)/OR/RR/PR with 'other' disease <18 years [A] Specify other
	Proportion (%)/OR/RR/PR of children with psoriasis who develop JPsA [A]
Long-term outcomes <u>Guidance</u> *To extract data on the longer-term outcomes for children with psoriasis. To answer the questions ''What is the*	Proportion (%) of children with psoriasis who's skin disease persists into adulthood Proportion (%) of children with psoriasis who's skin disease in adulthood is defined as 'moderate' or 'severe' Proportion (%) of children with psoriasis who have spontaneous remission of psoriasis Proportion (%) of adults with psoriasis who first developed psoriasis in childhood

likelihood of child-onset psoriasis persisting into adulthood (or remitting) and the likelihood of severe disease?' and 'What impact does child-onset psoriasis have on an adult psoriasis patient's QOL and is this greater than those with adult-onset psoriasis?'	QOL measurement in adults with child-onset psoriasis Y or N Specify how was QOL was measured Has QOL in child-onset been compared to adult-onset Y or N Is QOL lower in child-onset Y or N Specify difference
	Other

Main study limitations (reviewer's comments)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

1. diagnos$.mp.
2. differentiat$.mp.
3. discriminat$.mp.
4. determinin$.mp.
5. confirmat$.mp.
6. ascertainment.mp.
7. detect$.mp.
8. characteris$.mp.
9. characteriz$.mp.
10. identification.mp.
11. identify.mp.
12. exp diagnosis/

13. criteria.mp.
14. criterion.mp.
15. classification.mp.
16. clinical feature.mp.
17. clinical features.mp.
18. diagnostic feature.mp.
19. diagnostic features.mp.
20. validat$.mp
21. accura$.mp
22. specificity.mp.
23. sensitivity.mp.
24. reproducibility.mp.
25. diagnosis/cl, st [Classification, Standards]
26. exp validation studies/
27. exp sensitivity and specificity/
28. exp predictive value of tests/

29. psoriasis.ti,ab

30. OR/1-12
31. OR/13-28
32. 29 AND 30 AND 31

Ovid EMBASE 1974 to 2015

1. diagnos$.mp.
2. differentiat$.mp.
3. discriminat$.mp.
4. determinin$.mp.
5. confirmat$.mp.
6. ascertainment.mp.
7. detect$.mp.
8. characteris$.mp.
9. characteriz$.mp.
10. identification.mp.
11. identify.mp.
12. exp diagnosis/

13. criteria.mp.
14. criterion.mp.
15. classification.mp.
16. clinical feature.mp.
17. clinical features.mp.
18. diagnostic feature.mp.
19. diagnostic features.mp.
20. validat$.mp
21. accura$.mp
22. specificity.mp.
23. sensitivity.mp.
24. reproducibility.mp.
25. exp validation studies/
26. exp “sensitivity and specificity”/
27. exp predictive value/

28. psoriasis.ti,ab

29. OR/1-12
30. OR/13-27
31. 28 AND 29 AND 30

Title	
Lead author	
Year of publication	
Country of the research group	
Funding source	
Study aim (either specified in or inferred from the paper)	
Study type (circle as appropriate)	Case-series, cross sectional, case-control
Study population (circle as appropriate)	Secondary care, primary care, population based, unclear Adults, children (<18 years), adults and children Any further details:
Sample size	
Reference/gold standard	
Diagnostic criteria/tool tested	
Key findings (if given include sens and spec)	
Strengths/limitations	
Diagnostic accuracy study (circle and appropriate) **If yes go on to critically appraise with the QUADAS-2 tool**	Yes, No

Study aim:

If possible take the study aim from the objectives of the study (often at the end of the introduction). If this is not specified then summarise what the study aimed to achieve.

Study type
If stated take this from the methods section. Otherwise define as:
Case-series – a selected group of individuals are investigated
Cross sectional – all eligible individuals within a population (eg consecutive recruitment) are investigated
Case-control – patients are identified on their disease status and the diagnostic criteria/tool applied

Study population:
In any further details please include information which might be relevant to the generalisability of the findings eg ethnicity, psoriasis subtype etc

Sample size
The number of patients in the study, document cases and controls separately

Reference or gold standard
This is what the criteria/tool is compared to, for example a clinical assessment by a dermatologist

Diagnostic criteria/tool
What name was given to the criteria/tool tested?

Key findings
How did the criteria/tool perform – give a very short summary of the findings

Strengths/limitations
Can you spot any particular strengths or important problems with the conduction of the study or interpretation of the findings?

Diagnostic accuracy study
Was the study designed to test the diagnostic performance of the criteria/tool?

1. Scale and erythema involving the hairline
2. Scale growing down the hair shaft
3. Retro-auricular erythema and/or fissures (including behind the earlobes)
4. Well demarcated erythematous facial lesions with fine or absent scale
5. Well demarcated periorbital lesions with fine or absent scale
6. Scaly erythematous plaques on the trunk triggered by a sore throat or other infection
7. Scaly erythematous plaques on the extensor surfaces of the elbows and knees
8. Fine scaly patches involving the upper thighs and buttocks
9. Well demarcated erythematous annular lesions in the axilla
10. Nappy rash
11. Erythema in the umbilicus
12. Well demarcated erythematous rash in the napkin area involving the crural folds
13. Natal cleft erythema and/or fissures
14. Nail pitting
15. Onycholysis of the nail(s)
16. Subungal hyperkeratosis of the nail(s)
17. Family history of psoriasis
18. Koebner phenomenon
19. Sleep not disturbed by itch
20. Absence of skin xerosis
21. Fusiform swelling of a toe or a finger suggestive of dactylitis

DIPSOC
Developing Diagnostic criteria for Psoriasis in Children

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

Case Report Form (CRF)

Participant ID

☐☐ ☐☐ ☐☐

Site no. Participant no. Initials

Sponsor: University of Nottingham

About this CRF

- To record information from the research visit and medical record.

- Information from the medical record must only be added to this CRF after the diagnostic criteria assessment has been performed to maintain blinding of the assessor.

- The section to complete from the medical record is separated at the end of this CRF and starts on page 14.

- All data fields in the CRF must be completed in capitals using black ballpoint pen. Missing data will be queried.

- This CRF must be securely retained by the site until the end of the study. A copy should be transferred to:

DIPSOC
FAO Dr Esther Burden-Teh
Centre of Evidence Based Dermatology
Kings Meadow Campus
University of Nottingham
Nottingham
NG7 2NR

dipsoc@nottingham.ac.uk
Fax: +44 (0) 115 84 68618

Guidance on completing this CRF

Participant ID

- The ID is a six digit code consisting of a 2 digit site number, 2 digit participant number (for the site), and first and surname initials. The participant ID should be recorded in these boxes at the top of each page.

Dates

- All dates should be entered in the format DD-MMM-YYYY.

MMM is for the first three initials of the month.

Active disease at the time of assessment

- Check with participant that they have a rash present on the day of assessment

Research visit

• **Remind the participant <u>not to share</u> the name of their skin disease.** • Please send a copy of the consent form and the contact details page separately from the CRF.	
	Please complete or tick as appropriate
Date of visit	_ _ / _ _ _ / _ _ _ _ DD MMM YYYY
Signed informed consent Date of consent	☐ Yes ☐ No _ _ / _ _ _ / _ _ _ _ DD MMM YYYY
Eligibility checks	☐ Age <18 years ☐ Eligible diagnosis ☐ Active skin disease at the time of assessment
Name of the study investigator completing the research visit	

Demographic information about the participant

	Please complete or tick as appropriate
Date of birth	_ _ /_ _ _ /_ _ _ _ DD MMM YYYY
Sex	☐ Male ☐ Female ☐ Other ☐ Prefer not to say
Ethnicity	☐ White ☐ Mixed/multiple White and Black ☐ African/Caribbean ☐ Mixed/multiple White and Asian ☐ Mixed/multiple other ☐ Asian ☐ Black/African/Caribbean ☐ Arabic ☐ Other ☐ Prefer not to say
What is the occupation of the adults in the household?	

Performing the diagnostic criteria assessment

Which participants should have two diagnostic criteria assessments?

- Diagnostic criteria assessment by two separate assessors is needed for the first 40 participants (where two assessors are available) recruited to the whole study. An update from the DIPSOC study coordinator will be sent to all recruiting sites when this total is reached.

- The double assessment is to check for variability between assessors. Therefore, each assessor must perform their assessment independently.

- A second diagnostic criteria assessment form has been produced as a separate sheet and should be attached to the CRF.

	Please tick as appropriate
Participant is within the first 40 participants recruited.	☐ Yes ☐ No
Participant is within the first 40 participants AND a second assessor is available.	☐ Yes ☐ No **If yes please remember to attach the completed diagnostic criteria assessment 2 form to the CRF.**

Diagnostic criteria assessment 1

- The data from the diagnostic criteria assessment is for the study's primary objective. It is therefore critical this section is fully completed.
- All assessors must have completed the training manual prior to undertaking the assessment and passed the quiz. The training manual can be used as a reference aid.
- In the assessment you are looking for the presence or absence of each diagnostic criterion (i.e. is the skin change present – yes or no). You are not trying to make a diagnosis or decide if the rash is psoriasis.
- The criteria have been ordered so you can carry out examination from head to toe.
- Some of the criteria also involve asking a question. These should be directed to the participant and/or guardian.

		Please tick as appropriate
1	Scale and erythema in the scalp involving the hairline	☐ Yes ☐ No
2	Retro-auricular erythema (including behind the earlobes)	☐ Yes ☐ No
3	Scaly erythema inside the external auditory meatus	☐ Yes ☐ No
4	Persistent well-demarcated facial rash with fine or absent scale *Remember to ask about how long the rash has been present.*	☐ Yes ☐ No
5	Persistent well-demarcated erythematous scaly rash anywhere on the body *Remember to ask about how long the rash has been present.*	☐ Yes ☐ No

6	Scaly erythematous plaques on the trunk triggered by a sore throat or other infection *Remember to ask about the trigger*	☐ Yes ☐ No
7	Raindrop plaques typical of guttate disease on the trunk or limbs	☐ Yes ☐ No
8	Persistent erythema in the umbilicus *Remember to ask about how long the rash has been present.*	☐ Yes ☐ No
9	Scaly erythematous plaques on the extensor surfaces of the elbows and/or knees	☐ Yes ☐ No
10	Nail pitting	☐ Yes ☐ No ☐ Not assessable
11	Onycholysis of the nail(s)	☐ Yes ☐ No ☐ Not assessable
12	Subungal hyperkeratosis of the nail(s)	☐ Yes ☐ No ☐ Not assessable
13	Fusiform swelling of a toe or a finger suggestive of dactylitis	☐ Yes ☐ No
14	Fine scaly patches involving the upper thighs and/or buttocks	☐ Yes ☐ No

15	Well-demarcated erythematous rash in the napkin area involving the crural folds	☐ Yes ☐ No
16	Natal cleft erythema and/or skin splitting	☐ Yes ☐ No
17	Koebner phenomenon	☐ Yes ☐ No
18a	Positive family history of psoriasis – mum, dad, brother or sister	☐ Yes ☐ No
18b	Positive family history of psoriasis – grandparent, aunt, uncle or cousin	☐ Yes ☐ No
	Who is completing the diagnostic criteria assessment?	☐ Dermatology consultant ☐ Paediatric consultant ☐ Dermatology registrar/clinical fellow ☐ Other doctor ☐ Nurse with dermatology training ☐ Nurse without dermatology training ☐ Other study investigator

Completed by (signed) _____ (initials) _____ (date) _ _ / _ _ _ / _ _
DD /MMM/YYYY

Quality of life questionnaires

	Please tick as appropriate
Is the participant aged between 4-17 years?	☐ No – Quality of life questionnaires are not required. Please go page 10. ☐ Yes – Please complete the CDLQI and the CHU9D quality of life questionnaires.

- A CDLQI questionnaire and a CHU9D must be completed for all participants aged 4-17 years.
- The text or cartoon CDLQI can be used, depending on participant preference.
- There are two versions of the CHU9D depending on the age of the participant. For children aged 4-6 years the proxy version should be completed by a parent or guardian.
- Please mark who the questionnaire was completed by.
- **Remember to collect and attach completed CDLQI and CHU9D to the CRF.**

	Please complete and tick as appropriate
How old is the participant in years?	
CDLQI (text or cartoon) Text Cartoon Completed by	 ☐ Completed ☐ Completed ☐ Participant ☐ Parent/guardian ☐ Both
CHU9D (Proxy CHU9D or CHU9D) Proxy CHU9D for participants aged 4-6 years CHU9D for participants aged 7 years and older Completed by	 ☐ Completed ☐ Completed ☐ Participant ☐ Parent/guardian ☐ Both

Vouchers

- Vouchers should be given to the participant or parent/guardian at the research visit.
- Voucher information is to be recorded for accountability and monitoring voucher stock at each site.
- A £10 voucher is to be given as a thank you for taking part in the study. A further £10 voucher can be given, if required, to cover additional expenses from attending the research visit. Please indicate the amount given.

	Please complete or tick as appropriate
Date voucher was given	_ _ / _ _ _ /_ _ _ _ DD MMM YYYY
Name of person voucher given by	
Value of the voucher(s)	☐ £10 ☐ £20
Voucher code(s)	
Tick if voucher not given	☐
Tick if voucher declined	☐

Un-blinding

	Please complete or tick as appropriate
Was the person performing the diagnostic criteria assessment aware of the participant's diagnosis before the study?	☐ Yes ☐ No
Did the person performing the diagnostic criteria assessment become aware of the participant's diagnosis during the assessment?	☐ Yes ☐ No
If yes to either question, please briefly describe the circumstances leading to the un-blinding.	

Contact details

- **A copy of this page should be sent <u>separately</u> to the copy CRF to ensure data protection is maintained. It is essential the <u>participant ID</u> is completed at the <u>top of the page</u>.**

- Participants can optionally agree to share their contact details. Please indicate which option(s) the participant has consented to, and if agreed please record their contact details here.

	Please tick as appropriate
Did not consent for contact details to be recorded.	☐
Agreed for contact details to be transferred so a questionnaire can be sent after the end of the study.	☐
Agreed to receive a summary of the results at the end of the study.	☐
Agreed to receive information about other skin research that is being carried out by the University of Nottingham.	☐
If consented, please record contact details here. *House/flat number or name* *Street name* *Town* *County* *Postcode* *Telephone number* *Email address* Preferred option to be contacted on.	☐ Post ☐ Email

Confirmation of data accuracy

Signature of the study investigator to confirm the information recorded in this CRF from the research visit is, to their knowledge, accurate.	

The next section should be completed from the medical record.

This information should be collected by a different person from the diagnostic criteria assessor to prevent un-blinding

Information collected from the medical record

- Information should be taken from the most recent consultation where this is documented.
- The data from the dermatologist's diagnosis is for the study's primary objective. It is therefore critical this section is fully completed. If the diagnosis is not clear from the medical record then please check with the participant's clinical team.
- Check the participant ID number on the front cover of this CRF against the consent form and documentation in the medical record.

	Please complete or tick as appropriate
Name of the study investigator completing this section	
At the time of recruitment was the participant a new or follow-up patient?	☐ New patient ☐ Follow-up patient
From the most recent consultation where this is documented, what is the dermatologist's diagnosis? Please choose one of the following: Psoriasis Indeterminate/possible psoriasis Other skin disease	☐ ☐ ☐ If yes to other skin disease please specify:
When did the participant first receive this skin diagnosis from a dermatologist? At what age did the skin symptoms/rash start?	_ _ / _ _ _ / _ _ _ _ DD MMM YYYY _____ (years) ☐ Not documented

Has the participant had a skin biopsy? If yes, what is the diagnosis or possible diagnoses reported on the histology report?	☐ Yes ☐ No _____
From the most recent consultation where this is documented, what is the current severity of the participant's skin disease? If recorded, how is severity described? (This can include disease severity scores) If the diagnosis is psoriasis, what is current PASI score from the most recent consultation where this is documented?	☐ Mild or very mild ☐ Moderate ☐ Severe or very severe ☐ Not documented _____ PASI score: - _____ ☐ Psoriasis but no PASI score recorded
From the medical record, does the participant have psoriatic arthritis?	☐ Yes ☐ No
From the most recent consultation where this is documented, what is the participant's current <u>skin</u> medications? Topical (applied to the skin)	*List the medications by name, but dose and frequency are not needed*. ☐ No topical medications ☐ Yes, please specify

Systemic (including oral medication and injected drugs)	☐ No systemic medications ☐ Yes, please specify
Phototherapy (light treatment)	☐ No phototherapy ☐ Yes, please specify

Clinical photographs

- Participants can optionally agree to allow the photographs of their skin rash that are taken as part of normal care to be transferred to the Centre of Evidence Based Dermatology. Please indicate which option(s) the participant has consented to, and if agreed how the images will be transferred.
- Photographs only need to be transferred for cases (participants with psoriasis).

	Please tick as appropriate
Did not consent for photographs to be transferred.	☐
Agreed for photographs to be transferred for assessment by an independent group of dermatologists to check for consistency of the diagnosis.	☐
Agreed for photographs to be transferred for use in academic publications and shown at academic presentations	☐
If consented, please detail how the images will be securely transferred.	☐ Not applicable (not a case)

Confirmation of data accuracy

Signature of the study investigator to confirm the information recorded this CRF from the medical record is, to their knowledge, accurate.	

What to do next

	Done
• Keep a recruitment log of the participant's name, DOB, local hospital number or NHS number, participant's ID and whether they are a case/control/indeterminate psoriasis at the study site in the site file.	☐
• Document the participant's ID on the front and at the top of each page of the CRF.	☐
• Check for missing data. Pay particular attention that all parts of the diagnostic criteria assessment and the dermatologist's diagnosis are completed. These details are for the primary objective of the study.	☐
• If completed, attach the diagnostic criteria assessment 2 to the CRF.	☐
• Attach quality of life questionnaires (cDLQI and CHU9D) to the CRF.	☐
• If consented and a case, transfer photographs of the participant's rash to the Centre of Evidence Based Dermatology.	☐
• Transfer a copy of the CRF (including quality of life questionnaires and diagnostic criteria form 2 if completed) to the Centre of Evidence Based Dermatology. Make sure a copy of the contact information page (if consented) and consent form is transferred separately. DIPSOC FAO Dr Esther Burden-Teh Centre of Evidence Based Dermatology Kings Meadow Campus University of Nottingham Nottingham NG7 2NR dipsoc@nottingham.ac.uk Fax: +44 (0) 115 84 68618	☐
• File the original CRF in a secure place such as a locked room, or locked cupboard or cabinet.	☐
• Please add the participant to the recruitment update. The update should be sent monthly to dipsoc@nottingham.ac.uk.	☐

Protocol deviation

Protocol date and version number	
Record any changes or deviations from the above protocol here.	

Dr Esther Burden-Teh is funded by a National Institute for Health Research Doctoral Research Fellowship (DRF-2016-09-083). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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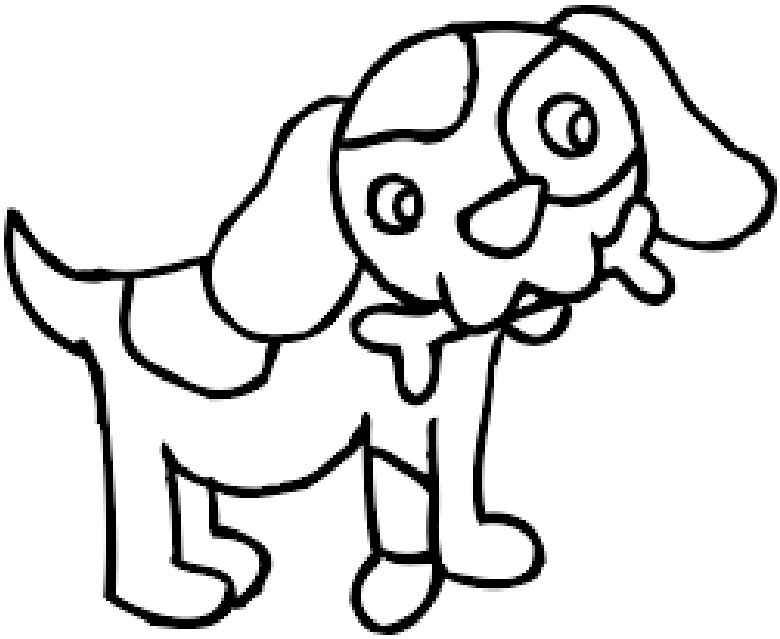
Developing Diagnostic criteria for Psoriasis in Children

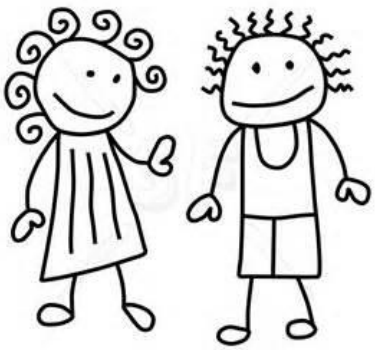
Local trust logo

Please read me if you are aged 3 to 6 years



Dizzy and their skin

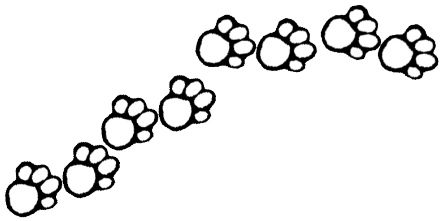
Please colour me in



My name is Dizzy and I'm visiting the hospital today to have my skin looked at.

The doctor or nurse want to know if I have a rash, but shhhhhhhh I can't tell them the name of it.

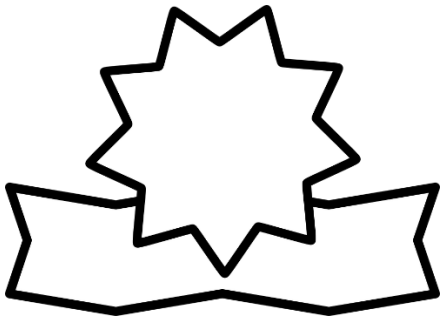
They will also ask my mummy and daddy some questions.



When I am at the hospital the doctors or nurse will want to have a look all over my skin.

They will look ……

- In my hair
- Under my arms
- At my tummy and even in my belly-button
- On my bottom



At the end I will get a certificate or a sticker to show I have taken part.

All finished and time to go home.

Goodbye and thank you for coming along.

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An Information Sheet for children aged 7 to 11 years

Lots of children have rashes on their skin. Doctors try to give these a name so the best medication can be given.

Sometimes it can be hard to give a rash a name. It can help doctors to have a list of skin changes to look for that are special to that rash. We call this list diagnostic criteria.

Some children have a rash called psoriasis. This rash can sometimes be difficult for doctors to spot.

We are looking for children to help us with our investigation. We need about 320 children with skin rashes to help us. Some of you will have psoriasis and some of you will have other skin rashes.

320

Everybody taking part will have their skin looked at by a doctor or nurse. We will want to look all over your skin including .....

In your hair, under your arms, on your tummy, in your belly-button, on your bottom, and on your hands and feet. We will do this in a private space.

The doctors or nurse will also want to ask your mum, dad or carer some questions about you and your rash.

It is very important not to tell the nurse or doctor what the name of your rash is. This is because we want to test how well the list works.

For our investigation we only need to look at your skin once – in a small number of children this will be done by two doctors or nurses. So when this is finished we are all done. Thank you!

Taking part is up to you.

The results from the investigation will tell us how well our list works. We can then use the list to help children with psoriasis get the medications they need.

Everyone who takes part gets a certificate or a sticker. Thank you!

If you would like to chat about this or have any questions then please ask your parent or carer, or one of the doctors or nurses.

We will only need to see you on this one occasion. The visit will take about 30 mins.

What are the benefits and possible harms of taking part?

Our study will, in the future, help children and young people with psoriasis to be diagnosed earlier. To say thank you for taking part we would like to give everyone a certificate and a voucher.

Our study does not involve any blood tests or medications. We will have to look your skin in more private body sites such on your bottom.

Is there anything else I should know?

It is up to you if you want to take part in our study. If you don't, then that's fine, you'll be looked after at the hospital just the same.

Any personal information we collect about you will stay confidential: this means, we will not share it with anybody who isn't working on the study. The information we collect, called data, is also kept anonymous: this means that we use a special code to label it, and we do not use your name.

If you have any questions, you can ask your parent/guardian, the researcher, or the doctor.

Who are the research team?

Prof Kim Thomas

Chief Investigator – the person at the top who oversees the whole study

Centre of Evidence Based Dermatology

University of Nottingham

Dr Esther Burden-Teh

Study Coordinator – the person managing the study day to day

Centre of Evidence Based Dermatology

University of Nottingham

An information leaflet for young people aged 12 to 15 years

DIPSOC

Developing Diagnostic criteria for Psoriasis in Children

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What are the best skin changes to look for and questions to ask (diagnostic criteria) when making a diagnosis of psoriasis in children?

We would like you to help us with our research study. Our study will test how well a list of diagnostic criteria work at diagnosing psoriasis. Diagnostic criteria are a list of special skin changes or questions a doctors or nurse may ask when making a diagnosis. We can think of making a diagnosis as giving a name to a disease. For example, calling a rash psoriasis, eczema or acne.

In the study we would like to ask you and your parent/carer some questions. After this we would like have a look at your skin on different parts of the body. We only need to do this once and it will take about 30 minutes.

If you would like to help please read the rest of the leaflet.

Why is this study important?

Psoriasis can cause a rash anywhere on your body. It can have a big effect on how you feel about yourself.

Sometimes psoriasis can be hard to recognise in children and young people. It can be hard because the skin changes can look different in this age group and sometimes doctors/nurses are less familiar with it.

We know that it is important for everyone with psoriasis to be diagnosed as quickly as possible. Early diagnosis helps people get specific treatment for psoriasis. We therefore want to create diagnostic criteria to help make sure children and young people get an early diagnosis.

What would we like to know?

We would like to test how well a list of skin changes and questions, known as diagnostic criteria, work at diagnosing psoriasis. We will do this by testing the diagnostic criteria on two groups of children/young people, one group with psoriasis and another group with other skin rashes. We will be looking to see how well the diagnostic criteria separate these two groups.

Why have I been asked to help?

We need about 320 children/young people to take part in our study. This number includes people with psoriasis and people with other skin rashes. We need people like you to take part in our study.

What will I have to do if I help?

If you decide to help us you will see a member of the research team on one occasion. **It is very important that you don't tell the researcher the name of your skin disease.**

At the visit the researcher will ask you and your parent/carer some questions. The researcher will then look all over your skin. Some of the places we will want to look are in your hair, under your arms, on your stomach, in your belly-button, on your bottom, and on your hands and feet. It is up to you if you would like your parent/carer to be with you when we look at your skin.

We will give you a quick questionnaire to complete about how your skin disease affects you. We may also like to include some photos of you rash in the study, but only if it is OK with you.

In a small number of children/young people two researchers will need to do the same assessment one after the other to check for consistency.

We will only need to see you on this one

An information booklet for young people aged 16-17 years

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Developing Diagnostic criteria for Psoriasis in Children

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Contents

First, an introduction and a quick summary

Participant information sheet 16 and 17 years Diagnostic criteria for psoriasis in children
10.02.2017 Final v1.2 IRAS ID: 220116

You are invited to take part in our research study

- It is important you understand why the research is being done, and what it will involve.
- If you have any questions about this information or this study, talk about it with others: your parents, the researcher or your doctor.
- It is up to you whether you want to take part. If you choose not to, this won't change anything about the quality of care you receive or will receive in the future for your skin disease.

A quick summary of what you need to know

- We want to improve the diagnosis of psoriasis.
- Our study will test how well a list of diagnostic criteria (skin changes to look for and questions to ask) work at diagnosing psoriasis.
- We only need to see you once and it will take about 30 minutes. We may want to contact you by post after the study. It is important you don't tell the researcher the name of the skin disease.
- There are no tests or medications in this study. If it is OK with you we may want to include some photos of your rash in our study.

PART A

1. Why is this study important?

Psoriasis (pronounced sor-aye-asis) can cause skin changes anywhere on the body. For many people it can be a long-term condition and have a significant impact on their quality of life.

Psoriasis can be associated with other diseases such as arthritis, which causes swelling and damage to the joints. It is therefore important that psoriasis is diagnosed early and accurately. This will help people receive specialist psoriasis treatment quickly.

Psoriasis in children and young people (17 years or younger) can be harder for non-specialist doctors and nurses to recognise. The development of diagnostic criteria will help non-specialist doctors and nurses recognise psoriasis.

2. What are the aims of the study?

Our study aims to test how well each item on the list of diagnostic criteria work at diagnosing psoriasis. This list has been created with experts in psoriasis from around the world. Using the results from the study we will create an improved list of diagnostic criteria.

We will test the criteria by inviting children/young people with psoriasis and those with other skin diseases to take part. We will investigate how well the diagnostic criteria separate the two groups.

3. Who is leading this research and has it been approved?

The study is being led by a dermatology (skin) doctor, Dr Esther Burden-Teh, from the University of Nottingham. This is a combined project with doctors and nurses in the NHS, researchers from Universities of Nottingham and Rotterdam, and people with psoriasis.

This study has been reviewed and approved by the Research Ethics Committee (REC). The REC looks after the rights, wellbeing and dignity of people invited to take part in research studies. The study has also been reviewed by children, young people and adults with psoriasis.

4. Why have I been invited to take part?

To help us answer our research question we are inviting about 320 children/young people to take part. We will invite people with psoriasis and other skin diseases, like you, to help with the study.

5. What will I have to do and how long will it take?

If you decide to take part in the study you will see a member of the research team on one occasion. **It is very important that you don't tell us the name of your skin disease.**

At the visit we will ask you, and if needed your parent/carer, some questions. We will then look at your skin in many different places. Some of the places we will want to look are in your hair, on your stomach, in your belly-button and flexures (armpits and groin).

If you would like anyone else with you whilst you are being examined, for example a family member or a nurse/doctor, please ask. The examination will take place in a private space and you will have the option to wear a gown.

We will give you a quick questionnaire to complete about how your skin disease affects you. We may also like to include some photos of your rash (which have been taken as part of your usual care) in the study, but only if it is OK with you. Please ask if you would like to see the photos.

We will send some children and young people a questionnaire, after the main study has closed, to find out what has happened to their skin disease.

If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form.

For our study we only need to see you on this one occasion. The visit will take about 30 minutes.

Thank you for reading this far. Read on to Part B for more information about the study

PART B

6. Are there possible disadvantages?

The study does not involve any tests or medications. We will need to look at your skin in more private body sites such as the groin. The study does not change your individual medical treatment and will not improve your skin disease.

7. Are there possible benefits?

The results from the study will hopefully help children and young people in the future to be diagnosed with psoriasis earlier and more accurately. Everyone who takes part will receive a certificate and a gift voucher to say thank you.

8. Will my information be kept confidential?

We will use ethical and legal guidelines to make sure we handle all information about you in confidence (not sharing it with anyone who isn't working on the study or who you haven't given us permission to share it with). If you join the study, some parts of your medical records and the data collected for the study will be looked at by the research team at the University of Nottingham. Anyone who sees your data will be required to keep everything they see confidential and respect your right to privacy.

All information which is collected about you during the course of the research will be kept strictly confidential, stored in a secure and locked office, and on a password protected database. Any data about you which leaves the hospital will have your name removed (anonymised) and a unique code will be used instead so that you cannot be recognised.

All research data will be kept securely for 7 years. After this time your data will be disposed of securely. During this time, everyone involved in the study will make sure that your right to privacy is protected. Anonymised data may be used to support research in the future and shared with other researchers.

If you agree to it on the consent form, your contact details will also be kept securely at the Centre of Evidence Based Dermatology after the end of the study so we are able to contact you about the results of the study, what has happened to your skin disease and future related studies. If you don't want your contact details to be kept and used in this way, or if in the future you decide you no longer want us to hold your personal details that is fine. You can let us know and we will remove your details from our database.

9. Will I find out the results of the study?

The results from this study will be published in medical journals, presented at medical conferences and shared with patient groups/relevant charities. We will send you a newsletter with a summary of the study findings, unless you ask us not to.

10. What if there is a problem?

If you have a concern or questions about any part of this study, you can speak to your research nurse or dermatologist working on the trial (their contact details are on the front page of this leaflet).

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure by emailing england.contactus@nhs.net (ensuring you state 'For the attention of the complaints manager' in the subject line) or via the Local Patient Advisory and Liaison Service (PALS).

Thank you for reading this booklet

Contact details

Local contact details:

Central contact details:

Email address: dipsoc@nottingham.ac.uk

Postal address: Centre of Evidence Based Dermatology, Kings Meadow Campus, University of Nottingham, Nottingham, NG7 2NR

Lead researchers

Dr Esther Burden-Teh

Study Coordinator – the person managing the study day to day

Centre of Evidence Based Dermatology

Prof Kim Thomas

Chief Investigator – the person at the top who oversees the whole study

Centre of Evidence Based Dermatology

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DIPSOC
Developing Diagnostic criteria for Psoriasis in Children

DIPSOC training manual for performing the diagnostic criteria assessment

DIPSOC Training Manual Final v1.0 04.12.2017

Funded and supported by NHS National Institute for Health Research

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What is the purpose of the training?

This training has been designed to ensure all individuals who will be performing the diagnostic criteria assessment receive the same information and perform the assessment in the same way.

This standardisation is important because different individuals at multiple centres will be performing the diagnostic criteria assessment.

Remember – please only follow the training and diagnostic criteria assessment checklist. Leave any pre-existing knowledge behind.

DIPSOC
Developing Diagnostic criteria for Psoriasis in Children

What will the manual cover?

- Background to the diagnostic criteria.
- Each individual diagnostic criterion. Including photographic examples and a plain language explanation.
- Hints and tips.
- Following the training there is a short quiz to check your understanding of the material.

Background to the diagnostic criteria

- The diagnostic criteria were developed through a consensus study with a group of psoriasis experts from the International Psoriasis Council.
- There is some repetition of terms in the criteria, but these are the items that experts identified as being important for the diagnosis of psoriasis in children.
- There are 18 items in the diagnostic criteria.

First steps

Remember - you are looking for the presence or absence of each diagnostic criterion (i.e. is the skin change present – yes or no). You are not trying to make a diagnosis or decide if it is psoriasis.

There is no option for 'not sure'. Either the criterion is present or absent. By default if you are unsure it is not present.

First steps

Remember - you are looking for the presence or absence of each diagnostic criterion (i.e. is the skin change present – yes or no). You are not trying to make a diagnosis or decide if it is psoriasis.

There is no option for 'not sure'. Either the criterion is present or absent. By default if you are unsure it is not present.

Performing the assessment

- The order of the criteria has been chosen to take you though the examination from head to toe.
- This is the same order as the criteria are presented in the case report form (CRF).
- Some of the criteria also involve asking a question. These should be directed to the young person and/or guardian.
- Redness in darker skin types can appear as a darkening of the skin.

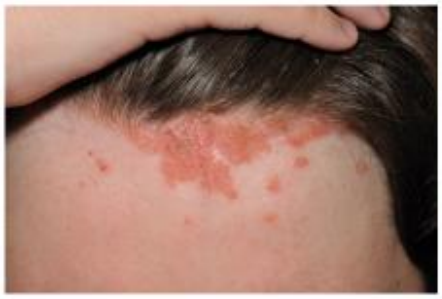
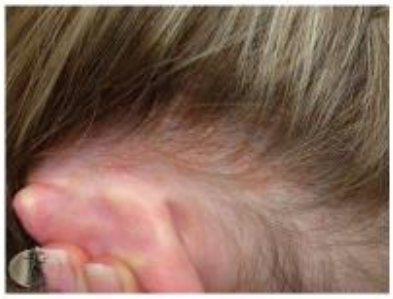
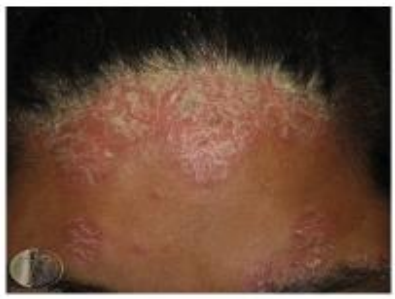
Using the training manual

- Some of the photographs depict more than one of the diagnostic criteria. In these cases an arrow has been used to highlight the clinical sign.
- Some of the criteria require a prompt question to be asked to help the assessor decide whether the criterion is present or absent.

Diagnostic criterion 1

Scale and erythema in the scalp involving the hairline

- Is there flaky and red/pink skin in the scalp and hairline?

Hints and tips

- The scalp changes must involve the hairline.

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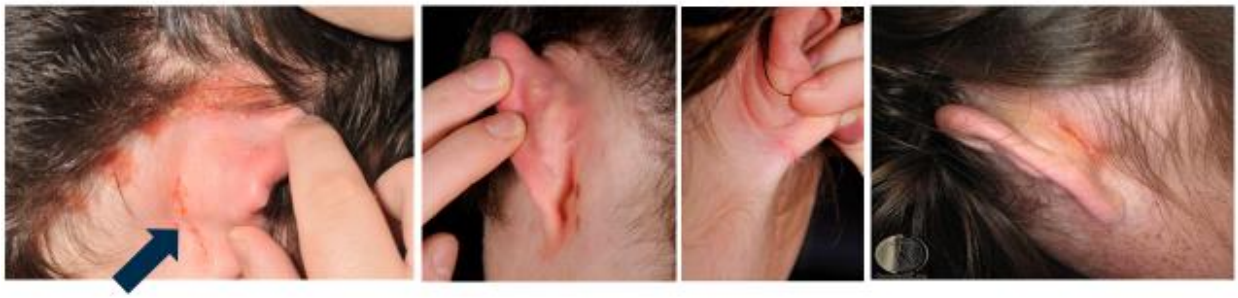
Diagnostic criterion 2

Retro-auricular erythema (including behind the earlobes)

- Is there red/pink skin behind the ears or in the crease behind the ears? Remember to look behind the earlobes.



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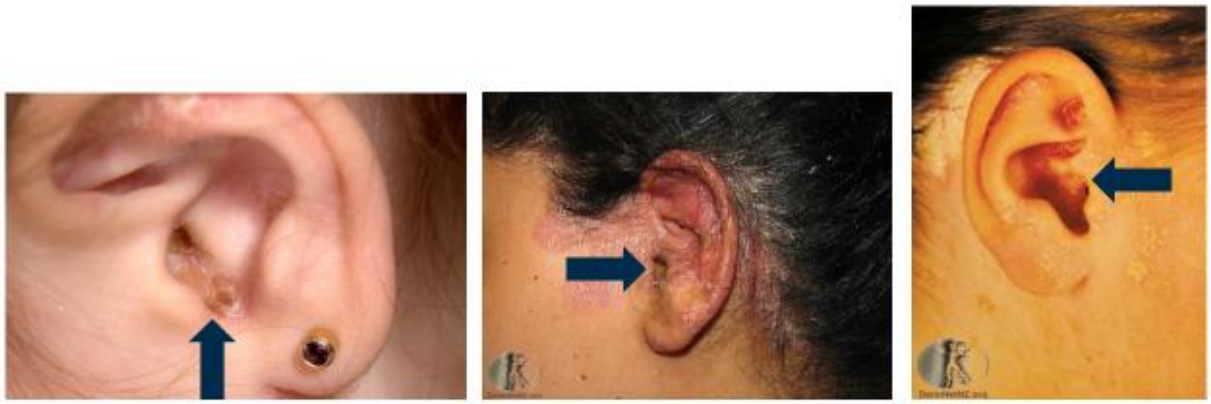
Diagnostic criterion 3

Scaly erythema inside the external auditory meatus

- Is there flaky and red/pink skin inside the ear?



Hints and tips

- You only need to look inside the ear with the naked eye.
- The skin changes can be visible in one ear or both.

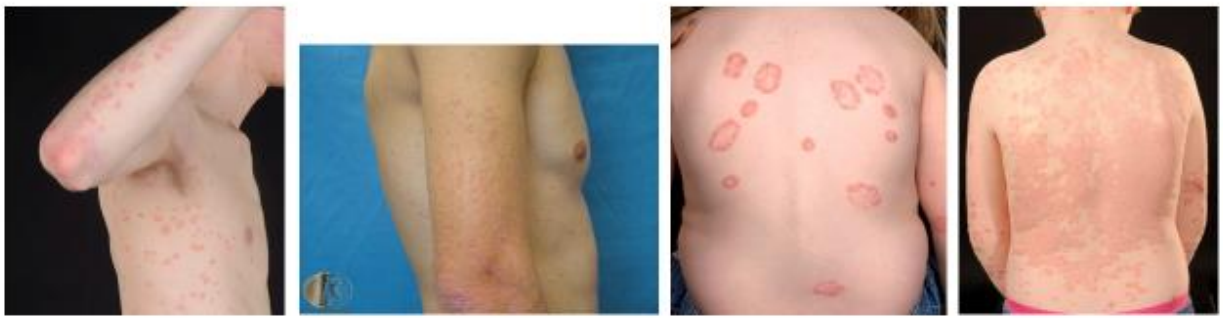
Hints and tips

- If you are looking to see if the rash is well demarcated imagine you are holding a pen and trying to trace the outline.
- If you are looking to see if the rash is flaky gently rub the surface to see if any flakes of skin come away.

Diagnostic criterion 5

Persistent well-demarcated erythematous scaly rash anywhere on the body

- Is there a red/pink flaky rash with an edge you can easily draw around anywhere on the body? Remember to ask – 'Has the rash been there continuously over the past 2 weeks?'



Hints and tips

- If you are looking to see if the skin changes are raised remember to feel the skin.

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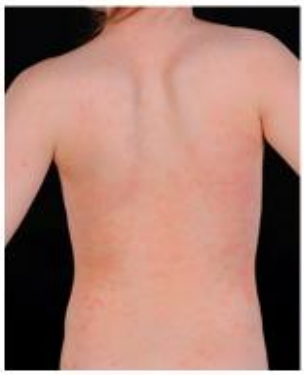
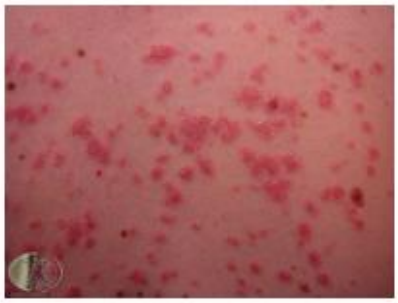
Diagnostic criterion 7

Raindrop plaques typical of guttate disease on the trunk or limbs

- Are there lots of small raised red/pink flaky areas of skin with an edge you can easily draw around on the body or arms or legs?





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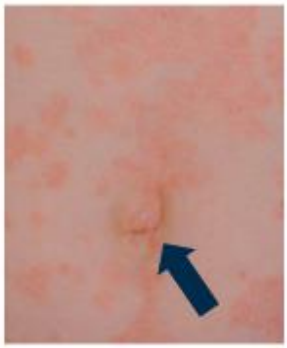
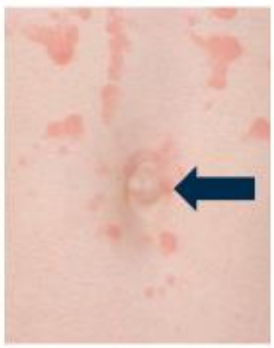
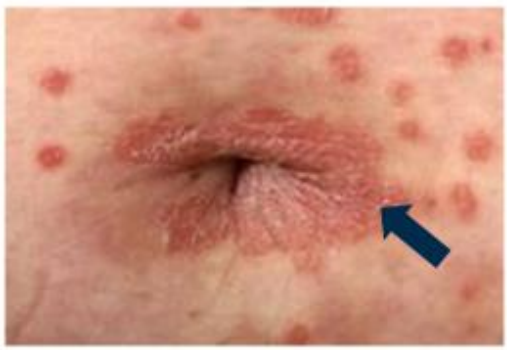
Diagnostic criterion 8

Persistent erythema in the umbilicus

- Is the skin inside the belly-button red/pink? Remember to ask – 'Have the skin changes been there continuously over the past 2 weeks?'



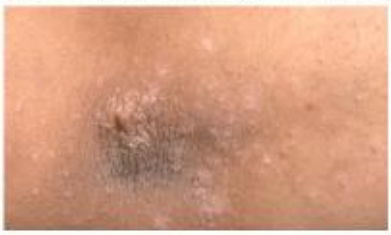


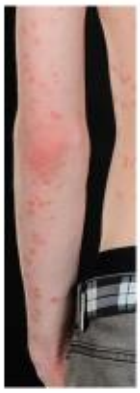


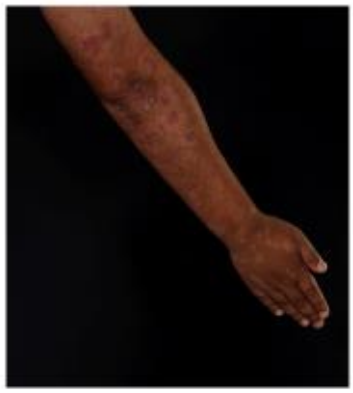
Diagnostic criterion 9

Scaly erythematous plaques on the extensor surfaces of the elbows and knees

- Are there raised red/pink flaky areas of skin on the bony side of the elbows and/or knees?







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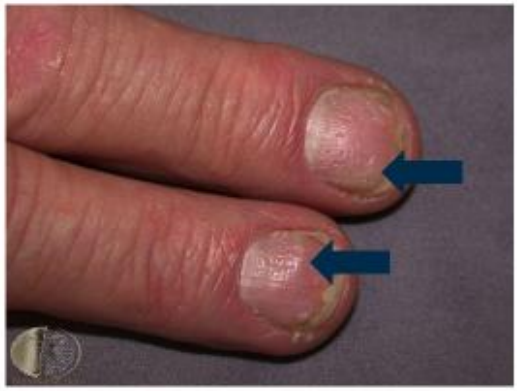
- The skin changes only need to be seen on the elbows or knees (or both).

Diagnostic criterion 10

Nail pitting

- Are there little pin-point dents in the nails? Remember to look at the finger and toe nails.



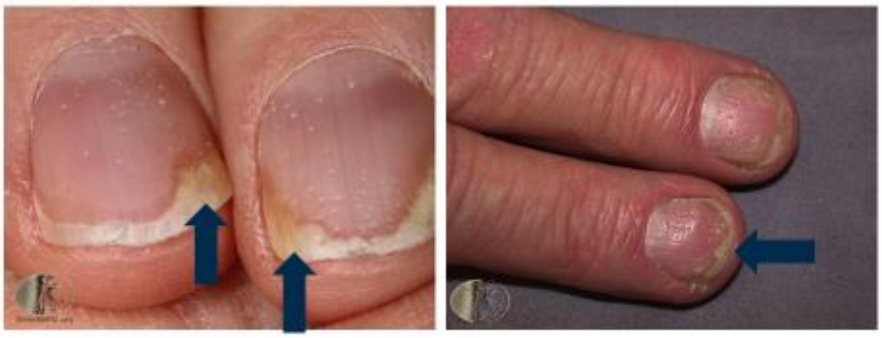
Hints and tips

- The nail changes only need to affect one (or more) finger/toe nail(s).
- If the participant is wearing nail varnish, please ask whether they would be happy to remove it. If this is not possible please tick the 'not assessable' box.

Diagnostic criterion 11

Onycholysis of the nail(s)

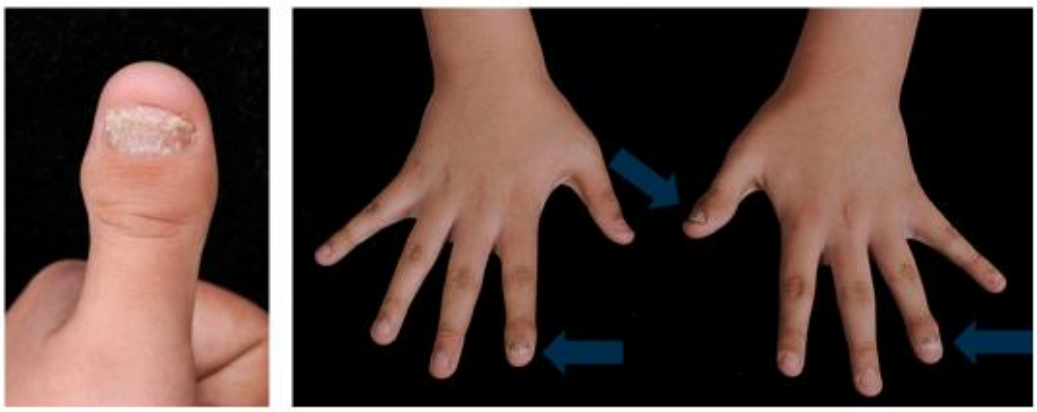
- Is there lifting up of the nail edge so it has separated from the skin below? Remember to look at the finger and toe nails.



Diagnostic criterion 12

Subungal hyperkeratosis of the nail(s)

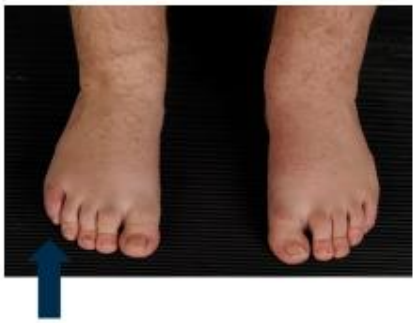
- Is there thickening of the underside of the nail or the nail itself? Remember to look at the finger and toe nails.

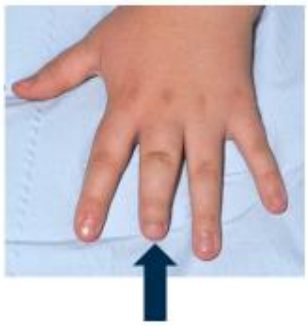


Diagnostic criterion 13

Fusiform swelling of a toe or a finger suggestive of dactylitis

- Is there swelling of a finger or toe causing a sausage-like appearance?





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- The skin changes only need to be seen on the thighs or buttocks (or both).

Hints and tips

- The skin changes must involve the area of skin that would be covered by a nappy in a younger child and the groin creases.

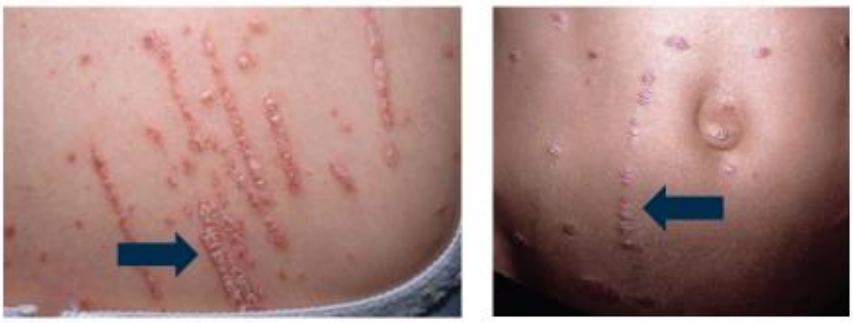
Hints and tips

- To have a look at the natal cleft gently part the cheeks of the bottom.

Diagnostic criterion 17

Koebner phenomenon

- Look to see if red/pink flaky skin changes have developed in an area of skin injury, for example a cut, graze or scratch.



Diagnostic criterion 18

Positive family history of psoriasis

Ask –

- 'Does (the child's/young person's) mum, dad, brother, or sister have psoriasis?
- 'Does (the child's/young person's) grandparent, aunt, uncle or cousin have psoriasis?'

Hints and tips

- **Remember – you aren't trying to make a diagnosis. You are only trying to decide if each criterion is present or absent.**
- Red or pink skin changes in darker skin types can appear as a darkening of the skin.
- The scalp changes must involve the hairline.
- You only need to look inside the ear with the naked eye. The skin changes can be visible in one ear or both.

Hints and tips

- If you are looking to see if the rash is well demarcated imagine you are holding a pen and trying to trace the outline.
- If you are looking to see if the rash is flaky gently rub the surface to see if any flakes of skin come away.
- If you are looking to see if the skin changes are raised remember to feel the skin.
- The skin changes only need to be seen on the elbows or knees (or both).

Hints and tips

- The skin changes only need to be seen on the thighs or buttocks (or both).
- The nail changes only need to affect one (or more) finger/toe nail.
- The napkin area is the area of skin that would be covered by a nappy in a younger child. Remember, the groin creases must be involved as well.
- To have a look at the natal cleft gently part the cheeks of the bottom.

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At the end ....

- Thank the participant and ask them to get dressed.

- If you are completing the research visit remember to:
  - ask the demographic questions
  - complete the quality of life questionnaires
  - complete (if consented) the contact details page
  - offer a certificate, sticker and voucher

Dr Esther Burden-Teh is funded by a National Institute for Health Research Doctoral Research Fellowship (DRF-2016-09-083). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Funded and supported by NHS National Institute for Health Research

Appendix 15 DIPSOC study recruiting site newsletter

Hello from the DIPSOC study coordinating team!

DIPSOC
Developing Diagnostic criteria for Psoriasis in Children

Dr Sonia Ratib	**Dr Esther Burden-Teh**	**Prof Kim Thomas**	**Dr Ruth Murphy**
Study Statistician	Study Co-ordinator	Chief Investigator	Medical Expert
Assistant Professor	NIHR Doctoral Research Fellow	Professor of Applied Dermatology Research	Consultant Adult and Paediatric Dermatologist

Dear DIPSOC investigators,

April and particularly May have been fantastic months for DIPSOC recruitment. **We have passed the 100 mark and congratulations to Oxford who recruited the 100th participant!** 111 participants have been recruited so far (end May 2018).

We still need more double assessment, so please continue with these whenever two assessors are available. Well done Nottingham, Coventry, Sheffield and Oxford. Get in contact if you would like more assessors to be trained.

Remember, the **recruitment target for DIPSOC is 320 participants**. For our top recruiters we would like to increase your local recruitment target. Thank you Nottingham for increasing your target to 30 cases and 30 controls.

Four new sites are in the process of opening. Welcome St George's (London) and Plymouth who have just completed their SIV. Blackpool and Cardiff are also soon to be joining us.

How are we doing? (Up to the end of March 2018)

	Number of participants recruited	Number of double assessments
Nottingham	37	18
Barts London	2	0
Middlesbrough	13	0
Cambridge	9	0
Coventry	4	1
Sheffield	0	0
Glasgow	1	0
Dorchester	2	0
Oxford	*Just opened*	*Just opened*

How can you help?

If you can help with any of the following then please get in touch at dipsoc@nottingham.ac.uk

- Do you know any departments who might be interested in becoming a DIPSOC recruiting site?
- Do you have recruitment or research visit tips to share? Please share them with us and we will develop a 'DIPSOC tips' section of the newsletter.

Noticeboard

- We will be holding an **open teleconference session on Thursday 24th May 13.00 to 13.30.** This is an opportunity to ask any questions, share experiences or meet other recruiting sites.
  https://www.freeconferencecall.com/participant-instructions
- Esther will be at the British Association of Dermatologist's Annual Meeting 3-5th July in Edinburgh. If you are attending and would like to meet up, let us know.
- We are awaiting agreement from the HRA for a small amendment to the consent form. The amendment covers adding a statement that a copy of the consent form will be sent to the coordinating centre. When agreed, the details will be circulated.