PROTOCOL TITLE:

A multi-centre, prospective, cohort study to establish clinically relevant pharmaco-genetic markers of systemic treatment outcomes in patients with severe psoriasis

SHORT TITLE:

Bio-markers of Systemic Treatment Outcomes in Psoriasis

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- See Appendix 7 for ongoing list of Collaborating Sites

1. Background and Rationale

The significant reduction in quality of life and psychosocial disability suffered by people with psoriasis underline the need for prompt, effective treatment, and long term disease control (reviews[1;2]). Whilst localized, limited disease can usually be managed satisfactorily with topical agents, patients with severe disease often require treatment with one of several 'standard' systemic therapies including ciclosporin, methotrexate and acitretin[3]. In the last 5 years, 'biologic therapies' have also become available with those that target the cytokine tumour necrosis factor (TNF) - adalimumab, etanercept and infliximab (TNF-antagonists) - constituting >90% of all biologics used, plus the very recent addition of biologics targeting the interleukin 12/23 pathway - ustekinumab and briakinumab[4].

Despite the extensive range of available treatments, patients demonstrate high levels of dissatisfaction (83% in a recent UK survey)[5-7] citing inefficacy or side effects as the principal reasons. Short-term efficacy data from randomised controlled trials (RCT) support this perception: for example the percentage of patients achieving an adequate response by 3-4 months (ie: 75% improvement in baseline Psoriasis Area and Severity Index, PASI) ranges between 28-85% for ciclosporin[8], 35-69% for methotrexate[9], 30-34% for etanercept (25mg biweekly), 71% for adalimumab and 75.5 to 87.9% for infliximab[4], whilst the monthly incidence rates of adverse events ranges from 16.1% (lowest, ciclosporin) to 17.8 (highest, infliximab)[8]. Longer term data are scarce, although with respect to TNF antagonists, there appears to be a gradual loss of efficacy over time[4;8]. These data reflect the inherent limitations of drug therapy in psoriasis and inter-individual variability in treatment outcomes since drugs are not reliably effective either in the short or long term and are complicated by side effects. Identifying those patients at risk of side effects or poor response prior to treatment initiation has the potential to deliver enormous benefits including optimal management of psoriasis, reduced drug toxicity and significant health care savings.

Whilst a proportion of inter-individual variability in drug response relates to 'external' factors (for example, concordance with therapy, incorrect dosing), individual genome variation is also critical. Genes encoding drug-metabolising enzymes, transporters and drug targets all may be subject to functionally relevant polymorphisms and overall, are estimated to account for 15%-30% of inter-individual variation in drug response[10]. Pharmacogenetics (the study of the relationship between individual gene variation and drug effect) offers the potential to identify those at risk of adverse drug reactions and those likely to respond (or not) to a particular treatment prior to drug exposure.

To date, most pharmacogenetic research of relevance to psoriasis has used a candidate gene approach, and has comprised small, retrospective, case cohort studies with often conflicting results[11-13]. Nevertheless, potentially important single nucleotide polymorphisms (SNPs) have been identified for methotrexate[12;13], ciclosporin and TNF antagonists[14]. Although a number of genes of putative importance in the TNF pathway have been investigated in rheumatoid arthritis[15;16] with no evidence of association with TNF response, there is some evidence to indicate that genetic polymorphisms in tumour necrosis factor gene itself may be relevant. This gene is located on chromosome 6p21.3, with at least 44 known polymorphisms. Two G-to-A transitions in the promoter region at the –238 and –308 sites appear to influence TNF-expression[17] and are considered as functional SNPs. The -308 G/A variant, which is also associated with increased susceptibility to, and severity of, rheumatoid arthritis[18], has been the focus of a number of (small) studies investigating treatment response to TNF antagonist; a recent meta-analysis concluded that whilst the -308(A) variant appeared to predict poor response to TNF inhibitors, there is a need for large scale prospective studies to validate these findings[14]. Interestingly, both the -238G>A and -308G>A polymorphisms have been implicated in psoriasis risk[19] . Very recent genome-wide studies by others, and our group (Principal Investigator, R

Trembath)[20-22] have identified further disease susceptibility loci that also may be of potential relevance including TNFAIP3 (TNF-induced protein 3) and TNIP1 (TNFAIP3 interacting protein 1)[20], whose gene products work downstream of TNF to regulate NF-kB28, and C6orf10 which is activated by TNF[21]. Furthermore, psoriasis disease susceptibility loci that are not necessarily clearly related to the TNF pathway may still be of relevance in shaping treatment response, as indicated by the example in rheumatoid arthritis and the influence, albeit modest, of loci AFF3 and CD226 and TNF response[23].

Given that the pharmacokinetic and pharmacodynamic profile of a particular drug reflects the sum of multiple processes, each of which is potentially subject to genetic variation, and also, that the mechanism of action (and therefore relevant genetic pathways) of some of the drugs used in the treatment of psoriasis remains poorly understood, there are limitations to the candidate gene approach of investigation. Genome-wide association studies (GWAS), using response (efficacy or toxicity) to a particular drug as the phenotype, is an alternative, increasingly used 'hypothesis-free' approach[24], and has successfully identified a number of important, novel associations between drug response and clinically relevant loci in other (non dermatological) disciplines[25]. However, such studies require large numbers (>2000) of well characterised treatment cohorts and are extremely expensive to perform.

Almost without exception, pharmacogenetic studies in psoriasis (and in fact, in many areas of medicine as a whole) have been underpowered, and have lacked robust, prospectively acquired data with clear delineation of disease response and adverse events, such that major advances in this important area have not been made. To address this research gap, we plan to establish a UK Interventions for Psoriasis Bio-bank, matching clinical data with collection of relevant biological samples in order to investigate potentially relevant genetic and other surrogate markers of treatment outcome. To achieve this we plan to utilise patient data available through an established registry, the British Association of Dermatologists Biological Interventions Register (BADBIR – EC Ref: 07/MRE08/9). The BADBIR registry is an established, longitudinal study, of psoriasis patients on systemic and biological therapies, capturing a comparable dataset to that described in section 4.2., and by capturing BADBIR datasets we will not therefore be in conflict with BADBIR. Recruitment of BADBIR patients to this study will provide the necessary sample number for statistical analysis, as described in section 4.4. Written Informed Consent will be obtained from BADBIR patients to ensure that they are willing for the information held on them by BADBIR to be released to the Chief Investigator. The use of information held on the BADBIR database has been approved by the BADBIR Steering Committee and so minuted.

2. Trial Objectives and Design

2.1. Trial Objectives

Primary Objectives

1. To identify and characterise biomarkers of response (efficacy and toxicity) to systemic treatments for psoriasis

Secondary Objectives

1. To integrate any identified biomarkers of treatment outcome with clinical, investigational and other predictors (known or to be identified) of treatment response, in order to develop clinically useful treatment algorithms, and improved patient outcomes.

2. To secure a comprehensive collection of biological samples (DNA all subjects, RNA, cells, serum on designated subsets) to match corresponding clinical datasets largely already available through the BAD Biologics Interventions Register (Interventions for Psoriasis Biobank), thereby establishing a critical resource for future use by investigators to improve outcomes in psoriasis.

2.2 Study Design

The hypothesis is that there is a gene, or genes, that determine the response to systemic treatments in psoriasis. This is a observational, prospective, cohort study in patients with psoriasis exposed to standard systemic therapy (methotrexate, ciclosporin, acitretin and Fumaric acid esters), TNF antagonist therapy (etanercept, adalimumab, infliximab) and anti IL-12/23 therapy (ustekinumab). For each of these treatments, genetic and biological profiles will be compared in (a) non responders and responders (short and long term) and (b) those who develop drug toxicity and those who do not. These data will be used to identify robust markers of treatment outcome. Genetic studies will use both candidate gene and genome wide association approaches. To this end we aim to recruit 5,500 patients in total to this study (see Section 4.3 for details).

3.0 Subjects

3.1 Inclusion Criteria

I. Patients able to give written informed consent
II. Patients with psoriasis
III. ≥16 years
IV. Either or both:
    a. Enrolled in the BADBIR study
    b. Within 6 months of initiating or switching to a biologic or systemic therapy for the treatment of psoriasis

3.2 Exclusion Criteria

I. patients unable to give written informed consent
II. blood transfusion within 4 weeks (where DNA is being secured via whole blood).

3.3 Recruitment strategies and procedures

A. Approaching Patients in Clinic

Eligible patients attending at a clinic will be approached by a member of the hospital research team who will discuss the study with them and they will be given a 'Patient Information Sheet' to read and given sufficient time to decide if they wish to take part in the research. If they wish to participate a member of the research team will obtain written informed consent from the patient and they will asked to provide DNA and other relevant biological samples, together with clinical data (as dictated by the protocol).

B. Approaching Patients by Post

Eligible patients may be approached via post prior to their clinical visit using the Patient Invitation Letter to allow the patient extra time to consider the study.

The letter will include contact details for the Principal Investigator at the participating site and may also include contact details for the Research Nurse at the site. The Patient Information Sheet may be included with the letter.

C. Recall of Patients

In cases where genetic or other biomarkers of disease and/or treatment outcomes require further phenotypic and biological validation we may wish to recall individual patients for clinical phenotyping and /or collection of additional biological samples for additional functional studies. This recall is entirely voluntary as stated in the Patient Information Leaflet. The patient will sign a separate line on the Consent Form indicating their agreement. If it is necessary to contact the patient in the future a member of the study team will contact the patient by letter or approach them at their next clinic visit and asked if they are

still willing to provide further clinical data and biological samples. This is still optional for the patient at this stage.

3.4 Withdrawal of Subjects

A patient may voluntarily discontinue participation in this study at any time. This will not affect his/her current or future treatment. The study investigator or co-investigator may also, at his or her discretion, discontinue the subject from participating in this study at any time. If a blood sample has been collected and it is determined that the patient does not meet the inclusion and exclusion criteria for participation, or if the patient withdraws consent from the study, then the study physician must complete the appropriate documentation (Appendix 1) to request sample destruction. It is the responsibility of the study investigator to destroy the sample and to keep a record of that destruction in the study file.

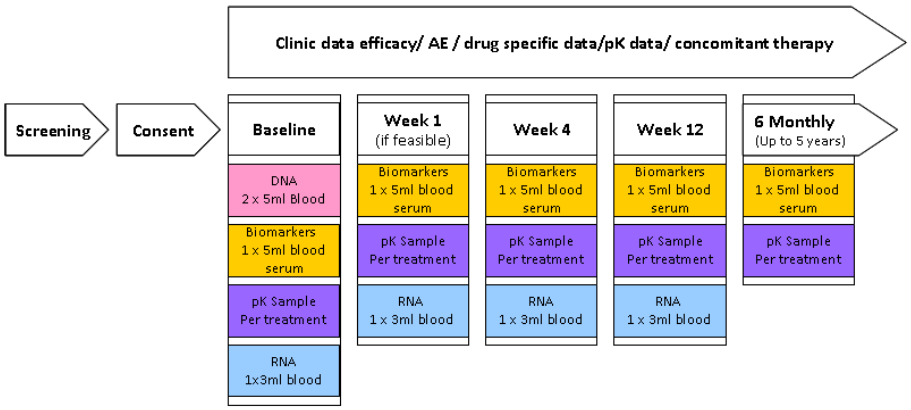
4.0 Investigational plan

4.1 Visit schedule

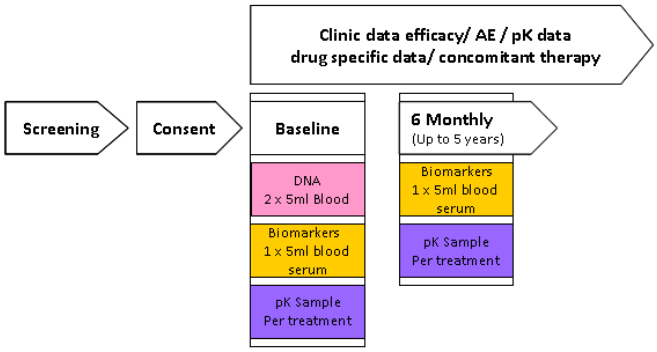
The visit schedule follows 6-monthly schedule for up to 5 years or for the duration of the patient's involvement in the BADBIR study. When possible, investigators should align (make concurrent) patients' BSTOP and BADBIR visit schedules.

Additionally, patients who are starting new treatment (new starters) or returning to treatment after 3+ months washout period, will be asked to provide additional visits at week 1 (if feasible), week 4, and week 12 . These visits will enable investigation of short term treatment outcomes (and allow comparison to published cohorts and trial data sets).

Patient Cohort 1: New Starters
Visit schedule for patients who are starting a new treatment or returning to treatment after 3+ month washout period:



Patient Cohort 2: Patients on Established Treatment Regimen
Visit schedule for all other eligible patients not in cohort 1 above:



4.2 Sites

Sample collection and patient follow up will be determined according to each site's resources and capabilities. Sites are divided into three categories with different levels of participation.

The Site categories are:

i) Supersites
Supersites will collect the full compliment of biological samples and complete the full follow-up schedule as determined for each patient by their Patient Group.

ii) Longitudinal Sites
Longitudinal sites will complete a limited follow up schedule and collect limited samples as determined by the CI.

iii) Single Sample Sites
Single sample sites will collect patient DNA at baseline visit only.

4.3 Measurements And Evaluations

a) Clinical data
The following clinical data will be collected at baseline and all subsequent follow up visits up to 5 years. Clinical data may also be collected if a patient changes their systemic psoriasis treatment.

Baseline visit:

i. demographics, disease phenotype, presence of psoriatic arthritis, co-morbidities,
ii. past treatment history (for psoriasis), and date and dose of previous systemic therapies for psoriasis
iii. clinical assessments: weight, waist, height, blood pressure and disease severity (PASI,PGA, BSA,)
iv. intervention of interest: drug, frequency, dose, time and date of last dosing
v. ongoing concomitant therapy
vi. FBC, creatinine, ALT, lipids, CRP, ESR
vii. Patient questionnaires: demographics, smoking history, alcohol history, DLQI and EQ-5D.

Follow up visit:

i. clinical assessments: weight, waist, height and disease severity assessment scores since the time of last follow up (PASI, PGA,BSA, DLQI)
ii. intervention of interest: drug, frequency, dose (or any change)
iii. drug toxicity and adverse events (reported according to standardised criteria for BADBIR).
iv. any new therapy (for psoriasis or other indication)
v. FBC, creatinine, ALT, AST, lipids, CRP, ESR
vi. Patient questionnaires: smoking status, alcohol units, DLQI and EQ-5D.

b) Biological Sample collections (see also Appendices 2 & 3 for SOP on sampling, transport, storage at partner sites and transfer to central co-ordinating sites)

DNA samples – Collected from all patients across all sites

- 2 x 6mls of blood will be collected in EDTA vacuette tubes (pink top) for DNA extraction (The blood is collected in EDTA coated tubes as this prevents blood from clotting. It is preferable to using heparin as an anticoagulant, as heparin may interfere with subsequent amplification of DNA by PCR).

- Where blood collection for DNA is not feasible, saliva sampling may be collected. A total of 1 x 2mls of saliva will be collected using the Oragene®-DNA self-collection kit from DNA Genotek (www.dnagenotek.com). Saliva DNA is stable in this format at ambient temperature and the patient can return the kit via Royal Mail Freepost service.

Pharmacokinetic (pK) samples – Collected at Supersites and designated Longitudinal Sites
Poor concordance with therapy and intra individual variation and development of drug antibodies in drug pharmacokinetics are known to impact on treatment response. The following samples will therefore be collected at selected centres to ascertain drug levels in participants at baseline and all subsequent follow up visits :

- **Methotrexate:** Patients on Methotrexate will provide 1 x 4 ml EDTA tube (purple top) of whole blood for methotrexate polyglutamates (to be taken 24 hours before dose of methotrexate ideally)
- **Ciclosporin:** Patients on Ciclosporin treatment will provide on 1 x 4 ml EDTA tube (purple top) of whole blood for ciclosporin level at trough level; where possible, an additional sample should be collected 2 hours post dosing (when feasible)
- **Biological drug levels:** Patients on biologic treatment will provide 1 x 5mls of blood collected in a serum separating clotting factor vacuette tube (yellow top). This will be collected based on the treatment as described below. Note time of last dosing.
    - **Adalimumab:** prior to dosing with window up to 3 days
    - **Etanercept**: prior to dosing with window up to 3 days
    - **Infliximab:** prior to infusion
    - **Ustekinumab:** prior to dosing and also at week 4 of each treatment cycle
- **Other drug levels:** - Patients on other biologic or systemic treatment not described above will provide 1 x 5mls of blood collected in a serum separating clotting factor vacuette tube (yellow top).

Samples for identification of potential biomarkers of treatment outcome
Serum – Collected at Longitudinal Sites and Supersites
Patients will provide serum samples at baseline and all subsequent follow up visits.

- 1 x 5mls of blood will be collected in a serum separating clotting factor vacuette tubes (yellow top)

RNA – Collected at Supersites and other designated sites

- RNA samples will be taken from patients starting new treatment or returning to treatment after 3+ month washout period, at baseline, week 1, week 4, & week 12 - this is an accepted point for determining treatment success.

- 1 x 3mls of blood into Tempus^{TM} tubes for RNA isolation.

DNA Sample Collection by Post – Site-specific upon approval from Central Co-ordinating Site
In exceptional circumstances where a patient is not able to attend clinic, is lost to follow up or is not able to give blood, the patient may be asked to provide a saliva sample for DNA via post.

The Principal Investigator at the participating site will approach the patient by post, including the 'Patient Information Leaflet' and a reply slip which they will be asked to return if they wish to participate. If they reply agreeing to participate they will then be sent a 'Consent Form' and a DNA sample donation pack (either blood or saliva depending upon their preferences) and asked to sign and return the 'Consent Form' and return the sample pack. Those subjects who do not reply to the initial letter will be followed up four weeks later by a member of the study team, by either telephone or letter, and asked if they wish to participate.

Dependent upon local R&D approval, the subsequent mail-out (i.e. Consent and DNA collection kit) may be administered centrally from the Skin Therapy Research Unit, St. John's Institute of Dermatology, Guy's and St. Thomas' NHS Foundation Trust.

4.4 Definition of treatment outcomes

Treatment response
Patients will be defined as responders, non-responders or indeterminate responders at 3-4 months, 6 months and yearly thereafter according to the following definition:

Responders:
≥ 75% reduction in the PASI score from commencement of treatment (PASI 75).
AND
the individual has continued treatment

Non-responders*:
< 50% improvement in PASI score from when treatment started
AND
the individual has continued treatment

*Non responders will be stratified for primary failures (ie no response at any time) and secondary failures (ie loss of response, following response at the first time point of evaluation - 3-4 months).

Indeterminate responders:
Patients with a PASI ≥50% and <75%.

Adverse outcomes

Adverse outcomes of special interest will be investigated as listed below. Additional adverse outcomes may be added during the time of the study from the BADBIR registry and other sources if relevant.
(i) drug discontinuation due to development of an adverse event
(ii) serious infection (inc TB)
(iii) cancer
(iv) drug induced hepatitis / fibrosis
(v) bone marrow suppression
(ie >50% reduction in Hb/ total WCC /neutrophils /lymphyocytes/platelets
(vi) death
(vii) any significant adverse events identified in the BADBIR register eg: Major cardiac event, neurological events

4.5 Data Analysis Methods

(i) Investigation of candidate SNPs for treatment response to TNF-antagonist therapy

We plan to test the hypothesis that variations in genes implicated in pathways targeted by TNF-antagonist therapy and/or disease susceptibility loci are relevant to treatment outcomes. Selected candidate genes will only be confirmed at the initiation of the study so as yet undescribed loci can be examined in this well defined cohort. Around 20 candidate genes will be investigated, including those involved in TNF pathways identified in published psoriasis GWAS namely TNFAIP3, TNIP126, C6orf1027, -308 G/A TNF promoter variant (SNP)20, novel genes identified in our present Wellcome Trust supported GWAS in psoriasis (results in press33) and those identified following interrogation of multiple data sources including proprietary gene expression analysis, and public databases (OMIM, Jackson Lab, NCBI) (see table 1). SNPs will be selected to cover these genes based on a combination of linkage disequilibrium tagging and direct functionality criteria. SNPs will be tested across the discovery cohorts using the state of the art core genome facility established to enable high throughput genotyping. Where evidence for association is observed, we will aim to replicate findings in the further (replication) cohort using in house TaqMan technology. We will seek the causal variants focusing particularly on variants that have high probability of having functional effects, e.g. non-synonymous SNPs (nsSNPs) or polymorphisms known to be strongly associated with other diseases. Where necessary additional variants will be sourced from available and emerging databases including the 1000 genome project.

Table 1 Candidate genes for investigation

Chr	Position	Gene/Locus	Chr	Position	Gene/Locus
1p31	67478546	IL23R	12q13	55024240	IL23A
1q21	1.51E+08	LCE3D	20q13	47988384	ZNF313
5q31	1.32E+08	IL13	2p16	60935046	REL
5q33	1.5E+08	TNIP1	2q24	1.63E+08	IFIH1
5q33	1.59E+08	IL12B	5q15	96127700	ERAP1
6p21	31371195	HLA-C	6q21	1.12E+08	TRAF3IP2
6q23	1.38E+08	TNFAIP3	14q13	34902417	NFKBIA
6p21	31652271	TNF gene	19p13	10333933	TYK2

(ii) Sample size

Investigation of candidate SNPs for treatment response to TNF antagonist therapy
Power calculations indicate that with the planned discovery sample size of 1000, assuming 400 of them will be non-responders to TNF-antagonists, we have 85% power to detect an additive genetic effect given an allele frequency of 0.1 with odds ratios of 1.5 for the heterozygous individuals and 2.25 for the homozygous individuals using a cut-off p-value of 0.0001.

Establishment of Psoriasis Interventions Biobank
The results from recent GWAS studies have demonstrated that most complex traits have some genes of small effect require sample sizes of at least 1000. We therefore aim to collect a minimum of 2500 patients on TNF antagonist therapy, anti IL-12/23 therapy (ustekinumab) and 1000 patients on each of methotrexate, ciclosporin and acitretin respectively who have completed a minimum of 6 months follow up, giving a total of 5,500 patients recruited to the study.

5 Assessment of Safety

5.1 Safety Reporting

This observational study does not impact patient treatment and has low risk of causing adverse events.

The BADBIR study tracks and reports all serious adverse events (SAEs) related to the treatment of the participant in line with the National Research Ethics Service standard operating procedures.

Where a participant in this study is not enrolled in the BADBIR study, or where an adverse event occurs due to the collection of BSTOP related data, such as infection or injury caused by blood extraction, the Chief Investigator or Principal Investigator at participating sites will report to the main Research Ethics Committee any SAEs in line with the National Research Ethics Service standard operating procedure on reporting of SAEs as defined in Appendix 4.

6. Administrative Aspects

6.1 Good Clinical Practice

The planning, conduct and reporting of this study will be in the spirit of the International Conference on Harmonisation in Good Clinical Practice (ICH-GCP) 1996.

6.2 Declaration of Helsinki and Ethical Review

The study will be performed in accordance with the principles stated in the Declaration of Helsinki, 2008.

The final study protocol, including the final version of the Patient Information Sheet (Appendix 5) and Informed Consent Form (Appendix 6) to be used, will be approved by an Ethics Committee before enrolment of any subjects into the study. The opinion of the Ethics Committee will be dated and given in writing. A list of those present at the committee meeting (names and positions) should be attached whenever possible.

All correspondence with the Ethics Committee will be filed in the Investigator Site File

6.3 Subject Information and Consent

The Investigator will ensure that the subject is given full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue their participation in the study at any time. The subject will be given an appropriate amount of time to consider their participation in the study and the opportunity to ask questions.
If modifications are made according to local requirements, the new version will be approved by the main Ethics Committee. Written Informed Consent will be obtained from all subjects, before enrolment into the study. The subject should retain a copy of the Subject Information Sheet including the signed Informed Consent Form.

6.4 Subject Protection

Subjects will be assigned an anonymised study number to ensure subject confidentiality throughout the duration of the study. Only the subject number will be referenced in data summaries and study publications and presentations. The Principal Investigators will be responsible for keeping a Subject Identification Log of all subjects enrolled into the study and their corresponding study number. This information will be kept on a secure NHS server in a password protected file and will only be available to the PI and study personnel.

The subjects will also be informed in writing that authorised representatives of the Regulatory Authorities, may require access to those parts of the hospital/practice records relevant to the study, including medical history, for verification of data.

6.5 Direct Access to Source Data and Documents

Key investigators/ collaborators of the project will be the only personnel with access to patient and study data and all data will be stored in accordance with the Data Protection Act, 1998. The Chief Investigator will have overall control of, and act as the custodian for all data for the full duration of time.

The data will be available for internal monitoring (verification of data using hospital notes against the information recorded in the Case Report Form).

6.6 Peer review

This study plan has been reviewed externally, and approved to ensure the study is scientifically sound as part of the process in the achieving funding through the Psoriasis Association.

7.0 Other Study Issues

7.1 Monitoring

Monitoring includes the verification of data using source data (hospital notes) against the information recorded in the Case Report Form as defined in the BADBIR protocol. By participating in this study the Investigator agrees to comply with guidelines for Good Clinical Practice. Principal Investigators will be responsible, in accordance with their local NHS R&D research governance procedures, for maintaining the site investigator file, ensuring study data is recorded in the source notes for each patient and for the monitoring of clinical data to ensure accurate data capture. This process will also be reinforced by the auditing and monitoring that will be conducted by BADBIR on its clinical datasets. BADBIR are to employ a team of clinical research associates to audit and monitor the BADBIR study at participating sites across the UK and therefore the clinical data that is captured for this study on patients enrolled to BADBIR will be validated.

7.2 Training

The principal investigator will ensure that appropriate training relevant to the study is given to the medical, nursing and other staff involved, and that any information of relevance to the performance of this study is forwarded to the Principal and Co-Investigators and other staff involved.

7.3 Study Timetable

Total duration of trial for each subject – minimum 6 months; up to 5 years
Duration of the enrolment period – 3 years
Estimated start date (first patient in) – January 2011
Estimated end date (last patient out) – January 2020

7.4 Subject Medical Records

For every subject taking part in the study, clinical trials records/source documents should clearly indicate at least:

- that the subject participated in the study, e.g. by including subject identification (enrolment code and/or subject number) and study identification (study code or other)
- diagnosis(es) (past and current; both the diagnosis studied and others, as relevant)

7.5 Retention of Study Records

Copies of protocols, CRFs, test results, correspondence, informed consents and other documents relevant to the study must be kept on file by the Investigator and retained for at least 15 years after the completion or discontinuation.

7.6 Changes to the Protocol

The study must be conducted as defined in the present protocol.
All changes must be documented by signed protocol amendments or a revised protocol, which will be submitted to the appropriate REC for approval.
The Investigator is responsible for notifying and obtaining approval from the Ethics Committee and the Regulatory Authorities for any changes to the protocol before implementation. National requirements will be followed.

7.7 Publications

The results of the study will be reported and disseminated in peer reviewed scientific journals and conference presentations.

8.8 Study Termination

The study may be terminated at any time for reasons of safety and tolerability as determined by the principal investigator.

Reference List

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Appendices

Appendix 1

Destruction of sample request

Request for Genotyping Sample Destruction

Subject Number:	Subject Initials:
Subject DOB:	Investigator:

Date of REQUEST for sample destruction:

Reason for sample destruction

(Tick only one box)

- ☐ Consent withdrawal
- ☐ Screen failure
- ☐ Other, specify……..

Date of ACTUAL sample destruction:

Investigator Signature:……

Investigator Name (Print):……..

Date of Signature:……

Appendix 2

Standard Operating Procedure Number:

Standard Operating Procedure Title: Standard Operating Procedure for Clinical Data, Sample Collection and Partner Site Storage

Intended for: Clinical and Research Staff as so indicated

Written by: Robert Pleass	**Authorised by:**

Written: December 2010	**Date for review:** December 2011

Related SOPs

Inter-site Transport and Processing of Human Samples

Purpose / Scope

To provide a standard operating procedure for Sample Collection, Partner Site Storage and transport to Central Co-ordinating Site, Guy's campus, Tower Wing, 9th Floor..
NB Clinical samples eg blood, serum etc should NOT be handled in offices at any time and should be taken directly to the lab and not transited though offices where food and drink may be consumed. All sample labelling etc should take place in the lab or clinical area.
The appropriate study consent must be in place from participants prior to sample collection, processing and storage.

Requirements

Each site must have as a minimum:

- Venepuncture facilities
- Centrifuge
- -20°C freezer (where -70°C not available)
- Sample collection and storage tubes
- Site to enter relevant details
- Secure storage facilities for data and samples

Procedures

Sample Labelling:

- Prior to sample collection ensure all tubes are clearly labelled with the participant's anonymised study number and date of collection.

- For sample labeling use a Staedtler® Lumocolor® permanent marker, fine tip, black.

Sample Collection, Preparation and Storage:

- Blood samples from patients at Guy's or St.Thomas' (GSTT) campuses are stored at 4°C in Dermatology Out-patients prior to transfer to the 9th Floor Tower Wing, Guy's campus.

Whole Blood for DNA

- 12 ml of whole blood is collected in 2x 6ml K_3EDTA vacuette tubes (pink top) which are labelled with participant's surname and date of sample collection number using a permanent marker.
- For collaborating centres that cannot freeze samples, samples are transferred to GSTT within 3 days in postal safe boxes.
- For collaborating centres that are freezing samples, blood is stored at -20^{O}C and transferred to the central co-ordinating site within 1 month.

Whole blood for RNA

- 3ml of whole blood in a Tempus™ RNA isolation tube
- Vortex for 10s to ensure thorough mixing – see below weblink for details
- Transfer within 2 days for ambient transfer.
- For collaborating centres that are freezing samples Store at -20°C until transported to the central co-ordinating site
- https://products.appliedbiosystems.com/ab/en/US/adirect/ab?cmd=catNavigate2&catID=604151&tab=Overview

Whole blood for Serum

- 5ml whole blood in 1x 5ml serum separating clotting factor vacuette tube
- Invert 3x to mix blood with clotting factor
- Centrifuge at 1000g for 10mins at ambient temperature
- Centrifugation of samples will be completed within 4 hours of blood extraction. Serum samples should be stored in a 4°C refrigerator prior to centrifugation.
- Aspirate separated serum into 2ml eppendorf tubes
- Collaborating centres shall store serum at -20^{O}C and transferred to the central co-ordinating site within 1 month.

Whole blood for red-blood cell collection (Methotrexate study)

- 4ml whole blood in 1x K_2EDTA vacuette tube (purple top)
- Invert 5x to mix thoroughly
- Coordinating centres will post Methotrexate samples at ambient temperature in postal safe boxes on the day of collection to the central co-ordinating site.

Whole blood for Methotrexate study – Guy's and St. Thomas' campuses only

- 4ml whole blood in 1x K_2EDTA vacuette tube (purple top)
- Store at 4°C prior to transfer to Purine Laboratory, 4th Floor North Wing, St. Thomas' campus
- All samples must be transferred to Purine lab within 24 hrs.

Saliva

- 2ml saliva in a 1x Oragene®-DNA collection kit (DNA Genotek Inc., Canada)
- Ensure lid is affixed securely
- Placed inside a zip-lock specimen bag
- Store at ambient temperature until transported to central co-ordinating site within 1 month or when 10 samples have been collected, which ever is sooner.

Transportation of Samples to Central Site:

- See related SOP for transportation
- No patient identifiable documents or labels must be sent with the samples
- All patient identifiable paper-work must be sent by separate post

Appendix 3

Standard Operating Procedure Number:

Standard Operating Procedure Title: Inter-site Transport, Processing of Clinical Data and Samples and Long Term Storage

Intended for: Clinical and Research Staff as so indicated

Written by: Robert Pleass	**Authorised by: Dr. Catherine Smith**

Written: December 2010	**Date for review:** December 2011

Related SOP's:

Standard Operating Procedure for Clinical Data and Sample Collection, and Partner site Storage

Purpose / Scope:

To provide a standard operating procedure for the inter-site transport of human samples from partner sites and for transport between Guy's and St. Thomas' campus, and for processing of samples at the central laboratory at Guy's Campus. This SOP is written in accordance with the Human Tissue Act 2004, Regulations 2006 & 2007 and King's College London, Guidelines for the Transport of Biohazardous Goods, for the distribution of human samples where appropriate.

Procedures

1). At Partner sites

1.1) Sample Transport from Partner Sites

To maintain participant anonymity all samples shall be separated from their respective clinical data and transferred under separate cover. All sample tubes shall be labelled with a site specific study number, details provided by the central co-ordinating site. Samples collected at partner sites are transported to the Skin Therapy Research Unit, 9th Floor, Tower Wing, Guy's Hospital, London SE1 9RT.

- Prior to transport the partner site research team must ensure that the central co-ordinating site is aware that the samples are to be transported and are able to receive them upon arrival.
- Frozen blood (whole and cells; RNA Tempus® tubes) and serum samples are transported on dry-ice by specialist courier service – contact central co-ordinating site for details and packaging instructions

- Saliva samples are placed in Jiffy® bag, securely sealed and posted via Royal Mail Freepost service – supplied by central co-ordinating site

1.2) Transport of Relevant Clinical Information from Partner Sites

Participant consent forms and clinical data sets (CRFs) shall be labelled with the corresponding study number that relates to the respective sample in order for the clinical data to be matched to the sample at the central co-ordinating site. ~~Clinical data sheets shall be transferred under separate cover form participant consent forms in order to maintain participant anonymity~~.

A photocopy of all completed CRFs shall~~All paper-work is~~ be transferred to the central co-ordinating site using Royal Mail Freepost service. Original copies of the CRF shall be stored securely in the study site file at the partner site.

At partner sites' request, the central co-ordinating site will acknowledge to the partner site receipt of clinical data and samples within 24hrs vis e-mail or 'phone. Partner sites requesting acknowledgement of receipt shall include the request and contact details as a covering letter to be included with the shipment.

Participating sites will retain participant consent forms until the conclusion of the study, at which time the central co-ordinating site will make arrangements for the transfer of all study documents. Principle Investigators at participating sites shall ensure that up-to-date consent is received from study participants and kept securely in the study file. The central co-ordinating site shall accept acknowledgement of consent on the patient CRF as confirmation that patient is consented to participate in the study.

~~The central co-ordinating site will acknowledge to the partner site receipt of clinical data and samples within 24hrs vis e-mail or 'phone.~~

2). At Central Co-ordinating Site (applicable to Guy's and St Thomas' NHS Foundation Trust sites only)

~~2.1). Transport of Clinical Data and Samples between Guy's and St. Thomas' Campus:~~

Relates to samples collected in Dermatology Out-patients Guy's and St Thomas' Hospital campuses and received at the Skin Therapy Research Unit at Guy's and St. Thomas' Hospitals. As for 1). above all clinical data ~~and consents~~ must be transferred under separate cover from

samples. ~~In addition all clinical data sets and consent forms must be transferred under separate cover from each other.~~

- Use GSTS pathology service. Samples and clinical data for transport are taken to the GSTS drop off point at North Wing St. Thomas' campus and collected from 4th floor Southwark Wing at Guys, and *visa versa*.
    - Whole blood for DNA, serum and saliva is transferred to the Skin Therapy Research Unit, Guy's site at above address
    - Whole blood for methotrexate sampling is transferred to the Purine Laboratory, fao Prof. Marinaki, 4th Floor, North Wing, St. Thomas' Hospital.
- Samples are packed at ambient temperature in a Jiffy® bag clearly labelled with name, address and contact number of recipient. Delivery time from between campuses is 30 mins – 1 hour.
- Alternatively ambient samples may be transferred between Guys and St Thomas' campuses by specialist courier – MEDICAL COURIER (0207 014 1050, account number 51201)

~~3~~2.2) For samples received at either central co-ordinating site from partner sites:

Frozen samples* are transferred between sites on dry-ice in a secure biological material transfer container in accordance with UN PI650 (see KCL, Transport of Biological and Human Tissue Samples between College campuses**)** using a specialist courier service and transferred to the appropriate laboratories as above eg CITY SPRINT the KCL approved courier - 0207 880 1111

*Frozen samples include the following:

- Whole blood for DNA
- Serum
- Whole Blood for RNA

3). Clinical Data and Sample Processing

Relates to samples and data received in the Skin Therapy Research Unit, Guy' campus.

- Samples and clinical data will arrive from partner sites by separate post. There may be a lag of up to 7 days between receipt of clinical data and samples. All clinical data must be collated and matched to the respective sample to ensure that the patient has been consented to the study and the appropriate clinical information has been obtained.

- In the event of ~~missing clinical data sets or consent forms, or~~ missing or leaked samples, the central co-ordinating site shall contact the participating centre within 1 working day to request copies of paper-work or to alert them to missing/leaked samples.
- Where central co-ordinating site identifies missing clinical data, the central co-ordinating site will contact the Research Nurse or study co-ordinator at the partner site to request

Formatted: Bullets and Numbering

3.1). Sample Processing

- All samples collected at Guy's and St. Thomas' campuses and from partner sites are assigned a unique study number and the sample information entered onto the St. John's Medical Dermatology database and into the laboratory sample log book with the following information
    - Unique study number
    - Patient's name
    - Date of birth
    - Laboratory number – see below
    - Date of sample
    - Disease and Protocol
    - Gender
    - Ethnicity
- All samples are assigned a laboratory number, generated sequentially from the laboratory sample book. This number is written on the sample tubes prior to storage and recorded on the accompanying clinical data sheet and entered onto the St. John's Medical Dermatology database as above.

3.2). Clinical Data Processing

Once all clinical data, consents and samples have been collated all clinical data and sample information must be entered onto the St. John's Medical Dermatology database within 2 working days.

Security and Storage of Clinical Data and Samples

1). Storage

- Samples are stored in the appropriate manner prior to further analysis/extraction
    - Whole blood for DNA is to be stored at -80°C
    - Serum is to be stored at -80°C

- Saliva is to be stored at ambient temperature

2). Security

- All clinical data and consent forms are to be stored separately in study specific site files in a locked office at the central co-ordinating site. Access to the central co-ordinating site (9th Floor, Tower Wing, Guy's Campus) is by swipe access.
- All electronic information regarding clinical data and samples will be stored on a password protected secure NHS server
- All samples are stored within a secure laboratory at the central co-ordinating site. Access to this laboratory is by swipe access, as is access to the central co-ordinating site itself.

4). DNA Extraction and Long Term Storage

DNA will be extracted from whole blood and saliva within 7 working days from receipt of samples. All accompanying patient data will be removed to ensure patient anonymity. DNA will only be identified by the laboratory number assigned upon sample receipt and stored at -70°C at the central co-ordinating site, Guy's Campus, for long term storage

Appendix 4

Standard Operating Procedure Number:

Standard Operating Procedure Title: Safety Reporting for non-cTIMP Studies	
Written by: Robert Pleass	**Authorised by:**
Written: November 2010	**Date for review:** November 2011

Related SOPs:

National Research Ethics Service SOP, version 4.1, May 2010, Section 9.64.

Purpose / Scope:

To provide a standard operating procedure for the safety reporting of serious adverse events in non-cTIMP studies.

Procedures

Safety reporting for other research
In research other than CTIMPs, a Serious Adverse Event (SAE) is defined as an untoward occurrence that:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect; or
- is otherwise considered medically significant by the investigator

An SAE occurring to a research participant should be reported to the main REC where in the opinion of the Chief Investigator the event was:

- "Related" – that is, it resulted from administration of any of the research procedures, and
- "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the SAE report form for non-CTIMPs published on the NRES website.

The Chief Investigator should include a report on the safety of participants in the annual progress report.

Individual reports of SAEs should be reviewed at a sub-committee or Committee meeting.

There is no requirement to provide reports to RECs other than the main REC.

Appendix 5

Patient Information Sheet v. 4, 17/1/2013

TAKING PART IN PSORIASIS RESEARCH

STUDY TITLE: Bio-markers of Systemic Treatment Outcomes in Psoriasis

You are being invited to take part in a research study. Before you decide it is important to understand why the research is being done and what it will involve. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Please ask the study doctor or nurse to explain anything you do not understand

WHAT IS THE PURPOSE OF THE STUDY?

There are a large number of drugs available for psoriasis but not all of these work for every person. We know that the genetic and biological make-up of each person is very important in determining how they will respond to treatment. The overall research aim of this large, multi-centre study therefore seeks to discover which gene(s) and also other so-called 'biomarkers' -for example present in a blood sample) are important in determining good (or poor) responses to the drugs that are used to treat psoriasis. Once discovered, doctors will be able to use the genetic and biological blueprint of each patient to identify which treatments are most likely to work (and be the safest or least likely to cause side effects) rather than the current approach which is 'try it and see'.

WHY HAVE I BEEN INVITED?

You have been invited to take part because you have psoriasis and are taking, or are about to start systemic or biological therapy for your psoriasis.

You may also be taking part in "The British Association of Dermatologists Biologics Intervention Register - BADBIR". This research study is being run alongside, and with the approval of, BADBIR and we would like your permission for us to access data that you have already given to BADBIR. This way we will not need to ask you twice for the same data.

BENEFITS OF TAKING PART IN THE STUDY

You will not receive any financial benefit for taking part in this study and the results of the study will not be of any direct clinical benefit to you. However, by taking part in this study you will be providing vital information to the research team which we hope will lead to better treatments for people with psoriasis.

WHAT ARE THE RISKS OF TAKING PART IN THE STUDY?

There are no important risks to taking part in this study. Blood tests can sometimes be uncomfortable and cause bruising at the site. However we will try to take any research blood samples from you when you are having your routine blood tests taken to minimise discomfort.

Research Information

DO I HAVE TO TAKE PART?
No. Taking part is entirely voluntary and your clinical care will not be affected by your decision to participate or not participate in this study.

WHAT DO I HAVE TO DO?

You will be asked to sign a consent form
In order to participate in the study we will ask you to sign a consent form. A study doctor or nurse will go through the consent procedure with you and explain the study in detail.

You may be asked to make additional visits to clinic
We will collect follow up data and blood samples from you at your regular clinical visits. For most patients this will be every 6 months for up to 5 years. Where possible, some patients starting new treatment (or patients returning to treatment after being off treatment for a long time) may be asked to return to clinic for additional follow up visits after the first week, the fourth week or the twelfth week of the treatment. This is because treatments often have significant effects in the early stages, and we want to get a "snapshot" of these changes during this important stage. Some patients will not be required to return to clinic for a follow up at all. We can collect valuable information from you regardless of your stage of treatment or the frequency of your visit, Talk to the study nurse or doctor to find out how often they would like to follow up with you.

You will be asked to provide clinical information
We need to collect clinical information about how you are responding to treatment and whether you have developed any side effects to the drug that you are on for your psoriasis. We also need to know your ethnic group, your current medical condition, the history of your psoriasis and whether you are taking any other medication. We aim to collect this information (along with samples, see below) during your normal clinical appointments to minimise the number of times you come to hospital. To minimise the amount of time you need to spend at appointments to participate in this study with your permission, data will be collected from the BADBIR registry (if you are taking part in this) and your medical records by the research nurse or study doctor where ever possible. The study nurse will also measure your height, waist and weight.

You will be asked to complete patient questionnaires
You will be asked to complete the questionnaires and other survey forms about your health. You should note that some of the questions on these questionnaires may be of a sensitive or personal nature. You are not compelled to answer all of the questions.

You will be asked to provide biological samples
You will be asked to donate at least one sample of your DNA & RNA. This will be either in the form of a saliva sample or of a blood sample. To donate using saliva you will be asked to spit 2mls (approximately half a teaspoon) into a plastic pot or to donate using blood, 15ml (approximately 3 teaspoons) of blood will be taken will be taken from your arm. It is your choice which method you prefer in order to donate DNA to us.

In addition, to help us investigate how your treatment is being affected by your body, and how your body is being affected by the treatment, you will be asked to donate additional blood sample at each visit. The maximum volume requested at any one visit would be 5 teaspoons if you are on Methotrexate, 4 teaspoons for all other treatments.

You will be asked if you are willing to be recalled for future investigations

Psoriasis research is a rapidly changing field and there are frequent advances in our analytical techniques. In the event that new discoveries are made or new aspects to explore, the researchers are requesting permission to contact you again for future investigation. This is an optional request and if you don't wish to give consent to be contacted for future investigations,it will not impact your participation in this study nor will it impact your clinical care.

WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?

Yes. When you consent to take part in the study you will be assigned an anonymised study number. This number will used for all study-related material (including data). No person-identifiable information will be used in any correspondence. Only the study doctor will know which anonymised number relates to you.

WHAT WILL HAPPEN TO MY DATA?

All your data will be stored in accordance with the Data Protection Act 2004 and the International Conference on Harmonisation for Good Clinical Practice. Your data will held on a secure NHS database for the purposes of this study and only the Chief Investigator for this study, Dr. Catherine Smith, members of the research team and approved regulatory personnel will have access to your study records and medical notes.

WHAT WILL HAPPEN TO MY DNA, RNA AND MY OTHER SAMPLES?

All samples, including the DNA extracted from your blood cells or saliva, will be stored securely in accordance with the Human Tissue Act and according to national and local NHS Research Governance guidelines and will only be used for scientific research related to psoriasis. We plan to store your samples for as long as this and future studies of psoriasis continue at the main study co-ordinating centre (St. John's Institute of Dermatology, London).
We plan to store your biological samples for the duration of this study and, with your agreement store your samples anonymously for future research into skin disease in a research bio-bank at St. John's Institute of Dermatology, Guy's and St Thomas' NHS Trust: Ethics Approval Ref: 07/H0712/106; HTA License number 12521.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

When the study has been completed we will aim to publish the results in scientific journals/publications. Please let us know if you wish to be informed of the publication of the study and we will aim to keep you fully informed. You will not be identified in any publication.

WHO CAN I CONTACT FOR FURTHER INFORMATION ON THE STUDY?

Please contact Dr. Catherine Smith or the research nurse on 020 7188 6273 at any time if you have questions about the study.

WHAT HAPPENS IF I WISH TO WITHDRAW FROM THE STUDY?

If at any time you wish to withdraw from the study we will provide you with a form to complete and return to us asking us to destroy your samples and withdraw you from the study. Your samples, including your DNA and RNA will be removed from storage and destroyed and any research data we have collected about you will not be used in this study. Your participation is voluntary. None of these actions will affect your future treatment.

If you have understood all the information above and wish to participate in the study you will be asked to sign a Consent Form. You should keep a copy of this Information Sheet for yourself.

Research Team at Guy's and St. Thomas' NHS Trust

Dr. Catherine Smith: Chief Investigator and Consultant

Professor Barker: Co-investigator and Consultant

Kate Thornberry: Clinical Research Nurse;

Greg Kuenzig: Study Co-ordinator

Study Ethics reference: 11/H0802/7

Date of Study Approval: 01/03/2011

Appendix 6

CONSENT FORM (v.4, 17/1/2013)
Title of Study: Bio-markers of Systemic Treatment Outcomes in Psoriasis
Ethics Ref: 11/H0802-7
Date of Approval:

BSTOP ID

Name of participant:_____ Study Number: STRU-PG-02-201
Name of Chief Investigator: Dr. Catherine Smith

Please Initial box

1. I confirm that I have read and understand the Patient Information Sheet (Version 4 dated 17th January 2013) for the above study for psoriasis patients and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand, and agree, that members of the study team and the Chief Investigator will, if I am a participant in the BADBIR study, have access to my data from that study, as agreed by the BADBIR Steering Committee. ☐
4. I understand that sections of any of my medical notes may be looked at by hospital staff and members of regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
5. I agree to donate samples of my DNA, RNA and serum, and for personal data to be collected for the purposes of this research and for this material to be stored on a secure database in an anonymised manner for this study. ☐
6. I agree to complete the questionnaires and other survey forms about my health. ☐
7. I agree to personal information from which I can be identified being held by the research team at St. John's Institute of Dermatology in a secure NHS database, but held separately from my clinical information ☐

Please check "Yes" or "No" to items 8 & 9. You may participate in this study regardless of your responses to the below statements

	YES	NO
8. Following the completion of this study, my personal data and materials may be stored anonymously for future studies in psoriasis in the research bio-bank at St. John's Institute of Dermatology, Guy's and St Thomas' NHS Trust: Ethics Approval Ref: 07/H0712/106; HTA License number 12521. I understand that this part of the study is entirely optional.	☐	☐
9. I agree to be contacted in the future for the purpose of requesting consent for further clinical investigation and biological samples from me. I understand that this part of the study is entirely optional.	☐	☐

10. I agree to take part in the above study. ☐

_____	_____	_____
Signature	Name of participant	Date
_____	_____	_____
Signature	Name of researcher	Date
_____	_____	_____
Signature	Name of Investigator	Date

1 copy for participant, 1 copy for medical/research notes & 1 copy for department.

Signature(s) of Investigator(s)

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified in the study protocol, and according to the principles of Good Clinical (Research) Practice (GCP).

. . . . . .

DR. CATHERINE SMITH

CHIEF INVESTIGATOR

. . . . . .

DATE

APPENDIX 7

On-going list of collaborating sites

Aneurin Bevan Health Board
Royal Gwent Hospital, Dermatology
Cardiff Road
Newport
NP20 2UB
PI: Prof Alex Anstey

North Glasgow NHS Trust
Western Infirmary, Dermatology
56 Dumbarton Street
Glasgow
G11 6NT
PI: Dr David Burden

Salford Royal NHS Foundation Trust
Greater Manchester Dermatology Centre
Manchester
PI: Prof Christopher Griffiths

NHS Grampian
Dermatology
Aberdeen Royal Infirmary
Aberdeen
AB25 2ZR
PI: Dr Tony Ormerod

Newcastle Upon Tyne Hospitals NHS Foundation Trust
Newcastle
PI: Prof Nick Reynolds

Salford Royal NHS Foundation Trust
Manchester
PI: Dr Richard Warren

King's College London
St. John's Institute of Dermatology
Great Maze Pond
London
SE1 9RT
PI: Prof Jonathan Barker

Surrey and Sussex Healthcare Trust
Department of Dermatology
Canada Avenue
Redhill
RH1 5RH
PI: Dr Sandeep Cliff

County Durham and Darlington NHS Foundation Trust
Dermatology
North Road
Durham
DH1 5TW
PI: Dr Shyamal Wahie

Brighton and Sussex University Hospitals NHS Trust
Dermatology
Elm Grove
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