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 (BSTOP)

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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 15 years, 'biologic therapies' have also become available, with those that target the cytokine tumour necrosis factor (TNF) - adalimumab, etanercept and infliximab (TNF-antagonists) - plus the more recent addition of biologics targeting the interleukin (IL) 12/23 pathway (ustekinumab p40 subunit mAb), IL17 (secukinumab, ixekizumab) and Il23 (p19 subunit mAb, such as guselkumab). New 'small molecule' agents include a PDE4 inhibitor (apremilast) and janus kinase inhibitors (eg: tofacitinib)[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 indicate 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 Biologics and Immunomodulators Register (formerly 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 4.5. 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 has been minuted.

Introduction update (2019)

Since the set-up of the BSTOP study, research into the biomarkers of treatment response has progressed significantly. Major collaborations have been set up e.g. an MRC funded consortium (Psoriasis Stratification to Optimise Relevant Therapy, PSORT.org.uk, MR/L011808/1) and we have begun to work with an expanded range of investigators and research partners, including industry partners, within and outside the UK. This is in line with the original aims and objectives of the study and capitalises on the world leading, unique, large scale BSTOP bioresource. The possibility of obtaining additional samples (e.g. skin biopsies, microbiome samples and peripheral blood mononuclear cells) to more deeply phenotype a subset of patients will bring added value, given the opportunity to augment and allow comparison with existing PSORT psoriasis cohorts.

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 an observational, prospective, cohort study in patients with psoriasis being treated with systemic therapy. This includes, but is not limited to standard systemic therapy (methotrexate, ciclosporin, acitretin, fumaric acid esters, dimethyl fumarate) biologic therapies (including but not limited to etanercept, adalimumab, infliximab, ustekinumab, secukinumab, ixekizumab, guselkumab, brodalumab) and novel small molecules (apremilast). 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. Recent efforts to identify genetic markers of response in rheumatoid arthritis highlight the complexity of the 'response' phenotype[26]. We will therefore use other known or newly identified biomarkers of response (for example drug levels, transcriptomic, proteomic) alongside the clinical data to enhance power to discover genetic determinants and more generally, clinically relevant biomarkers of outcome. To this end we aim to recruit up to 9,500 patients in total to this study (see Section 4.3 for details).

2.3 Linkage to BADBIR:

Subject to patient consent, the BSTOP study is linked to BADBIR to enrich the clinical dataset and avoid duplication of effort. This also minimises study burden (time and visit number) and for subjects in the "single sample" cohort, provides sufficient data to allow meaningful analysis.

Following consent, BABDIR ID numbers and BSTOP numbers will be shared between the BADBIR and BSTOP study teams via the BSTOP coordinating centre to facilitate data linkage. As per the BADBIR data sharing agreement, local study centres are responsible for sharing BADBIR IDs with central study team on the case report forms (CRFs). The BADBIR ID, corresponding date of birth and matching BSTOP ID are shared with BADBIR (in accordance with **G**eneral **D**ata **P**rotection **R**egulation; 2018), who then use this to identify the patient records to be sent to the BSTOP team (see Figure 1).

Figure 1: BSTOP/BADBIR data linkage

2.4 Transitioning of patients participating in PSORT-D

All participants in the PSORT-D study (REC: 14/LO/1685) will be invited to participate in BSTOP (and also BADBIR). The longer term follow up afforded through BSTOP/BADBIR will greatly enhance the research value of the multi-omic dataset collected for PSORT-D where the follow up duration is limited to 12 weeks.

3 Subjects

3.1 Inclusion Criteria

I. Patients able to give written informed consent

II. Patients with psoriasis ≥16 years

III. Either or both*:

   a. Enrolled in the BADBIR and/or the PSORT-D study

   b. Within 6 months of initiating or switching to a systemic therapy (standard, biologic or small molecule) for the treatment of psoriasis

Note that patients recruited to the single sample ('DNA only') cohort (see 4.1.1 / page 17) must be enrolled in BADBIR to be eligible, to enable the linkage of one-off data collected to longitudinal data from the BADBIR dataset

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. Recall may also be requested if there is insufficient sample (for example if a DNA sample results in a low concentration after extraction or the samples taken have been exhausted). 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 team member should complete the appropriate documentation with the patient (BSTOP Withdrawal of consent form, latest version), where the patient agrees. If not completed, any instructions from the patient should be documented in a file note.

Patients consented to ICF v5 or later

Patients consented using ICF v5 or later will have consented to the retention of samples and data collected to date, in the event of study withdrawal.

Patients consented to ICF v4.1 or earlier

Patients who were consented using ICF v4.1 or earlier may request data deletion and/or sample destruction following withdrawal from the study. It is the responsibility of the local study investigator to ensure withdrawal of consent forms with these wishes documented, and/or clear instructions are shared with the coordinating centre by email. It is the responsibility of the study investigator to organise destruction of any samples collected from a patient from whom a request is received, and to keep a record of that destruction in the study file. It is also their responsibility to request sample destruction for any samples already shipped to the coordinating centre, through provision of the withdrawal of consent form or emailed instructions to the trial manager and study administrator.

The terms of the patient withdrawal specified, and version of ICF used to consent each patient are also documented in the patient record on the online study database, ‘CAPTURE’ (see section 6.5 below). It is

the responsibility of the study investigator to destroy any samples collected in error or at the request of the patient, and any data to be destroyed, and to keep a record of that destruction in the study file. It is also their responsibility to request sample and/or data destruction for any samples already shipped and/or data sent to the coordinating centre, through provision of the form to the trial manager and study administrator.

4 Investigational plan

4.1 Patient Cohorts and Site types

Sample collection and visit schedule will be determined by the patient's therapy, stage of treatment, site type (longitudinal or single sample) and patients' choice.

4.1.1 Participant Cohorts

Cohort 1: participants providing multiple samples ("longitudinal samples").
Cohort 2: participants who are donating a single DNA sample only.

4.1.2 Sites

Sample collection and patient follow up will be determined according to each site's resources and capabilities. Sites are therefore divided into 2 categories:

Longitudinal Sites: will collect samples from participants at multiple time points as per the visit schedule. Exact sample types to be confirmed by CI and study manager at set up

Single Sample Sites: will collect a sample for DNA at a single baseline visit only.

NB: longitudinal sites may also recruit patients as per single sample sites (i.e. for single DNA only sample) where indicated (for example, based on resources available at the time or patient's choice)

4.2 Measurements and Evaluations

The following data will be collected from participants:

4.2.1 Clinical data

The following clinical data will be collected at baseline and all subsequent follow up visits:

Baseline visit (all patients)

i. Secure consent for linkage to BADBIR
ii. Demographics, NHS number, disease phenotype, presence of psoriatic arthritis, co-morbidities, past and current systemic therapies for psoriasis including dates and dosing schedules
iii. Previous UV therapy
iv. Skin cancer risk factors, including the Fitzpatrick skin type and history of skin cancer
v. Clinical assessments: weight, waist circumference, height, blood pressure and disease severity measures - psoriasis area severity index (PASI), physicians global assessment (PGA), body surface area (BSA)
vi. Intervention of interest: drug, frequency, dose, time and date of last dosing
vii. Ongoing concomitant therapy
viii. FBC, Creatinine, ALT, lipids, CRP, ESR Patient questionnaires: demographics, smoking history, alcohol history, employment status, history of living in hot climates, DLQI, CAGE (in patients who drink alcohol), HAQ (only in patients with Psoriatic arthritis) and EQ-5D.

Follow up visits (cohort 1 only) – some or all of the following will be collected

i. clinical assessments: weight, waist circumference and disease severity assessment scores since the time of last follow up (including PASI, PGA, BSA)
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. any new diagnosis of psoriatic arthritis

FBC, creatinine, ALT, AST, lipids, CRP, ESR Patient questionnaires: smoking status, alcohol units, employment status DLQI, CAGE (in patients who drink alcohol), HAQ (in patients with Psoriatic arthritis) and EQ-5D.

4.2.2 Biological Sample collection

DNA samples - collected from all participants

- **2 x 6ml EDTA vacuette tubes (pink top)** of blood for DNA extraction/epigenetic studies. (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.
- **In exceptional circumstances, and only with prior arrangement with the central co-ordinating centre**, 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 should be returned to the central site via Royal Mail Freepost service.

Pharmacokinetic (pK) samples – collected from cohort 1

Poor concordance with therapy, inter-individual variation in drug pharmacokinetics and development of drug antibodies are known to impact on treatment response. The following samples will therefore be collected at selected centres **depending on therapy prescribed**, to ascertain drug levels in participants at baseline and all subsequent follow up visits:

Note - study site staff should consult the latest working documents for guidance on sampling

- **Methotrexate: 1 x 4 ml EDTA tube (purple top)** of whole blood for methotrexate polyglutamates (ideally taken 24 hours before dose of methotrexate where feasible).
- **Ciclosporin: 1 x 4 ml EDTA tube (purple top)** of whole blood for ciclosporin level at trough level (where feasible, an additional sample should be collected 2 hours post dosing)
- **Biologic treatment: 1 x 5ml serum separating clotting factor (yellow top)** of whole blood. This will be collected based on the treatment as described below. Ideally samples will be collected prior to dosing. However, there is flexibility around the dosing window and respective sampling. If a participant is due a follow up, collect the relevant samples and ***note the time of last dosing*** and whether there have been any interruptions in treatment.
    - **Adalimumab:** ideally prior to dosing with window up to 3 days
    - **Etanercept**: ideally prior to dosing with window up to 3 days
    - **Ixekizumab**: ideally prior to dosing with window up to 7 days
    - **Infliximab:** ideally prior to dosing with window up to 7 days
    - **Secukinumab:** ideally prior to dosing with window up to 7 days
    - **Ustekinumab:** ideally prior to dosing with window up to 7 days
    - **Guselkumab:** ideally prior to dosing with window up to 7 days

Pharmacokinetic (pK) samples – collected from cohort 1 *(continued)*

Other treatments: patients on other biologic or systemic treatments not described above will provide 1 x 5ml serum separating clotting factor (yellow top). Additional Pk samples may be requested for specific cohorts and by arrangement with the coordinating centre study team.

Biomarker samples – collected from cohort 1

Serum

- **1 x 5mls serum separating clotting factor (yellow top)** of blood at baseline and all subsequent follow up visits.

RNA - collected by designated sites only

- **1 x 3mls Tempus™ tubes (blue top)** of blood for RNA isolation taken at baseline, week 1, week 4, & week 12-16.

Additional samples – selected participants and selected sites

Some participants may be invited to provide optional additional samples to augment the analysis of longitudinal samples already collected. These are optional requests and by consenting to participate in BSTOP participants are not inherently consenting to additional sampling. Additional samples may be taken at any point in the study, though there will be a particular focus on additional sampling in the first 16 weeks of starting a new drug. Additional sampling may include:

(i) Blood samples

Samples for DNA, sera or RNA or for other biomarker analysis (e.g.: Peripheral Blood Mononuclear Cells, PBMCs) up to a maximum of 100ml per visit. Novel methods for sampling blood (e.g.: via finger prick devices, capillary tube sampling) may be used to minimise discomfort and inconvenience for PK sampling or other biomarker discovery programmes.

(ii) Skin microbiome samples (swabs)

Skin microbiome samples may be collected (from a maximum of 2 swabs at any one visit, one per lesional/non-lesional sample) using a non-invasive method which involves scraping the outer skin cells without puncturing the skin. Where sites for swabs are to be matched to biopsies taken at the same visit, microbiome sampling should precede skin biopsy sampling. This will follow a standardised protocol:

Where lesional and non-lesional samples required, start with the non-lesional sample. The skin should not be cleaned prior to sampling. Place the chamber on the skin, and pipette 1.5ml of sterile Phosphate Buffered Saline (PBS) into the chamber. Rub skin 10 times in one direction with a plastic inoculating loop, and then in the opposite direction with a plastic inoculating loop. Aspirate 0.75ml of the PBS solution into each eppendorf tube. Repeat for lesional sample if required.

Additional samples – selected participants and selected sites *(continued)*

(iii) Skin Biopsies

Skin biopsies may be collected (up to a maximum of 2 at any one visit, and a maximum of 6 throughout the life time contribution of the patient in this study) using standard clinical procedure as follows:

The skin is disinfected and local anaesthetic is infiltrated into the desired area prior to the sample being taken. A punch biopsy will be taken from the skin, in which a small circular blade of up to 6mm diameter will be used to puncture the skin. After removing the skin sample, the wound will be covered with a dressing or stitched as appropriate. Biopsy sites should not be allowed to get wet for the first 24-48 hours after taking the biopsy. The wound healing process will be followed by a research doctor and/or research nurses involved in the study, and in some cases may be delegated to the patient's general practitioner if appropriate.

4.3 Schedules

Participating centres will be confirmed as collecting either longitudinal or single samples (as per site types above, section 4.1). This then infers the specific sampling regimes (sample types to be collected detailed in Section 4.2). The visit schedule will continue for 5 years or until the participant completes their involvement in BADBIR, whichever is longer. Patients who have been consented to ICF v4.1 or earlier may be invited to continue participation according to these updated criteria, following reconsent to ICF v5 or later.

Wherever possible, investigators should align (make concurrent) participants' BSTOP and BADBIR visit schedules. The BSTOP sample collection should continue every 6 months, even after the BADBIR follow visits are annual. Any visits made outside of a BADBIR visit should be recorded on the 'in between BADBIR visit' case report form or else live on the study database.

Longitudinal Sample (Cohort 1) collection:

The time points for sample collection depend on where, in the treatment cycle, the participant is:

(i) new starters or switchers:

The following visits should be scheduled for all participants starting or switching to a new treatment.

Every effort should be made to recruit early but if participants are not consented in time, baseline may be completed at any point up to 12-16 weeks from start of treatment. The next visit will depend on the baseline time point i.e. if "baseline" is at 5 weeks post treatment start, the next visit at week 12-16.

Baseline	Week 1	Week 4	Week 12-16	Every 6 months
Before or on the day of treatment start (pre-dose)*	1 week post treatment start	4 weeks post treatment start	12-16 weeks post treatment start	6 months from treatment start

**Can be up to 12-16 weeks after treatment start*

To be most useful, samples should be taken **before** the next treatment dose is administered. Note that there is no need to restart the schedule where a patient begins adjunctive methotrexate in addition to their main treatment (e.g. initiated on methotrexate in combination with an existing biologic).

(ii) joiners:

These participants are joining BSTOP whilst established (>3 months) on treatment. If they plan to start a new treatment they should switch into the above schedule for new starters and start sample collection again

Baseline	Every 6 months
First BSTOP visit	6 months from treatment start

(iii) participants who are failing therapy prior to switching to a new therapy:

Participants who are failing therapy and plan to switch treatment should wherever possible be approached to provide an **additional serum sample** outside the above schedules. Please contact the study manager to confirm the samples needed if centres have patients in this position.

Additional visit	Baseline
Before switching treatment to collect serum sample	Before or on the day of treatment start (pre-dose)

Participants providing longitudinal samples who stop treatment will be followed up for one year, at 6 monthly intervals, after stopping. If the participant resumes treatment again, their follow up visits will recommence according to the visit schedule and the new drug start date.

Single Sample (Cohort 2) collection:

Collection of a single DNA sample alongside clinical data (with BADBIR data sharing if consent given). Participants in this cohort (Cohort 2) can donate at any point in their treatment course, even if off treatment.

Baseline
Single BSTOP visit

4.3.1 Figures: Patient Cohort Visit Schedules

Figure 1

Participant cohort 1: longitudinal visit schedule

Ongoing data collection throughout: *Clinic data / efficacy / AE / drug specific data / pK data / concomitant therapy*

Screening	Consent	Baseline *Pre- or post-drug start, choose next visit accordingly*	***POST-DRUG START DATE*** *(as applicable)*				
			Week 1	**Week 4**	**Week 12-16**	**6 months**	**6 monthly[1]**
		Blood for DNA 2 x 6ml	**Blood for Biomarkers** 1 x 5ml blood	**Blood for Biomarkers** 1 x 5ml blood	**Blood for Biomarkers** 1 x 5ml blood	**Blood for Biomarkers** 1 x 5ml blood	**Blood for Biomarkers** 1 x 5ml blood
		Blood for biomarkers 1 x 5ml blood	**Blood for pK[2]** per treatment	**Blood for pK[2]** per treatment	**Blood for pK[2]** per treatment	**Blood for pK[2]** per treatment	**Blood for pK[2]** per treatment
		Blood for pK[2] per treatment	**Blood for RNA[3]** 1 x 3ml blood	**Blood for RNA[3]** 1 x 3ml blood	**Blood for RNA[3]** 1 x 3ml blood		
		Blood for RNA[3] 1 x 3ml blood					
		Blood for PBMCs[4] Up to 4 x 10ml	**Blood for PBMCs[4]** Up to 4 x 10ml	**Blood for PBMCs[4]** Up to 4 x 10ml	**Blood for PBMCs[4]** Up to 4 x 10ml		
		Skin swab[4] 4 x 0.75ml	**Skin swab[4]** 4 x 0.75ml	**Skin swab[4]** 4 x 0.75ml	**Skin swab[4]** 4 x 0.75ml		
		Skin biopsy[4]	**Skin biopsy[4]**		**Skin biopsy[4]**		

Notes: *[1]**6 monthly** continues even when annual for BADBIR; [2]**Pk sample** determined by drug, MTX or otherwise; for MTX only take during treatment; [3]**Blood for RNA** only taken at longitudinal supersites; [4] **Additional optional samples below line** only on designated subsets of patients at limited centres; may also be taken at other visits*

Figure 2

Participant cohort 2: single sample visit schedule:

4.4 Definition of treatment outcomes

Treatment response (primary outcome)

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 (i.e. no response at any time) and secondary failures (i.e. 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 e.g.: Major cardiac event, neurological events

4.5 Sample storage

Samples will be collected and stored according to the latest working documents (see sample processing and storage manual). Samples for methotrexate (MTX) levels will be shipped ambient via approved methods to the coordinating centre as soon as possible after the sample is taken, to be analysed by the team at Viapath on receipt. Samples for DNA may be shipped together with accompanying MTX samples, or else stored at at least -20 before dry ice shipment. Samples for serum must also be processed according to the latest manual and stored at at least -20 until transfer. Courier shipments on dry ice will be paid for and organised by the coordinating centre, approximately every 50 patients or annually. Shipments at more regular intervals will need to be negotiated with the coordinating centre. Long term storage of samples will be at the St John's Institute of Dermatology research offices, King's College London, in Tower Wing, Guy's Hospital, London SE1. Samples for analysis may also be shipped to external collaborators. Any sample sharing will be in line with the participant informed consent. The transfer and use of samples will be covered through a material transfer agreement (MTA).

4.6 Ongoing bioresource

Fulfilling the aim of establishing a critical resource for future use by investigators to improve outcomes in psoriasis, samples will be stored for use in further ethically approved psoriasis studies in a research bioresource, and tracked on the secure NHS database, named CAPTURE (also referenced below in relation to linked clinical data in 6.5 Data Management). Separate ethical approval will be sought for the CAPTURE research database and bioresource, before anonymised samples will be shared with a third party collaborators for future ethically approved studies. Professor Catherine Smith will act as the data controller for all data stored on CAPTURE. Requests for sample use (and linked clinical data) for Research Ethic Committee (REC) and/or Health Research Authority (HRA) approved studies will be made through a structured, formal process, managed by an internal data access committee. Following an additional review by the independent data access committee, successful applicants may then be given access to specific samples and/or data fields as determined by their study requirements and study approvals.

4.7 Data Analysis Methods

The site and/or laboratory performing the analysis will depend on where the relevant expertise exists. This may be within the group of Professor Catherine Smith, other groups within King's College London, collaborating partners outside of King's College London, and potential future collaborators that may include industry partnerships. Collaborators may be inside or outside of the European Union. No data fields related to patients' BADBIR participation will be shared with external collaborators, in line with our data sharing agreement. All data analysis will be conducted on anonymised data and samples only.

4.7.1 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

4.7.2 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 1000 patients on each drug therapy respectively, with the aim of recruiting up to 9,500 patients 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.

Where a serious adverse event occurs due to the collection of BSTOP related data, such as infection or injury caused by blood extraction, the 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.

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 latest version of the study protocol, along with the latest version of the Patient Information Sheet and Informed Consent Form, will be approved by an Ethics Committee before enrolment of any subjects into the study using that documentation. 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 Anonymisation

Subjects will be assigned an anonymised study ID number to ensure subject confidentiality throughout the duration of the study. The Principal Investigators at each site will be responsible for keeping a Subject Identification Log of all subjects enrolled into the study and their corresponding study number, or will use our database CAPTURE as a log (more detail below).

Anonymised data only will be used in study analyses. Anonymised research data collected as part of the BSTOP study may also be shared with other collaborators which may include industry partners, inside and outside of the European Union, for the purposes of research and analysis only. This will not include data fields from BADBIR. See below (section 6.5) for further information on access to data.

The subjects will be informed that authorised representatives of the Regulatory Authorities, may require access to hospital records relevant to the study, including medical history and identifiable information, for audit and monitoring purposes.

6.5 Data Management

All data will be stored, managed and transferred in accordance with the Data Protection Act, 1998 and updated EU General Data Protection Regulation (GDPR; 2018). The Chief Investigator will have overall control of, and act as the custodian for all data for the full duration of the study.

Study data will either be collected on paper based case report forms (CRFs) and entered on to a secure research database or entered directly onto a secure research database. The database will be password protected and access restricted to named study individuals only. The database used may be one purpose built, developed and maintained by the NIHR Biomedical Research Centre at Guy's and St Thomas's NHS Foundation Trust (GSTT) and King's College London (KCL) known as CAPTURE (ChArting PaTient outcomes Using an online REsource).

CAPTURE is a web-based forms system used to record clinical research data for use in research studies and clinical trials. CAPTURE sits on the GSTT servers behind the NHS firewall and data stored within CAPTURE is afforded the same security controls as any clinical data held within the GSTT servers. CAPTURE will be used by GSTT and KCL staff onsite as well as third-party collaborators. External staff will access the system via the public internet, secured with industry standard SSL and SafeNet 2-factor authentication. Further details of the architecture of CAPTURE and additional CAPTURE specific security measures can be found in the CAPTURE Information Governance Policy.

Identifiable information held on the database will only be accessible by the Chief Investigator and approved delegated members of the study team. The level of data accessed (patient identifiable/anonymised) will be determined by the user's job role and location. All requests for all users will be authorised by Prof

Catherine Smith or a delegated staff member. Access to identifiable data at local study centres will only be granted following additional checks of delegation logs, and Principle Investigator approval. Identifiable data visible to the user at participating centre will be restricted to that from the relevant centre and study.
Paper based CRFs will be stored in a secure locked office at study sites and/or the coordinating centre and will be the responsibility of the principal investigator.

NHS numbers are collected on CAPTURE as unique identifiers. These will not be shared with research partners.

Fulfilling the aim of establishing a critical resource for future use by investigators to improve outcomes in psoriasis, data and samples will be stored for use in further ethically approved psoriasis studies on the secure NHS database, named CAPTURE. Separate ethical approval will be sought for the CAPTURE research database, before anonymised data will be shared with a third party collaborators for future ethically approved studies. The Capture database will be also used for sharing anonymised datasets with a third party collaborators for the purposes of analysis for the BSTOP study under the BSTOP ethical approval. An appropriate collaboration agreement will be executed before study data is shared under the BSTOP study. Professor Catherine Smith will act as the data controller for all data stored on CAPTURE. Requests for data for Research Ethic Committee (REC) and/or Health Research Authority (HRA) approved studies will be made through a structured, formal process, managed by an internal data access committee. Following an additional review by the independent data access committee, successful applicants may then be given access to specific data fields as determined by their study requirements and study approvals. Continued access to identifiable information, as above, would only be granted to members of Prof Smith's direct team for whom it was necessary to carry out their role.

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 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 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

Estimated start date (first patient in) – January 2011

Estimated end date (last patient out) – January 2020

Single sample only patients will only be seen once. Patients participating in longitudinal sampling will be followed up for up to 5 years, or until the patient has completed their involvement in the BADBIR study follow up visits, whichever is longer. Patients in the longitudinal arm who have been consented to ICF v4.1 or earlier may be invited to continue participation according to these updated criteria, following reconsent to ICF v5 or later. Patients in all cohorts who have provided consent to recall may also be invited to attend a further visit(s).

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. Following the end of the study and/or the closure of a study site, archiving of the trial master file will be carried out as per the latest policy published by the lead site and sponsor, Guys & St Thomas' NHS Foundation trust.

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, websites and other media used to disseminate science and in line with standard practice.

7.8 Study Termination

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

8 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)

_____ . 17.07.2019

PROFESSOR. CATHERINE SMITH DATE

CHIEF INVESTIGATOR

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_____ _____

PRINCIPLE INVESTIGATOR DATE

NAME: _____

SITE NAME: _____

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