1 Protocol details

1.1 Protocol title

Biomarkers and Stratification To Optimise outcomes in Psoriasis: a multi-centre, longitudinal, observational cohort study

SHORT TITLE: Biomarkers and Stratification to Optimise outcomes in Psoriasis (BSTOP)

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1.3 Protocol details

Version number 8
Final
Date 02 OCT 2023

2 Signature Page

The Chief Investigator and the R&D (sponsor office) have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol.
The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP, the UK Data Protection Act (2018), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator [Insert name of CI]		17 Jan 2024
	Signature	Date
Sponsor Representative R&D to Add GSTFT	R&D signature not required for non-CTIMP protocols	
	Signature	Date

This Protocol template is intended for use with UK sites only.

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4 List of Abbreviations and Definitions

AE	Adverse Event
AR	Adverse Reaction
BADBIR	British Association of Dermatologists Biologic and Immunomodulators Register
CAPTURE	Charting Patient outcomes Using an online Resource
CI	Chief Investigator
CRF	Case Report Form
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
ICF	Informed Consent Form
IMID	Immune-Mediated Inflammatory Diseases
ISF	Investigator Site File
KCL	King's College London
PBMC	Peripheral blood mononuclear cells
PI	Principal Investigator
PIS	Participant Information Sheet
PSORT	Psoriasis Stratification to Optimise Relevant Therapies
REC	Research Ethics Committee
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TSC	Trial Steering Committee

5 Summary/Synopsis

Title	Biomarkers and Stratification To Optimise outcomes in Psoriasis: a multi-centre, longitudinal, observational cohort study
Protocol Short Title/Acronym	Biomarkers and Stratification to Optimise outcomes in Psoriasis (BSTOP)
Protocol Version number and Date	Version 8, 02 Oct 2023
IRAS Number	71048
REC Reference	11/H0802/7
Study Duration	Start date (first patient in) January 2011 Estimated end date (last patient recruited) – January 2026
Sponsor name	Guys & St Thomas' NHS Foundation trust
Chief Investigator	Professor Catherine Smith
Funder	Psoriasis Association
Medical condition or disease under investigation	Psoriasis
Purpose of research	To better understand disease development, progression and treatment response, and so develop tools to improve outcomes for people with psoriasis.
Primary objective	(i) To identify biomarkers of disease severity, progression and response to treatments (ii) To provide a bioresource for psoriasis research in line with the James Lind Alliance top 10 priorities
Secondary objective (s)	(i) To describe the genetic architecture of psoriasis (all phenotypes) and how it relates to other immune-mediated inflammatory diseases (ii) To identify genetic and mechanistic determinants of disease severity, progression, and response to treatments (including drug-induced remission and recurrence following treatment withdrawal) (iii) To understand genetic and environmental determinants (and associated mechanisms) that trigger disease and fluctuations in disease severity
Number of Subjects/Patients	9500
Study Type	Observational, prospective, longitudinal cohort
Endpoints	**Primary endpoint** Identification of genetic variants associated with response to treatments, disease severity and disease progression **Secondary endpoints** • Change in abundance and activation status of cell types in skin and blood between baseline, day 3, day 14, month 3, month 6 and annually • Change in gene expression in skin and blood between baseline, day 3, day 14 and month 3 of different drugs • Change in abundance and activation status of cell types in skin or blood between baseline, day 3, day 14 and month 3 of different drugs • Change in immune proteins in skin or serum between baseline, day 3, day 14, and month 3 of different drugs

	• Biological sample and data accrual to inform the investigation of the cause, prognosis and treatment outcomes in psoriasis. • Identification of molecular biomarkers for the future stratification and personalisation of medicine and health.
Main Inclusion Criteria	1. Individuals who are able to provide written informed consent prior to performing any protocol-related procedures, including screening. 2. One of the following: i. Adult (16+) with a confirmed diagnosis of psoriasis ii. Adult (16+) with a confirmed diagnosis of psoriasis who is due to start, stop or switch systemic immune-modifying therapy, including those enrolled on BADBIR and/or PSORT D and or other related study. iii. Adult (16+) without psoriasis (healthy control) iv. Adult (16+) with a confirmed diagnosis of an immune-mediated inflammatory disease (IMID) including inflammatory bowel disease, rheumatoid arthritis or other arthritis (IMID control).

6 Introduction

Psoriasis is a common immune-mediated inflammatory disease (IMID) that presents with red painful skin plaques and is associated with multimorbidity and reduced life expectancy. 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[1;2]. Whilst localized, limited disease can usually be managed satisfactorily with topical agents, patients with severe disease often require systemic treatment. This involves either 'standard' systemic therapies, including ciclosporin and methotrexate[3], or biologic therapies, which target cytokines implicated in disease pathogenesis including tumour necrosis factor (TNF) or the interleukin (IL) 17/IL-23 pathway[4]. Small molecule agents inhibiting PDE4 (apremilast) and Janus kinase (e.g. tofacitinib) are also available[5]. Despite the extensive range of available treatments, patients demonstrate high levels of dissatisfaction[6-8], citing inefficacy or side effects as the principal reasons. Inter-individual variability in response and tolerability remain a problem, and the high cost of newer targeted agents add to the already considerable socio-economic burden of disease. Longer term data also indicate a gradual loss of efficacy over time[5,9].

Understanding the molecular determinants of treatment outcome is the first step towards the overall aim of choosing the right drug for each person, first time. A shift away from trial-and-error prescribing and towards intelligent data-driven drug allocation will optimise efficacy, reduce time to remission, avoid treatment switches, drug-related morbidity and improve cost effectiveness. It will inform drug withdrawal and dose minimisation strategies, in addition to drug innovation efforts for effective treatments with minimum off-target consequences. Individuals with psoriasis also bear a substantial risk of psychological, social, and multi-morbidity burden[10]. We know that this burden is associated with more severe disease although access to effective therapies is often delayed with pathways of care largely reactive rather than pro-active. There is thus also a need for biomarkers to enable identification of those most at risk of severe disease, disease progression or multi-morbidity to enable early intervention and reduced disease burden. Finally, we need to better understand the factors that trigger disease and fluctuations in severity, as these may enable disease modification and prevention. These aspects have all been identified as high priority by the Psoriasis Priority Setting Partnership with James Lind Alliance and the Psoriasis Association.

The BSTOP study addresses these important research gaps through large-scale prospectively acquired and deep phenotype data (clinical data and relevant biological samples including skin and blood). Since its inception, the BSTOP study has functioned in conjunction with the British Association of

Dermatologists Biologics and Immunomodulators Register (BADBIR, Ref: 07/MRE08/9), an established, longitudinal study of patients with psoriasis who are receiving systemic and biological therapies[11]. We also work with an expanded range of investigators, research collaborators and industry partners within and outside the UK, including as part of the MRC-funded Psoriasis Stratification to Optimise Relevant Therapy consortium (PSORT, Ref: MR/L011808/1), and European Commission funded consortia (BIOMAP[12] and HIPPOCRATES[13]). Since longitudinal studies involving large-scale data and sample collection are expensive, it is imperative that data captured in BSTOP are accessible and can be utilised to their full potential, allowing research into any aspect of psoriasis. To this end, we aim to link our dataset to other relevant datasets through NHS Digital, facilitating important collaboration with other studies and ensuring the efficient use of NIHR research resources. This is in keeping with both NIHR research objectives and the James Lind Alliance top 10 priorities for psoriasis research[14].

The BSTOP study dataset will also be enriched by a patient-facing self-reporting platform, 'mySkin', launched on 17 June 2023 (REC reference: 22/NI/0193). The aim of mySkin is to better understand inflammatory skin disease onset, progression and treatment outcomes over time, and to develop tools to improve disease outcomes. The study will collect longitudinal patient-reported outcomes, self-taken photographs and self-samples. BSTOP participants who have consented to recall for future studies will be invited to take part, as will future BSTOP participants. Their consent will be sought via the mySkin Informed Consent Form to link their mySkin data to their BSTOP data to validate/supplement self-report data, establish representation of disease severity within the self-reporting population, and address potential reporting bias. Full details of the mySkin study can be found in the mySkin protocol. The mySkin banner and/or flyers can be displayed at BSTOP sites to aid recruitment to mySkin.

7 Study objectives and purpose

Overarching Research Aim

To better understand disease development, progression and treatment response, and so develop tools to improve outcomes for people with psoriasis

Primary Objectives

(i) To determine biomarkers of response to systemic treatments for psoriasis in terms of efficacy and toxicity

Secondary Objectives

(i) To describe the genetic architecture of psoriasis (all phenotypes) and how psoriasis relates to other immune-mediated inflammatory diseases (IMIDs)

(ii) To understand genetic and environmental determinants (and associated mechanisms) that trigger disease and fluctuations in severity

(iii) To identify genetic and mechanistic determinants of disease severity, progression, and response to treatments, including drug-induced remission and recurrence following treatment withdrawal

(iv) To provide a bioresource accessible to investigators to investigate any aspect of psoriasis in line with the James Lind Alliance top 10 priorities for psoriasis research

8 Study design & Flowchart

8.1 Study Design

This is an observational, prospective, cohort study of people with psoriasis investigating determinants of treatment outcomes, disease severity and disease progression.

We will compare the genetic and immune profiles of people who:

(i) have responded to a systemic therapy of interest, where response encompasses measures of effectiveness (response, remission, relapse) and toxicity, compared to relevant comparator psoriasis populations

(ii) develop severe disease compared to people without severe disease

(ii) develop the index morbidity of interest compared to people with psoriasis without the index morbidity, and to other populations with IMIDs, and/or to relevant general populations

8.1 Primary endpoints

The identification of genetic variants (i.e.: genetic biomarkers) that are associated with response to treatments (including drug-induced remission and recurrence following treatment withdrawal), disease severity and disease progression.

8.2 Secondary endpoints

Change in abundance and activation status of cell types in skin and blood between baseline, day 3, day 14, month 3, month 6 and annually in responders, comparing the different drugs with each other.

Change in gene expression in skin and blood between baseline, day 3, day 14, month 3, month 6 and annually in responders, comparing the different drugs with each other.

Change in gene expression in skin and blood between baseline, day 3, day 14 and month 3 of different drugs, comparing (i) responders vs non-responders or (ii) individuals with vs without adverse events or (iii) individuals in remission who experience disease recurrence following drug withdrawal vs those in sustained drug-free remission.

Change in abundance and activation status of cell types in skin or blood between baseline, day 3, day 14 and month 3 of different drugs, comparing (i) responders vs non-responders or (ii) individuals with vs without adverse events or (iii) individuals in remission who experience disease recurrence following drug withdrawal vs those in sustained drug-free remission.

Change in immune proteins in skin or serum between baseline, day 3, day 14, and month 3 of different drugs, comparing (i) responders vs non-responders or (ii) individuals with vs without adverse events or (iii) individuals in remission who experience disease recurrence following drug withdrawal vs those in sustained drug-free remission.

Biological sample and data accrual to inform the investigation of the cause, prognosis and treatment outcomes in psoriasis.

Identification of molecular biomarkers for the future stratification and personalisation of medicine and health.

8.3 Flowchart

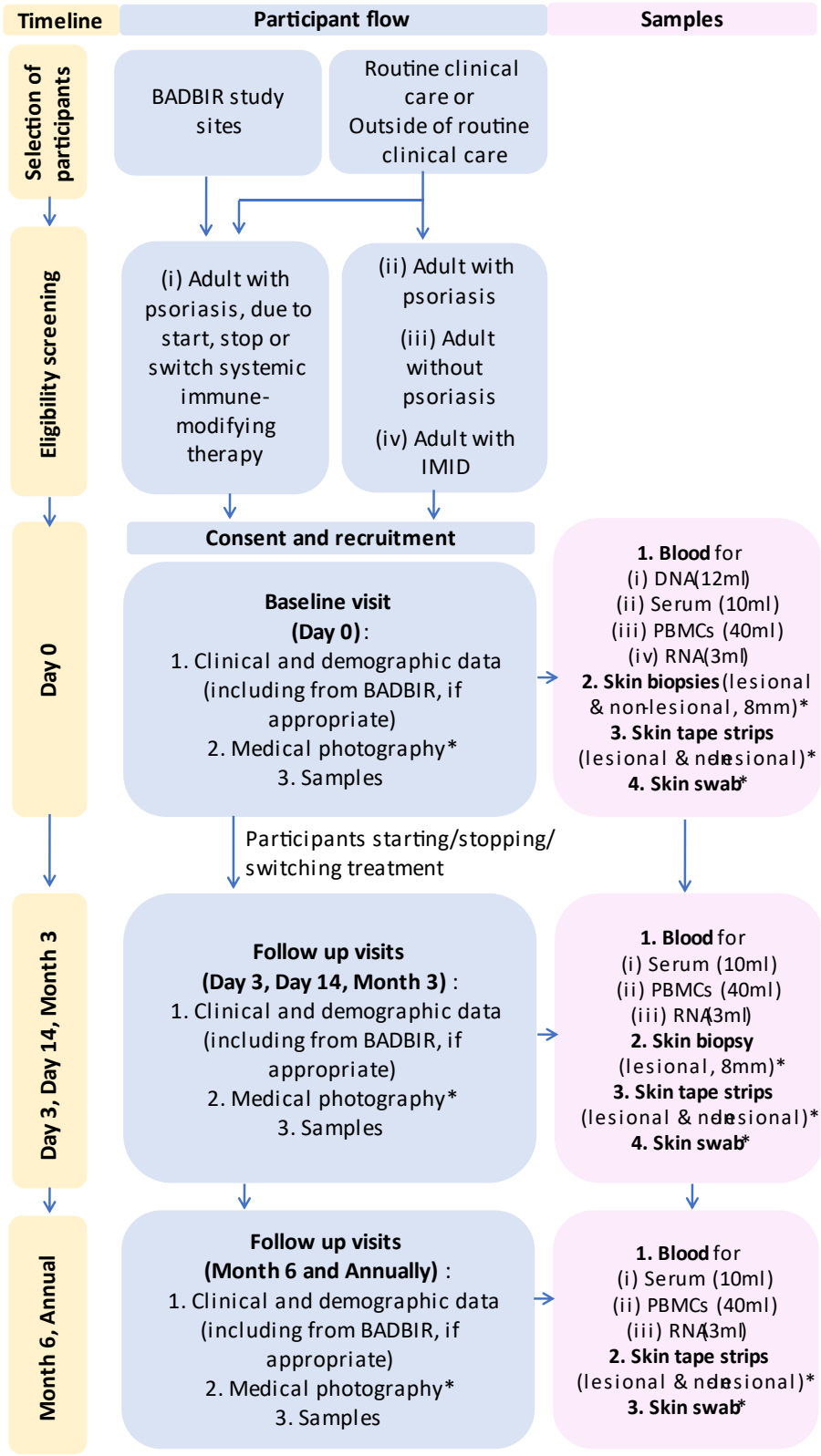

Figure 1: Study flow chart to show study design and flow of participants.

The collection of blood for PBMCs and RNA, skin biopsies, skin tape strips and skin swabs are to be performed at participating study sites that have the appropriate expertise and facilities (see 10.2).
*Optional (the participant can choose to donate any of these).

Baseline	Day 3	Day 14	Month 3	Month 6
✓				
✓	✓	✓	✓	✓
✓				
✓	✓	✓	✓	✓
✓	✓	✓	✓	✓
✓	✓	✓	✓	✓
✓	✓	✓	✓	
✓	✓	✓	✓	✓

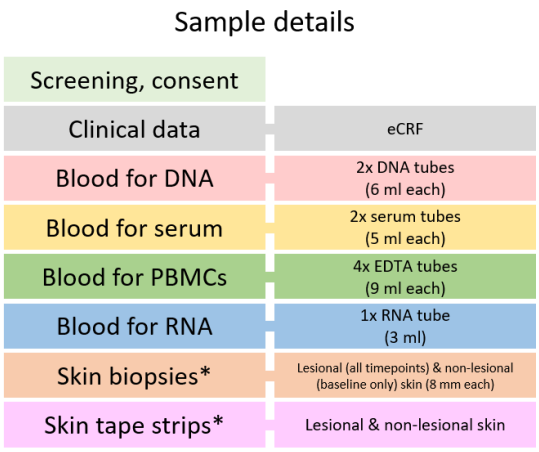

Figure 2: Sample collection overview.
The collection of blood for PBMCs and RNA, skin biopsies, skin tape strips, skin swabs and medical photography are to be performed at participating study sites that have the appropriate expertise and facilities (see 11.2). *Optional samples (the participant can choose to donate any of these optional samples).

9 Subject selection

9.1 Subject inclusion criteria

1. Individuals who are able to provide written informed consent prior to performing any protocol-related procedures, including screening.
2. One of the following (**nb** patients may fall into more than one category):
    i. Adult (16+) with a confirmed diagnosis of psoriasis.
    ii. Adult (16+) with a confirmed diagnosis of psoriasis enrolled on BADBIR and/or PSORT D and/or other related study
    iii. Adult (16+) with a confirmed diagnosis of psoriasis who is due to start, stop or switch systemic immune-modifying therapy
    iv. Adult (16+) without psoriasis (healthy control).
    v. Adult (16+) with a confirmed diagnosis of an immune-mediated inflammatory disease (IMID) including inflammatory bowel disease, rheumatoid arthritis or other arthritis (IMID control).

9.2 Subject exclusion criteria

1. Inability to give written informed consent.

2. Inability to participate in study-specific procedures.
3. Blood transfusion within 4 weeks (where DNA is being secured via whole blood).

10 Study procedures

10.1 Subject recruitment

Participants with psoriasis will be recruited via the following routes:

1. Routine clinical care visits. We will approach eligible patients attending study sites as part of routine clinical care (e.g. during outpatient visits). A member of the research team will approach them and discuss the study with them. They will be provided with the study communication material*.
2. BADBIR study sites. We will approach individuals who are consented to BADBIR at any time and provide the communication material*.
3. Outside of routine clinical care visits. We will identify eligible patients who are due to attend study sites (e.g. via search of new referrals, forthcoming clinic lists, pharmacy database) and provide the communication material*.
4. Existing participants of related research studies who have consented for recall. We will approach individuals with psoriasis who have provided consent to be approached for research in related research studies (for example PsoProtect*Me* (20/YH/0135), PSORT (14/LO/1685)) and provide the communication material*.
5. Routine clinical care settings in primary care. We will promote the study in primary care settings through primary care links. Potential participants identified via health care providers, or self-identified participants with psoriasis will be directed to seek more information via our website and invited to self-refer via the central co-ordinating site. Communication material will be provided with contact details of the nearest BSTOP study site.
6. Outside of routine clinical care settings. We will disseminate details of the study (communication material) via the study website, our Patient and Public Involvement events, collaborating patient organisations such as the Psoriasis Association, The Psoriasis and Psoriatic Arthritis Alliance, and other communication channels including social media*.

*__*Communication material*__ includes an outline study invitation, participant information sheet (PIS) and study team contact details and will be provided in print by hand or electronically (email/text with attachments/via a URL link to our website). The approach (in person or electronically) and the material

(by hand or electronically) will be selected based on whichever is most appropriate for the setting and/or convenient for the patient.

Participants without psoriasis (healthy controls) and participants with IMIDs (IMID controls):

1. Routine clinical care settings. We will approach individuals without psoriasis (e.g. staff members and accompanying friends/family members of patients) and those with IMIDs at study sites and in primary care.
2. Outside of routine clinical care settings. We will disseminate details of the study via the study website and other communication channels such as social media (including social media channels of King's College London and Guy's and St Thomas' NHS Foundation Trust).
3. Existing participants of related research studies who have consented for recall. We will approach healthy controls and individuals with IMIDs who have provided consent to be approached for research in related research studies and provide the communication material.

10.2 Consent

A member of the clinical care team will approach potential participants (see 9.1) and provide them with the communication material, including a study invitation, the participant information sheet and study team contact details, via a letter/email/text, whichever is most appropriate. All potential participants will speak to a member of the study team. This maybe at the same time that they are provided with the communication material or at a future arranged time – depending on the setting and how the individual has heard about the study (see 10.1). Potential participants will be given an appropriate amount of time to consider their participation in the study and the opportunity to ask questions. If they wish to participate, a member of the research team will obtain written informed consent using an electronic consent form (eConsent), which will be stored on the electronic data capture system (see section 16.2), or a paper consent form, which will be kept in the Investigator Site File at the participating site, and the consent process documented in the medical notes. Participants will be notified that they are free to withdraw their participation in the study at any time (see section 15.2).

10.3 Expected duration of study

Start date (first patient in) – January 2011

Estimated end date (last patient recruited) – January 2026

Patients participating in longitudinal sampling will be followed up for up to 5 years, or until the patient has completed their involvement in BADBIR study follow up visits, whichever is longer (see section 10.4.2 for details about longitudinal follow up schedule).

The study may be prematurely discontinued by the Sponsor, Chief Investigators or Regulatory Authority on the basis of new safety information or for other reasons given by the Study Management Committee or ethics committee concerned. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

10.4 Study procedures by visit

10.4.1 Baseline Visit

The baseline (day 0) visit for all participants will take place following written informed consent to participate. Informed consent can be taken on the day of the baseline visit, once participants have been provided with verbal and written study information and adequate time to consider taking part).

The baseline visit will include:

1. Written informed consent
2. Collection of clinical and demographic data (see section 11)
3. Medical photography (optional, to enhance the capture of disease severity)
4. Blood samples (see section 10.2 for details)

   (i) Blood for DNA analysis using standardised operating procedures (SOPs) at participating study sites that have the appropriate expertise and facilities. In exceptional circumstances, where blood collection for DNA is not feasible (such as in the case of a recent blood transfusion), saliva sampling may be collected. A total of 2mls of saliva will be collected as per SOPs.

   (ii) Blood for serum analysis using SOPs at participating study sites that have the appropriate expertise and facilities.

   (iii) Blood for RNA and peripheral blood mononuclear cells (PBMCs) using SOPs at participating study sites that have the appropriate expertise and facilities.
5. Skin biopsy samples (optional)

   (i) Lesional and non-lesional skin (preferred site lower back or buttock, see section 10.2for details).

6. Skin tape strip samples (optional)

   (i) Lesional and non-lesional skin (see section 10.2 for details).

7. Skin swabs (optional, see section 10.2 for details)

10.4.2 Follow up visits (day 3, day 14, month 3, month 6, then annually)

Follow up visits are only routinely required for participants starting, switching or stopping systemic therapies, and at selected sites depending on facilities. These follow up visits are distinct from unscheduled recall/follow up visits (see section 10.4.3)

Follow up visits occur at 3 days, 14 days, 3 months, 6 months and then annually after the start, cessation, or switch of systemic immune-modifying treatment. For participants also enrolled on BADBIR, study teams are encouraged to align BSTOP and BADBIR study visits for patient convenience. A window of +24 hours will be permitted for Day 3 and a window of ±48 hours will be permitted for Day 14 and subsequent visits.

Each follow up visit will include:

1. Collection of clinical and demographic data (see section 11.1)
2. Optional medical photography (to enhance the capture of disease severity)
3. Collection of blood for serum, RNA and PBMCs analysis and/or supplementary DNA, according to standard operating procedures, at participating study sites that have the appropriate expertise and facilities.
4. Optional collection of the following, according to standard operating procedures, at participating study sites that have the appropriate expertise and facilities:
   i. Skin biopsy (lesional skin, matched site to baseline visit biopsy) at day 3, day 14 and month 3
   ii. Skin tape strips (lesional and non-lesional) at day 3, day 14, month 3, month 6 and then annually
   iii. Skin swabs at day 3, day 14, month 3, month 6 and then annually

10.4.3 Unscheduled recall/follow up visits

In some circumstances a participant may need to return to clinic outside of the suggested follow up visits, for instance due to a disease flare or drug adverse event. We may also wish to recall individual participants for additional clinical phenotyping and/or collection of additional samples for further functional studies where mechanisms/biomarkers of treatment outcomes (including emergent adverse events) or disease severity/progression require phenotypic and biological investigation/validation. Recall is entirely voluntary (as stated in the Participant Information Sheet) and the participant will sign a separate line on the Consent Form indicating their agreement to be recalled. This will allow us to contact the participant (only). To recall the participant, a member of the study team will contact the participant by letter/text/phone/email or approach them at their next clinic visit and ask if they are willing to provide further clinical data and samples. It will be emphasised at this point to the participant that participation in further clinical data/sample collection is optional.

Unscheduled/recall visits (maximum 3 unscheduled visits per year) will include the following:

1. Collection of clinical and demographic data (see section 11.1)
2. Optional medical photography (to enhance the capture of disease severity)
3. Collection of **Blood** for serum, RNA and PBMCs and/or supplementary DNA, according to standard operating procedures, at participating study sites that have the appropriate expertise and facilities.
4. Optional collection of any of the following, according to standard operating procedures, at participating study sites that have the appropriate expertise and facilities:
    i. Skin biopsy (lesional and/or non-lesional)
    ii. Skin tape strips (lesional and non-lesional)
    iii. Skin swabs

A maximum of 2 skin biopsies will be collected at any one visit and a maximum of 6 skin biopsies will be collected from any one individual. (including biopsies from scheduled visits, see 10.4.1-10.4.2). A maximum of 100ml of blood will be drawn at any one visit, and a maximum of 500ml of blood will be drawn per year (including blood from scheduled visits, see 10.4.1-10.4.2).

10.4.4 Loss to follow up

If any of the study participants are lost to follow up contact will initially be attempted through the research team. If the lead investigator at the study participating centre is not the participant's usual

clinician responsible for their specialist care, then follow up will also be attempted through this latter clinician. Where possible, information on the reason for loss to follow up will be recorded.

11 Clinical data and biological sample collection

11.1 Clinical data

Clinical data will be collected at baseline and all subsequent follow up visits within the case report form (CRF) including (as appropriate):

1. Demographics e.g. age, sex, ethnicity
2. Psoriasis/IMID details e.g. disease phenotype, date of onset, current and prior treatment including dates, dosing schedules and adverse events*
3. Medical history including co-morbidities, concomitant medications
4. Family history of psoriasis/IMIDs
5. Other environmental variables including smoking, alcohol intake, factors that precipitate flares
6. Patient reported outcomes including dermatology life quality index (DLQI), mental health screens (PHQ-9, GAD-7), EQ-5D, CAGE (in patients who drink alcohol), HAQ (in patients with psoriatic arthritis), brief illness perception questionnaire (BIPQ)*
7. Clinical assessments
    a. General health including weight, waist circumference, height, blood pressure
    b. Disease severity measures including psoriasis area severity index (PASI), physician global assessment (PGA), body surface area (BSA)*
8. Medical photography (optional)*
9. Results of blood tests performed as part of routine clinical care including FBC, creatinine, ALT, AST, lipids, CRP, ESR*

*Not applicable to healthy controls

11.2 Biological sample collection

11.2.1 Blood samples

Peripheral blood samples will be collected using standard NHS protocols at participating study sites that have the appropriate expertise and facilities (see standard operating procedures for sample processing and storage manual). Up to 100ml (6-7 tablespoons) of venous blood will be drawn per visit, according to the study collection strategy (see section 8.3).

Blood sample collection: The following blood samples will be collected:

1. At least 12 ml of blood in EDTA tubes (pink top) for DNA extraction and analysis at baseline only.
2. At least 10 ml of blood in serum tubes (gold top) for serum isolation and serological analysis. This will be collected at baseline, day 3, day 14, month 3, month 6 and then annually.
3. At least 40 ml of blood in Sodium Heparin tubes (green top) or appropriate alternative for immune cell isolation and analysis. This will be collected at baseline, day 3, day 14, month 3, month 6 and then annually.
4. At least 3 ml of blood in dedicated tubes for RNA extraction and analysis. This will be collected at baseline, day 3, day 14, month 3, month 6 and then annually.

Novel methods for sampling blood (e.g. finger prick devices (sourced via NHS procurement), capillary tube sampling) may be used to minimise discomfort and inconvenience, where appropriate. Saliva samples are an option where for logistical or other reasons, blood collection for DNA is not feasible. In this case, 1 x Oragene saliva kit (2ml) from DNA Genotek should be used for DNA extraction.

Blood sample processing: Blood samples will be transferred to King's College London (KCL) for processing and/or storage in accordance with standard operating procedures in the sample processing and storage manual. Processing of samples will be undertaken by suitably experienced personnel in appropriate laboratories of the Sponsor and/or third-party collaborator(s) and/or third-party service provider(s), to be decided by the Sponsor and as further detailed at 10.2.7. Aliquots of immune cells (e.g. peripheral blood mononuclear cells [PBMCs]), serum, DNA and RNA will be stored appropriately and safely. Saliva DNA is stable at ambient temperature and should be returned to the central site via Royal Mail Freepost service.

11.2.2 Skin biopsy samples (optional)

Skin preparation: Participants will be asked to refrain from using topical treatments (except for emollients) at the future sites of biopsy for at least 48 hours before biopsies. All skin biopsy samples will be taken from site-matched areas (preferred site lower back or buttock).

Skin biopsy collection: Skin biopsies will be collected from centres with appropriate facilities in line with the study collection strategy (see 7.3) using standard NHS protocols (see SOPs in the sample processing and storage manual). One site-matched punch skin biopsy (up to 8mm) will be obtained from lesional skin of participants at baseline. For those starting or stopping treatment, or following a skin related adverse event such as paradoxical psoriasis, additional biopsies may be taken at day 3, day 14 and month 3. An additional biopsy may be sampled from non-lesional skin at baseline. Preferable sites of biopsies will be the lower back or buttock area but biopsies may be taken at other sites at the discretion of the investigator and participants, preferably close to the preferred sites. The site of biopsies will be recorded, ideally using a photograph of the site. Sequential site-matched biopsies will be taken with a minimum distance of 2cm between initial and subsequent biopsies.

Skin biopsy processing: Skin samples will be transferred to KCL for processing and/or storage according to SOPs in the sample processing and storage manual. Processing of samples will be undertaken by suitably experienced personnel in appropriate laboratories of the Sponsor and/or third-party collaborator(s) and/or third-party service provider(s), to be decided by the Sponsor and as further detailed at 11.2.7.

11.2.3 Skin tape strip samples (optional)

Study participants will be invited to provide skin tape strip samples at baseline. For those starting or stopping treatment, or following a skin related adverse event such as paradoxical psoriasis, additional biopsies may be taken at day 3, day 14, month 3, month 6 and then annually. If study participants decline skin biopsies, they will still be invited to provide skin tape strip samples.

Skin preparation: Participants will be asked to refrain from using topical treatments including emollients at the future sites of tape strips for at least 48 hours prior to the tape strips. All skin tape strip samples will be taken from site-matched areas

Skin tape strip collection: Tape strip samples will be collected at centres with appropriate facilities in line with the study collection strategy (see 7.3 and SOPs in the sample processing and storage manual). Consecutive D-squame tape strips will be applied topically on the skin for 5 seconds using the D-squame pressure applicator to ensure standardized pressure. The first tape strip will be discarded to eliminate possible contaminants. Subsequent tape strips will be placed in Eppendorfs according to SOPs in the sample processing and storage manual.

Skin tape strip processing: Tape strips will be transferred to KCL and processed and/or stored in accordance with SOPs in the sample processing and storage manual. Processing of samples will be undertaken by suitably experienced personnel in appropriate laboratories of the Sponsor and/or third-party collaborator(s) and/or third party service provider(s), to be decided by the Sponsor and as further detailed at 11.2.7.

11.2.4 Skin swabs (optional)

To assess the skin microbiome, study participants may be invited to provide skin swabs at baseline. For those starting or stopping treatment, or following a skin related adverse event such as paradoxical psoriasis, additional swabs may be taken at day 3, day 14, month 3, month 6 and then annually.

Skin swab collection: Five swabs will be collected at each visit: from non-lesional and lesional areas (adjacent location from biopsies, always collect the non-lesional swab before the lesional one), left antecubital fossa and left volar forearm and a negative control. The skin should not be cleaned prior to sampling, therefore microbiome sampling must be carried out before biopsies and venepuncture. The swab (e.g. Isohelix™) is wet with 2 drops of sterile normal saline and rubbed over a skin area of approximately 4cm^2 with a firm circular motion, 10 times on each side of the swab (once clockwise, and once in the opposite direction), and transferred into a sterile plastic collection tube. The negative control is obtained by holding the swab in ambient air for 5 seconds.

Skin swab processing: Collection tubes will be transferred to KCL and processed and/or stored in accordance with SOPs in the sample processing and storage manual. Processing of samples will be undertaken by suitably experienced personnel in appropriate laboratories of the Sponsor and/or third party collaborator(s) and/or third party service provider(s), to be decided by the Sponsor and as further detailed at 11.2.7.

11.2.5 Possible adverse effects related to sample collection

Based on our longstanding experience with the described routine procedures (11.2.1-11.2.4), we consider the associated risks of adverse events as low. When taking blood samples discomfort, hematoma and infection may occur. Skin biopsies carry the risk of bleeding, discomfort, infection, scarring and dyspigmentation. After injection of local anaesthesia for skin biopsies intolerance

reactions might occur but are very rare. Skin tape strips carry the risk of discomfort and dyspigmentation.

Where an adverse event does occur due to the collection of samples, the Chief Investigator or Principal Investigator at participating sites will report to the main Research Ethics Committee any unexpected and related SAEs in line with the National Research Ethics Service SOP on reporting of SAEs.

11.2.6 Sample handling

All samples will be labelled with a unique study ID, sample ID and collection date. No identifiable documents or labels will be sent with the samples.

11.2.7 Laboratories for sample analyses

The laboratory performing each analysis will be chosen according to where the relevant expertise exists. The chosen laboratories may be those of the study investigators or of participating site(s) or of external collaborator(s) (including industry partnerships) or of service providers, according to the specific expertise developed in each research centre/laboratory; these laboratories may be within or outside the UK. Sharing and use of samples and/or data (including personal data derived from the samples) will be transferred under an appropriate agreement, i.e.:

- a Material Transfer Agreement or Service Level Agreement for transfer of samples to a collaborator or service provider, respectively
- a Controller to Controller Data Sharing Agreement or a Data Processor Agreement for transfer of personal data to a collaborator or to a service provider, respectively (including where personal data will be derived from the samples by the Recipient). Where the recipient of any personal data is outside the UK, the 'restricted transfer' will be made in accordance with the requirements of the Information Commissioner's Office[15].

Sharing of samples with third parties will be in accordance with Participant Informed Consent. Sharing of personal data with third parties will be in accordance with the data privacy notice provisions of the Participant Information Sheet (also see section 17).

12 Outcome measures

Outcome measures include measures of treatment response and disease progression (e.g. requirement for systemic therapy; development of significant comorbidity such as psoriatic arthritis, metabolic syndrome, cardiovascular disease; psoriasis flare). Outcome measures will be defined using continuous or dichotomous measures according to national and international guidelines[4,10], and in line with emergent drug adverse events. For example, indicators of treatment response may include persistence on treatment, ≥ 90% reduction in the psoriasis area severity index (PASI) from commencement of treatment (PASI 90), PASI change over time, physician global assessment (PGA) of clear/nearly clear.

13 End of Study Definition

The date of the last visit of the last participant or the completion of any follow-up.

14 Assessment of Safety

14.1 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. All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

14.2 Ethics reporting

The study will abide by the principles of the World Medical Association Declaration of Helsinki (2013 amendment) and the principles of Good Clinical Practice and in accordance with all applicable

regulatory requirements. This protocol and related documents will be submitted for review to Health Research Authority (HRA) and Research Ethics Committee (REC). The study protocol will not be initiated until it has received the favourable opinion of a REC and the HRA. Subsequent to this, it must also undergo independent review at R&D offices at participating sites. The local R&D office should be sent the appropriate site-specific information form complete with the necessary authorisation signatures, plus any other documentation requested for review. A copy of local Research & Development (R&D) approval should be forwarded to the Study Co-ordinating Centre before the site is initiated and participants recruited.

There are no major ethical issues with this study, as it is observational in nature, embedded in routine clinical care. However, the following points have been considered:

- Medications under observation: It is the treating physician's responsibility to ensure that participants are suitable for the therapy, and that any standard of care treatment or clinical/safety assessments are provided by the patient's clinical team alongside participation in this observational study as per local requirements. The treatment of psoriasis in participants will not be compromised/affected by participation in the study.
- Blood testing: The risks of taking blood include temporary discomfort from the needle in the arm, bleeding, bruising, swelling at the needle site and, in rare instances, infection.
- Other (optional) tests for those who consent:
    - Skin biopsy: Every biopsy carries the risk of bleeding, discomfort, infection and scarring, and separate consent will be taken for this procedure. Local anaesthetic will be used to numb the skin beforehand, and intolerance reactions might occur but are very rare.
    - Tape stripping: this involves several applications of a sticky sellotape to the skin and is not uncomfortable.
    - Skin swabs: this is non-invasive and is not uncomfortable.

14.3 Study Management Committee

A Study Management Committee (SMC) is set up to provide overall supervision for the study on behalf of the study Sponsor and study Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's UK Policy Framework for Health and Social Care Research and the Guidelines for GCP.

The committee will aim to:

a) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress and
b) make recommendations concerning the continuation, modification, or termination of the study.

14.4 Ethics & Regulatory Approvals

The study protocol will not be initiated until it has received the favourable opinion of a REC and the HRA. Subsequent to this, it must also undergo independent review at R&D offices at participating sites. The local R&D office should be sent the appropriate site-specific information form complete with the necessary authorisation signatures, plus any other documentation requested for review. A copy of local Research & Development (R&D) approval should be forwarded to the Study Co-ordinating Centre before the site is initiated and participants recruited.

After the participant has entered the study, the clinician is free to change to an alternative treatment at any stage, if they feel it to be in the best interest of the individual. However, the reason for doing so should be recorded and the participant will remain within the study for the purpose of follow-up and data analysis. Similarly, the participant remains free to withdraw at any time from the study treatment and study follow-up without giving reasons and without prejudicing their further treatment (see section 15.2).

15 Compliance and withdrawal

15.1 Compliance

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.

15.2 Withdrawal

Withdrawal from study participation

Participants can withdraw from active participation in the study at any time with no impact on care. Participants may therefore choose to

(i) Withdraw from further sample collection only or

(ii) Withdraw from further sample AND clinical data collection

Should a participant decide to withdraw from the study, all efforts will be made by the investigator to report the reason for withdrawal as thoroughly as possible. The study investigator or co-investigator may also, at their discretion, withdraw a participant from the study at any time.

Withdrawal of consent for use of samples and/or data

In view of the nature of the study, and planned use for samples and data generated from those samples, participants will be made aware that clinical information, samples and data generated from those samples obtained prior to withdrawal of consent/study participation will be kept by the research team and cannot be withdrawn (redacted).

Withdrawal from study participation for participants consented to previous versions of this protocol

(i) Participants consented to ICF v5 or later

Participants 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.

(ii) Participants consented to ICF v4.1 or earlier

Participants 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 web-based forms/data capture system e.g. 'CAPTURE' . 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.

16 Archiving

Copies of protocols, CRFs, test results, correspondence, informed consent 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.

Research data will be retained intact in an appropriate format and storage facility according to relevant data legislation for a period of 5 years from the date of any publication which is based upon it. On completion of the study and all associated analyses, data will be retained for future use and with consent (see Patient Information Sheet). Where research data is not retained it will be disposed of according to Guy's and St Thomas' NHS Foundation Trust guidelines.

17 Data

17.1 Data Protection

The Chief Investigator will act as custodian for the study data for the full duration of the study. On completion of the study and all associated analyses, samples and data will be retained for future use (see Patient Information Sheet). Data will be handled, managed, and stored in accordance with the requirements of the UK data protection legislation (i.e. the Data Protection Act 2018 and the UK GDPR, as derived from the EU General Data Protection Regulation 2018) and with the requirements of the UK Information Commissioner's Office.

When processing personal data (i.e. collection, recording, organisation, structuring, storage, alteration, retrieval, consultation, use, disclosure, dissemination, restriction, erasure or destruction), the Sponsor will at all times comply with the data protection principles[17], in particular:

Principle 1 - Lawfulness, fairness and transparency

Personal data to be collected for the study is detailed at section 11.1. The participants are advised how their data will be used, and for what purposes, in the Patient Information Sheet. Whenever necessary, including but not limited to the use of any participant personal data for other research purposes by the Sponsor or by third parties, the Sponsor will update the 'Participants' sections of the Study website and provide timely and transparent information outlining the purposes for which their personal data is being used and by which organisations or sectors, and the locations where processing will take place, together with the contact details of the Data Custodian and the Sponsor's Data Protection Officer.

Principle 2 - Purpose limitation

UK GDPR 5 (1b) permits further processing for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes (subject to compliance with other requirements).

Principle 3 - Data minimisation

Personal data will be shared with collaborators and/or service providers only when necessary and will be relevant and limited to what is required to answer the research questions.

Principle 4 – Accuracy

See Section 17.2.3 for audit and quality control measures.

Principle 5 - Storage limitation

See Section 16 for data archiving plans.

Principle 6 - Integrity and confidentiality (security)

All participants will be assigned a pseudo-anonymised study ID. Participant enrolment and clinical/sample data will be held on a web-based forms system used to capture clinical research data for use in research studies and clinical trials (e.g. CAPTURE) and access restricted to authorised study staff only.

Also see detailed measures at Sections 17.2.2 (data security) and 17.2.4 (confidentiality).

Principle 7 - Accountability

Many of the 'accountability' requirements are undertaken at an organisational level, but the Chief Investigator will:

- communicate with the Sponsor's Data Protection Officer (i) to determine if a Data Protection Impact Assessment is required, and (ii) to promptly report any suspected or actual data breaches
- be responsible for setting up and maintaining Records of Processing[18]
- ensure that appropriate contracts are in place before permitting third party access to personal data (except as may be required for regulatory purposes).

In all cases the Chief Investigator will comply with the Sponsor's organisational policies and procedures relating to data protection and will consult with and involve appropriate offices of the Sponsor, as required by those policies and procedures.

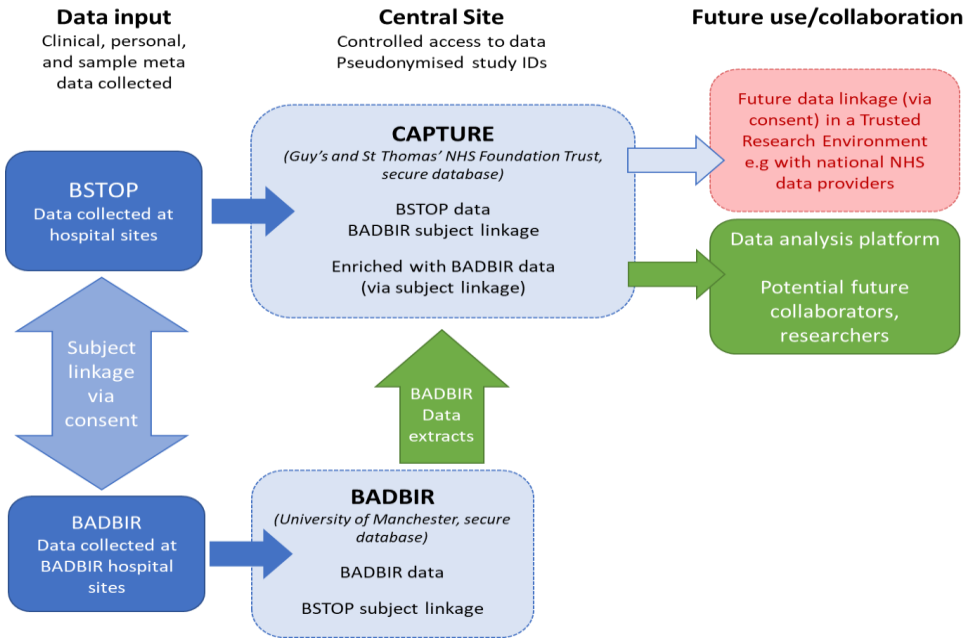

Figure 3: Data flow

17.2 Data Management

17.2.1 Case Report Form

Study data will be entered directly onto the web-based forms system (i.e. electronic case report form, eCRF) approved for use in research studies and clinical trials. Paper-based case report forms (CRFs) will be used if the eCRF is unavailable and data subsequently entered onto the web-based forms system when available. Where paper-based CRFs are the source, these will not be destroyed once

reconciled with the eCRF. The CRF/eCRF will include fields relating to variables including demographics (e.g. age, sex, ethnicity), psoriasis/IMIDs (e.g. date of onset, current/prior treatment, severity), medical history (e.g. comorbidities, concomitant medications), family history, smoking/alcohol intake, patient reported outcomes (e.g. dermatology life quality index) and skin examination findings (see 10.1). Primary source data will be collected through direct eCRF data entry by a clinician or nurse at point of care (hence eCRF can be source data) or through paper CRFs; information will be sourced directly from patients, electronic/paper participant questionnaires and medical notes. All mandatory and marked as 'required' fields on the eCRF must be completed within 21 days of original data collection.

All photographic images are stored securely and processed in accordance with the Data Protection Act 2018. All images will remain strictly confidential and access to information will be restricted at all times to researchers with clear purpose to access it.

All study data will be pseudo-anonymised by participant study ID. Enrolment data containing patient identifiers and any contact information will be collected and held separately on GSTT servers. Study participation will be recorded in the hospital patient medical record and in a separate secure site file that will contain patient identifiable data with the pseudo-ID study number along with confirmation of consent. If the eCRF is temporarily unavailable, alternative data entry on paper will be possible, and these data will be transcribed by the study team at the earliest opportunity.

Exceptional circumstances: In case a face-to-face visit cannot be arranged at site, we allow data collection over the phone, via video calls/virtual visits and also by mail/email. The method of the data collection has to be written in the medical notes alongside the name of the staff member who collected the data. The answers given to the questionnaires can also be collected remotely, as described above, by the local study teams and transcribed into the eCRF.

17.2.2 Data security

The study data will be protected by several means keeping data secure and accessible only to appropriate personnel. Access to identifiable data at local study centres will only be granted following additional checks of delegation logs, and Principal 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. Photographs will be saved on a secure NHS database within Guy's and St Thomas' NHS Trust (GSTT). If photographs are taken at peripheral sites, they will be transferred via secure nhs.net email and saved onto the NHS database within GSTT. Clinical and sample data will be entered onto a web-based forms/eCRF system used to capture clinical research data for use in research studies and clinical trials such as 'CAPTURE' (ChArting PaTient outcomes Using an online REsource). CAPTURE has been developed by the NIHR Biomedical Research Centre at GSTT and King's College London. CAPTURE sits on the GSTT servers behind the NHS firewall and data stored within CAPTURE is therefore afforded the same security controls as any clinical data held within the GSTT servers.

Personal information collected within CAPTURE using the eCRF that could identify individuals will remain strictly confidential. Access to the information will be restricted at all times to approved delegated members of the research team with clear purpose or need to access it. All requests for all users will be authorised by Prof Catherine Smith or a delegated staff member. All data held within CAPTURE is processed in accordance with the Data Protection Act 2018 and UK GDPR.

CAPTURE is built on a number of established technologies:

- **Microsoft SQL Server 2012 R2** hosts the GSTT CAPTURE database. This includes the tables storing the data, and a number of stored procedures to get, set and process data using custom business logic.
- **K2 Blackpearl** provides a data abstraction layer to translate between logical 'Smart Objects' and SQL tables and stored procedures. Smart Objects are used in the forms to get and set data.
- **K2 SmartForms** is used for the user interface and data capture forms.
- **SharePoint 2013** (https://collaborate.gstt.nhs.uk) is a fully supported technology stack already live in the Trust. It is responsible for hosting SSRS reports to be presented through the CAPTURE front-end, and can also be used to host relevant documents, training videos etc.

CAPTURE will be used by GSTT/KCL staff members onsite as well as third-party collaborators. Third-party collaborators will only have access to de-identified data. Security to the application is managed at a number of different layers.

- **Web Application Proxy**: In order for users to access the system over the internet, CAPTURE is published through the DMZ Web Application Proxy (WAP) gateway. This is a secure way of publishing web-based content out over the internet. Any request for https://capture.gstt.nhs.uk

will need to be authenticated – and the WAP layer depends on internally managed ADFS servers for authentication. This layer is owned and managed by the IT Infrastructure team.

- **ADFS & SafeNET 2-Factor Auth**: When accessing CAPTURE internally on the GSTT network, each user authenticates against ADFS, supplying their normal GSTT credentials to be authenticated against the Trust Directory. All external user accounts will be created and managed in a separate Active Directory. The external directory is also supported by the Service Desk. Any member of staff accessing CAPTURE externally, or a non-GSTT staff member accessing CAPTURE will also need to authenticate via SafeNET 2-factor authentication. This is a fully supported solution implemented by GSTT. Any user wishing to access the system externally will need to be enrolled on SafeNET and supplied with a token. They then connect that token to the SafeNET mobile app on their personal smartphone device. When logging in they supply their account credentials along with the SafeNET "OTP" (One-time-passcode), given to them via the app. This ensures that even if a malicious user is able to gain access to a staff member's username and password, they will not be able to gain unauthorised access to CAPTURE.

17.2.3 Data audit and quality control

Central auditing of data quality and completeness will be undertaken by a dedicated Data Manager. Any suspect data will be returned to the site in the form of data queries, electronically generated by the Study Co-ordinating Centre. Sites will respond to the queries providing an explanation/resolution to the discrepancies. Appropriate corrections will then be made on the central database.

17.2.4 Confidentiality

Data will be stored in accordance with the Data Protection Act 2018 and the UK General Data Protection Regulation (GDPR). Please also see section 17.1 for details on data protection. Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. The Study Co-ordinating Centre will preserve the confidentiality of participants taking part in the study. Identifiable data may also be used by the site investigators or members of the central study team to contact patients willing to be invited to partake in further research or to reach those lost to follow-up or for whom data is missing only where participants have consented to this. All CRFs and study data will be archived onto an appropriate media for long-term accessible storage (see section 16).

17.2.5 Data linkage to national healthcare data providers

It is recognised that there is potential for participants to be lost to follow-up in the mid to long term or for events to be missed during the data collection process. To mitigate against this risk, the study will link data to relevant datasets held by certain national providers of healthcare data for long term follow up and health economic research. These include Hospital Episodes Statistics (HES), mortality, Clinical Practice Research Datalink (CPRD), and NCRS (National Cancer Registry Service) such as by NHS Digital in England, for long term follow up. These data will supplement that acquired via the dermatology team and provide a more comprehensive picture of each participant's health. Personal identifiable data (PID) will need to be used for this purpose; these data will be encrypted and stored, and only the minimum amount of identifiable data will be used as sufficient to provide a robust linkage, often only NHS number (or equivalent outside the UK), date of birth, and postcode, avoiding patient name where possible, being transferred to the relevant organisation for the purpose of linkage. The linkage will occur in a highly secure data environment (i.e. Trusted Research Environment) and only de-identified data will be returned. Although this linkage will not happen immediately, consent of all participants will be sought on study entry.

17.2.6 Data linkage to BADBIR

Subject to participant 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 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 UK General Data Protection Regulation), who then use this to identify the patient records to be sent to the BSTOP team (see Figure 4).

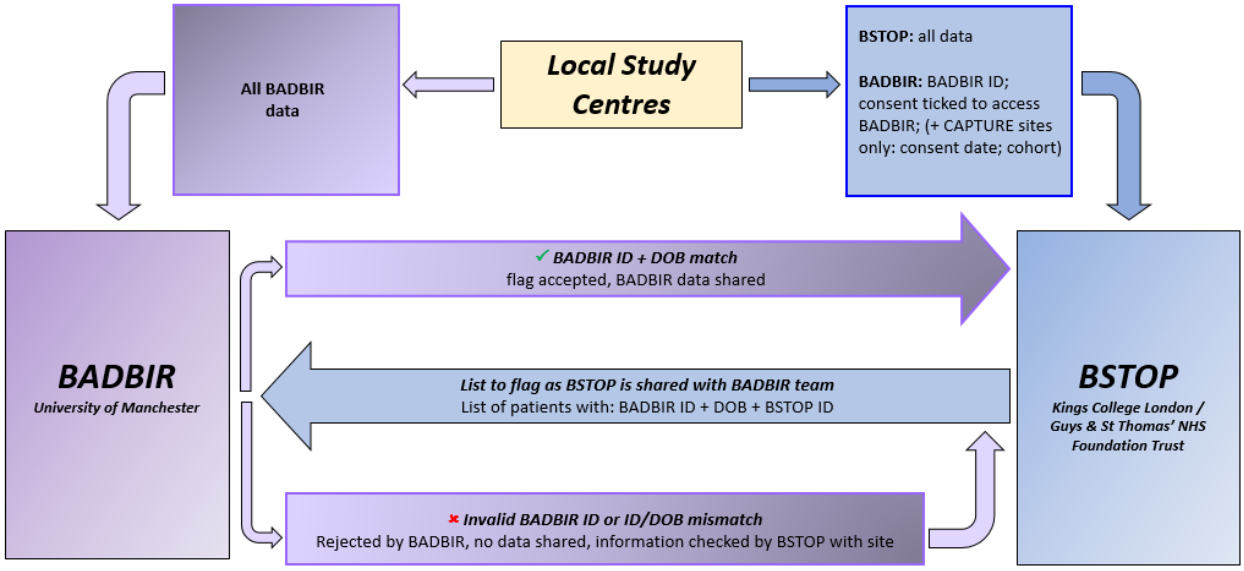

Figure 4: BSTOP/BADBIR data linkage

17.2.7 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.

17.2.8 Data linkage to mySkin

BSTOP participants who have consented to be contacted about future studies may be invited to participant in mySkin. Individual level data from BSTOP will be linked to the participant's mySkin data to enhance the research value of the datasets. Personal identifiable data will need to be used for data linkage; these data will be encrypted and stored, and only the minimum amount of identifiable data will be used as sufficient to provide a robust linkage, often only NHS number (or equivalent outside the UK), date of birth, and postcode, avoiding patient name where possible, being transferred to the relevant organisation for the purpose of linkage. The linkage will occur in a highly secure data environment (i.e. Trusted Research Environment) and only de-identified data will be returned.

17.3 Data monitoring

Monitoring includes the verification of data using source data (e.g. health care records) 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 employ a team of clinical research monitors 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.

18 Statistical considerations

18.1 Sample size calculation

As indicated in 18.2, samples and data generated will support a number of analyses and related research questions. The overall sample size is based on results from genome-wide association studies[19] that demonstrate that most complex traits have some genes of small effect require sample sizes of at least 1000. We aim to collect a minimum of 9,500 patients to the study. The study size and recruitment target may be revised depending on the outcome of ongoing analyses to explore determinants of treatment outcome.

18.2 Analysis

Blood samples (see section 11.2.1) will be analysed as detailed below and in the SOPs in the sample processing and storage manual:

- DNA and RNA will be isolated and used for further molecular analysis including, but not limited to DNA sequencing/genotyping (e.g. genome-wide association studies), RNA-sequencing, RT-PCR, epigenetic analysis.
- Immune cells will be analysed using, but not limited to: single cell RNA sequencing, single cell combined transcriptome and surface proteome analysis (CITE-seq), antibody staining, flow and imaging flow cytometry. Immune cells will also be used for *ex vivo* functional experiments and further molecular biology assays.

- Serum will be prepared for the analysis of analytes including, but not limited to drug levels, anti-drug antibody levels, proteomic and metabolomic analysis.
- Proteins will be extracted and used in molecular biology assays such as western blot, proteomics and metabolomics.

Skin biopsy samples (see section 11.2.2) will be profiled using, but not limited to: single nuclear/cell RNA sequencing, spatial transcriptomics, RNAscope, immunostaining and confocal microscopy. Further biological analysis will also take place including epigenetics, proteomics and metabolomics.

Protein will be extracted from tape strip samples (see section 11.2.3) and skin swabs (see section 11.2.4) and used for further analysis including, but not limited to proteomics and metabolomics.

BSTOP data will thus support a range of research projects addressing a series of linked research questions. Consequently, statistical analysis details will vary based on the nature of each specific research project. Analyses will typically study the relationship between an exposure and an outcome of interest, which may include psoriasis susceptibility or severity, quality of life, development of comorbidities, or response to medication (both effectiveness and adverse events). Projects making use of the BSTOP resource will generally assess the role of molecular measures (such as genotype) as exposures or as modifiers of other exposures. This may be done in a hypothesis-driven way (such as assessing genetic variants in specific genes highlighted in other work) or a hypothesis-free way (such as genome-wide association studies). In either case, researchers applying to use BSTOP data will be required to demonstrate to the steering committee a robust statistical plan based on up-to-date methods. Typical analysis approaches are expected to employ basic parametric/non-parametric hypothesis testing and linear or logistic regression approaches, potentially including interaction tests. More sophisticated modelling approaches may be warranted for complex analysis, including prediction modelling approaches, particularly where longitudinal outcomes are under study. Due attention should be given to the risk of bias and confounding, and appropriate measures employed to mitigate against this. Users of BSTOP data will be encouraged to seek independent datasets in which independent replication of results can be undertaken, and the steering committee can provide advice regarding suitable external data sources. The steering committee will also require that publications based on BSTOP data draw conclusions that are directly supported by correct interpretation of statistical findings.

19 Financial Aspects

The study is funded through a grant from the Psoriasis association (reference: RG2/10: RG2/10). Individuals who participate in this study will be reimbursed the cost of their travel if they attend study visits outside of their routine clinical care. They will also receive up to £60 per visit if they donate skin biopsies or up to £30 per visit if they donate tape strip samples.

20 Reporting and dissemination

It is intended that the results of the study will be reported and disseminated widely to all stakeholders through international clinical and scientific conferences, in peer-reviewed scientific journals, the study website, engagement with the public and patient community (including Psoriasis Association). All transcriptomic data will be deposited in public repositories (e.g. Gene Expression Omnibus, Array Express) together with relevant meta-data. Data objects will be provided for re-use by researchers, including through freely accessible browsable web portals. Summary statistics for genetic and flow cytometry studies will be included in publications.

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Appendix A

Genomics profilin (genotyping/GWAS)
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Sanquin (for Drug level/anti-drug antibody evaluation)
Sanquin Diagnostic Services
Biologicals Laboratory
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Viapath (for Methotrexate polyglutamate and other analyte evaluations)
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Genomics UK (for Transcriptomics)

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