British Association of Dermatologists Biologics and Immunomodulators Register

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1. Background

Biologic interventions using highly specific immuno-modulatory agents represent a rapidly developing therapeutic approach to the treatment of patients with moderate to severe psoriasis, especially those in whom other agents have failed, are contra-indicated or are for other reasons unsuitable. The scientific basis, mode of action, effectiveness and safety of these interventions have been more rigorously tested than many prior systemic psoriasis therapies but the initial evidence is based on short-term randomised clinical trial interventions, commonly 3 – 6 months. However psoriasis is generally a lifelong illness, most commonly starting before 40 years of age and often presenting initially in childhood or early adulthood. Patients with severe disease are known to have a significantly increased mortality, particularly from

cardiovascular disease (Mallbris et al.;Wong et al.;Gladman et al.). They tend to require interventions over long periods of their life and many of these expose them to toxic and potentially fatal side effects. For photochemotherapy this includes squamous carcinoma and melanoma; for methotrexate, haematopoietic failure, cirrhosis and pulmonary fibrosis; and for ciclosporin, renal impairment hypertension and its consequences. Paul et al. noted a doubling of the incidence of malignancies in 1252 patients treated with ciclosporin due to a higher (six fold) incidence of squamous carcinoma, particularly in patients treated with ultraviolet A combined with psoralen (PUVA) and more than two years of ciclosporin (Paul et al.). With acitretin there may be the development of skeletal hyperostosis, hyperlipidaemia and its consequences, and hepatotoxicity. Side effects such as nausea, vomiting, headache, hair loss, myopathy etc. can prevent the use of an agent in some patients. The long term effects and relative risks with each of the modalities or combinations of these modalities are poorly studied and poorly understood.

Retrospective cross sectional studies have been carried out in large populations of patients with severe psoriasis. A cohort of 8991 patients hospitalised for psoriasis (Mallbris et al.) showed that patients with severe disease, as indicated by frequent admission and earlier age of onset, is associated with an increased risk of cardiovascular death standardised mortality rate (SMR) 2.62; 95% confidence interval (CI) 1.91-3.49). Olsen (Olsen, Moller, and Frentz) reported on 6910 patients with psoriasis and found an increase in cancer of the larynx relative risk (RR) 2.8) and pharynx (RR2.9) in men and colon RR (1.6) and kidney (RR 2.3) in women. In a community-based study of more than 100,000 people aged over 65 years, Gelfand (Gelfand et al.) found there to be an increased incidence of lymphoma amongst the 2718 patients with psoriasis (Relative rate 2.95; CI 1.83-4.76): only 1.5% of these patients received ciclosporin and the cohort pre-dated the widespread use of this drug, and the finding pertained even when methotrexate patients and those developing mycosis fungoides were excluded. Boffetta (Boffetta, Gridley, and Lindelof) reported increased cancer risks in a cohort of 9773 patients with psoriasis standardised increased risk (SIR) 1.37; 95% CI 1.28 – 1.47), most notably squamous carcinoma of the skin (2.64), vulva (3.24) and penis (4.66). Interestingly, malignant melanoma was reduced in incidence (SIR 0.32; 95% CI 0.10-0.74). In addition several malignancies associated with smoking and alcohol was increased. A similar Finnish study by Anna Hannuksela-Svahn et al (Hannuksela-Svahn et al.) examining 5687 patients who had been hospitalised for psoriasis revealed an increased incidence of Hodgkin's disease (RR 3.3; CI 1.4-6.4) and squamous carcinoma of the skin (SIR 3.2; 95% CI 2.3-4.4), non-Hodgkin's lymphoma (SIR 2.2; 95% CI 1.4-3.4) and laryngeal carcinoma. Melanoma incidence was reduced (SIR 0.8; CI 0.3-1.6). Margolis (Margolis et al.) studied 1101 patients with severe psoriasis requiring second line therapy and 16519 patients with less severe disease. They used patients with severe eczema, hypertension or organ transplantation as controls. They found a similar incidence of cancer in severe psoriasis patients to that found in the organ transplants (RR 2.12; 95% CI 1.8-2.5) with males and older patients having the greatest risk. The risk ratio for lymphoma was 7.95 (95% CI 4.94-12.79). Non-melanoma skin cancer accounted for most other malignancies in their patients but the sample was of insufficient power to compare differences between treatments. The increased risk in the

non-severe psoriasis patients was only slightly increased (RR 1.13; 95% CI 1.03-1.25). Whether these effects are a consequence of disease severity or the use of therapies cannot be ascertained.

Excess mortality related to alcohol and smoking is also found to be associated with severe psoriasis (Poikolainen, Karvonen, and Pukkala). Overall SMR was 1.62 (95% CI 1.52 –1.71) for men, and for women 1.54 (95% CI 1.43-1.64). For causes related to alcohol the SMR for men was 4.46 and for women 5.6. Similar ratios have been found for patients with psoriatic arthritis (SMR 1.59 for males and 1.65 for females) (Wong et al.). Potentially, disease modification can have beneficial effects on disease associated co-morbidity. This has been established for low dose methotrexate (Prodanowich et al.) and for TNF blockers in rheumatoid arthritis (Jacobsson et al.)

Thus psoriasis itself is associated with health risks that may relate to disease severity and may alternatively be modified by interventions with immunosuppressive and UV based therapies. The disease is a long term condition for which optimal long term management has little evidence to guide the clinician.

We do not know whether powerful but toxic interventions lead to a net benefit or a net adverse effect for patients.

2. Rationale for the Establishment of a Biologic Interventions for Psoriasis Register

The primary purpose of establishing a biologics registry for psoriasis was to follow a large cohort of patients treated with biologic agents so that their long-term safety could be monitored. These long-term safety data cannot be determined from short-term clinical trials in selected patients. A subsidiary aim was to collect information on their long-term efficacy.

Eleven originator biologics are currently licensed for treatment of psoriasis and approved by NICE. These comprise four inhibitors of TNF (Cimzia, Enbrel, Humira, Remicade), three IL-17A inhibitors (Cosentyx, Kyntheum, Taltz), three IL-12 inhibators (Ilumetri, Skyrizi, Tremfya) and one IL12/23 p40 inhibitor (Stelara). As the patents on these molecules expire, biosimilar agents are being developed, and currently biosimilars of adalimumab, etanercept and infliximab and approved in the UK and ROI are in clinical use. Other biologic agents are being evaluated for psoriasis (e.g. bimekizumab) and if these are licensed they could be integrated into the register. Biologic agents are generally free from the traditional end organ toxicities of existing systemic agents but have other common side effects such as infusion reactions, injection site reactions and development of antidrug antibodies.; additional rare side effects include serious infection e.g. tuberculosis, cardiac failure and demyelinating disease. They offer considerable benefits in safety and quality of life for those with moderate to severe psoriasis but

questions remain regarding long-term safety, safety in particular circumstances (e.g. pregnancy and childhood), optimal treatment sequence, relative drug survival, and the use of co-therapies Although some of these questions might be answered by carefully designed randomised controlled trials, there will inevitably be many uncertainties about the "real world" use of these therapies and much is being learned from registries. To date BADBIR has published, in the scientific literature, analyses of the demographics of patients receiving systemic and biologic treatment in the UK and Republic of Ireland, the frequency of associated co-morbid diseases (Iskander *et al.* 2015), the factors influencing treatment selection (Davison *et al.)*, drug survival of first biologic (Warren *et al.*), and the impact of treatment on health-related quality of life (Iskander *et al*. 2017). Comparable registries have been set up for biologic treatment of psoriasis and other immune-mediated inflammatory diseases. In Europe, several of these registries are affiliated to PSONET to facilitate collaboration, for instance to investigate rare but potentially important side effects that are beyond the power of individual country registries to identify, and to replicate observations between cohorts.

2.1 Rationale for the inclusion of children Use of Biologic Therapy and Conventional Systemic Therapy in Children

Etanercept (Enbrel) was the first biologic licensed for use in children with plaque psoriasis. In February 2015, the European Medicines Agency (EMA) granted a positive opinion for Humira (adalimumab) for the treatment of severe chronic plaque psoriasis in children and adolescents from four years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies. However, a recent survey (Lam et al.), of all dermatologists in the UK undertaken by the BAD revealed variation in how paediatric patients with psoriasis are managed, with ustekinumab and with conventional systemic treatments also being used. This survey indicated that the numbers of children (the majority were aged 8 years or over) currently being treated are small relative to the numbers of adults.

2.2 Importance of Long-term Safety and Efficacy of Biologic Therapies in Children with plaque psoriasis

To date, there has been very little published on the "real-world" safety and effectiveness of etanercept or other biologics in children with psoriasis. Possible malignancy risk is likely to be over a much longer time frame than any currently reported safety follow-up studies. Thus, there is a need for ongoing formalised study of children receiving new therapies beyond that of the short-term clinical trial, such that this risk can be evaluated. Therefore, it remains important that the long-term safety is evaluated in this group as the combination of exposure to immunosuppressive therapy on an immature immune system and a potentially high lifetime exposure (due to the chronic nature of the disease) may result in a different safety profile than that seen in adults and potentially place them at a higher risk. In addition to specific issues around safety, there are the additional challenges of understanding the effects of cytokine blockade in children as they grow, develop and mature into adults. As psoriasis is a lifelong disease it

is more prudent to incorporate this relatively small group of paediatric of patients within BADBIR as it allows for their seamless follow up as they move into adulthood

2.3 Rationale for the inclusion of a third cohort of non-biologic

At its inception, BADBIR was designed to compare biologic agents with the standard systemic treatments that were in clinical practice at that time (2007). These systemic treatments consisted principally of methotrexate and ciclosporin, and also acitretin, fumaric acid esters, hydroxyurea and PUVA. Most recently, new non- biologic systemic therapies (small molecule immunotherapies) have been licensed or are in late phase development for the treatment of moderate to severe psoriasis. These include apremilast, dimethylfumarate and Janus kinase inhibitors. The place of these small molecule inhibitors in the therapeutic pathway is uncertain, but in UK clinical practice they are generally considered after standard non-biologic systemic therapy with similar indications for their use as biologic treatments. This is a diverse group of treatments but collectively their expected long-term safety and efficacy is likely to be significantly different to the biologic agents. For this reason, a third cohort will be created to encompass these drugs.

3. Methods

3.1 Aims

The primary purpose of establishing a biologics register for psoriasis was to ascertain whether there is an importantly increased risk of serious adverse events following the introduction of these agents in the treatment of psoriasis compared to that expected from a conventionally treated cohort with comparable disease severity. This assessment includes potential adverse effects, which have not been detected in the relatively short-term clinical trials and those which are theoretically or currently perceived as important. Specifically this includes cancer especially lymphoma, non-melanoma skin cancer especially squamous cell carcinoma, demyelinating disease and tuberculosis. A further aim is to ascertain the relative long-term safety and efficacy of novel non-biologic small molecule systemic therapies.

A subsidiary aim will be to collect information on the long-term efficacy of these therapies. A number of subsidiary questions will also be addressed which include the evaluation of differences between these agents, multiple agents concurrently or in sequence in terms of serious adverse effects.

Further, it is proposed that the register will seek to identify all available data on patients who become pregnant on treatment and to follow up the outcome of those pregnancies.

The BADBIR will also correct for the influence of potential confounders on these outcomes such as psoriasis severity, alcohol and cigarette smoking; non-biologic concomitant or previous therapy; and phototherapy.

This initial proposal is based on outcomes to be ascertained within 5 years of start of treatment though it is accepted that longer term follow up may be required for serious adverse events with a greater latency.

The results will inform clinical practice for long-term management of this chronic, often lifelong disease.

3.2 Design

This is a prospective cohort study consisting of three cohorts comparing patients treated with biologic interventions, small molecule immunotherapies and a comparator group with similar disease characteristics but exposed only to traditional non-biologic systemic therapies. The comparator group includes patients treated with PUVA, methotrexate, ciclosporin and acitretin. The protocol will be submitted for MREC approval. Analysis will take into account switching between the cohorts.

The register was initially modelled on the existing British Society for Rheumatology Biologics Register, BSRBR, and co-located at Manchester University. Staff of the BSRBR will be partners in running this new register. BADBIR will promote registration of biologic therapies, small molecule therapies and of controls to all dermatologists prescribing these interventions on all patients they treat that satisfy the inclusion criteria and that consent to take part. The register aims to recruit all patients receiving each agent until the required cohort size has been attained. Numbers required need to be achievable and sufficient to enable worthwhile comparisons to be made. It is anticipated that 2000-4000 will be required in each biologic and small molecule intervention. In order to account for the smaller number of patients exposed to each agent than originally anticipated, recruitment to other agents can be extended to 6000 patients. The total for the conventional cohort will continue past 4000 to help provide a more contemporaneous comparison group for biologic cohort patients recruited in the later years of the study. A maximum target for the conventional cohort will be 7000.
It is recognised that recruitment may be affected by external factors such as:

1) NICE technology assessment
2) NICE indicates the need for pharmacovigilance and recommends patients are registered in this registry.
3) Funding by NHS
4) Uptake by prescribing dermatologists
5) Local issues

These external factors contributed to the discontinuation of recruitment to Remicade (infliximab) on 31st July, 2013, to Enbrel (etanercept) in July 2016 and to Humira (adalimumab) in July 2019 as the predicted cohort numbers were not achieved.

Following registration, for the duration of the study, BADBIR will approach the dermatologists to update the records of all patients whether or not they continue on therapy. This will be captured primarily as

web-based data entry. Dermatologists will be able to view data on their patients and add to this without unnecessary repetition. Where responses from physicians are delayed there will be repeated reminders and phone calls if necessary to ensure the most complete data possible is obtained.
Data completed directly by participants are also collected, including questionnaire and lifestyle information. Data can be collected at outpatients clinic appointments or entered directly by participants to a web-based application. Study end is defined as when the last participants have completed their final visits.

With support of the BAD, external validity will be maintained by urging involvement of all dermatologists in the registration process. BAD guidelines and guidance from NICE will all state that patients treated with biologic or new small molecule therapy should be registered. Failure to do so can be construed as not complying with normal clinical practice.

The study will be restricted to the United Kingdom and the Republic of Ireland and will be co-ordinated by a steering group acting on behalf of the BAD.

3.2.1 Linkage to National Healthcare Data Providers

It is recognised that there is potential for patients to be lost to follow-up or for events to be missed during the data collection process To mitigate against this risk, the study will link to relevant national providers of healthcare data (e.g. NHS Digital in England) to receive information in three areas:

- Mortality
- Malignancy
- Inpatient hospital admissions

This data will supplement that acquired via the dermatology team and provide a more comprehensive picture of each participant's health. Patient identifiable data (PID) will need to be acquired from the dermatology team for this purpose. All PID will be encrypted and stored at University of Manchester and will only be transferred to the relevant organisation for the purpose of linkage. When formal follow-up of the last patients entered in the register is complete, BADBIR will continue to link the register to the national providers of healthcare data. Patient data will need to be acquired and stored with patient specific information. This will be pseudonymised (e.g. patient number) to protect confidentiality.

3.2.2 Biologic Exposed cohort

Inclusion criteria

1. Patients commencing or switching treatment with a biologic agent in the previous six months for their psoriasis.

or Biologic-experienced patients commencing or switching to new non-biologic small molecule immunotherapy in the previous six months for their psoriasis

2. Willingness to give informed consent for long term follow-up and access to all medical records **(**if patient is under the age of 16, there must be willingness from a parent / guardian to provide this consent. The patient must also provide separate assent).

To reduce bias between this and the active intervention group BADBIR will also collect at baseline the reasons for treatment with the chosen agent, whether the patient is either intolerant or contraindicated or failed to respond to other therapies.

3.2.3 Non-Biologic Small Molecule Immunotherapy Exposed Cohort

Inclusion criteria

1. Patients commencing or switching treatment with a non-biologic small molecule immunotherapy in the previous six months for their psoriasis

2. Willingness to give informed consent for long-term follow-up and access to all medical records **(**if patient is under the age of 16, there must be willingness from a parent / guardian to provide this consent. The patient must also provide separate assent).

Exclusion criteria

Patients must never have been exposed to biologic therapy
To reduce bias between this and the other enrolled groups, BADBIR will also collect at baseline the reasons for treatment with the chosen agent, whether the patient is either intolerant or contraindicated or failed to respond to other therapies.

3.2.4 Traditional Systemic Therapy Comparator cohort

Many patients with similar disease severity will continue to be treated with traditional interventions. The severity of disease requiring a systemic intervention is likely to compare quite closely with that of the exposed cohorts. Most frequently a decision to use biologic and small molecule therapy will be based more on unsuitability or unresponsiveness to existing therapy than on disease severity. There are likely to be differences, for example in the responsiveness to standard agents, compared to patients in the

exposed cohorts; these cannot be quantified other than by fully documenting previous systemic treatment for psoriasis. These random heterogeneous effects should be similar over a large sample.

The controls will be recruited across all contributing centres, with participants encouraged to register one control for every patient registered. This will ensure high recruitment of controls and reduce the risk of selection bias in the controls.

Analysis will take into account switching between groups to different treatments within groups, such that the person years of follow-up in the comparator group switch to the exposed group if biologic therapy is initiated.

Inclusion criteria

1. Patients initiating or switching conventional therapy with PUVA, ciclosporin, methotrexate, fumaric acid esters, acitretin or hydroxycarbamide.
2. If not switching therapy, patients must have severe psoriasis meeting the severity criteria for biologic therapy as in the BAD guideline (rule of 10s)
3. Informed consent to participate in long-term follow-up and access to all medical records (if patient is under the age of 16, there must be willingness from a parent / guardian to provide this consent. The patient must also provide separate assent).

Exclusion criteria

1. Patients must never have been exposed to biologic therapy or non-biologic small molecule immunotherapy

Note: If a patient was subsequently started on biologic therapy or non- biologic small molecule immunotherapy, then he/she would switch from the control cohort to the appropriate cohort as the design is to include all eligible patients in that cohort.

4. Statistics, Sample size and statistical power (see also appendix 1)

The initial analyses will consist of comparisons in baseline status between the individuals in the treatment cohorts. For the purposes of analysis (initially) follow-up time will be censored in both cohorts if there is switching to another class of biologic therapy and censored in the standard therapy group if there is switching to a biologic agent. The adverse events of interest are calculated per person time of

follow-up, after the start of therapy. Depending on the events, separate analyses are undertaken (i) restricting consideration to time on drug, which include the period within 90 days of last injection and (ii) all person time following start of therapy. Standard time-dependent regression analyses will be undertaken to compare event rates between groups after adjusting for baseline and other differences.

The size of the comparison cohort will be under our control. However, it is difficult to anticipate the magnitude of rate differences for adverse events between the cohorts as patients from all groups are likely to have had prior exposure to immunosuppressive drugs. Cancer is likely to have a low incidence, which may also be increased by having severe psoriasis. Using crude incidence figures in psoriasis patients, approximated from previous studies (Hannuksela-Svahn et al.), (Boffetta, Gridley, and Lindelof) these would be as follows:

SQ Ca with high CSA use	1 in 320
Non-melanoma skin cancer 100/ 100,000	1 in 1,000
Melanoma in high dose PUVA	1 in 1,666
Melanoma in normal person 10/100,000	1 in 10,000

Any adverse events with a frequency of up to 1 in 2,000 in the control group should be addressed within the power of the register. (See assumptions in appendix 1). Bold figures, above, indicate those outcomes which the register is powered to address to an increase risk of 3 or 4 fold over 5 years.

Other potential adverse effects with biologic have been shown to have a strong signal which would be detected by the register by virtue of the many fold increase in risk of a rare outcome e.g. Tuberculosis increased by a factor of 5 with anti-TNFα agents.

SLE	1 in 4,608 (Voss, Green, and Junker)
SLE on infliximab	1 in 118 (De et al.)
Tuberculosis on infliximab	1 in 192 (Wolfe et al.)
Tuberculosis Western Population	1 in 17,241(Wolfe et al.)
Multiple sclerosis	1 in 10,000

The sample size required in each group for a 2 sided significance of alpha < 0.05 to be detected with 80% power has been determined in patient years. Grey shaded areas in appendix 1 indicate predictions within the scope of the register.

Estimating the risk of rare adverse effects with a smaller signal, especially lymphoma will be facilitated by long-term linkage to the national cancer registry (in addition to the control group). The risk window for cancer being defined as once exposed always at risk. Where two biologics have been used, the proportion of time spent on each will define its possible contribution to risk. Where the adverse event is

rare or where a biologic intervention is under-represented in the register, the numbers of patient's data can also potentially be increased by sharing data with other compatible registers such as those operating in Sweden, Italy, and Germany.

5. Auditing the conduct of the study and research governance

The following coordinated program will ensure quality control

a. Training of staff – including a program of training for nurses in PASI scoring and how to use the register. A coordinated program is underway.
b. An on-line manual will be provided for dermatologists to send in quality data, including worksheets for collection of data.
c. Quality checks will be made for data received (i.e. manual scanning for completeness, errors and then checks at data entry stage for inconsistencies).
d. Selected serious adverse events (SAEs) will be checked against a set of predefined validation criteria.

6. Summary Study flow chart

Data captured	**Baseline**	**Follow up (months) 6, 12, 18, 24, 30, 36**	**Follow up (months) 48, 60,72, 84, 96, 108,120 etc.**
Consent (for patients under 16, this is Assent and Consent from parent / guardian)	✓		
Patient ID	✓		
Psoriasis details	✓		
Basic laboratory values Hb, WCC, Platelets, Creatinine, Transaminase, Lipids	(if applicable**)**	(If applicable)	
Systemic treatments	✓	✓	✓
Phototherapy history	✓	If applicable	If applicable
Skin cancer	✓		
Co-morbidity	✓		
Concomitant medications	✓	✓	✓
Biologic /small molecule therapies	✓	✓	✓
Examination	✓	✓	✓
PASI or GPPASI	✓	✓	✓
PGA or GPPGA	✓	✓	✓
DLQI or cDLQI	✓	✓	✓
Euroqol or EQ-5D-Y	✓	✓	✓
HAQ or CHAQ	If applicable	If applicable	✓
HADS	✓	✓	✓
CAGE	If applicable	If applicable	✓
Adverse events		✓	✓
*ESI		✓	✓
Employment	✓	✓	✓
Drinking / smoking	✓	✓	✓
Self-Administered PASI (SAPASI)	✓	✓	✓
PGA (patient completed)	✓	✓	✓

*Events of Special Interest (ESI) eg. Pregnancy: Targeted additional questionnaire for events of particular interest to the study outcome.

7. Baseline data.

This will necessarily be comprehensive to identify potential confounding factors.
A unique identifier will be assigned on registration of the patient. Ascertainment of data will be from a combination of patient interview, examination and examination of hospital medical records, performed by a doctor or trained deputy e.g. nurse.

7.1.1 Patient identification and Demographics (encrypted)

- Surname
- Forenames
- Address
- NHS number (Chi number Scotland) (health and care number Northern Ireland)
- Hospital unit number

7.1.2 Patient identification and Demographics

- Date of Birth
- Gender
- Patient identification unique number
- Date of consent

7.2 Psoriasis details

Type of psoriasis

Chronic plaque with guttate
Chronic plaque without guttate
Erythrodermic
Generalised pustular
Localised pustular
Nails
Flexural (inverse)

Scalp

Acrodermatits continua of Hallopeau

Year of onset of psoriasis

Family history of psoriasis in first degree relatives yes / no

Psoriatic arthritis

Has the patient a diagnosis by a rheumatologist of psoriatic arthritis? Y/N Date of Diagnosis

Patients with arthritis – HAQ/CHAQ score to be obtained via patient questionnaires every 6 months up to Follow up 6 (month 36) and annually thereafter (month 48, 60 etc.).

7.3 Baseline severity

- Psoriasis Area and Severity Index (PASI) and date taken
- Physician Global Assessment (PGA) and date taken
- Generalised Pustular Psoriasis diagnosis: Generalised Pustular Psoriasis Area and Severity Index (GPPASI) and date taken
- Generalised Pustular Psoriasis diagnosis: Generalised Pustular Psoriasis Physician Global Assessment (GPPGA) and date taken

7.4 Current Treatment

- Registration Treatment name, starting date, dose and frequency (For all cohorts)
- Name and start date of any other systemic treatment

7.5 Prior therapy

Has the patient previously received and total exposure (months):

Conventional Systemics

- Apremilast
- Azathioprine
- Ciclosporin
- Fumaric acid esters
- Hydroxycarbamide
- Methotrexate
- Mycophenolate mofetil
- Oral retinoids

Biologics

- Amevive (alefacept)

- Amgevita (adalimumab biosimilar)
- Benepali (etanercept biosimilar)
- Bimzelx (bimekizumab)
- Cosentyx (secukinumab)
- Enbrel (etanercept)
- Hyrimoz (adalimumab biosimilar)
- Idacio (adalimumab biosimilar)
- Ilumetri (tildrakizumab)
- Imraldi (adalimumab biosimilar)
- Inflectra (infliximab biosimilar)
- Humira (adalimumab)
- Mabthera (rituximab)
- Orencia (abatacept)
- Raptiva (efalizumab)
- Remicade (infliximab)
- Remsima (infliximab biosimilar)
- Kyntheum (brodalumab)
- Simponi (golimumab)
- Stelara (ustekinumab)
- Skyrizi (risankizumab)
- Taltz (ixekizumab)
- Tremfya (guselkumab)
- Zessly (infliximab biosimilar)

New Small Molecule Immunomodulatory Therapies

- Otezla (apremilast)
- Skilarence (dimethyl fumarate)

Additional treatments may be added to this list following marketing approval.

7.6 UV therapy History:

1.	Broadband UVB	Number of Treatments
2.	Narrowband UVB	Number of Treatments
3.	Oral PUVA	a) Number of Treatments
		b) Cumulative dose (J/cm²) if known
4.	Topical PUVA	a) Number of Treatments
		b) Cumulative dose (J/cm²) if known

7.7 Comorbidities

Year and date of all pre-existing conditions including but not limited to these areas:

● Hypertension

●Cardiovascular disease (Angina, Myocardial Infarction, Stroke/Cerebrovascular Disease, Dyslipidaemia)

● Diabetes (Type 1, Type 2)

● Autoimmune disorders (Thyroid Disease, Alopecia Areata, Vitiligo, Psoriatic Arthritis)

● Thrombosis (Deep Vein Thrombosis, Pulmonary Embolism, Asthma, COPD (including chronic bronchitis, emphysema))

● Liver disease (NAFLD (non-alcoholic fatty liver disease, including fatty liver and NASH), Alcoholic Liver Disease, Viral Hepatitis, Autoimmune Hepatitis, Inherited Liver Disease (inc. haemochromatosis))

● Kidney disease (Chronic Kidney Disease, Glomerular Disease, Renovascular Kidney Disease, Inherited Renal Disease (polycystic kidney disease))

● Peptic ulcer

● Demyelination (Optic Neuritis, Multiple Sclerosis, Transverse Myelitis, Chronic Inflammatory, Demyelinating, Polyneuropathy, Guillain-Barre Syndrome)

● Epilepsy

● Non Skin Cancer

● Psychiatric (Depression, Anxiety)

● Inflammatory bowel (Crohns, Ulcerative Colitis)

7.8 Skin

Fitzpatrick Skin Type (Fitzpatrick,1975)	1-6
Outdoor occupation	Yes=1 No=0
Residence in tropical/subtropical countries	Yes=1 No=0
History of prior Neoplastic or pre-cancerous lesions:-	Yes=1 No=0

Melanoma, Melanoma in situ (give site and date for each), SCC (give number), BCC (give number), yes tick for Keratoacanthoma, Actinic Keratosis, Bowen's Disease.

7.9 Laboratory investigations

Basic blood results will be captured including: haemoglobin, white cell count, platelets, creatinine, transaminase (ALT), and where possible fasting lipids. These will be recorded in the register at baseline and every 6 months up to 36 months.

7.10 Additional Measurements

- Blood Pressure
- Weight
- Waist Circumference
- Height

7.11 Patient Completed Questionnaires

- Patient Baseline Questionnaire (including birth place, ethnicity, working status, alcohol intake, current and historic smoking).
- DLQI or cDLQI
- EuroQol or EQ-5D-y
- CAGE
- HAQ (if patient is diagnosed with inflammatory arthritis) or cHAQ
- HADS
- Self-Administered PASI
- PGA (patient completed)

8. Follow up data

Recorded at 6 monthly intervals for 3 years and annually thereafter, the following data will be required –

8.1 Appointment

- Did the most recent follow-up take place in-person or remotely (e.g. phone, video) ?
- Date of most recent appointment

8.2 Treatment

- Have there been any changes to the patient's psoriasis therapy (biologic/conventional/small molecule therapy) ?
- If yes record drug, date started and stopped, dose and frequency
- Infliximab**/**ustekinumab dates of all administrations
- Reasons if discontinuing
    - Lack of efficacy
    - Remission
    - Adverse events
    - Inefficacy and adverse events
    - Patient non-compliance

- Titration
- Financial consideration
- Patient choice

Any additional phototherapy since baseline or last follow-up

Any additions or changes to systemic treatments for any other condition (I.e. not psoriasis)

8.3 Lab Values

- Basic blood results will be captured including: haemoglobin, white cell count, platelets, creatinine, transaminase (ALT), and where possible fasting lipids. These will be recorded in the register every 6 months up to 36 months

8.4 Adverse Events

- Event Description
- Start and Stop date
- Is the event ongoing?
- Is the event thought to be related to treatment with a particular biologic / small molecule treatment
- Was a yellow card completed?
- Is the event classified as serious by the study's definition?
- Can the event by categorised as an Event of Special Interest (ESI)?
- Was the patient hospitalised (if yes, provide admission and discharge dates)
- Outcome of event

8.5 Disease Severity

- All PASI completed since last follow-up
- BSA for patients with pustular psoriasis, GPPASI & GPPGA if GPP diagnosis.
- Physician Global Assessment
- Whether there has been a new diagnosis of inflammatory arthritis

8.6 Additional Measurements

- Weight (kg)
- Waist Circumference (cm)
- For patients under the age of 16 on the date of follow-up, height (cm)

8.7 Data acquired directly from patients at follow up six monthly to Month 36 (Year 3) and annually thereafter (year 4+)

Participants have opportunity to complete data at clinic attendance or through electronic means:

- Any new hospital referrals and reason Y/N
- Any new hospital admissions and reason Y/N
- Any new drugs since last follow-up Y/N
- Occupation and working status
- DLQI (or cDLQI for paediatric patients)
- Euroqol (or EQ-5D-y for paediatric patients)
- CAGE
- HAQ (or CHAQ for paediatric patients)
- HADS
- Self-Administered PASI
- PGA (patient completed)
- Current smoking
- Current alcohol intake

8.8 Patient Withdrawals/Lost to Follow up

Three potential scenarios as follows:
i) Patient Discharged from clinic/ Continued non attenders
Mark next 12 months of follow-ups as 'missed / data cannot be recorded'.
This means the clinician will not get repeatedly reminded about the follow-up data and also that the BADBIR office gets at least an annual update on whether the patient is still not attending.

ii). Patient Transferred to Unknown Hospital
Mark all remaining follow-ups as 'missed / data cannot be recorded'. If BADBIR are made aware that patient starts to attend another centre involved in BADBIR, the follow up will continue via the new centre.

iii) Patient does not want to continue with BADBIR:
a) Ask the patient if they would be happy if only clinical data is collected via the dermatology team (i.e. no patient reported data - questionnaires). In this case continue to follow up the patient and provide a comment as follow in the database feedback section "patient questionnaires not completed'.
or
b) If the patient does not want to be followed at all:
All remaining follow-ups will be recorded as 'missed / data cannot be recorded' no further prompts for further information will be given. Flagging with cancer and malignancy database will be discontinued. All data collected by the study to the point of withdrawal will be retained.

8.9 Participation in Clinical Trials

Patients registered with BADBIR are not precluded from entering clinical trials. The following procedure has been developed to deal with the various scenarios:

Procedure for handling data on patients who are registered with BADBIR who enter into Clinical Trials

i) If a patient registered with BADBIR enters into an un-blinded investigator sponsored clinical trial, the patient data may be collected and processed in the usual way.

ii) If a patient registered with BADBIR enters into an un-blinded clinical trial sponsored by a pharmaceutical company then subject to the consent of the pharmaceutical company the patient data may be collected and processed in the usual way. As BADBIR may have no formal contract with this pharmaceutical company, the relevant Principal Investigator would negotiate this with the pharmaceutical company and communicate the response to BADBIR.

iii) If a patient registered with BADBIR enters into a blinded clinical trial, the data would be censored at the time of entry onto the clinical trial. The patient could later be reinstated once the blind has been opened with the proviso that we could collect the BADBIR data relevant to that period. The responsibility for this would be with the Principal Investigator as BADBIR may have no formal agreement with this pharmaceutical company.

9.0 Analysis of the data

9.1 Primary endpoints for evaluation

- Any malignancy
- Any infection requiring hospitalisation
- Serious adverse event other than death
- Death and cause of death

9.2 Hypotheses to test

- Increased risk is related to the duration of therapy
- Baseline characteristics determine increased risk, especially prior therapy
- Certain longitudinal combinations of treatment carry higher risks
- In addition the benefits of therapy will be assessed using a variety of objective scores, PGA and PASI, and quality of life DLQI, HADS, Euroqol. (or cDLQI and EQ-5D-y for paediatric patients)

9.3 Analytic approach

The initial analyses will consist of comparisons in baseline status between the individuals in the treatment cohorts. For the purposes of analysis (initially) follow up time will be censored in both cohorts if there is switching to another class of biologic therapy and censored in the standard therapy cohort if there is switching to a biologic agent. The adverse events of interest are calculated per person time of follow up, following the start of therapy. Depending on the events, separate analyses are undertaken (i) restricting consideration to time on drug, which includes the period within 90 days of last injection and (ii) all person time following start of therapy e.g. malignancy. Time-dependent regression analyses will be undertaken to compare event rates between groups after adjusting for baseline and other differences. Within the biologic cohort, there are distinct modes of action amongst the available treatments (e.g. Anti-TNF and IL12/23 inhibitors). Where appropriate power is reached, it will be additionally possible to make comparisons between these treatment groups.

Interim Analyses

Interim analyses will be undertaken at appropriate intervals when 5000 person years of exposure have been accumulated in any of the exposed groups. Such analyses will be a guide to the ultimate levels of recruitment and length of follow up required. Decisions as to the timing of publications and the need for continued follow up and/or recruitment can only be taken in the light of results from such analyses. A Data Monitoring Committee (DMC) has been established, analogous to a Data Safety & Monitoring Board established for major clinical trials. The DMC will be independent of the principal investigators and also of any of the pharmaceutical industries involved, and will have the power to request interim analyses and advise on the timing and nature of any publications. The DMC should include at least one epidemiologist, a dermatologist and a statistician.

10. Roles of interested parties

The BAD will seek funding and a generic contract with the pharmaceutical companies whose products are being monitored. The University of Manchester will be the sponsor of the study. The project will be steered by a steering group, DMC and ethics committee under the auspices of the BAD and will operate independently from direct industry involvement..

10. 1 Role of the Pharmaceutical companies

The goals of industry and the dermatological community are similar in seeking accurate estimates of any increased risk of adverse events. It may also be a pre-requisite for drug license approval, that a study such as the one proposed is established. It is accepted that it is beneficial that any study, such as the one proposed, should be independent of any direct industry involvement. Thus decisions on

analyses, interpretation and publication should be independent of any industrial contribution. Industry can have a crucial role in stimulating registration after licensing, and also contributing their experience into the nature and type of data to be collected. Timely serious adverse event data will be shared with the relevant manufacturer according to agreed standardised protocols (schedule 3). Aggregated data relating to a particular product will be shared with industry in confidence, though individual identifiable patient data will not be released. A participant company has the option of requesting specific analyses and will be shown drafts of any publications, reports, abstracts or other material prior to submission for presentation or publication. They can ask for clarifications or amendments to such material but the final decision on these would rest with the principal investigators and the DMC. All the principal investigators and members of the DMC have to complete an annual 'Declaration of conflict of interests', which will be added to all publications.

There will be an annual joint pharmaceutical companies meeting to discuss contractual issues and also to update on study progress.

10.2 Role of BAD

BAD will be the owner of the data that emerge from the study. The BADBIR Programme Manager will report on a quarterly basis to such committees or sub-committees that BAD deems appropriate. The membership of the DMC will be subject to the approval of BAD.

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Appendix 1 Statistical Power and numbers converted to patient years

Number pt years required in each cohort (controls and biologics)
Shading indicates likely power of the register in 5years (dark) to 10 years (light)

Relative risk Incidence of event in controls	1.5	2	3	4
1 in 500	39738	12309	2760	2568
1in 1000	79311	24561	8694	5121
1 in 2000	158460	49068	17364	10221

Using stat calc (epi info) 95% confidence level 80% power 1 to 1 ratio in each cohort

Chart of accrual of patient years given scenario of 1000 per year patients registered on biologics or 500 per year registered runs to 14 years which may be relevant for longer term e.g. melanoma data.

Number of years of register	year 1	year 2	year 3	year 4	year 5	year 6	Year 7	**person years**
1	500							**500**
2	1500	500						**2000**
3	2500	1500	500					**4500**
4	3500	2500	1500	500				**8000**
5	4500	3500	2500	1500	500			**12500**
6	5500	4500	3500	2500	1500	500		**18000**
7	6500	5500	4500	3500	2500	1500	500	**24500**
8	7500	6500	5500	4500	3500	2500	1500	**31500**
9	8500	7500	6500	5500	4500	3500	2500	**38500**
10	9500	8500	7500	6500	5500	4500	3500	**45500**
11	10500	9500	8500	7500	6500	5500	4500	**52500**
12	11500	10500	9500	8500	7500	6500	5500	**59500**
13	12500	11500	10500	9500	8500	7500	6500	**66500**
14	13500	12500	11500	10500	9500	8500	7500	**73500**

	year 1	year 2	year 3	year 4	year 5	year 6	Year 7	**person years**
1	250	0	0	0	0	0	0	**250**
2	750	250	0	0	0	0	0	**1000**
3	1250	750	250	0	0	0	0	**2250**
4	1750	1250	750	250	0	0	0	**4000**
5	2250	1750	1250	750	250	0	0	**6250**
6	2750	2250	1750	1250	750	250	0	**9000**
7	3250	2750	2250	1750	1250	750	250	**12250**
8	3750	3250	2750	2250	1750	1250	750	**15750**
9	4250	3750	3250	2750	2250	1750	1250	**19250**
10	4750	4250	3750	3250	2750	2250	1750	**22750**
11	5250	4750	4250	3750	3250	2750	2250	**26250**
12	5750	5250	4750	4250	3750	3250	2750	**29750**
13	6250	5750	5250	4750	4250	3750	3250	**33250**
14	6750	6250	5750	5250	4750	4250	3750	**36750**