British Association of Dermatologists Biologics and Immunomodulators Register

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1. Background to Introduction of Biologic Interventions

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.

Twelve originator Biologics are currently licensed for treatment of psoriasis and approved by NICE. These comprise of four inhibitors of TNF (Cimzia, Enbrel, Humira, Remicade), four IL-17A inhibitors (Cosentyx, Kyntheum, Taltz and Bimzelx), three IL-23 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 are approved in the UK and ROI and are in clinical use. Other biologic agents are being evaluated for psoriasis 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

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 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, dimethyl fumarate and deucravacitinib. 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.

2.4 Summary of Current Position

Since the introduction of biologic therapies for psoriasis, several academic studies have researched safety outcomes using real world data. BADBIR data were used to compare rates of serious infection between patients receiving biologic and non-biologic systemic therapies (Yiu et al.). This analysis found no significant overall increase in the risk of serious infection between the two cohorts. Similar conclusions regarding infection risk were reported in comparable studies conducted in France (Couderc et al.) and the United States (Dommasch et al.).

BADBIR data have also been used to assess the risk of major adverse cardiovascular events (MACE) in patients receiving adalimumab, etanercept, or ustekinumab compared with methotrexate (Rungapiromnan et al., 2020). This analysis demonstrated no significant increase in cardiovascular risk among patients exposed to biologic therapies. Similarly, a 2016 study by Curtis et al. using a large administrative cohort in the United States compared rates of MACE between biologic and non-biologic systemic therapies. This study also found no significant difference in cardiovascular risk between the biologic and conventional systemic treatment groups.

Research into malignancy risk has also been conducted using BADBIR data. This includes an analysis of skin cancer risk in patients without prior malignancy (Mason et al., 2021), which found that biologic therapies were not associated with an increased risk of incident basal cell carcinoma (BCC) or squamous cell carcinoma (SCC). More recently, an abstract assessed the risk of incident cancers overall (excluding keratinocyte carcinoma) using BADBIR data (Esse et al., 2024). This study concluded that exposure to biologic therapies does not increase the risk of developing cancer in the short to medium term compared with conventional systemic therapies. However, it highlighted the need for further investigation into site-specific cancers (e.g. breast and prostate), with longer follow-up required. Latency also remains a key consideration in malignancy research, and future analyses will benefit from extended follow-up across all treatment groups.

Collectively, these findings have improved understanding of the real-world safety profile of first-generation biologics, including TNF inhibitors (TNFi) and IL-12/23 inhibitors. As a result, emerging

research is increasingly focused on comparisons between different classes of biologics, rather than solely against conventional systemic therapies. A summary of the statistical power required for such comparisons between modes of action is provided in Appendix 2.

3. Methods

3.1 Aims

The primary purpose of establishing a register for psoriasis was to ascertain whether there is an importantly increased risk of serious adverse events following the introduction of biologic and small molecule agents which have relatively small amount of “real world” safety data in the treatment of psoriasis. These cohorts of patients can be compared to a conventionally treated cohort which has long term “real-world” safety data. The conventional cohorts will consist of patients with a comparable disease severity to those in the biologic and small molecule cohorts.

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 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, patients will be managed on the BADBIR database. Queries will be raised on missing data or if additional data is required on an entered serious adverse event. Patients who are due a follow-up will be highlighted on the database. Centres will receive a monthly email to notify them how many patients were recruited that month, how many follow-ups are overdue and how many queries remain unsolved. Dermatologists will be able to view data on their patients and add to this without unnecessary repetition.

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 British Association of Dermatologists (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 England) to receive information in four areas:

- Mortality
- Malignancy
- Inpatient hospital admissions
- Medical prescriptions

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.

3.3 End of the Study

Patient recruitment will end on 31/07/2037 all patients on the register will continue to be followed-up until 31/07/2038. As of 31/07/2038 no data collected from sites will be inputted into the database.

4) STUDY PARTICIPANTS

4.1 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

4.2 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

Exclusion criteria

Patients must never have been exposed to biologic therapy

4.3 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 conventional comparator patients will be recruited across all contributing centres.

Analysis will take into account switching between cohorts. If a patient is exposed to a biologic or small molecule therapy, they will switch cohorts and they will start at baseline in their new cohort.

Inclusion criteria

1. Patients initiating or switching methotrexate, If not switching therapy, patients must have moderate to severe psoriasis. This is identified by a patient meeting a PASI of 10 or above and a DLQI of above 10.
2. If switching between conventional therapies the patient needs a history of moderate to severe psoriasis. The patient does not need to meet a PASI or DLQI criterion but does need a historic PASI of 10 or above 10 and a DLQI of above 10.
3. Informed consent to participate in long-term follow-up and access to all medical records.
4. If patient has a diagnosis of Generalised Pustular Psoriasis they can be initiating or switching to methotrexate, ciclosporin and acitretin. These patients do not need to meet the PASI and DLQI eligibility criteria above to be eligible.

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.

4.4 Paediatric patients

Inclusion Criteria

1. Patient starting or commencing systemic therapy in the last six months.
2. The patient can be starting on any systemic treatment for psoriasis. The treatment does not need to be listed in our eligible drugs list.
3. For patients under the age of 16 a Child Dermatology Life Quality Index (cDLQI) of 10 or above is not required for the patient to be eligible.
4. Informed consent to participate in long-term follow-up and access to all medical records Consent (for patients under 11 this is consent from parent/guardian. Patients between ages 11-16 an Assent and Consent from parent / guardian will be required)

Note: Patient should be re-consented at their next clinic appointment on turning the age of 16. A reminder will be added to the BADBIR database in the form of a data query that an updated consent form is required.

5) RECRUITMENT

5.1 Postal consent

Postal consent was introduced to BADBIR in Amendment 5 on 05/05/2011.
Eligibility criteria remains the same for patients recruited using postal consent. Please refer to the eligibility page for full information, but in summary:

- The patient has to sign the consent form within 6 months of starting their registration drug
- A DLQI is required for all registrations, dated as close to the start date of their registration drug as possible
- A PASI is required for all registrations, dated as close to the start date of their registration drug as possible

When you have identified a potential recruit for BADBIR, you can send them the patient invitation letter and the patient information sheet for them to look at, along with the consent form and baseline questionnaires to complete and return if they decide they would like to join.
When recruiting patients through postal consent, use the same consent materials as used in clinic. Localised versions can be found in your electronic site file.
When you are ready to send the documents to the patient, you can:

- Post the documents to the patient for them to return by post
- Post the documents to the patient for them to complete before taking a photo/scan and emailing it back to the dermatology department
- Email the documents to the patient for them to print out and complete, before taking a photo/scan to email back to the dermatology department

Email should only be used for sending or receiving consent forms if you have local approval to do so. If you have local approval, we have no objection. If email is used to exchange documentation, this must be in line with your local policies regarding information security.
For patients recruited through postal consent, it's acceptable for the date of signature for patient and person-taking-consent to differ.

5.2 Contacting participants about similar studies

An additional consent statement has been added to all consent form variants enabling the participant to indicate their willingness (or otherwise) to be contacted by the University of Manchester about similar studies. The statement clarifies that this is optional and that the participant can participate in the study without agreeing to this.

Patients who opt-in to the above will be contacted using patient data already collected and stored as part of the recruitment process. Email address is collected in the Baseline CRF for this purpose. The patient is free to unsubscribe at any point by contacting the study team, whose contact details are provided on consent materials and when contacted. Contact details are encrypted within patient database tables. Data is retained in line with study end data retention.

6. 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 conventional cohortif 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 dose 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 thecontrol 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.

7. Auditing the conduct of the study and research governance

The following coordinated program will ensure quality control:

a. Training of staff – All staff will be required to complete online training prior to being given access to the database.
b. Paper questionnaires are available to ensure dermatologists are able to collect all relevant data in clinic. Quality checks will be made for data received There are manual quality data checks and the database includes a data entry validation.
c. Database Query System
d. Selected serious adverse events (SAEs) will be checked against a set of predefined validation criteria.
e. Centres audits to verify source data.

8. 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 11 this is consent from parent/guardian. Patients between ages 11-16 an Assent and Consent from parent / guardian will be required)	✓		
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/ conventional 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.

9. 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.

9.1.1 Appointment

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

9.1.2 Patient identification and Demographics (encrypted)

- Surname
- Forenames
- Postcode (note this will be used to derive data for Index of Multiple Deprivation and will stay within the BADBIR infrastructure without being shared externally via fully offline, deterministic processing).
- NHS number (Chi number Scotland) (health and care number Northern Ireland)
- Hospital unit number

9.1.3 Patient identification and Demographics

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

9.2 Psoriasis details

Type of psoriasis

Chronic plaque with guttate
Chronic plaque without guttate
Erythrodermic
Generalised pustular
Has the patient recently been hospitalised for a Generalised Pustular Psoriasis Flare?
Yes/No

If Yes
Date of admission:
GPPGA on admission:
Time to pustular clearance:
GPPGA/GPPASI at Week 1, Week 2 and Week 3
Possible trigger for flare:

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.).

9.3 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

9.4 Current Treatment

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

9.5 Prior therapy

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

Conventional Systemics

- 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)
- Hulio (adalimumab biosimilar)
- Humira (adalimumab)
- Hyrimoz (adalimumab biosimilar)
- Idacio (adalimumab biosimilar)
- Ilumetri (tildrakizumab)
- Imraldi (adalimumab biosimilar)
- Inflectra (infliximab biosimilar)
- Mabthera (rituximab)
- Orencia (abatacept)
- Pyzchiva (ustekinumab biosimilar)
- Raptiva (efalizumab)
- Remicade (infliximab)
- Remsima (infliximab biosimilar)
- Simponi (golimumab)
- Skyrizi (risankizumab)

- Spevigo (spesolimab)
- Stelara (ustekinumab)
- Steqeyma (ustekinumab biosimilar)
- Taltz (ixekizumab)
- Tremfya (guselkumab)
- Uzpruvo (ustekinumab biosimilar)
- Wezenla (ustekinumab biosimilar)
- Zessly (infliximab biosimilar)

  Yuflyma (adalimumab)

New Small Molecule Immunomodulatory Therapies

- Otezla (apremilast)
- Skilarence (dimethyl fumarate)
- Sotyktu (deucravacitinib)

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

9.6 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

9.7 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)

9.8 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.

9.9 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.

9.10 Additional Measurements

- Blood Pressure
- Weight
- Waist Circumference
- Height

9.11 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)

10. Follow up data

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

10.1 Appointment

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

10.2 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 administrationsReasons 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)

10.3 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

10.4 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

10.5 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

10.6 Additional Measurements

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

10.7 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

10.8 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.

10.9 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.

11.0 Analysis of the data

11.1 Primary endpoints for evaluation

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

11.2 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)

11.3 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.

12. 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.

12. 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.

12.2 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	1.5	2	3	4
Incidence of event in controls				
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**

Appendix 2 Statistical Power for Biologic-class Comparison

Event-based simulation demonstrated that projected statistical power (statistical power is the probability of detecting a significant treatment effect when that effect is real and beyond what can be attributed to chance) varied substantially across pairwise comparisons, reflecting differences in event accrual and the number of initiators within each treatment class. Power estimates incorporated both currently observed malignancy events and projections based on observed incidence rates over an additional 10 years of follow-up.

As illustrated in Figure 1, power increases consistently with both effect size and duration of follow-up, but the rate of gain differs markedly across comparisons. Comparisons between non-biologic and biologic therapies are already well powered, exceeding 80% power at relatively modest effect sizes (hazard ratios ~1.15–1.2), confirming that the study is already capable of detecting small but clinically relevant differences.

In contrast, biologic class comparisons show a clear dependence on extended follow-up. TNF versus IL-12/23 inhibitors is expected to exceed 80% power at hazard ratios just under 1.25, and 90% power at approximately 1.3, indicating that the proposed extension will enable robust detection of clinically meaningful differences. TNF versus IL-17 inhibitors demonstrates more gradual gains in power, crossing 80% at approximately 1.3 and approaching 90% only at larger effect sizes, highlighting the importance of additional follow-up to improve precision.

Notably, TNF versus IL-23 inhibitors remains underpowered across much of the clinically relevant range, only approaching adequate power at higher effect sizes (≥1.35). This reflects the relatively recent introduction and lower cumulative exposure to IL-23 inhibitors. However, the figure also demonstrates a clear upward trajectory, indicating that continued follow-up will progressively close this evidence gap. These patterns are driven by real-world prescribing trends, in which newer biologics have lower initial uptake but are rapidly increasing in use. As exposure accumulates over time, the number of malignancy events in these groups will rise, directly translating into improved statistical power.

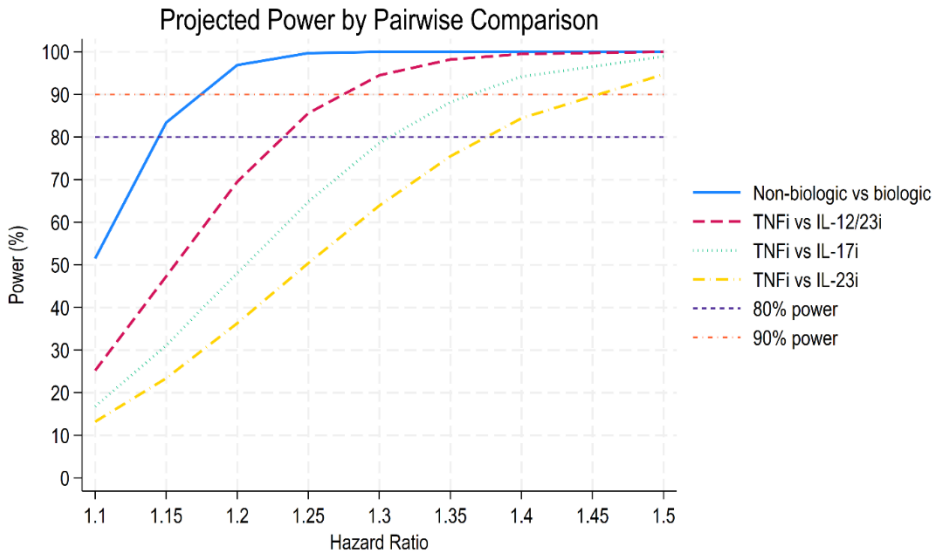

Figure 1. Projected statistical power to detect differences in malignancy risk across pairwise treatment comparisons, based on expected event accrual following 10 additional years of follow-up. Power exceeds 80% for moderate effect sizes in non-biologic versus biologic and TNF inhibitor versus IL-12/23 inhibitor comparisons. TNF inhibitor versus IL-17 inhibitor comparisons demonstrate moderate power, while TNF inhibitor versus IL-23 inhibitor comparisons remain underpowered, achieving adequate power only at larger effect sizes. Hazard ratios shown on the x-axis represent a range of plausible effect sizes specified a priori for the simulation, reflecting clinically meaningful differences in malignancy risk informed by prior literature and study feasibility considerations.