British Association of Dermatologists Biological Interventions Register

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1. Background

Biological interventions using highly specific immuno-modulatory agents represent a new therapeutic approach to the treatment of patients with 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 standard psoriasis therapies but the evidence is based on short term clinical trial interventions, commonly 3 –6 months; there is, however, some limited data up to three years with certain of these agents and considerably more experience from use in other diseases with others (infliximab and etanercept).

Psoriasis tends to be 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 (rare in psoriasis patients); 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 PUVA and more than two years of ciclosporin (Paul et al.). With acitretin there may be the development of skeletal hyperostoses, 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 (SMR 2.62; 95% 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 (RR2.8) 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 (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 Biological Interventions for Psoriasis Register

The primary purpose of establishing a "biologicals" registry for psoriasis is to follow a large cohort of patients treated with biological agents so that their long-term safety can be monitored. This long-term safety data cannot be determined from short-term clinical trials in selected patients. A subsidiary aim will be to collect information on their long-term efficacy.

In the UK, three agents (infliximab, efalizumab and etanercept) are licensed for treatment of psoriasis and two are undergoing technology approval by NICE (efalizumab and etanercept). These agents are free from the traditional end organ toxicities of existing systemic agents but have other side effects such as infusion reactions, chills, injection site reactions and development of antinuclear antibodies (infliximab and etanercept); additional rare side effects include thrombocytopenia (efalizumab), rebound or flare (efalizumab), serious infection e.g. tuberculosis (infliximab and etanercept), cardiac failure and demyelinating disease (infliximab and etanercept). They are likely to offer considerable benefits in safety and quality of life for those with more severe disease but questions remain regarding long term safety and rare side effects. Other biological agents are being evaluated for psoriasis (e.g. adalimumab) and when these become licensed they could be integrated into the register.

We need to have a better understanding of the advantages and disadvantages of these agents for maintaining suppression of severe psoriasis over years and of how these compare with existing agents. Such understanding will inform the place of each treatment in long-term treatment strategies, e.g. in what sequence should they be given and should they be used in combination with existing drugs or with each other? 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 could be learned from a registry. Establishing a registry of all UK patients exposed to biological therapy for psoriasis and a control group given conventional therapies including ciclosporin, methotrexate and acitretin will help to answer these questions.

In a prospective follow-up study of 1380 patients treated with PUVA alone over a 20 year period, Stern, Nichols and Vakeva observed a five fold increase in the relative risk for melanoma (Stern, Nichols, and Vakeva). This was in an American population where there is a higher background incidence of melanoma than in the UK. Latency was as long as 10-15 years and the crude incidence was only of 8 more melanomas than expected. A similar follow up of 4799 Swedish patients treated

with PUVA failed to show an increase in the risk of melanoma following systemic PUVA (Lindelof et al.). The proposed register will probably include a number of patients who have received large cumulative doses of PUVA in the past. Current UK practice, however, is to rely more on narrow band UVB for which the carcinogenic risks are thought to be less but where there is a lack of long-term data.

Comparable databases have been set up in Europe and USA for anti-TNFα therapies in other indications and initial findings are starting to be reported. In the Stockholm register for inflammatory bowel disease, with 217 infliximab treated patients (Ljung et al.), the risk of adverse events was increased in elderly patients with severe inflammatory bowel disease and lymphoma had a 1.5% incidence. A Spanish register of 1,540 patients treated with infliximab (86%) and etanercept (14%) showed a 1.1-1.9% incidence of tuberculosis in patients treated for rheumatoid arthritis (Gomez-Reino et al.)

The American national register for rheumatic disease studied by Wolfe (Wolfe and Michaud) included 18,572 patients with RA and showed an overall SIR for lymphoma in patients treated for RA with anti TNFα therapies of 2.9 (95% CI 1.7-4.9), but this may be due to patients with more severe disease being represented in these treatment cohorts and the authors could not establish a causal relationship between RA treatment and the lymphomas observed.

Rationale for the inclusion of children Use of Biological 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]

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

3. Methods

3.1 Aims

The primary purpose of establishing a "biologicals" register for psoriasis is 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 is to include 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 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-biological 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 two cohorts comparing patients treated with biological interventions to a control group with similar disease characteristics but exposed only to non-biological systemic therapies. The comparison group would include patients treated with PUVA, methotrexate, ciclosporin and acitretin. The protocol will be submitted for MREC approval. Analysis will take into account switching from the control group to a biologic agent or from one biologic agent to a different one.

The register will be modelled on the existing British Society for Rheumatology Biologics Register, BSRBR, and run on a similar platform and co-located at Manchester University. Staff of the BSRBR will be partners in running this new register. BADBIR will promote registration of biological 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 biological intervention. Recruitment for one agent would cease if the 4000 patient target is reached. **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.**

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 physicians are delayed there will be repeated reminders and phone calls if necessary to ensure the most complete data possible is obtained.

When formal follow-up of the last patients entered in the register is complete, BADBIR will continue to link the register to the national cancer register and to the death register. Patient data will need to be acquired and stored with patient specific information. This will be pseudonymised (e.g. patient number) to protect confidentiality.

3.2.1 Exposed cohort

Inclusion criteria

1. Patients commencing or switching treatment with a biological agent 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.

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 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.

3.2.2 Non-exposed 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 those exposed to biological interventions. Most frequently a decision to use biological 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 biological group; 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 from one group to another or to different biologics such that the person years of follow-up in the control group switch to the biological group if biological 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 biological 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 biological therapy

Note: If a patient was subsequently started on biological therapy, then he/she would switch from the control cohort to the biological 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.

Sample size of the biologics exposure group will be limited or determined by external factors:

1) NICE technology assessment 103 and recommendation of the agents with etanercept failure being a criteria for the use of efalizumab
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

After discussion with sponsors, industry, health administration and opinion leaders we feel that over 5 years collecting 4000 patients in each of the biological intervention arms and in the control cohort is likely to be achievable.

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 psoriatic 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 biologicals 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 biologicals 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 biological 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.

The aim is to recruit 4,000 patients on conventional treatments and 2,000 to 4,000 on each biological intervention (depending on the uptake of these drugs in clinical practice). NICE guidelines indicate that in the UK etanercept should be used first and it is likely to be used much more than the others. 4,000 patients in each cohort, biologicals and conventional treatment would give an exposure of 12,000 patient years in each group. This would give power to detect at least a 3 or 4 fold increase in risk of events occurring at a frequency of 1 in a 1000 or 1 in 2000 patients. Rarer events would be detected if the relative risks were higher. nQuery advisor (version 5, JD Elashoff) was used to calculate the person years of follow-up required using a 95% confidence level and 80% power 1 to 1 ratio in each cohort. This would be sufficient to detect for example the risk of non melanoma skin cancer which is a particular concern in these patients who have been exposed to phototherapy.

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**
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	✓	✓	✓
Biological medications	✓	✓	✓
Examination	✓	✓	✓
PASI	✓	✓	✓
PGA	✓	✓	✓
DLQI **or cDLQI**	✓	✓	
Euroqol **or EQ-5D-Y**	✓	✓	
HAQ **or CHAQ**	If applicable	If applicable	
CAGE	If applicable	If applicable	
Adverse events		✓	✓
*Pregnancy	✓	✓	✓
Employment	✓	✓	
Drinking / smoking	✓	✓	

*Pregnancy: Specific prompts in the consultant follow-up forms with additional questionnaires if yes to follow specific 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 Patient identification (separately stored for confidentiality)

- Surname
- Forenames
- Address
- Telephone number

- Gender
- Date of Birth
- NHS number (Chi number Scotland) (health and care number Northern Ireland)
- Hospital unit number if above not known
- Consultant Dermatologist
- Code for centre

7.2 To appear in the register

- Patient identification unique number
- Code for centre
- Gender
- Date of Birth
- Date of registration
- Working Yes / No

7.3 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).

7.4 Baseline severity

- PASI score
- DLQI from patient questionnaire (**or cDLQI for paediatric patients)**
- EuroQol (5 questions) **(or EQ-5D-Y for paediatric patients)**
- CAGE questionnaire (if patient drinks alcohol) for alcohol dependence

7.5 Baseline examination

- Blood pressure (mmHg)
- Weight (kg)
- Height (m)
- Waist circumference (cm)

7.6 Prior therapy

Has the patient previously received and total exposure (months)

1. Methotrexate
2. Ciclosporin
3. Oral retinoids
4. Hydroxycarbamide
5. Azathioprine
6. Mycophenolate mofetil
7. Fumaric acid esters
8. Infliximab (biologicals group only)
9. Etanercept (biologicals group only)
10. Efalizumab (biologicals group only)
11. Adalimumab(biologicals group only)
12. Alefacept (biologicals group only)
13. Ustekinumab (biologicals group only)

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

UV therapy:

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 Risk factors for skin cancer

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.

7.8 Co morbidity data

Any co-morbidity including

High blood pressure
Angina
Heart attack
Stroke

Epilepsy
Asthma
Chronic bronchitis/emphysema
Peptic ulcer
Liver disease
Hepatitis
Abnormal LFTs
Renal disease
Raised creatinine
TB increased risk
Demyelination
Diabetes
Thyroid disease
Depression
Non skin cancer
Type free text, site free text, date
Blood dyscrasia
Immunodeficiency syndromes

Smoking

1. Current, 2.ex-smoker or 3.never-smoked

a) Number of cigarettes currently smoked

b) Number of cigarettes smoked when a smoker

Do you drink alcohol Y/N

Current alcohol intake: number of units per week (give examples on the form)

7.9 Concomitant medications

List drugs patient is taking – (predictive text on field)

A specific prompt will be made for topical tacrolimus and pimecrolimus use.

7.10 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

8. Follow up data

Recorded at 6 monthly intervals for 3 years and yearly for up to 7 years the following data will be required –

8.1 Consultant Follow up

- Have there been any changes to the patient's biological therapy?
- If yes record drug, dose started and stopped
- Infliximab/ustekinumab dates of all administrations
- Reasons if discontinuing

    - Lack of efficacy
    - Adverse effect
    - Patient preference
    - Psoriasis remission
    - Other
- Any change in the patient's oral anti-psoriatic medication?
- Anti-psoriatic drug treatment, dose, started and stopped?
- Any further phototherapy?

    - PUVA
    - Narrowband
    - Broad band
    - Number of doses and total Joules (PUVA) for the episode

- Has your patient experienced an adverse event or new illness?
- Adverse event detail (allow for input of several)
- Specific prompt for skin cancer and non-cutaneous cancer and tuberculosis or serious infection
- Was patient on biological therapy at the time of onset of event?
- Date of last injection
- Did this result in death, hospitalisation, loss of function, significant disability, congenital malformation or was in any other way life threatening?
- Do you believe that there is a reasonable possibility that this event was related to the patient's biological therapy?
- Was a yellow card filled in for the adverse reaction?

8.2 Current psoriasis severity

- PASI
- Physicians global assessment (PGA) (See appendix 5)
- Patients with a rheumatologist's diagnosis of inflammatory arthritis will have the HAQ assessed at baseline and subsequent visits

8.3 Vital status

- Alive
- If no, date of death
- Contact details for person completing the form
- Patient follow up details
- Add any missing data from registration
- Adverse events will be classified according to the new pharmaceutical standard MedDRA coding
- If pregnancy occurs follow up to include outcome
    - Still pregnant
    - Miscarriage
    - Maternal outcome
    - Foetal outcome

8.4 Data acquired directly from patients at follow up to Month 36 (Year 3)

- Any new hospital referrals and reason Y/N
- If yes name of hospital consultant in charge and reason
- Any new hospital admissions and reason Y/N
- If yes name of hospital, consultant in charge and reason
- Any new drugs and reasons
- DLQI (up to Follow up 6 (Month 36) **(or cDLQI for paediatric patients)**
- Euroqol (up to Follow up 6 (Month 36) **(or EQ-5D-y for paediatric patients)**

- CAGE
- HAQ **(or CHAQ for paediatric patients)**

Patient Withdrawals/Lost to Follow up

Patients 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.

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, 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.

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. BAD will have ownership of the data. The project will be steered by a steering group and data monitoring and ethics committee (DMC) under the auspices of the BAD and will operate independently from direct industry involvement. The manufacturer of a product will have access to aggregated data from subjects exposed to their product but not to named individual data.

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 study co-ordinator 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**