British Association of Dermatologists' Biological Interventions Register

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Steering group members
Anthony Ormerod (Chair)
Alex Anstey
Prof. Jonathan Barker
David Burden
Robert Chalmers
David Chandler (PAA)
Prof Andrew Finlay
Prof. Chris Griffiths
Karina Jackson
Neil McHugh
Kevin Mckenna
Prof N Reynolds
Catherine Smith

Study Team

Principal Investigator	Prof Chris Griffiths
Chief Investigator	Dr A.D. Ormerod
Chief Investigator	Prof Deborah Symmons
Study Director	Dr Kath Watson

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 were 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.

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 and 4000 controls. Recruitment for one agent would cease if the 4000 patient target is reached.

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. Paper forms will be available as a substitute for those unable to use the web.

The co-ordinating centre will mail patients with paper forms to gain additional information on their quality of life, drinking and smoking habits, medication and any health care problems according to the protocol.

Where responses from patients or 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 with psoriasis commencing treatment with a biological agent for therapy of their skin disease.
2. Willingness to give informed consent for long term follow-up and access to all medical records.

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 will be co-ordinated by a Board/ 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** or acitretin.
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.

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. Ongoing analyses will be conducted for any outliers between centres
e. End point evaluation for serious adverse events (SAEs) will be validated by obtaining copies of medical records.

6. Summary Study flow chart

Data captured	Baseline	Follow up (months) 6, 12, 18, 24, 30, 36, 48, 60
Consent	✓	
Patient ID	✓	
Psoriasis details	✓	
Basic laboratory values Hb, WCC, Platelets, Creatinine, Transaminase, Cholesterol, triglycerides	✓	6, 12, 18, 24, 30, 36, 48, 60
Systemic treatments	✓	If applicable
Phototherapy history	✓	If applicable
Skin cancer	✓	If applicable
Co-morbidity	✓	If applicable
Concomitant medications	✓	✓
Biological medications	✓	✓
Examination	✓	✓
PASI	✓	✓
PGA	✓	✓
DLQI	✓	✓
Euroqol	✓	✓
HAQ	If applicable	If applicable
CAGE	✓	✓
Adverse events		✓
*Pregnancy	✓	✓
Patient diary	✓	✓
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 all possible 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 inflammatory arthritis? Y/N

Patients with arthritis - HAQ score to be obtained via patient questionnaires every 6 months.

7.4 Baseline severity

- PASI score
- DLQI from patient questionnaire
- EuroQol (5 questions)
- CAGE questionnaire for alcohol dependence

7.5 Baseline examination

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

6.6 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)

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

Skin Type	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

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 Cholesterol and triglyceride. These will be recorded in the register at baseline and every 6 months

8. Follow up data

Recorded at 6 monthly intervals for 3 years and yearly for a further 2 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 dates of all infusions
- Reasons if discontinuing
  - Lack of efficacy
  - Adverse effect
  - Patient preference
  - Psoriasis remission

- 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

- 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
- Euroqol

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 EQ-5D.

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.

The data will also need to be subject to interim analysis so that any early trends that could affect practice are picked up in a timely fashion and serious events are considered. Too frequent analysis however will diminish the statistical power and increase the likelihood of false positive errors. For each class of adverse event relative risks (RR) can be determined against the control population and analysed by time dependent regression analysis. Multivariate analysis could be used to identify interaction of exposure factors associated with adverse events e.g. PUVA and biological therapy. These might be age related, co-morbidity related, related to prior therapy or concomitant therapy. Data will be analysed for trends that identify predictors of response, response to therapy or adverse events.

9.4 Role of the pharmaceutical industry sponsors

The pharmaceutical industry shares the goal of ascertaining the relative risks of long-term therapy. The EMEA stipulate a minimal requirement for follow up but for certain events, particularly skin cancer longer-term follow-up is required. Timely adverse event data will be shared with the relevant manufacturer according to agreed standardised protocols. Companies will also be given access to the

aggregated data on patients exposed to their product and anonymous control data. There will be a common goal of pharmacovigilance whereby identification of potential signals can be acted upon as a preventative measure and do not await the final analysis of the cohort.

The BAD will seek sponsorship and a generic contract with the companies whose products are being monitored. The BAD will be the sponsor of the study and will have ownership of the data. The project will be steered by a steering group 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.

A participating company will have the option of requesting specific analyses. They will be shown the drafts of any publications, reports or abstracts prior to submission for presentation or publication with the sole and rare exception of bringing attention to matters of factual error they have no role in the interpretation or preparation of material for publications. Full responsibility for all data, results, analyses, interpretation of findings rests solely with the authors and principal investigators. All principal investigators will have to complete an annual declaration of conflict of interests which will be added to all publications.

There will be a regular sponsor's forum meeting (initially every 4 months) to meet the needs of sponsors and adverse event reporting and also to update on progress and setting up the register.

10. Reporting timelines

We aim to begin recruitment in early 2007 with pilot sites. Thereafter there would be an annual report describing the frequency and types of adverse events without any formal hypothesis testing or statistical adjustments. Each company would receive the data for their drug and for the controls, and the MHRA and EMEA would receive all the data annually from the date of first registration. These data would include demographics, gender age and patient numbers together with baseline characteristics; cumulative follow up time; and counts and incidence rates of the specific adverse events of interest. In addition, annual reports will present adverse event rates stratified by duration of exposure to the biologic agents.

Serious adverse events (potentially life threatening or resulting in hospitalization) would be expedited and notified within 48 hours of the register becoming aware. Reporters in the scheme would be actively encouraged to report this in real time rather than at the next register update (6 monthly). After 5 years there would be a full report and statistical analysis evaluating subgroups and relative risks against risk factors.

A data monitoring committee will have access to all the data in the event of particular severe adverse events or safety concerns would investigate these to decide if reporting was necessary, particularly in respect of any unexpected adverse events.

Participating dermatologists will be kept informed of the progress of the project by 6 monthly newsletters and will receive feedback on the primary outcome measures, incidence of serious adverse events, tuberculosis and other infections, lymphoma, skin cancer, and demyelinating disease. On request, individual reporters could receive a spreadsheet of the data for their own patients for local audit and for their patient records. Participating dermatologists will thus be in a position to further inform their patients of the progress of the study and at the end of the study the final outcomes.

At the end of the five years BADBIR will continue to link patient identifiers to the UK national cancer registry and death registry. These links will remain in place indefinitely to capture adverse events with long incubation times such as melanoma and to ascertain any events that were not captured by the dermatologists. After 5 years, once registration is complete, a comprehensive analysis will compare the rates of key adverse events of interest in the biologics cohort to that in the unexposed psoriasis cohort, adjusting for potential confounders.

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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 DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick 4 one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all Not relevant
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all Not relevant
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all Not relevant
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all Not relevant
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No Not relevant
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all Not relevant
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little

		Not at all Not relevant
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all Not relevant

Please check you have answered EVERY question. Thank you.

Appendix 3 EuroQol

Generic Health Utility Index – Patient Baseline EuroQol

For each of the five activities below please indicate which statements best describe your own

1. Mobility ***(Please tick one box)***

-I have no problems in walking ◯

-I have some problems in walking ◯

-I am confined to bed ◯

2. Self Care ***(Please tick one box)***

-I have no problems with self care ◯

-I have some problems washing or dressing ◯

-I am unable to wash or dress ◯

3. Usual Activities *(Please tick **one** box)*

-I have no problems performing my usual activities (e.g. work, study, housework, family/leisure activities) ◯

-I have some problems performing my usual activities ◯

-I am unable to perform my usual activities ◯

4. Pain/Discomfort ***(Please tick one box)***

-I have no pain or discomfort ◯

-I have moderate pain or discomfort ◯

-I have extreme pain or discomfort ◯

5. Anxiety/Depression ***(Please tick one box)***

-I am not anxious or depressed ◯

-I am moderately anxious or depressed ◯

-I am extremely anxious or depressed ◯

Compared with my general level of health over the past 12 months, my health state today

(Please tick one box)

Better ◯

Much the same ◯

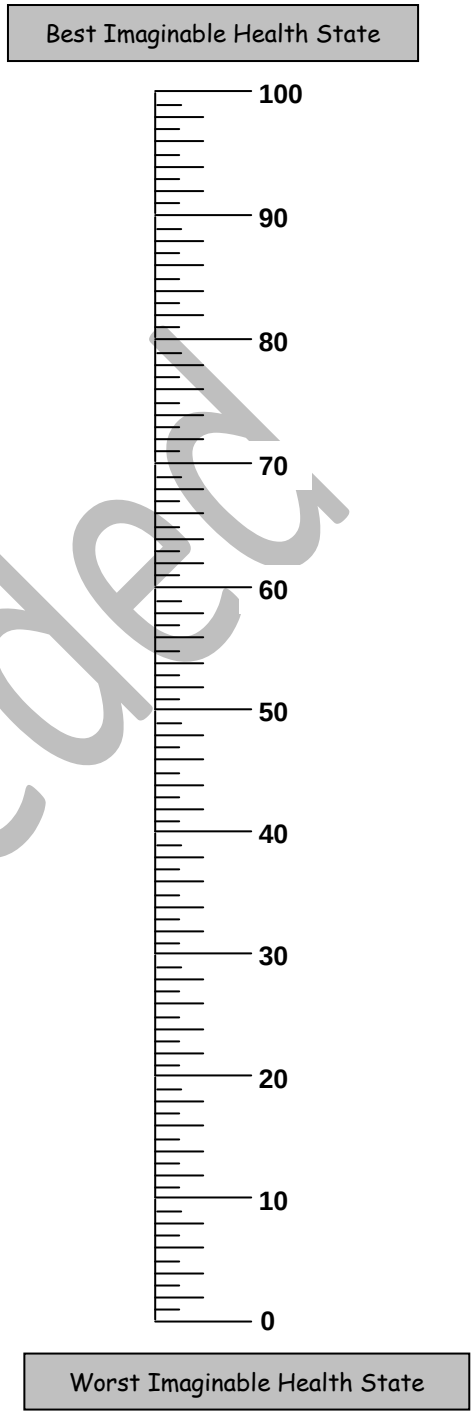
Worse ◯

Please turn over!

We would like you to indicate on this scale how good or bad is your health today, in your opinion.

Please do this by drawing a line from the box below to whichever point on the scale indicates how **good or bad your current state is.**

How do you feel today?



Patient Name:

Date Completed:

Appendix 4 PASI scoring

The Psoriasis Area & Severity Index (PASI) is scored by body region, and combines a 0-6 scale of body surface area (BSA) involvement with three separate 0-4 severity scales for the plaque qualities of erythema, induration and scaling (E,I,S). PASI is used to generate a single global score, ranging from 0-72, that is a weighted sum of the scores for the individual body regions

- When considering the different regions, remember:
- The neck counts as part of the head
- The axillae and groin count as part of the trunk
- The buttocks count as part of the lower extremities
- If the plaque qualities differ clinically within the same body area, try to score an average.
- Half values for erythema, induration and scaling are not allowed.
- **While the total PASI score may range from 0 - 72, most cases fall in the range of 0 – 25**
- Although you are not required to calculate the total PASI score for this study, the score may be calculated as follows or using a supplied spreadsheet

• PASI = (0.1) H + (0.2) UE + (0.3) T + (0.4) LE
• H = Head = $(E_H + I_H + S_H)\ A_H$
• UE = Upper Extremities = $(E_{UE} + I_{UE} + S_{UE})\ A_{UE}$
• T = Trunk = $(E_T + I_T + S_T)\ A_T$
• LE = Lower Extremities = $(E_{LE} + I_{LE} + S_{LE})\ A_{LE}$
• E = Erythema Score (0-4), I = induration Score (0-4), S = Scaling Score (0-4) and
• A = Area Grade (0-6) 0% =0; <10% =1; 10-29%=2; 30-49%=3; 50-69%=4; 70-89% = 5; 90-100%=6

SCORE	ERYTHEMA	INDURATION	SCALING
0 None	No evidence of erythema	Flat no elevation	No scaling
1 Slight	Pink colour	Slight definite elevation above normal skin	Mainly fine scales, lesions partially covered
2 Moderate	Red colour	Moderate elevation with round, sloped edges	Courser scales, lesions partially covered
3 marked	Very red colour	Marked elevation with very hard sharp edges	Coarser scales lesions covered, rough surface
4 Very marked	Extreme red colour	Very marked elevation with very hard sharp edges	Coarse very thick scales lesion covered very rough

Appendix 4 PASI worksheet (to do)

Physicians Global Assessment

Static PGA: Measured at each visit

Example of a Psoriasis Global Assessment (PGA)

Severe
Very marked plaque elevation, scaling, and/or erythema
Moderate to severe Marked plaque elevation, scaling, and/or erythema
Moderate
Moderate plaque elevation, scaling, and/or erythema
Mild
Slight plaque elevation, scaling, and/or erythema
Almost clear
Intermediate between mild and clear
Clear
No signs of psoriasis (post-inflammatory hyperpigmentation may be present)
Note: Various PGAs with different descriptions and scores have been used in clinical trials; most are similar to the above example.

Appendix 6 Patient information sheet (to be printed on hospital headed paper)

PATIENT INFORMATION SHEET

STUDY TITLE: Are new treatments for skin conditions harmful to long term health?

You are being invited to participate in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information and ask for anything that is unclear to be explained.

What is the purpose of the study?

The purpose of the research is to assess whether some of the new treatments used in the treatment of skin conditions, particularly psoriasis, have a greater risk of serious side effects and long term health problems than established treatments. The study therefore involves following up patients taking a number of different drugs for psoriasis (and other skin conditions) and assess the frequency that long-term side effects occur.

Why have I been chosen?

You have been chosen to participate as either you have been started on one of the new treatments called "biologic therapy" or you have been started on one of the established treatments and can provide useful comparison information.

Do I have to take part?

You do not have to take part. If you do decide to take part, you can keep this sheet and will be asked to sign a consent form. Your participation will not interfere with the standard of care you receive.

What will happen to me if I take part? Your

participation will involve the following:

(i) Agreement to complete the questionnaires and other survey forms about your health;
(ii) Agreement with your specialist to provide information from your medical records to the researchers;
(iii) Agreement for your name to be registered with national databases including the National Health Service Central Register, part of the General Register Office such that in the unlikely event you develop a cancer or die during the research, the researchers will be notified directly.

At this stage we do not know how long we will want to collect this information from you and about you. It is likely to be for at least five years.

Will the research influence the treatment I receive?

The research does not alter the treatment you receive. Your specialist will start and stop treatments as determined by your clinical condition.

Will my taking part in the study be kept confidential?

Identifiable information about you will be held by the research team at Manchester University Medical School, and the National Health Service Central Register, together with the data collected during the study**. This information will be collected via a computer system. Data will be sent using a secure network system and will be held at the University of Manchester.** No-one outside the research team will have access to any identifying information and all identifiable information will be kept securely.

Who is organising and co-ordinating the study?

The study is being sponsored by the British Association of Dermatologists, a society of dermatologists aiming to give the best patient care to individuals with skin diseases. The study is being co-ordinated by the University of Manchester and the lead researchers, Dr Anthony Ormerod and Professor Christopher Griffiths, can be contacted for further details. Results of the study, which are unlikely to be available for at least five years will be sent to your consultant (Tel: ########## Fax: ######### Email: ################) whom you should contact for information.

Local contact | | **Version 3: Date: 30/11/2007**

Appendix 7 Patient consent form *(to be printed on hospital headed paper)*

PATIENT CONSENT FORM

Title of Project: **Are new treatments for skin conditions harmful to long term health?**

Name of Researchers: Dr Anthony Ormerod
Professor Christopher Griffiths

Please initial box

1. I confirm that I have read and understand the information sheet dated …**30/11/2007 (version3)** for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that my record will be flagged on the National Health Service Central Register, part of the General Register Office. I give permission for these individuals to have access to my records. ☐
4. I agree to complete the questionnaires and other survey forms about my health. ☐
5. I agree that my specialist Dr _____ may provide the researchers with information from my Health Records that is relevant to this Study. ☐
6. I agree to information, from which I can be identified, being held by the research Team at Manchester University Medical School together with data collected during the study. ☐
7. I agree for my name to be registered on the national database as explained to me by _____. ☐

Name of patient	Date	Signature
Name of Person consent	Date	Signature
Researcher	Date	Signature

1 copy for patient; 1copy for researcher; 1 copy to be kept with hospital notes

Appendix 8 Questionnaires

Consultant Questionnaires
(i) Consultant baseline questionnaire
(ii) Consultant baseline supplementary questionnaires (DLQI, EuroQol, CAGE, HAQ)
(iii) Consultant follow-up questionnaire
(iv) Control Consultant follow-up questionnaire

Patient Questionnaires
(v) Patient baseline questionnaire
(vi) Patient 6 monthly diary
(vii) Patient follow-up form (includes DLQI, EuroQol, CAGE, HAQ)

Serious Adverse Event Further Information Forms
(viii) Aplastic anaemia further information rapid fax
(ix) Congestive heart failure further information rapid fax
(x) Serious infection further information rapid fax
(xi) Central demyelination further information rapid fax
(xii) Lymphoproliferative tumour further information rapid fax
(xiii) Tuberculosis further information rapid fax
(xiv) Pregnancy outcome questionnaire