

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at <http://eudract.emea.eu.int/document.html#guidance>.

To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available at <http://www.nres.npsa.nhs.uk/applicants/review/after/amendments.htm>.

Details of Chief Investigator:

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Full title of study:	British Association of Dermatologists Biological Interventions Register
Name of main REC:	North West England
REC reference number:	07/MRE08/9
Date study commenced:	16/08/07
Protocol reference (if applicable), current version and date:	BADBIR Study Protocol – Version 13 (14/05/2009)
Amendment number and date:	Amendment Seven 05/12/2012

Type of amendment (indicate all that apply in bold)

(a) Amendment to information previously given on the NRES Application Form

Yes

If yes, please refer to relevant sections of the REC application in the “summary of changes” below.

(b) Amendment to the protocol

Yes

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

Yes

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Is this a modified version of an amendment previously notified to the REC and given an unfavourable opinion?

No

Summary of changes

Briefly summarise the main changes proposed in this amendment using language comprehensible to a lay person. Explain the purpose of the changes and their significance for the study. In the case of a modified amendment, highlight the modifications that have been made.

If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

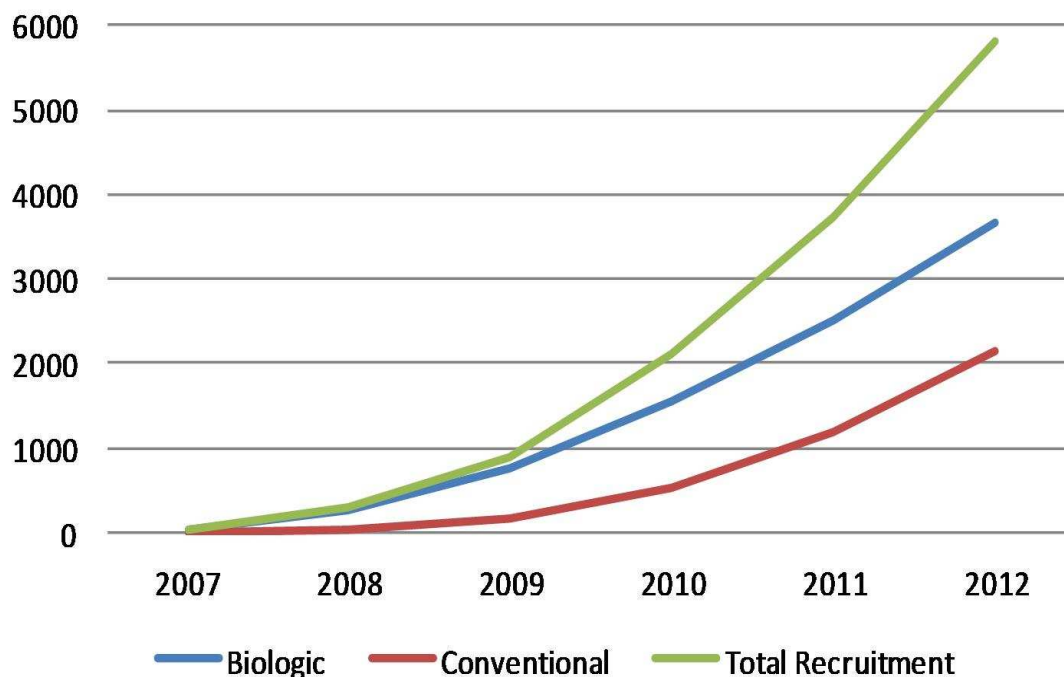
a) Recruitment

The criteria regarding required levels of recruitment in order to be able to fulfil the primary outcomes of the study are stated within the study protocol as below.

Primary outcome	Non-melanoma skin cancer
Incidence in psoriasis	1 in 1000
Number of patients	2000-4000 per drug (in order to obtain approx. 20,000 py on biologics)
Number of controls	4000
Recruitment period	2008-2013
Follow-up period	2008-2018 (5 yrs per patient)

However, recent analyses of recruitment indicate that there is a risk of not reaching the levels of recruitment required to evaluate all of the primary endpoints in the presently stated recruitment period. A number of factors have contributed to this including delays obtaining NHS approvals and lack of research infrastructure at dermatology sites. Currently, 135 sites are recruiting and since April 2010 when BADBIR was accepted onto the NIHR portfolio recruitment has significantly improved (Figure 1). Several strategies have been used to maximise recruitment and promote the project including monthly newsletters to dermatology teams, awards for centre with highest recruitment each month and promotion of BADBIR at professional events e.g. British Association of Dermatologists Annual Meeting and the effects of these are now becoming increasingly evident.

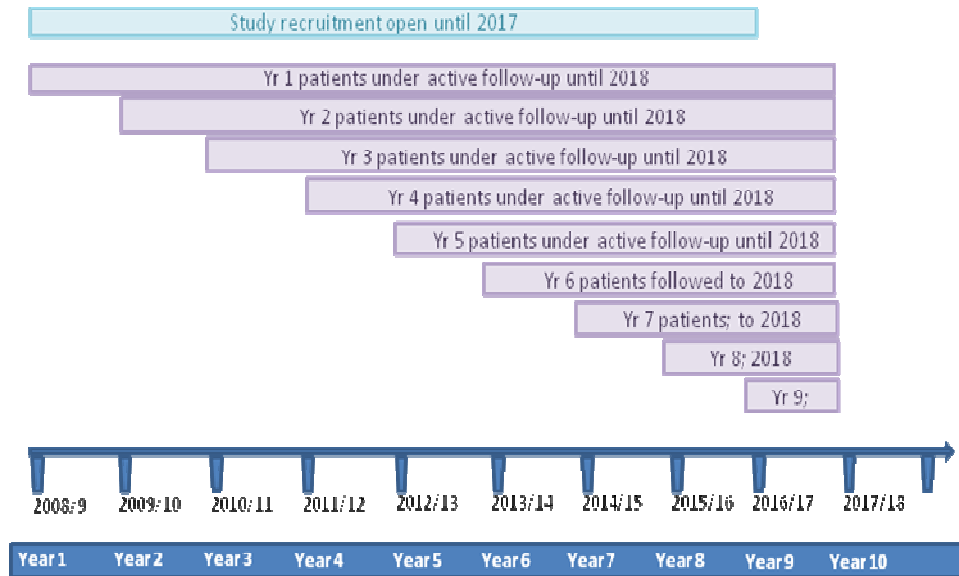
Figure 1 BADBIR Recruitment



Two important factors have been considered when looking at the possibility of extending the period of study recruitment and/or follow-up; i) ensuring that enough data are acquired to evaluate the primary endpoints of the study and; ii) to consider whether it is worthwhile following patients for a longer period of time to increase the likelihood of identifying adverse events which may have a greater latency.

Having considered the various options the following is the preferred option

Recruitment ends 2017, follow-up ends 2018 (i.e. extend both recruitment period and follow-up)



Benefits:

- Significantly increases *pyrs follow-up in all cohorts
- Enable detection of latent events, i.e. up to 10 years
- Enhance NHS IC national cancer and death register data
- Eligible for portfolio support until 2017
- By extending study recruitment period to 2017, will reflect current medical practice in the UK until 2017, i.e. prospective cohorts

Risks:

Although the overall cost of the project is not increased from the predicted budget, the yearly costs will be different. This is currently under discussion with the funders.

The study end date of July 2018 will remain unchanged. The Patient Information and Consent Form do not require amendment as these currently state that patients will be followed up for a minimum of 5 years.

b) Amendments to the Protocol

- 1) The Steering Committee propose discontinuation of data collection at follow ups as outlined below::
 - i) All Follow –ups: Patient Diary (currently this information is duplicated)
 - ii) Follow up 7 onwards (beginning of Year 4 to end of study)

- Validated PROs (i.e. DLQI, CAGE, EQ 5D, HAQ)
- Current smoking
- Current drinking
- Current employment status
- Blood results

iii). Follow up 9 onwards (beginning of Year 6 to end of study):

- Weight
- Waist Circumference

It is possible that refining data collection could improve patient retention as completion of the questionnaires is one of the main reasons given for withdrawal of consent.

Section 6 Table, Section 7.10 and Section 8 have been amended to reflect these changes

2) Procedures have been developed to deal with patient participation in clinical trials transfer to other hospitals, missed follow ups and withdrawals as follows:

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:

- 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.
- 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.
- 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.

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 is 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 BABDIR:

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.

These procedures have been included in Section 8 (page 15) of the BABDIR protocol

3. Some minor textual changes have also been made to the protocol for clarification and these are summarised in the following table:

Section	Text	Added	Deleted	Replaced
	Steering Committee and Study Team			✓
1	were			was
3.2 Design	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”. from patients or”		✓	
7.3 Psoriasis details	psoriatic” Date of Diagnosis	✓		inflammatory
7.7 Risk factors for skin cancer	“(Fitzpatrick,1975)”	✓		
7.8 Comorbidity data	“Any”	✓		
Reference List	Fitzpatrick TB: Soleil et peau. J Med Esthet 1975;2:33034”	✓		

Reduction of per patient Fees to centres

Per patient fees from Year 4 to end of follow up will be reduced from £30 to £15 per follow up.

The proposed protocol changes would justify this reduction to the centres and this would be included as an amendment to the current contracts which are all due to expire in July 2013.

c) BADBIR Patient Poster

Several centres have reported that it would be beneficial to have BADBIR posters sited in outpatient waiting rooms. This would provide interested patients with the opportunity to ask the BADBIR research team at their hospital for further information.

Text will include:

Do you have Psoriasis?

Are you taking tablets or using injections to treat your condition?

Would you like to take part in a research study aiming to assess the safety and effectiveness of current psoriasis treatments?

If the answer is yes, our local BADBIR team would like to hear from you!

For further information or to discuss your eligibility to participate, please ask your dermatologist or specialist nurse about BADBIR.

www.badbir.org

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.

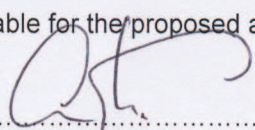
List of enclosed documents

Document	Version	Date
BADBIR Protocol	14	12/12/12
BADBIR Patient Poster	1	16/07/2012

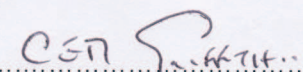
Declaration

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.

Signature of Chief Investigator:



Print name:



Date of submission:

