Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
Toxicity from Anti-TNF Therapy

REC details:

Name of main REC:
North West 5 Research Ethics Committee

REC Reference Number:
00/8/53

NRES form lock code:

1. Select one category from the list below:

- ○ Clinical trial of an investigational medicinal product
- ○ Study only involving data or tissues not identifiable to the researcher

If your work does not fit any of these categories, select the option below:

- ◉ Other study

2. Does the study involve the use of any ionising radiation?

○ Yes ◉ No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☑ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- ◉ England
- ○ Scotland
- ○ Wales
- ○ Northern Ireland
- ○ This study does not involve the NHS

4. Do you plan to include any participants who are children?

○ Yes ◉ No

5. Do you plan to include any participants who are adults unable to consent for themselves through physical or mental incapacity?

○ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

6. Is the study or any part of it being undertaken as an educational project?

○ Yes ◉ No

NOTICE OF SUBSTANTIAL AMENDMENT
Please use this form to notify the main REC of substantial amendments to all research other than clinical trials of investigational medicinal products (CTIMPs).
The form should be completed by the Chief Investigator using language comprehensible to a lay person.

Details of Chief Investigator:

	Title	Forename/Initials	Surname
	Prof	Kimme	Hyrich
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Full title of study:	Prospective observational study of the long term hazards of anti-TNF therapy in rheumatoid arthritis
Lead sponsor:	University of Manchester
Name of REC:	North West 5 Research Ethics Committee
REC reference number:	00/8/53
Name of lead R&D office:	Manchester University NHS Foundation Trust
Date study commenced:	01/12/2000 (date of original ethical approval)
Protocol reference (if applicable), current version and date:	Main protocol dated 06/10/2003. Two current sub-study protocols: 1) certolizumab and anti-TNF (v3 15/10/2010) tocilizumab (v1.1: 17/01/2011)
Amendment number and date:	Amendment 26: 19/09/2018

Type of amendment

(a) Amendment to information previously given in IRAS

◉ Yes ○ No

If yes, please refer to relevant sections of IRAS in the "summary of changes" below.

(b) Amendment to the protocol

○ Yes ◉ No

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 ○ No

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 and not approved?

○ Yes ◉ No

If yes, please explain the modifications made under "Summary of changes" below

Summary of changes

Briefly summarise the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study.
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.

Currently, the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) primary objective is to study the long term safety of biologic, biosimilar and other advanced targeted therapies in the treatment of RA. The longitudinal nature of the study has allowed the collection of disease activity and drug continuation data to assist in the analyses of the predictors of treatment response.

Treatment response can be explained primarily by genetic and disease factors but also by non-genetic patient-specific factors. Disease and genetic factors had been investigated in treatment response in rheumatoid arthritis (RA) patients (Hyrich et al. 2006; Hider et al. 2006). However, little attention had focussed on the role and contribution of patient-specific factors to treatment response and there had been little evidence on the role of patient psychosocial factors to adherence and ultimately the role of adherence in predicting treatment response. As reported treatment adherence rates varied between 30-78% (Belcon et al. 1984; Miller 1997; Owen et al. 1985; Viller et al. 1999) in RA patients, it had become clear that adherence remained a problem in this disease group.

Interestingly, studies suggest that while biologic therapies are fast acting and have significant improvement on disease outcome, the withdrawal rates from treatment are comparable to those of disease-modifying anti-rheumatic drugs (DMARDs). The consequence of treatment withdrawal or non-adherence, not only reduces the health benefit for the patient, but has financial implications for the future and availability of biologic and other advanced therapies. Conversely, if predictive factors could be identified to identify those patients likely to adhere well to medication and achieve a good response, prescription to biologic therapy can be targeted efficiently and effectively being both beneficial to patient, practice and NHS resources.

The role of psychosocial factors in predicting adherence and the role of adherence in predicting treatment response therefore warranted further investigation.

As part of substantial amendment 7 (REC approved 14th March 2007), the BSRBR-RA sought approval to further examine the influence of patient-specific factors on treatment response, specifically the influence of patient adherence on treatment response, via the introduction of an additional booklet (Views on illness, treatment and general health, v1.1 - 05/03/2007). This new booklet was to be sent alongside the patient baseline questionnaire and comprised a number of validated questionnaires. In addition, an extra page was added to the 6 monthly patient follow up questionnaires containing the validated patient self-completed Compliance Questionnaire for Rheumatology (CQR), to enable adherence to also be assessed at 6, 12 and 24 month follow up points.

This data was analysed in the publication 'The influence of behavioural and psychological factors on medication adherence over time in rheumatoid arthritis patients: a study in the biologics era' (Morgan et al. 2015) which concluded that:

"wider recognition of the importance of psychological factors, particularly medication beliefs, in driving medication adherence could have substantial clinical and health economic benefits in RA. The psychological factors we have identified are putative targets for strategies to improve adherence in RA."

Although the BSRBR-RA stopped capturing adherence data in 2011, since this time, recruitment of patients

commencing newer targeted therapies has been approved. The adherence and factors affecting adherence to these newer targeted therapies has not been previously investigated in the BSRBR-RA cohort. The nature of the BSRBR-RA study design will still enable adherence data to be collected and assessed effectively. In addition, with the readily available data such as disease activity, functional disability and treatment response data in addition to standard socioeconomic and demographic data will provide invaluable factors to be able to further explore true treatment adherence in the RA population.

The BSRBR-RA would therefore like to restart the collection of data around treatment adherence by reintroducing an amended version of the 'Views on illness, treatment and general health' booklet updating it to version 2, 31/08/2018.

The new version of this booklet consists of the following validated questionnaires:

Section A: 'Brief Illness Perception Questionnaire' (Brief-IPQ) (Broadbent et al. 2006)
Section B: Medication Adherence Report Scale (MARS-5) (Horne et al. 2002)
Section C: Compliance Questionnaire Rheumatology (CQR) (de Klerk et al. 1999; de Klerk et al. 2003)
Section D: Beliefs about medicines questionnaire (BMQ) (Horne et al. 1999)

All of the questionnaires in the booklet are represented in their full validated form.

The CQR and BMQ questionnaires remain from the previous version of the booklet whilst the Brief IPQ and MARS-5 questionnaires are new additions. The 'Illness Perception Questionnaire-Revised' (IPQ-R) (Moss-Morris et al. 2002), 'Stone & Neale Coping Questionnaire' (Stone et al. 1984) and 'Hospital Anxiety and Depression score' (HADs) (Zigmond et al. 1983) from version 1.1 of the booklet have been removed completely.

This reduces the number of questions participants are asked to complete significantly. In addition we would like to reduce the frequency of this data collection, to baseline, 6 month and 12 month follow up points only, alongside the current BSRBR-RA Patient 6 Monthly Follow-up Questionnaire (v7, 17/07/2017) approved as part of substantial amendment 25 (REC/HRA approved on 24/08/2017). Patients will be mailed a reminder, in line with the current BSRBR operating procedures.

We have continued to keep all of these validated questionnaires within a single booklet for ease of completion by the patient. However, we have also taken care to ensure that the questionnaires appear separate and distinct in the following ways:

• Each individual questionnaire has been identified under its own headings in the booklet.
• Throughout the study literature, the series of questionnaires are referred to as a "booklet" rather than a "questionnaire".
• A description on the covering page to the booklet explains the booklet contains a number of different questionnaires.

In addition, as with the previous version, some of the questions contained in the new booklet could be considered of a sensitive nature. This is addressed in the current BSRBR-RA participant Information Sheet (v9, 17/07/2017) approved as part of substantial amendment 25 (REC/HRA approved on 24/08/2017) which includes the following statement:

"You may find some of the questions to be of a sensitive or personal nature. You are not obliged to answer all questions".

References

Belcon, M. C., Haynes, R. B., and Tugwell, P. (1984). A critical review of compliance studies in rheumatoid arthritis. Arthritis Rheum, 27, (11). 1227-1233.

Broadbent, E., Petrie, K. J., Main, J., and Weinman, J. (2006). The brief illness perception questionnaire. J Psychosom Res. 2006 Jun; 60(6). 631-637.

de Klerk, E., van der Heijde, D., Landewe, R., van der Tempel, H., and van der Linden, S. (2003). The compliance-questionnaire-rheumatology compared with electronic medication event monitoring: a validation study. J Rheumatol, 30, (11), 2469-2475.

de Klerk, E., van der Heijde, D., van der Tempel, H., and van der Linden, S. (1999). Development of a questionnaire to investigate patient compliance with anti-rheumatic drug therapy. J Rheumatol, 26, (12), 2635-2641.

Hider, S.L. (2006). Methotrexate in Rheumatoid Arthritis: Clinical and genetic factors that influence drug related outcomes. PhD Thesis.

Horne, R., Weinman, J. (2002). Self-regulation and Self-management in Asthma: Exploring The Role of Illness Perceptions and Treatment Beliefs in Explaining Non-adherence to Preventer Medication. Psychol Health, 17, 17-32.

Horne, R., Weinman, J., and Hankins, M. (1999). The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health, 14, 1-24.

Hyrich, K. L., Watson, K. D., Silman. A. J., Symmons. D.P. M., and The BSRBR (2006). Predictors of response to anti-TNF-α therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology, 45, 1558-1565.

Miller, N.H. (1997). Compliance with treatment regimens in chronic asymptomatic diseases. Am J Med, 102(2A), 43-49.

Morgan, C., McBeth, J., Cordingley, L., Watson K., Hyrich K.L., Symmons D. P., Bruce I.N. (2015). The influence of behavioural and psychological factors on medication adherence over time in rheumatoid arthritis patients: a study in the biologics era. Rheumatol, 54, (10), 1780-1791.

Moss-Morris, R., Weinman, J., Petrie, K. J., Horne, R., Cameron, L. D., and Buick, D. (2002). The revised Illness Perception Questionnaire (IPQ-R). Psychol Health, 17, (1), 1-16.

Owen, S. G., Friesen, W. T., Roberts, M.S., and Flux, W. (1985). Determinants of compliance in rheumatoid arthritic patients assessed in their home environment. BrJ Rheumatol, 24, (4). 313-320.

Stone, A. A. and Neale, J. M. (1984). New measure of daily coping: development and preliminary results. J Pers Soc Psychol, 46, 892-906.

Viller, F., Guillemin, F., Briancon, S., Mourn, T., Suurmeijer, T., and van der Heuvel, W. (1999). Compliance to drug treatment of patients with rheumatoid arthritis: a 3 year longitudinal study. J Rheumatol, 26, (10), 2114-2122.

Zigmond, A. S. and Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand, 67, 361-370.

Any other relevant information

Applicants may indicate any specific issues relating to the amendment, on which the opinion of a reviewing body is sought.

List of enclosed documents

Document	*Version*	*Date*
Views on illness, treatment and general health	2.0	31/08/2018

Declaration by Chief Investigator

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

Date of submission: 24/09/2018

Signature: 

Declaration by the sponsor's representative

I confirm the sponsor's support for this substantial amendment.

Signature: .....

Print Name:

Post:

Organisation:

Date: *(dd/mm/yyyy)*

Does this amendment involve new types of exposure or increased exposure to ionising radiation?

◯ Yes ◉ No

If Yes, please provide details below:

Does this amendment involve inclusion of adults lacking capacity or a change to the arrangements relating to adults lacking capacity?

○ Yes ◉ No

If Yes, please provide details below:

Declaration by Sponsor's Representative

This section was signed electronically by Mrs Stacey Body on 21/09/2018 12:05.

Job Title/Post:	Research Governance Officer
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