Northumbria Healthcare NHS Foundation Trust

Adherence to Methotrexate in Rheumatoid Arthritis: Effect of an Information Booklet on Methotrexate Levels

Methotrexate Adherence Project

Protocol Version 2 dated 20/08/2018

Northumbria Healthcare NHS Foundation Trust

RESEARCH REFERENCE NUMBERS

PROTOCOL VERSION NUMBER 2 20th August 2018

Sponsor: Northumbria Healthcare NHS Foundation Trust

IRAS Number: 189766

CPMS 37811

TRIAL SUMMARY

Trial Title	Adherence to Methotrexate in Rheumatoid Arthritis: Effect of an Information Booklet on Methotrexate Levels	
Internal ref. no. (or short title)	Methotrexate Adherence Project	
Clinical Phase	IV	
Trial Design	Mixed Methods	
Trial Participants	Subjects with Rheumatoid Arthritis on a stable dose of Methotrexate	
Planned Sample Size	100 participants	
Treatment duration	3 – 6 months	
Follow up duration	none	
Planned Trial Period	18 months	
	Objectives	Outcome Measures
Primary	Does Education using an Information Booklet have an impact on Methotrexate Adherence and Disease Management	The responses of 100 patients with RA on Methotrexate to the Methotrexate Adherence Questionnaire and the Rheumatoid Arthritis Knowledge Questionnaire will be analysed qualitatively and quantitatively
Secondary	Do changes in Methotrexate Polyglutamate Assays detect Methotrexate Adherence	Methotrexate Polyglutamate Assays will be measured in venous blood samples of the study population

FUNDING AND SUPPORT IN KIND

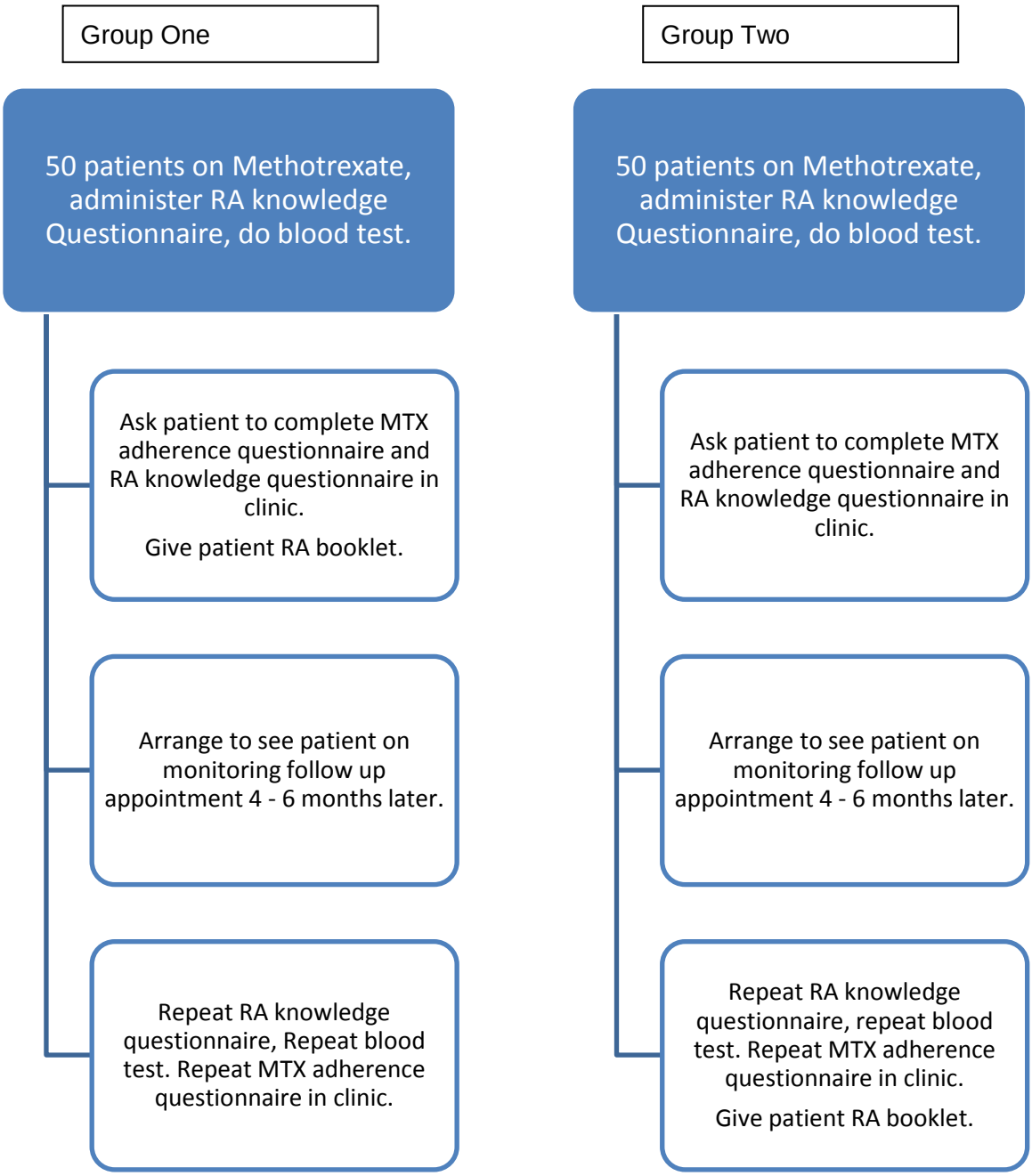
FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
Chugai Pharmaceuticals Ltd UK	Financial support given
University of Newcastle Upon Tyne	Processing of blood samples
Northumbria Healthcare NHS Foundation Trust	Study Sponsor

KEY TRIAL CONTACTS

Chief Investigator	Sandra Robinson Senior Research Nurse Northumbria Healthcare NHS Foundation Trust Co-Investigator: Dr David Walker Consultant Rheumatologist Northumbria Healthcare NHS Foundation Trust
Trial Co-ordinator	Sandra Robinson Senior Research Nurse sandra.robinson3@nhct.nhs.uk 0191 2934322
Sponsor	Northumbria Healthcare NHS Foundation Trust North Tyneside General Hospital Clinical Trials Office, Rake Lane North Shields, Tyne and Wear. NE29 8NH
Joint-sponsor(s)/co-sponsor(s)	N/A
Funder(s)	Chugai Pharmaceuticals Ltd UK
Clinical Trials Unit	N/A
Key Protocol Contributors	Dr David Walker
Statistician	N/A
Trials pharmacist	N/A
Committees	The INFLAME patient group, North Tyneside

LIST of CONTENTS

TRIAL FLOW CHART



STUDY PROTOCOL

Adherence to Methotrexate in Rheumatoid Arthritis: Effect of an Information Booklet on Methotrexate Levels.

1 BACKGROUND

The aim of this study is to explore any effect of the Rheumatoid Arthritis information booklet (Chugai/Roche 2014a) on the disease management and drug adherence of patients with Rheumatoid Arthritis (RA) taking Methotrexate. We also wish to explore the usefulness of red cell glutamate levels in determining Methotrexate Adherence levels.

Methotrexate is the default disease modifying drug (DMARD) for treatment of RA. It is a drug which has a delayed onset of action and where the majority of patients, even those continuing on treatment, have side effects that they tolerate in order to stay on the drug (Walker et al 2014). Poor drug adherence can give the impression that the therapy has failed which could lead to an economic impact (O'Niell 2011).

The definition of adherence is not straightforward, Haynes et al (2002), describe it as "the extent to which a person's behaviour coincides with medical or health advice" or Kelly (1995) who suggests "following medical advice sufficiently to achieve the therapeutic goal'. We think that patients can be divided into "Non Adherence": those patients who stop their prescriptions completely and do not pick up repeat prescriptions; Partial adherence, divided into those who partially adhere but whose disease is under good control; and those who miss medications often enough for their disease not to be under good control.

The reasons for incomplete adherence are only partly understood. They may relate to the tolerance problems (Hill 2005). Some patients find adhering to medication regimes a chore (Duerden 2013). Understanding why they are taking the drugs has been shown to improve adherence (Hill 2005). Jackson (2014) has divided the reasons into Capability; Opportunity and Motivation.

A World Health Organisation survey of a long term drug use indicates that as many as 40% of patients do not take their prescriptions as intended (2003). Patients have admitted to us of not always taking the Methotrexate and to taking a "Methotrexate holiday" when they can't face taking it (Walker et al 2014). They are often reluctant to divulge this to the healthcare staff they see. There are many reasons for this ranging from embarrassment, not wanting to "upset" their health care provider to fearing that their drugs may be stopped.

Educating patients about the drug and why they are taking it has been shown to improve adherence (Quinlan 2009) “The finding that health knowledge, especially medication knowledge, is influenced by health literacy, age, income and education”. Chugai/Roche have recently produced a booklet for people who have Rheumatoid Arthritis (Chugai/Roche 2014a). This has been designed with psychology input to prompt the patients to think about and then assess using a scale from 0 – 10 how their treatment suits them across 7 domains. These domains reflect drug use, efficacy, side effects and drug concerns. A low score in a domain prompts the user to turn to a certain section in the booklet for more information. A pilot study of the booklet has shown it to be well received and useful to patients (Chugai/Roche 2014b).

Measuring adherence is also a problem as patients may not be entirely open about how they take their drugs. Questionnaires have been used, but we suspect from talking to patients and health care professionals, that, who delivers the questionnaire and how it is delivered may make a difference to responses. Methotrexate is quickly cleared from the blood, but metabolites known as polyglutamates collect in the red cells (RC-polyglutamates) and give a longer look at drug taking. We plan to measure these for comparison with the Methotrexate dose and the adherence data.

Benefits of the Study to the NHS

The World Health Organisation (2003) reports that around 40% of patients do not take medication as prescribed; this could lead to poor disease management, waste, prescription of more expensive drugs and increased in-patient attendance. All of these factors could potentially have a financial burden on the NHS. The NHS FIVE Year Forward View (NHS 2014) describes “empowering patients”, encouraging patients to manage their own health, make informed treatment choices and provide opportunities for self-management education (NHS 2014:12). We want to understand how patients self-manage their own treatment, what impact this has on their disease and how far this could impact on the financial burden of the NHS. We want to be able to recognise and understand those situations where patients are self-managing well and when they are not. We also want to understand if education around their disease and treatment could make a positive impact on drug adherence and therefore disease management which would contribute to the financial plan of the NHS Five Year Forward View (NHS 2014:36).

This study has been given financial support from Chugai Pharmaceuticals Ltd UK. It underwent formal internal review by Chugai Clinical Support Group and Clinical Finance Group. A CPU Investigator Initiated Study Agreement is in place between the Sponsor, Northumbria Healthcare NHS Foundation Trust and Chugai Pharmaceuticals Ltd, UK.

2 RATIONALE

We are interested to explore whether this booklet, used by patients, would improve self-management of disease and adherence to Methotrexate. Our primary outcome measures will be the responses to a Methotrexate Adherence questionnaire and a Rheumatoid Arthritis Knowledge questionnaire. We will also have the opportunity to compare the Methotrexate Adherence questionnaire with an objective blood test measuring the RC-MTX polyglutamate blood levels to the prescribed dose of Methotrexate.

2.1 Assessment and management of risk

This trial is categorised as:

- Type A = No higher than the risk of standard medical care

See Appendix 1

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

The primary objective of this project is to determine if a Rheumatoid Arthritis information booklet increases understanding of Rheumatoid Arthritis in patients with this disease and leads to better disease management through drug adherence.

3.2 Secondary objectives

The secondary objective is to measure blood Methotrexate levels in order to detect drug compliance.

3.3 Outcome measures

3.3.1 Primary endpoint/outcome

The primary outcome measure is the responses to the Methotrexate Adherence and the Rheumatoid Arthritis Knowledge questionnaires. Subjects will be randomised 50:50 to receive the Rheumatoid Arthritis information booklet. Those participants who do not receive the booklet at randomisation will receive it 3 – 6 months later when the participant returns for their routine Methotrexate blood monitoring appointment. The aim of this is to determine whether the intervention of the Rheumatoid

Arthritis information booklet has an impact on patient Methotrexate management. All patients will be given the Methotrexate Adherence questionnaire and the RA Questionnaire at screening and again 3 – 6 months later.

3.3.2 Secondary endpoints/outcomes

The secondary outcome measure is the measurement of RC-MTX polyglutamate levels in a venous blood sample at two timepoints from all study patients to detect if Methotrexate Adherence correlates with RC-MTX polyglutamate levels.

4 TRIAL DESIGN

A parallel group design where each group of participants receives only one of the study treatments. The participants will be randomised to one of two groups of 50 participants each. One group will receive the Rheumatoid Arthritis information booklet at screening and both groups with have blood taken for RC-MTX polyglutamate levels at screening and 3 – 6 months later, the group who did not receive the booklet will receive the Rheumatoid Arthritis information booklet when they return 3 – 6 months later. Following a peer review of the protocol, participants who have to stop taking Methotrexate due to eg infection or abnormal blood laboratory result, will be able to continue in the study provided they have been on their original stable dose of MTX for at least 4 weeks prior to taking the second blood tests.

5 STUDY SETTING

This will be a single centre study in a secondary care setting. No PIC sites will be used. Potential participants will be invited to take part in the study when they attend for their routine Methotrexate blood monitoring. All potential study subjects will be approached first by the clinical team and then referred to the researcher if they are interested in taking part in the study. All interested potential participants will be given the study Patient Information Sheets. The study team will ensure that potential participants have as much time as they need to decide whether to take part in the study, and will be available to answer any questions. However subjects can be consented on the same day if they and the study team feel that they have had sufficient time to make an informed decision to take part.

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Subjects capable of giving informed consent in English
- Male or female
- Over the age of 18 years

- Diagnosis of Rheumatoid Arthritis
- On a stable dose of Methotrexate for at least 3 months

6.2 Exclusion criteria

- Subjects who are unwilling or unable to take Methotrexate
- Subjects who are unwilling or unable to return for their Methotrexate blood monitoring 3 – 6 months later
- Subjects who are unable to read the Rheumatoid Arthritis booklet or the Methotrexate Adherence and Rheumatoid Arthritis Knowledge Questionnaire.
- Subjects who are unable to read English

7 TRIAL PROCEDURES

7.1 Recruitment

Potential study participants will be recruited at their routine Methotrexate blood monitoring clinic having been identified by the clinical team first Potential participants will be given a Patient Information Leaflet describing the study, which will describe “Methotrexate Management” rather than “Methotrexate Adherence”. Using the word “Adherence” may affect the way the participants take their medication in order to be compliant with Methotrexate whilst on the study and we wish to avoid that bias. A diagnosis of Rheumatoid Arthritis will be determined by consulting the patients’ notes with their consent. All data collected on the study will be anonymised and each participant will be given a unique study number for identification and safety.

The following data will be collected:

- age
- gender
- ethnicity
- Dose of Methotrexate
- How long on this dose
- Route of administration

- Day of the week Methotrexate is taken
- Other concomitant medication

7.2 Consent

The Chief Investigator (CI) will retain overall responsibility for the informed consent of participants at their site and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is acceptable then details will be provided.

Informed consent will be obtained prior to the participant undergoing any study specific procedures.

The right of a participant to refuse participation without giving reasons will be respected.

The participant will remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the trial.

There will be:

- discussion between the potential participant or his/her legally acceptable representative and an individual knowledgeable about the research about the nature and objectives of the trial and possible risks associated with their participation
- the presentation of written material e.g., information leaflet and consent document which has been approved by the REC and be in compliance with GCP, local regulatory requirements and legal requirements
- the opportunity for potential participants to ask questions
- assessment of capacity. For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. A capable person will:
    - understand the purpose and nature of the research
    - understand what the research involves, its benefits (or lack of benefits), risks and burdens
    - understand the alternatives to taking part
    - be able to retain the information long enough to make an effective decision
    - be able to make a free choice

- be capable of making this particular decision at the time it needs to be made

7.2.1 Additional consent provisions for collection and use of participant biological specimens

- all biological specimens will be acquired and stored during the trial.
- biological specimens will be used for submission to ethically approved research tissue banks for future specified or unspecified research
  - participants may opt out but still participate in the main study
  - consent for the use of their data and specimens to be stored for further research will be required
  - consent for use in future research unrelated to the clinical condition under study

7.3 The Randomisation Scheme

A block randomisation schedule will be generated by:

Sealed Envelope Ltd. 2016.
https://www.sealedenvelope.com/simple-randomiser/v1/lists

7.4 Baseline Data

The following data will be collected at baseline:

- Age in years
- Gender
- Ethnic Origin
- Dose of Methotrexate the subject is currently taking
- Route of Administration
- Date the subject was first prescribed Methotrexate
- Medical history
- Concomitant Medication

7.5 Study Assessments

- Baseline and follow up Methotrexate Adherence questionnaire
- Baseline and follow up Rheumatoid Arthritis knowledge questionnaire
- Two blood test for RC-MTX polyglutamate levels

7.6 Withdrawal criteria

Participants will be withdrawn from the study if:

- They withdraw consent
- Stop taking Methotrexate or change their stable dose
- Are unable to return to clinic for their routine 3 – 6 month blood monitoring appointment
- In the PI's opinion it is in the best interests of the participant to withdraw from the study

7.7 Storage and analysis of samples

Blood sampling will be undertaken by a trained phlebotomist in accordance with Northumbria-Healthcare Foundation Trust Policy.
The samples will be transported in UN 3373 packaging to the University of Newcastle Upon Tyne.
Approximately 10mls of blood will be drawn from the subject during their routine blood monitoring clinic.
If a subject does not have good venous access and refuses more than one attempt at blood draw, this participant will be withdrawn from the study.
The Sponsor will provide the collection bottles.
The samples will be tested at the University of Newcastle Upon Tyne.

7.8 End of trial

The sponsor will notify the REC within 90 days of completion of the study.

8 STATISTICS AND DATA ANALYSIS

8.1 Planned recruitment rate

It is expected that the project should run for 18 months from the date of R&D approval being given. It is estimated that 10 – 15 patients per month will be recruited, until a total of 100 patients have been recruited into the study.

8.2 Statistical analysis plan

Sample size estimation

This is a pilot study, and as such key outcomes of interest relate to recruitment rates, drop outs a/loss to follow up and data quality and missing data for completion of the adherence questionnaire. We will also collect data on change in adherence with medication and change in polyglutamate levels in red blood cells from baseline to follow-up in each group. This will help inform a sample size calculation for a fully powered clinical trial. For an external pilot study designed to establish the sample size for a definitive randomised controlled trial, with a normally distributed continuous primary clinical outcome, Teare, et al[1] recommend a minimum sample size in each group of 35. To allow for a maximum drop-out rate of 30% at follow-up, we aim to recruit 50 subjects per group (100 in total).

8.3 Primary outcome analysis

Data analysis will be supported by standard statistical software (e.g. SPSS, SAS) and supervised by a statistician. Given the pilot nature of the study, and the stated outcomes of interest, much of the analysis will be of a descriptive nature using standard summary outcomes (e.g. frequency, mean, median, range, standard deviation). Where appropriate (e.g. assessment of effect size) for clinical outcomes of interest, inferential analysis will be conducted using standard tests depending on the distribution and nature of the data (e.g. t-test, Mann-Whitney U test, Wilcoxon signed ranks test, Chi-squared test). Significance will be set at 5% and two tailed tests used as appropriate.

8.4 Subject population

The subject population under study are patients with Rheumatoid Arthritis over the age of 18 and who have been on a continuous stable dose of Methotrexate for at least 3 months.

9 DATA HANDLING

9.1 Data collection tools and source document identification

Source Data

ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

Source Documents

ICH E6 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

Case report forms

The lead study nurse and the PI will ensure that:

- adequate collection of data has been performed
- proper paper trails will be kept to demonstrate the validity of the trial (both during and after the trial)
- only the data required by the protocol are captured in the CRF (using the CRF to capture secondary data not required for the study may be a criminal beach of the Data Protection

Act, makes the CRF unnecessarily complicated, and can make it more difficult to extract the primary data for analysis)

10 Data handling and record keeping

- Data will be entered onto paper CRFs and patients' hospital notes. This data will be checked by the lead study nurse and the CI.
- All data will be stored in study files which are located in a locked office in The Clinical Trials Office at North Tyneside Hospital. No identifiable data will leave Trust facilities.
- No identifiable data will be transferred out of Northumbria Healthcare NHS Foundation Trust. No identifiable data will be recorded on blood samples only the subject's unique study number.
- All study participants will be allocated a unique study number as and when they give informed consent and study enrolment. This will be carried out by the research team.
- The lead study nurse is responsible for data entry and quality.
- Study personnel are responsible for data analysis.

11 ACCESS TO DATA

Direct access will be granted to authorised representatives from the Sponsor and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11.1 Archiving

- archiving will be authorised by the Sponsor following submission of the end of study report
- The sponsor will be responsible for storing all trial related documents
- all essential documents will be archived for a minimum of 5 years after completion of trial
- destruction of essential documents will require authorisation from the Sponsor

12 MONITORING, AUDIT & INSPECTION

Monitoring of the study will be conducted internally by the Research and Development Department. All study documentation will be available for monitoring and audit purposes.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review& reports

- before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters
- substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study
- all correspondence with the REC will be retained in the Trial Master File/Investigator Site File
- an annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended
- it is the Chief Investigator's responsibility to produce the annual reports as required.
- the Chief Investigator will notify the REC of the end of the study
- if the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination
- within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC

13.2 Public and Patient Involvement

The study will be discussed with a local patient group who meet on a regular basis.

We will discuss:

- Design of the research
- Management of the research
- Undertaking the research

13.3 Regulatory Compliance

The study will not commence until all of the following approvals have been obtained:

- Ethics Committee Approval
- HRA Approval
- Trust Research and Development Approval
- Caldicott Approval (if necessary)

13.4 Data protection and patient confidentiality

All investigators and trial site staff will comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

- All data will be collected on Northumbria Healthcare NHS Foundation Trust premises. All study documents will be kept locked in the clinical Trials Office at North Tyneside Hospital and only the research team will have access to the documents. No identifiable personal data will be used and to further protect the identity of participants, the name of the patient will be replaced by a study number.
- Data will be stored for 15 years in accordance with Trust Policy.
- The chief Investigator is the Data Custodian.

13.5 Indemnity

The study will be covered by the NHS Indemnity Scheme.

13.6 Amendments

Any study amendments will be notified to the Sponsor NHS R&D department, The Research Ethics Committee will be notified of any substantial amendments.

13.7 Post trial care

All participants will be given the opportunity to receive the study results when they have been published.

13.8 Access to the final trial dataset

All of the study team will have access to the final dataset. In order to disseminate the results more widely the data will be submitted for presentation either as a poster or oral abstract at the British Society of Rheumatology Annual National meeting and will be prepared for publication if accepted.

14 REFERENCES

Chugai/Roche 2014a *Get the most from your RA treatment* Chugai/Roche June 2014 RCUKACTE01043E

Chugai/Roche 2014 *Non Adherence Discussion Guide: Pilot Findings and Recommendations* RCUKACTE01043r

Duerden M, Avery T, Payne R 2013 *Polypharmacy and Medicines Optimisation Making it Safe and Sound* The Kings Fund London

Haynes RB, McDonald H, Garg AX (2002). *Interventions for Helping Patients to Follow Prescriptions for Medications* Cochrane Review Oxford.

Hill, J 2005 Adherence with Drug Therapy in the Rheumatic Diseases Part One: A Review of Adherence Rates *Musculoskeletal Care* Vol 3 No 3 pp 61-73

Jackson Eliasson Barber & Weinman 2014 Applying COM-B to medication adherence: a suggested framework for research and interventions. *The European Health Psychologist.* http://www.ehps.net/index.php?option=com_content&view=article&id=302&Itemid=323

Kelly J (1995). Making sense of drug compliance by patients. *Nursing Times* 91: 40–1.

O'Neill, C 2011 Importance of Adherence and the role of Nonfinancial Barriers Editorial *Clinical Therapeutics* Vol 33 No 9

Quinlan P 2009 *The Relationship Between Health Literacy, Health Knowledge and Adherence to Treatment in Patients with Rheumatoid Arthritis* Doctoral Thesis Columbia University USA

Teare MD, Dimairo M, Shephard N, Hayman A, Whitehead A, Walters SJ. 2014 Sample size requirements to estimate key design parameters from external pilot randomised controlled trials: a simulation study. Trials. 2014;15:264

Walker et al 2014 A multi-centre Survey of Tolerability Problems for Patients on Regular Methorexate. *Arthritis and Rheumatology* Vol 66 No 11 (Suppl) p 1064 November 2014

World Health Organization (2003). *Adherence to Long-Term Therapies. Evidence for Action*. Geneva: World Health Organization.

16. APPENDICIES

16.1 Appendix 1-Risk

Risks associated with trial interventions

☒ LOW ≡ Comparable to the risk of standard medical care

☐ MODERATE ≡ Somewhat higher than the risk of standard medical care

☐ HIGH ≡ Markedly higher than the risk of standard medical care

A low risk questionnaire will be administered twice during the study. A blood test will be taken twice during the study, but this will only occur at a routine blood monitoring appointment where blood tests are taken under normal clinical care. The extra blood test will be taken at this time to minimise the discomfort and inconvenience to the subject.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
none	Circulatory	Blood test	twice	Taken when routines tests are being carried out.

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.)

N/A

16.2 Trial documentation and archiving

The PI will be responsible for archiving the trial data. This will be done in accordance with Northumbria Healthcare NHS Foundation Trust Policy

16.3 Required documentation

The local documentation required prior to site initiation are:

- CVs of the Research Team
- Laboratory Reference Ranges
- Ethics Approval
- R&D Approval

16.3.1 Principal Investigator responsibilities

The PI's legal responsibilities are listed in the Participating Site Agreement, The PI will ensure that all new members of the team are trained in the protocol and its procedures, ensure that the ISF is accurately maintained, disseminate important safety or trial related information to all stakeholders within the site.

16.4 Appendix 4 – Schedule of Procedures

Procedures	Screening	Baseline
Informed consent	X	
Demographics	X	
Concomitant medications	X	X
Laboratory test	X	X
Eligibility assessment	X	
Randomisation	X	
Assessment 1 Adherence Questionnaire	X	X
Assessment 2 RA Knowledge Questionnaire		
Adverse event assessments		X

16.5 Appendix 6 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.