PEAC

CLINICAL PROTOCOL

Version 2

TITLE:

Pathobiology of Early Arthritis Cohort (PEAC)

FUNDING BODY:

MRC

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Ethics Approval:

TITLE: PATHOBIOLOGY OF EARLY ARTHRITIS COHORT (PEAC)

REC reference number: 05/Q0703/198

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1 Study Rationale

Rheumatoid arthritis is one of the most important chronic inflammatory disorders in the UK. It affects approximately 1% of adults, causes considerable morbidity, reduces quality of life and increases mortality and results in large medical costs (over £1.2 billion/year) (1). As severe RA leads to structural damage within two years of onset, if effective disease control is not achieved (2), early aggressive treatment is recommended (3, 4). Treatment protocols are guided by some well-established prognostic algorithms (5) that include clinical parameters and positive autoantibodies such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP). However, particularly at presentation when patients with synovitis might fall into different diagnostic (RA vs non-RA including undifferentiated poly arthritis UPA) as well as disease severity categories, these markers are insufficiently sensitive to reliably identify individuals that will progress to destructive arthritis and hence functional and economic decline (5) (6).
Despite being a common disease there have been few cohorts in the UK that have systematically collected clinical, radiological, genetic and biological data. PEAC will provide such a unified approach. It will lead to a step change in the way in which clinical, imaging and immune- pathologic data is collated and integrated in the UK allowing UK rheumatologists to have a unique resource to compete within the EU arena, where complementary but distinct approaches in the Netherlands and Scandinavia have proven to be highly informative and successful.

Of critical relevance, even when the 'diagnosis' is established by virtue of composite diagnostic criteria, RA behaves clinically as a heterogeneous condition with a variable clinical course and major differences in joint damage scores: 10-12 fold after 10 years of disease (7). Thus, it is critical to tailor treatment on an individual patient basis according to prognosis-severity categories. Thus, it remains of critical importance to develop better prognostic/predictive (bio)-markers of joint erosion at presentation not only to determine the most effective allocation of expensive biologic disease modifying therapies but, above all, to prevent disability and the consequent considerable costs for individuals and society.

The development of a prospective early arthritis cohort with high quality clinical and imaging data together with a comprehensive collection of biological samples will provide a unique resource to search for early predictors of disease evolution as well as to enable early proof of concept/mechanistic studies with stratified entry according to the imaging and immunological profile. Thus, this cohort will represent an ideal platform for clinical trials of novel substances. In particular, it is envisaged that time integrated US/PDU imaging will improve on currently employed composite clinical assessment tools permitting earlier evaluation of response to therapy and development of prognostic algorithms of structural damage progression. Equally, the comprehensive collection of samples (particularly synovial tissue through a US guided minimally invasive biopsy) will enable scientists to test and generate hypotheses on the disease origin, natural course and response to treatment.

2 Design

This is a prospective, observational study in patients with early symptomatic inflammatory arthritis (3-12 months duration). Patients will be categorized, monitored and treated according to best practice and established prognostic algorithms as summarised in appendix 1.

3 Sample size

The target size of PEAC is 300-400 patients recruited in 24 months, so that practical end points of the study can be completed within 36 months while still allowing extra time for recruitment if necessary. Current recruitment rates at the participating Centers (5 patients/month/Centre) indicate that 600 patients will be eligible in 24 months. Depending on attrition rates for 1st and 2nd biopsy (section 4.2), it is estimated that 420 patients will be recruited to the study if 30% decline biopsy. Current biopsy consent rates, using US guided minimally invasive technique exceed 80%. Nonetheless, even allowing for 50% of patients declining biopsy, 300 patients (our target population) will be available. Formal power calculations for testing of hypotheses generated from this population will be possible as pilot data emerge for the primary and exploratory analyses. However, based on many observational and interventional studies, this population size is considered to have enough power to detect statistically significant differences at alpha value of 0.05.

4 Objectives and hypothesis

The purpose of PEAC is to develop a biomedical resource with a comprehensive collection of clinical, radiological and tissue samples form patients with early onset inflammatory arthritis.

The main hypothesis that will be tested is that there are distinct molecular and cellular phenotypes within the synovial tissue (genetically and / or environmentally driven) that define specific disease subsets and provide characteristic prognostic implications providing an explanation for disease heterogeneity and response to therapy.

Other specific programmes of the PEAC Consortium applicable to this proposal include: a) the development of novel diagnostic-prognostic algorithms using clinical, histopathological and imaging (US/PDU) categories and b) pathogenetic studies to further investigate the relationship between cytokines, hypoxia, angiogenesis and bone & cartilage damage. Questions to be address include the relationship between the early development of erosions and:

(i) Synovial thickening and volume (assessed by 2 and 3D high frequency ultrasonography (US) and synovial vascularity and vascular morphology, by 2 and 3D Power Doppler (PDU).
(ii) Degree of synovial inflammation both in terms of cellular make up and extent of lymphoid organisation (that would lead to higher levels of B cell activation and differentiation)
(iii) Specific gene expression signatures production of a range of cytokines and chemokines.

The potential identification of novel clinical biological correlates will lead to more efficacious disease management as well as early evaluation of clinical trials with rapid translational value.

5 Inclusion / Exclusion criteria

5.1 Inclusion Criteria

1. Adults aged 18 or over
2. Capable of giving consent to enrollment
3. Patients has at least one swollen joint which is amenable to synovial biopsy
4. Evidence of active arthritis shown by 1 or more swollen joint
5. Patient is judged to be in good health based upon medical history, physical examination, vital signs, and routine laboratory tests

5.2 Exclusion Criteria

1. Patients in whom biopsy is contra-indicated (e.g. taking anticoagulants)
2. Patients in whom there is no suitable joint for synovial biopsy.
3. Patients with a serious underlying medical disorder (e.g. end stage renal disease)

6 Patient Recruitment

Patients with early symptomatic inflammatory arthritis (less than 12 months duration) will be recruited from designated 'Early Arthritis' Clinics at each of the consortium sites.

Patients will be asked to consent at enrollment prior to any further assessment. The Patient information and consent form (REC reference number: 05/Q0703/198) pertaining to the study will be reproduced on the site headed note paper. A copy will be given to the patient, a copy will be placed in the patients notes and a copy retained for the study folder.

7 Data and donated tissues will be used for the following purposes

a) Clinical data will be collected at recruitment and every 6 months for a period of 2 years. Health assessment questionnaire, European Quality of life score, fatigue scores and DAS 28 score will be recorded as normally done in the RA clinic in our Unit.

b) Radiological data will be collected at presentation and 6 months for a period of 2 years
c) Screening blood tests will be carried out as per routine clinical assessment. In addition, 20 mls of blood will be obtained for cytokine/chemokine analysis, auto antibody analysis and DNA analysis for research purposes.

d) Within 2 weeks of recruitment (time 0) for each patient, an arthroscopic or ultrasound guided biopsy will be carried out and 10-15 specimens will be collected and processed for histological evaluation and gene microarray analyses. A second biopsy will be performed and serum collected after 6 months for the above tests to be repeated. This arm of the project will allow identification of the initial histomorphological pattern of cellular infiltrate in the synovial tissue, show any change over time and correlate this with defined measures of disease outcome. This is the only way to address prospectively the main scientific questions describe above.

e) Biopsy material will provide tissue for histology for the presence of "follicular" vs diffuse synovitis (H&E staining) and RNA extraction for gene expression profiling by microarrays. This will apply to both specimens from cross-sectional (for which ethical approval has already been granted) and prospective patient groups. Serum samples collected from each participant for cytokine and autoantibody determination. X-rays (hands and feet) will be collected on entering the study and at determined time points (6 and 12 months).

f) Urine: Urine will be collected at each routine clinic visit. The urine sample will be transferred from a collecting cup to a sterile universal container. The specimen will be stored at -80oC for metabolomic analysis.

g) US Data: Data from routine Ultrasound examinations of patient's joints at routine clinic visits will be collected. Power Doppler and Greyscale images will be scored retrospectively by both quantitative and qualitative methods. This data will be used to better characterise the group of patients with aggressive arthritis who have a poor functional outcome at the end of the study period.

8 Clinical Research Forms

8.1 Recruitment and follow up visits

Data from the initial visit, prior to treatment will be collected on specific data forms. Data to be collected at this visit includes

8.2 Demographics

Name
Date of Birth - Please specify: dd / mm / yyyy
Age - years
Hospital number
Gender - Male / Female
Marital status - Please specify: Single / Married / Divorced / Separated / Widowed.
Ethnicity - Please specify: White Caucasian / European / Bangladeshi / Black African / Black Caribbean / Pakistani / Indian / Chinese / other.
Occupation
Education - Please specify: Junior School / Secondary education / University degree / other

8.3 Medical history

Please provide the patients previous medical history from the patient's notes.

8.4 Concomitant Medications

Please list all current medication, start dates and the conditions being treated.
Recent steroid therapy - Patients who are already receiving steroid therapy may still be recruited to the study but should have their treatment amended to align with the designated treatment algorithm for PEAC. Prior to synovial biopsy patients should **not** have received:

i. Oral Predniolone > 7.5mg for 4 weeks
ii. Intra-articular steroid in the joint to be biopsied for 6 weeks

8.5 Family History of Rheumatic disease

If there is a family history of Rheumatic disease please specify in the table the relationship to the participant and the diagnosis of the condition.

8.6 Concomitant Medication

Please list all current medication, start times and the conditions being treated.

8.7 Cardiovascular risk factors

Smoking history - please specify whether the patient is a previous or current smoker and the number of pack years. This can be calculated by multiplying how many packs of cigarettes are smoked per day by the number of years the patent has been smoking. This applies to both ex-smokers and current smokers.
BMI - see under VITALS section
Alcohol consumption - please specify in units / week
Previous cardiovascular events - please specify nature and year of onset
Family history of cardiovascular events - please specify in the table the relationship to the participant and the nature of the event.

8.8 Vital Signs

Weight (kg)
Height (m) - this should be calculated without footwear
BMI (kg/m2) - calculated as weight / $(height)^2$
Blood pressure & pulse - these parameter should be measured in mmhg, with the patient resting for 5 mins.

8.9 ACR Criteria

Please tick appropriate response for each of the criteria.
If the patient has a positive rheumatoid factor please record the titre from the local laboratory result

8.10 Visser's Prognostic Features

Please indicate on the CRF table which indicators are present or absent. This will influence treatment decisions based upon the agreed therapeutic algorithm.
MTP Squeeze - the patients metatarsal joints should be pressed firmly holding the 5th and 1st metatarsal heads on the medial and lateral sides respectively. If this is painful in either foot a positive result should be recorded.
Length of symptoms prior to presentation - please record the number of weeks since symptom onset.
Anti-CCP & Rheumatoid factor- if positive please record the titre from the local laboratory

8.11 Diagnosis

Please record the appropriate response in the table provided in the CRF. For those patients classified as having Rheumatoid or Undifferentiated Arthritis, please indicate whether they have a good or bad prognosis. This will determine the treatment regime followed (see Appendix 1).

Rheumatoid arthritis - Bad prognosis will be inferred if there is the presence of (i) DAS-28 over 5.1; (ii) seropositivity for rheumatoid factor or anti-CCP; (iii) one or more radiographic erosions in the hands and feet. Other wise the patient will be assumed to have a good prognosis

Undifferentiated Arthritis - Bad prognosis will be inferred by the presence of anti-CCP antibodies or Vissers score > 6.

8.12 Joint Assessment

If any patients have joints which cannot be assessed then please indicate by N/A. Please specify which joints are unable to be assessed.

The following 28 joints will be assessed for both tenderness and swelling. Tenderness will be assessed in response to pressure and/or passive motion. Finger Proximal Interphalangeal Joints, thumb interphalangeal joint, metacarpophalangeal (MCP), wrists (includes carpometacarpal, intercarpal, and radiocarpal), elbows, shoulders, and knees.

Joint pain with palpation or pain on passive motion (either is sufficient) will be scored as:

0 - No pain

1 - Pain as stated by patient

Joint swelling will be scored as:

0 - No swelling

1 - Swelling

8.13 Visual Analogue Scores

Patients should complete the first three visual analogue scores (VAS) by transecting the line. Please record the value in mm within each box provided. The assessor should complete the final VAS and once again record the score in mm.

8.14 Disease Activity Score

The primary measure of disease activity in this study is the DAS28(ESR). This consists of the number of tender joints (28 joint count), swollen joints (28 joint count), a Global Health Index (100 mm VAS), and the ESR. The formula for determining the DAS28(ESR) is as follows:

$$DAS28 = 0.56 \surd (TEN28) + 0.28 \surd (SW28) + 0.70 \ln (ESR) + 0.014 (GH)$$

8.15 HAQ: Disability scale

Patients will respond to the Stanford Health Assessment Questionnaire disability scales (HAQ-DI) at inception at each subsequent visit. The HAQ – Disability Index questionnaire is in Appendix 2.

9 Radiological Assessment

9.1 X-rays

Digital radiographs of hands, wrists and feet will be taken using standardised views at each centre. Coded, anonymised baseline and follow-up radiographs will be assessed centrally for image quality. Radiographs will be read using the modified van der Heijde/Sharp score by two observers “blinded” for Centre and treatment. These images will be recorded at baseline (TIME 0) and at 1 year.

9.2 Ultrasound assessment

Patients will be imaged by ultrasound at baseline at 3 monthly intervals. Data will be stored locally and be copied and transferred to a central repository. A core data set of US data will be collected - Transverse PDU images of all 10 MCP joints. US imaging will also be retrieved form the biopsied joint prior to the procedure. See Ultrasound Manual for PEAC for more details.

10 Synovial Biopsy

A synovial biopsy will be performed at time 0 (within 2 weeks of recruitment) and at 6 months. The synovial biopsy will be performed by trained personnel at each centre and use arthroscopic procedure with or without ultrasound guidance.
Synovial tissue, blood and urine will be collected at these time points. A laboratory manual is available to cover the acquisition and processing of these tissues prior to transportation to the central repository.

11 Blood samples

Blood will be taken for local laboratory investigations at each routine clinic visit. At recruitment (TIME 0) blood local laboratory results for Cholesterol / HDL / LDL / GLUCOSE should be recorded.

Bloods TIME 0 & 1 YEAR
FBC / U+E / LFTs / CRP / ESR / RF / CCP / Cholesterol / HDL / LDL / GLUCOSE

Routine bloods for follow up (minimum data set)
FBC / U+E / LFTs / CRP / ESR

12 Therapy

Therapy will be initiated according to a set treatment protocol (see Appendix 1) depending upon classification of the early arthritis and in the case of Rheumatoid arthritis and Undifferentiated arthritis, whether they have good or bad prognostic features (see Vissers Criteria above). Patients will be considered for therapy modification at 3 monthly intervals. Treatment will be maintained/escalated according to EULAR response criteria: good, moderate or poor. Patients failing DMARD therapy will be treated with a TNF blocking agent. Approximately 30-40% of these patients will not respond to TNF-blockade and will be managed in line with best practice

13 Data Management.

A central database will be created to act as a central repository for all project data. This database will be anonymised and maintained within the Barts and The London Genome Centre on secure servers with password access only and local automated nightly backup. As describe above BLGC currently houses a number of large scale projects, similar in structure to the proposed study. Patient data will be collected at each of the sites and input into the database via a custom built web browser interface. Submission of this data will be via an encrypted and password protected link. The server will run a MySQL database and Apache webserver on a linux operating system in a common stack of software known by the acronym of'LAMP'. Both the MySQL database and Apache webserver applications are enterprise level systems used widely in mission critical, high usage environments.

14 Analyses and Statistics

(i) The paired student t test will be used to compare the DAS28 and HAQ scores in patients with different degrees of lymphoid aggregation and other biomarkers (e.g. CD68) in the initial synovial biopsy; Chi square statistics will be used to examine the relationship between the number of patients requiring additional treatments and/or the number of patients requiring TNF-inhibitors and the levels (above or below) of specific synovial biomarkers and lymphoid aggregation thresholds.
(ii) Multivariate complex regression models will be used to compare the relationship between synovial biomarkers and lymphoid aggregation thresholds, specific gene expression signatures, cytokine production patterns, erosive outcomes, other risk factors such as rheumatoid factor and treatment with disease modifying drugs.
(iii) Novel statistic algorithms developed by Dr Falciani with Prof Buckley's group in Birmingham will be also used

15 Governance

Patient recruitment and participation in the proposed study requires Ethical approval, which has been obtained by the Coordinating Centre (Ref n 05/Q0703/198) to include all participating Centres for the collection of data and patient's samples following informed consent (form attached).
The PEAC Biomedical Resource will be based at the Human Tissue Resource Centre (HTRC) and the Barts and The London Genome Centre (BLGC). These structures are core facilities provided by Barts and The London NHS Trust and School of Medicine with a track record in managing large biomedical and database resources including the MRC BRIGHT Study, NESTEGG, GAINS and Genetics of Sepsis and Septic Shock (GENOSEPT) studies (attached letter of Prof. M Caulfield). The teams managing these core facilities have considerable experience in overseeing: governance, ethics, compliance, audit and the application of uniform management and usage policies in accordance with data protection legislation and Human Tissue Act 2004.
The curator of the PEAC Biomedical Resource will be the Coordinator of the Consortium assisted by the PEAC Steering Committee and Scientific Advisory Board

16 Bibliography

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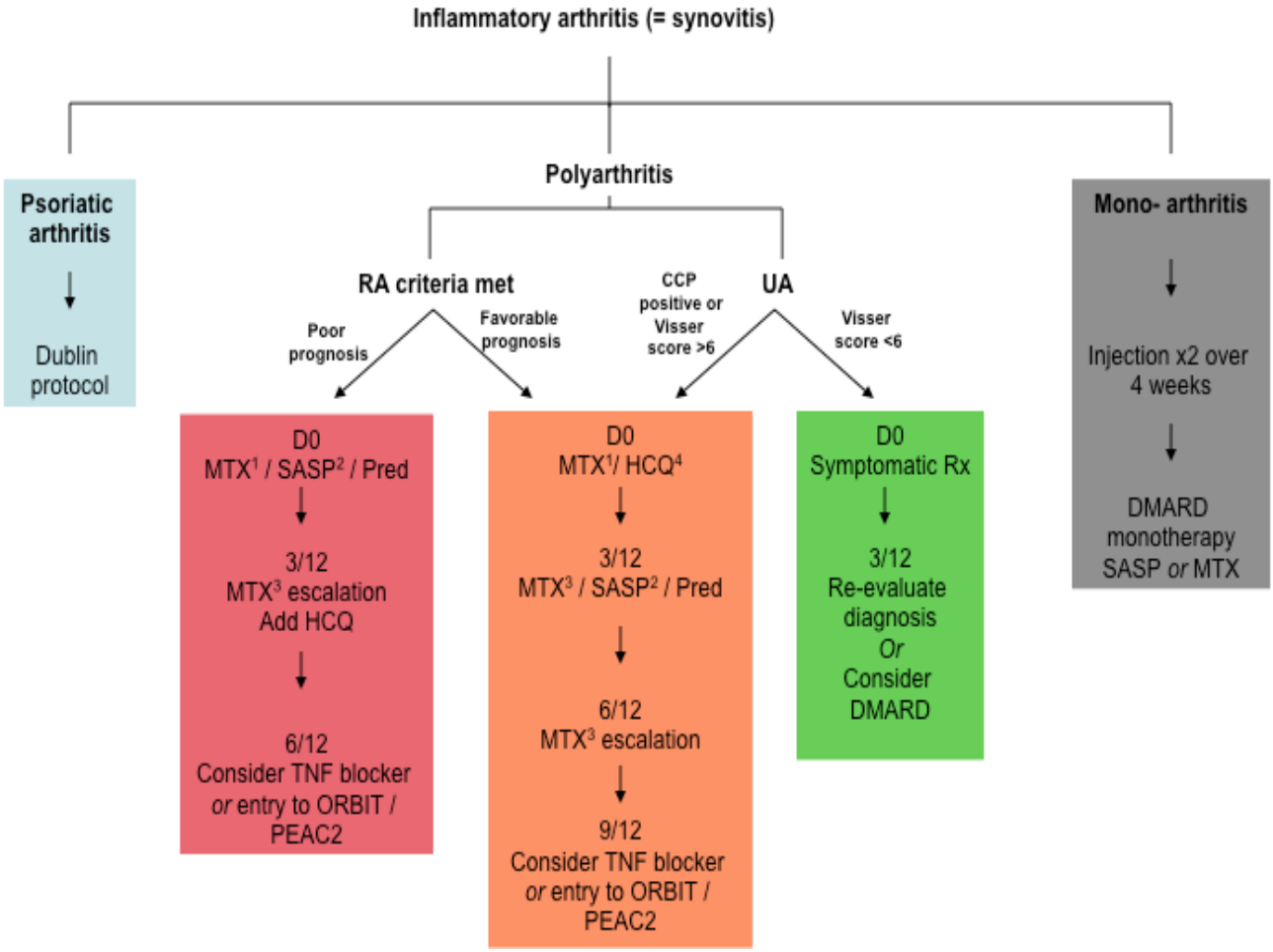
Appendix 1: Therapeutic treatment algorithm



Footnotes to protocol

1. MTX dose commencement: Oral dose of 7.5mg per week together with 5 mg per week of folic acid. Escalate MTX by 2.5mg increments every two weeks as tolerated. This will achieve dose of 20mg per week by week 12 evaluation. Monitoring required per local practice. Non mandatory interim reviews may be necessary at the discretion of the treating rheumatologist
2. SASP dose commencement: Oral sulphasalazine 500mg per day increased in 500mg increments weekly to target dose 2g per day or maximum dose tolerated. Monitoring required per local practice.
3. MTX further dose escalation: At week 12 assessment post MTX commencement, increase in 2.5mg increments every two weeks to target dose 25mg per week or as tolerated. Consider resort to parenteral MTX administration if no therapeutic response.
4. HCQ commencement: oral dose 200mg per day if patient <63kg and 400mg per day if >63kg, adjust higher dose down pending tolerance. Visual screening as per local practice.

Concomitant steroid rules

1. No steroid to a joint within 6 weeks pre-biopsy
2. 120-200mg depomedrone allowed at presentation and 6-8 weekly thereafter in appropriate prognostic groups
3. Oral prednisolone if used per protocol should be prescribed at 7.5mg p.o.
4. Intra-articular steroid injection allowed in addition - 10mg triamcinolone per small joint; 20mg triamcinolone to medium joint; 40mg triamcinolone to large joint. Dose equivalent steroid preparation may be used according to local practice.

Disease activity assessment

1. Should be evaluated 3 monthly through year 1
2. Therapeutic escalation performed every three months per protocol guidance. Escalation of therapy required if therapeutic failure since last evaluation. Defined as *either* DAS28 fall is <1.2 *or* DAS28 fall > 1.2 but residual DAS28 score is >3.2.

Appendix 2: HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)©

Name: _____ Date: _____

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
DRESSING & GROOMING				
Are you able to:				
Dress yourself, including shoelaces and buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
Stand up from a straight chair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
Cut your own meat?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Devices used for Dressing (button hook, zipper pull, etc.)
☐ Built up or special utensils
☐ Crutches
☐ Cane
☐ Wheelchair
☐ Special or built up chair
☐ Walker

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and grooming ☐ Arising ☐ Eating ☐ Walking

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
HYGIENE				
Are you able to:				
Wash and dry your body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
Open car doors?	☐	☐	☐	☐
Open previously opened jars?	☐	☐	☐	☐
Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
Run errands and shop?	☐	☐	☐	☐
Get in and out of a car?	☐	☐	☐	☐
Do chores such as vacuuming or yard work?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Raised toilet seat
☐ Bathtub bar
☐ Long-handled appliances for reach
☐ Bathtub seat
☐ Long-handled appliances in bathroom
☐ Jar opener (for jars previously opened)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene
☐ Reach
☐ Gripping and opening things
☐ Errands and chores

Your ACTIVITIES: To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

COMPLETELY	MOSTLY	MODERATELY	A LITTLE	NOT AT ALL
☐	☐	☐	☐	☐

Your PAIN: How much pain have you had IN THE PAST WEEK?
On a scale of 0 to 100 (where zero represents “no pain” and 100 represents “severe pain”), please record the number below.

Your HEALTH: Please rate how well you are doing on a scale of 0 to 100 (0 represents “very well” and 100 represents “very poor” health), please record the number below.
