



French multicentre cohort

Code no. P070302

SPONSOR	Assistance Publique – Hôpitaux de Paris Department of Clinical Research and Development Hôpital Saint-Louis 1, avenue Claude Vellefaux 75475 Paris cedex 10	<u>Project manager:</u> Yannick Vacher Tel: +33 (0)1 44 84 17 30 Fax: +33 (0)1 44 84 17 88
COORDINATING INVESTIGATOR	Professor Maxime Dougados GHU Cochin Service de Rhumatologie B 27 rue du Faubourg St Jacques 75014 Paris	Tel: +33 (0)1 58 41 25 62 Fax: +33 (0)1 43 54 92 56 E-mail: maxime.dougados@cch.aphp.fr
MANAGEMENT CENTRE	URC Paris Centre GH Cochin - Hôpital Tarnier 89 rue d'Assas 75006 Paris	Professor Jean-Marc Treluyer Tel: +33 (0)1 58 41 11 82 Project manager: Sabine Helfen Tel: +33 (0)1 58 41 11 90 Fax: +33 (0)1 58 41 11 83



TEAM CONTACT DETAILS

Scientific manager	Prof. Maxime Dougados Service de Rhumatologie B GHU Cochin 27 rue du Faubourg St Jacques 75014 Paris	Tel: +33 (0)1 58 41 25 62 Fax: +33 (0)1 43 54 92 56 E-mail: maxime.dougados@cch.aphp.fr
Statistician	Prof. Jean-Pierre Daures CHU Caremeau DIM - Bâtiment polyvalent Place du professeur Robert Debré 30029 NIMES Cedex 9	Tel: +33 (0)4 66 68 34 03 E-mail: daures@iurc.montp.inserm.fr
Centralised test laboratory	BIOLOGICAL RESOURCES CENTRE Dr Joëlle Benessiano CRB, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris	Tel: +33 (0)1 40 25 71 51 E-mail: joelle.benessiano@bch.aphp.fr
Founding members committee	AP-HP: Prof. Jean-Marc Treluyer INSERM: Prof. Francis Berenbaum SFR: Prof. Maxime Dougados Wyeth: Prof. Claude Griscelli	
Coordination committee	Doctor Joëlle Benessiano, Hôpital Bichat, Paris Professor Francis Berenbaum, Hôpital Saint-Antoine, Paris Professor Pascal Claudepierre, Hôpital Henri-Mondor, Créteil Professor Bernard Combe, CHU Lapeyronnie, Montpellier Doctor Patricia Dargent, INSERM U-149, Villejuif Professor Jean-Pierre Daures, IURC-INSERM, Montpellier Professor Maxime Dougados, Hôpital Cochin, Paris Professor Philippe Goupille, CHU Bretonneau, Tours Professor Alain Saraux, CHU La Cavale Blanche, Brest Professor Jean-Marc Treluyer, URC Paris Centre Professor Daniel Wendling, CHU Jean Minjoz, Besançon	
Scientific committee	Doctor Maria-Antonietta d'Agostino, Hôpital Ambroise Paré, Boulogne sur Seine	

	<p> Doctor Joëlle Benessiano, Hôpital Bichat, Paris Professor Francis Berenbaum, Hôpital Saint Antoine, Paris Professor Maxime Breban, Hôpital Ambroise Paré, Boulogne sur Seine Professor Alain Cantagrel, Hôpital de Rangueil, Toulouse Professor Pascal Claudepierre, Hôpital Henri-Mondor, Créteil Professor Bernard Combe, CHU Lapeyronnie, Montpellier Professor Anne Cotten, CHU Roger Salengro, Lille Doctor Patricia Dargent, INSERM 149, Villejuif Professor Jean-Pierre Daures, IURC-INSERM Montpellier Professor Maxime Dougados, CHU Cochin Professor Bruno Fautrel, Hôpital La Pitié-Salpêtrière, Paris Doctor Antoine Feydy, Hôpital Cochin, Paris Professor Philippe Goupille, CHU Tours Professor Désirée van der Heijde, Maastricht Doctor Corinne Miceli, Hôpital Bicêtre, Le Kremlin Bicêtre Doctor Pascal Richette, Hôpital Lariboisière, Paris Doctor Thao Pham, CHU La Conception, Marseille Professor Christian Roux, Hôpital Cochin, Paris Doctor Martin Rudwaleit, Berlin Professor Alain Saraux, CHU La Cavale Blanche, Brest Professor Daniel WENDLING </p>	
Permanent guests of the coordination committee and scientific committee	<p>Doctor Isabelle Logeart, Wyeth</p>	

ABSTRACT

Study title and code	<i>Cohorte Française sur le DEvenir des Spondylarthropathies Indifférenciées Récentes</i> (French cohort for the evaluation of the outcome of recent onset undifferentiated spondyloarthritis)
Coordinating investigator	Professor Maxime Dougados GHU Cochin Service de Rhumatologie B 27 rue du Faubourg St Jacques 75014 Paris
Primary objectives	<ol style="list-style-type: none"> 1) Study the natural history of recent onset inflammatory rachialgia 2) Identify predictive factors of development of spondyloarthritis and factors of progression of the disease, including genetic, ethnic and environmental factors 3) Study the human and economic effects on patients with recent onset inflammatory rachialgia
Inclusion criteria	<ul style="list-style-type: none"> - Men or women aged over 18 years and under 50 years with - Recent onset inflammatory rachialgia defined by: <ul style="list-style-type: none"> - Pain in the lumbar spine or thoracic spine or buttock - Meeting the Calin or Berlin criteria or both: <ul style="list-style-type: none"> Calin criteria (at least 4 of the 5 following criteria must be met) (ref. 25) <ul style="list-style-type: none"> Insidious onset Onset before the age of 40 Persistence for at least three months Morning stiffness lasting for ≥ 30 minutes Improving with exercise Berlin criteria (at least 2 of the 4 following criteria must be met) (ref. 26) <ul style="list-style-type: none"> Morning stiffness lasting for ≥ 30 minutes Improvement with exercise and absence of improvement at rest Pain in the second part of the night Buttock pain upon pelvic rocking - Symptoms lasting longer than 3 months and less than 3 years - Symptoms likely to be related to spondyloarthritis according to the doctor (≥ 5 on a visual numerical scale of 0 to 10) - Initial medical examination (section L.1121-11 of the French code of public health) - Informed and free consent given and form signed and dated
Non-inclusion criteria	<ul style="list-style-type: none"> - Patients with formally diagnosed painful spine disorder, other than spondyloarthritis (e.g.: symptomatic mechanical discopathy) - Pregnant women - History of alcoholism, drug abuse, psychological disorders, severe co-morbidity which may invalidate informed consent or limit patient compliance with the study protocol - Patients having received or receiving maintenance treatment such as Salazopyrine, Methotrexate or Imurel can be included. However, history of biotherapy treatment and notably anti-TNF therapy is a non-inclusion criterion.

	<ul style="list-style-type: none"> - Patients having received or receiving corticotherapy can be included on the conditions that it is <ul style="list-style-type: none"> - Stable for at least 4 weeks at the time of inclusion. - Administered at a daily dose lower than 10 mg prednisone. - Contraindication to MRI scans - Non registration with a social security scheme
Total number of patients per treatment group	700
Total study duration	2 years' inclusion and 10 years' follow-up Total study duration: 12 years
Patient participation period	2 years minimum
Methodology	National, multicentre, non-randomised study
Investigational treatments	none
Tests	<p>Physical examination</p> <p>Biological tests (40 to 120 ml blood sample depending on the visit)</p> <p>Genetic test: <ul style="list-style-type: none"> - DNA collected at the start of the study, - RNA collected at the start for AP-HP centres </p> <p>Urine test at each visit over 2 years</p> <p>Radiological examinations: <ul style="list-style-type: none"> - standard x-ray - MRI scan </p> <p>Bone densitometry</p> <p>Enthesis ultrasound</p>
Primary and secondary endpoints	Percentage of patients with radiological evidence of sacroiliitis, after 5 years' progression, according to the presence or absence of inflammatory lesions in the sacro-iliac area on the MRI scan at the start of the study

BIOMEDICAL RESEARCH PROTOCOL - COORDINATING INVESTIGATOR AND SPONSOR'S REPRESENTATIVE SIGNATURE PAGE

Biomedical research code: **P070302**

Title: Cohorte Française sur le DEvenir des Spondylarthropathies Indifférenciées Récentes
(French cohort for the evaluation of the outcome of recent onset undifferentiated spondyloarthropathy)

Version No. 4 Date: 20 July 2009

Coordinating investigator:

Prof. Maxime Dougados

Date: _____ / _____ / _____

GHU Cochin
Service de Rhumatologie B
27 rue du Faubourg St Jacques
75014 Paris

Signature:

Olivier Misse

Assistance Publique – Hôpitaux de Paris
Inter-regional Clinical Research Delegation

Date: _____ / _____

Hôpital Saint-Louis
75010 PARIS

Signature:

The research received a favourable opinion from the Ile de France III Ethics Committee on 4 September 2007.

A favourable opinion was issued for amendment no. 1 on 11 December 2007

A favourable opinion was issued for amendment no. 2 on 25 March 2008

CONTENTS

1. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION OF THE RESEARCH	9
1.1 SCIENTIFIC KNOWLEDGE - SUMMARY	9
1.1.1 <i>The concept of spondyloarthropathy</i>	9
1.1.2 <i>Usefulness of a French cohort</i>	12
1.2 BENEFITS / RISKS.....	13
1.3 POPULATION.....	13
1.4 BIBLIOGRAPHIC REFERENCES	13
2. STUDY OBJECTIVES	14
2.1 PRIMARY OBJECTIVES	14
2.2 PRIMARY ENDPOINT(S).....	15
3. STUDY DESIGN	15
3.1 STUDY TYPE	15
3.2 SCHEDULE.....	16
3.3 VISIT PROCEDURES:	17
3.3.1- <i>Acceptable authorised interval for visits after inclusion</i>	17
3.3.2- <i>Tests and management of data measured or generated</i>	17
3.3.3 <i>Biological procedures and collections</i>	22
3.4 PATIENT INCLUSION PROCEDURE.....	24
3.5 PATIENT PARTICIPATION AND FOLLOW-UP METHODS.....	24
4. EARLY TERMINATION OF THE TRIAL	25
4.1 REASONS AND DESCRIPTION.....	25
4.2 PROCEDURES.....	25
4.3 CONSEQUENCES	26
5. POPULATION SELECTION AND TERMINATION OF THE STUDY.....	26
5.1 NUMBER OF PATIENTS (OR VOLUNTEERS).....	26
5.2 INCLUSION CRITERIA	26
5.3 NON-INCLUSION CRITERIA	27
5.4 STUDY TERMINATION CRITERIA.....	27
6 SAFETY EVALUATION	28
6.1 DESCRIPTION OF SAFETY EVALUATION PARAMETERS	28
6.2 METHODS AND SCHEDULE.....	28
6.2.1 <i>Founding members' committee</i>	29
6.2.2 <i>Independent monitoring committee</i>	29
6.2.3 <i>Coordination committee</i>	29
6.2.4 <i>Scientific committee</i>	30
6.3 PROCEDURES FOR REGISTRATION AND NOTIFICATION OF ADVERSE EVENTS	31
6.3.1 <i>Non-serious adverse events</i> :.....	31
6.3.2 <i>Serious Adverse Events (SAE)</i> :.....	31
6.4 PRE- AND POST STUDY PROCEDURES.....	32
7. STATISTICAL ANALYSIS.....	33
7.1 STRATEGY FOR THE ANALYSIS OF DATA AND STATISTICAL ANALYSIS METHODS	33
7.2 NUMBER OF PATIENTS / SUBJECTS REQUIRED.....	33
8. RIGHT OF ACCESS TO DATA AND SOURCE DOCUMENTS	35
9. QUALITY CONTROL AND ASSURANCE	35
9.1 MONITORING PROCEDURES.....	35
9.2 TRANSCRIPTION OF DATA IN THE CASE REPORT FORM	36
9.3 QUALITY CONTROL BY AN AUDIT TEAM	36
9.4 QUALITY CONTROL BY HEALTH AUTHORITIES.....	37
10. ETHICAL CONSIDERATIONS	37
10.1 APPLICABLE TEXTS	37
10.2 INVESTIGATION CENTRE SELECTION.....	37

10.3	AUTHORISATION REQUEST TO THE DGS (FRENCH HEALTH MINISTRY)	37
10.4	REQUEST FOR OPINION FROM THE FRENCH ETHICS COMMITTEES	38
10.5	AMENDMENTS	38
10.6	DATA CONFIDENTIALITY AND DECLARATION TO THE CNIL (FRENCH DATA PROTECTION AUTHORITY)	38
10.6.1	Computerised data file	39
10.6.2	Non-anonymous file	39
10.8	FINAL RESEARCH REPORT	40
12.	FINANCING AND INSURANCE	41
12.1	INSURANCE	41
12.2	SCIENTIFIC COMMITMENT	41
12.3	FINANCING	41
13.	PUBLICATION RULES	41
14.	LIST OF APPENDICES	42
	APPENDIX 1: LIST OF CENTRES AND INVESTIGATORS	43
	APPENDIX 2: INVESTIGATION CENTRE CHARTER	45
	APPENDIX 3: SCIENTIFIC COMMITMENT	47
	APPENDIX 4: SAE DECLARATION FORM	48
	APPENDIX 5: SAE TABLE	50
	APPENDIX 6: COHORT ORGANISATION	51
	APPENDIX 7: COHORT ACCESS REQUEST APPROVAL	53
	APPENDIX 8: BASG SCALE	55
	APPENDIX 9: BASDAI SCALE	56
	APPENDIX 10: BASFI SCALE	57
	APPENDIX 11: HAQ SCALE	58
	APPENDIX 12: SF36 SCALE	61
	APPENDIX 13: ASQOL SCALE	66
	APPENDIX 14: MEDICAL AND ECONOMIC QUESTIONNAIRE	68
	APPENDIX 15: MODIFIED SHOBER TEST	72
	APPENDIX 16: CHEST EXPANSION	73
	APPENDIX 17: OCCIPUT TO WALL DISTANCE	73
	APPENDIX 17: OCCIPUT TO WALL DISTANCE	74
	APPENDIX 18: TRAGUS TO WALL DISTANCE	75
	APPENDIX 19: FINGER TO FLOOR DISTANCE	76
	APPENDIX 20: LATERAL SPINAL FLEXION	77
	APPENDIX 21: CERVICAL SPINE ROTATION	77
	APPENDIX 21: CERVICAL SPINE ROTATION	78
	APPENDIX 22: INTERMALLEOLAR DISTANCE	79
	APPENDIX 23: BASMI SCORE	80
	APPENDIX 24: RADIOLOGICAL DATA ACQUISITION METHODS	81
	APPENDIX 25: mSASS RADIOLOGICAL SCORE	85
	APPENDIX 26: BASRI RADIOLOGICAL SCORE	86
	APPENDIX 27: ANKYLOSING SPONDYLITIS CLASSIFICATION CRITERIA MODIFIED NEW YORK CRITERIA	87
	APPENDIX 28: SPONDYLOARTHROPATHY LESIONS MRI SCAN	88
	APPENDIX 29: BONE DENSITY ACQUISITION METHODS AND EVALUATION	90
	APPENDIX 30: ENTHESES ULTRASOUND ACQUISITION METHODS AND EVALUATION	93
	APPENDIX 31: GENERAL BIBLIOGRAPHY	95

1. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION OF THE RESEARCH

1.1 Scientific knowledge - summary

1.1.1 The concept of spondyloarthropathy

1.1.1.a. Diseases in the spondyloarthropathy family

The concept of spondyloarthropathy covers various arthritic diseases represented by inflammatory rheumatic disorders (1). The various diseases include ankylosing spondylitis, at the top of the list, reactive arthritis, of which Reiter's syndrome, psoriatic arthritis, inflammatory rheumatism associated with inflammatory bowel disease (ulcerative colitis, Crohn's disease) currently grouped under the umbrella term CIBD (chronic inflammatory bowel diseases) and undifferentiated spondyloarthropathies.

Confusion may arise from three of the terms frequently used: Ankylosing spondylitis, spondyloarthropathy and undifferentiated spondyloarthropathy, depending on whether doctors highlight the concept of a sub-group (e.g. ankylosing spondylitis) or the concept (spondyloarthropathy). For example, a patient with a history of uveitis and heel pain, carrying the HLA-B27 antigen and suffering from inflammatory rachialgia, but without radiological evidence of sacro-iliitis will be described:

- By some, as suffering from possible spondyloarthropathy with axial involvement (by emphasising current clinical symptoms and the fact that the patient formally meets the diagnostic criteria for spondyloarthropathy, even though the sacro-iliac x-rays are normal).
- By others, as suffering from undifferentiated spondyloarthropathy (by first emphasising the fact that the patient formally meets spondyloarthropathy classification criteria, but also by emphasising the fact that they meet none of the classification criteria for sub-groups of the disease, and notably that they do not meet New York criteria, where there is radiological evidence of sacro-iliitis) thus the proposed term "undifferentiated".

Therefore to enable better understanding of the protocol, either the term ankylosing spondylitis could be used when referring to modified New York criteria, or the term spondyloarthropathy when referring to Amor and/or ESSG criteria for diagnosing spondyloarthropathy.

1.1.1.b. Spondyloarthropathy - clinical presentation

The various diseases have clinical similarities: Axial involvement with typical pelvic-spine syndrome (inflammatory rachialgia, sacro-iliac involvement); peripheral joint involvement possible (asymmetrical oligoarthritis), specific "sausage digit" appearance or dactylitis. The possibility of enthesitis (points at which tendons insert into the periosteum and bone) involvement completes and suggests the rheumatologic picture.

Extra-rheumatologic clinical manifestations are also common to this group of disorders: in particular, ophthalmic involvement (uveitis, conjunctivitis) cardiac involvement (heart rhythm and conduction disorders, valvular heart disease, in particular late onset aortic involvement), skin disorders (psoriasis, erythema nodosum, pustuloses); digestive involvement (way in to reactive arthritis, chronic inflammatory bowel disease, asymptomatic ileal histological lesions similar to Crohn's disease).

Finally, a symptom (e.g. uveitis) or disorder (e.g. chronic inflammatory bowel disease) from the spondyloarthropathy group is found in one third of cases in individual patients or in their family.

The frequency of the presence of the HLA B27 antigen (50 to 85 % of patients versus 7 to 8 % of Caucasian subjects) confirms the notion of genetic background, encouraging the appearance of the disease.

1.1.1.c. Epidemiology

The prevalence of spondyloarthropathy has been estimated at between 0.6 and 1.9 % of white adults, with a prevalence of ankylosing spondylitis between 0.1 and 1 % (2, 3). In France, the Epirhum II survey approximated the prevalence of spondyloarthropathy at 0.31 % of the adult population, and at 0.14 % for ankylosing spondylitis, 0.11 % for psoriatic arthritis (4), homogenous between the various regions of France.

Predominance in men (60-80 %) and onset of symptoms between 20 and 40 years in the majority of cases completes the typical epidemiological description.

1.1.1.d. Diagnosis

Criteria

Ankylosing spondylitis and /or spondyloarthropathy is diagnosed on the basis of clinical elements and imaging and laboratory tests. These elements are grouped into several criteria systems, which are more so classification criteria than diagnostic criteria (5). Three systems are currently recognised and used, in therapeutic and pathophysiological studies in particular. The criteria of the ESSG (European Spondyloarthropathy Study Group) (6), and Amor criteria (7) concern spondyloarthropathies as a whole. The modified New York criteria are used to classify ankylosing spondylitis (8).

These criteria systems are not effective for early diagnosis and this may explain late diagnosis, estimated at 8 years in certain studies (9, 10).

Contribution of additional tests

The role of additional tests, whether laboratory tests (HLA B27 typing, CRP) or radiological examinations (standard x-rays, CT-scan, MRI scan, bone scintigraphy, ultrasound) is not standardized.

From a biological standpoint, ankylosing spondylitis comes with an inflammatory syndrome of varying degrees of intensity, often more moderate than in other chronic inflammatory rheumatic disorders and sometimes absent at initial onset of symptoms.

Radiological lesions often appear late on and contribute little to early diagnosis. Typical lesions initially show images of inflammatory erosion, followed by sub-ligament ossification. This sequence represents the aspects usually described at sites of predilection: sacroiliac joints, spine (spondylitis, syndesmophytes, enthesopathies), and synovial joints (e.g. coxitis) (11). These symptoms appear late on.

Magnetic resonance imaging (MRI) is able to reveal inflammation. The MRI scan could be an effective tool for diagnosing patients with spondyloarthritis, from onset of the disease. The role of the MRI scan in measuring the activity of the disease would appear to be important and must be explored further. One of the major questions remains the existence or not of correlation between the MRI scan and disease activity, and between the MRI scan and radiological progression.

Ultrasound would also appear to be promising in the detection of the first signs of undifferentiated spondyloarthritis.

1.1.1.e. Natural history of the disease

The most frequent clinical manifestations are pain, morning stiffness and gradual disability. Gradual loss of spinal mobility and/or functional ability is not only due to inflammation of the vertebral ligaments but also to their ossification. Progression of the disease also varies in terms of intensity and course, independently of the intensity of the pain, inflammation and stiffness.

Due to the insidious nature of the symptoms, a considerable number of patients with ankylosing spondylitis are not diagnosed within the first few years of development of the disease. With the arrival of new therapeutic strategies, of which new substances such as anti-TNF, early identification of patients is becoming genuinely necessary. Recent-onset ankylosing spondylitis (or undifferentiated spondyloarthritis) usually begins as inflammatory rachialgia. However, not all patients with inflammatory rachialgia will develop ankylosing spondylitis.

It is therefore necessary to distinguish and identify patients with inflammatory rachialgia that will later develop ankylosing spondylitis, from those that will not. As we will see again further on, this is the primary objective of this cohort. Among those patients with undifferentiated spondyloarthritis, it is also important to identify those that will develop a severe form of the disease.

1.1.1.f. Therapeutic principles of the disease

Treatment essentially includes physiotherapy and rehabilitation, in particular for the axial component, and the use of non-steroid anti-inflammatory agents (12, 13). The role of slow release treatments remains to be specified: Salazopyrine has demonstrated a certain level of effectiveness on peripheral joint symptoms only and there is no convincing data available for Methotrexate. Biotherapies, in particular anti-TNF agents, have shown clinical and biological effectiveness and an effect on quality of life and imaging results, in particular on axial involvement; new therapies significantly affect the way in which these diseases are managed. However their cost and potential side effects require discussion with respect to indications and time of initiation in the disease (14-17).

1.1.1.g. Medical, social and economic impact of the disease

Spondyloarthropathies, ankylosing spondylitis in particular, are chronic diseases affecting young adults, and are therefore the cause of loss of functional capacity and sick leave to a greater extent than in the general population (18). Excess mortality has also been reported in this disease (19). Such considerations provide a tentative explanation for the negative social and economic consequences of the disease (20). Loss of functional capacity predicts the total costs of the disease (21). However, overall prognosis of the disease is highly variable from one patient to another (10). This highlights the need to have prognostic criteria as of onset of the disease in order to offer the most appropriate treatment. Some factors have been put forward (22), but need to be confirmed.

Finally, there is currently little prospective data on the long-term social and economic impact of the disease, and even less concerning patients suffering from the early form. The impact of the disease (inflammatory rachialgia) on occupational status, insurance, income, leisure time, sick leave, home care, transport, home, adaptation to the environment, help, bracing and use of health resources (e.g. hospital admissions and treatments) in the first few years, is little known. Better knowledge of the predictive factors of the social and economic impact will provide an insight into the total impact of inflammatory rachialgia and will provide tools for managing patients.

1.1.2. Usefulness of a French cohort

None of the cohorts to date have made it possible to study the natural history of inflammatory rachialgia, either because the patients included had confirmed inflammatory rheumatism at the time of inclusion in the study, or because the monitoring period and number of patients did not make it possible to come to a conclusion.

We have seen the importance of early diagnosis and also of identifying elements suggesting particularly severe outcome as of onset of the disease.

To answer these questions, it is necessary to include a high number of patients, at an early stage, and to monitor them for at least 10 years, bearing in mind that late diagnosis of spondyloarthropathy is made 7 years after onset of the disease. France is one of the few European countries able to recruit a high number of patients for such a study. Furthermore, the multiethnic nature of the population, and in particular the large North African population, is a definite advantage for our epidemiological study. More severe clinical symptoms have previously been reported according to ethnic origin of patients, and notably a very clear difference as to the probability of suffering from coxitis (symptom testifying to the severity of the disease) after 10 years' progression, depending on whether the study was carried out in France or in Maghreb, was observed (23, 24)

Finally, the French cohort will be the only cohort to gather all possible determining data for identifying future cases of spondyloarthropathy, that are clinical, biological (RNA collection especially), and iconographic data, but also MRI results. During their follow-up, some patients will undergo standard x-rays, MRI scans and ultrasound scans, to not only determine the predictive signs of progression of the disease but also to determine their development over time.

Many French research centres have the human, technical and intellectual resources to conduct fundamental and/or translational research studies. Collection of data from French patients will make access to quality research material easier.

1.2 Benefits / risks

Participation in this cohort will make it possible to improve knowledge of the disease, in terms of the clinical, pathophysiological and prognostic aspects. Participation carries no specific risk, as the foreseen investigations are those generally conducted in this disease, and there will be no interference with standard management in terms of treatment.

Asymptomatic patients will be monitored according to protocol procedures. This means that additional tests, not usually carried out on this category of patients will be conducted, but this also implies more effective and earlier management of pain.

1.3 Population

The population studied shall meet the inclusion and non-inclusion criteria described in section 5.

1.4 Bibliographic references

Worldwide cohorts

Europe

To our knowledge, the first routine monitoring study of patients with an axial form of spondyloarthritis is the OASIS-Outcome in Ankylosing Spondylitis International Study. This study began in the 90s and included all patients with the disease for three consecutive months in 3 European centres (Cochin-Paris, France; Ghent, Belgium and Maastricht, Holland).

This study included patients for whom average progression was 12 years.

Although this study has always been and still is useful for better understanding the natural history of the disease, 3 characteristics of this cohort sparked off other studies in this field:

1. Absence of routine biological sample collection;
2. Heterogeneity of patients, with inclusion of patients consulting voluntarily in hospital reference centres for the disease;
3. Absence of notion of progression of the disease from onset.

A cohort including all patients (not only patients in the early stages of the disease) suffering from spondyloarthritis is underway in Spain (REGISPONSER study). It is coordinated by Professor Eduardo Collantes and almost 1,400 patients have been included to date.

To our knowledge, only 2 cohorts are selecting patients in the early stages of the disease: one (the largest) in Germany, coordinated by Martin Rudwaleit (GESPIC cohort) and the other in Holland (EsPac cohort), coordinated by Désirée van der Heijde.

The GESPIC cohort is a multicentre study (3 centres: Berlin, Hanover and Mainz). The patients monitored meet at least one of the following criteria: ESSG spondyloarthropathy criteria, Amor spondyloarthropathy criteria or modified New York ankylosing spondylitis criteria at the time of inclusion. They are therefore patients with possible spondyloarthropathy without undifferentiated inflammatory rachialgia. Patients were classified into ankylosing spondylitis, non-ankylosing spondylitis spondyloarthropathy and undifferentiated oligoarthritis. The recent nature depends on the disease:

- Ankylosing spondylitis < 10 years
- Non-ankylosing spondylitis spondyloarthropathy < 5 years
- Undifferentiated oligoarthritis < 1 year

Data collected includes clinical, medical and economic data, standard laboratory test results, serum bank and DNA bank data, synovial fluid and synovial material collection and standard x-rays.

The study is to last 30 months with a visit every 6 months (x-rays at baseline and after 2 years).

The EsPac (Early Spondyloarthropathy Clinic) cohort aims to study the progression of inflammatory rachialgia, to identify those patients that will go on to develop ankylosing spondylitis and to evaluate the social and economic impacts of the patients. However, follow-up is expected to last 2 years only and the 3 recruiting centres aim to monitor 70 patients in total. The data collected includes clinical, medical and economic, biological, radiographical and MRI data (one yearly consultation).

All cohorts are monitored according to ASAS (ASsessment of Ankylosing Spondylitis) according to fully transparent procedures. Désirée van der Heijde and Maxime Dougados are the international experts for the GESPIC cohort. Maxime Dougados is consultant for the REGISPONDER cohort. Désirée van der Heijde and Martin Rudwaleit are members of the scientific council for this project.

USA

There are no cohorts on this theme in the United States.

See appendix 31 for bibliographic references.

2. STUDY OBJECTIVES

2.1 Primary objectives

The specific objectives are the following:

- Study the natural history of recent onset inflammatory rachialgia
- Identify predictive factors of development of spondyloarthropathy and factors of progression of the disease, including genetic, ethnic and environmental factors
- Study the human and economic effects on patients with recent onset inflammatory rachialgia

This cohort essentially aims to meet the aforementioned specific objectives. However, collection of clinical, biological and radiological data will represent a single source of data, enabling research teams in coming years to access the relevant data for answering various specific relevant questions (pathophysiological, diagnostic, prognostic, medical and economic) according to the state of knowledge of this disease.

2.2 Primary endpoint(s)

Percentage of patients with radiological evidence of sacroiliitis, after 5 years' progression, according to the presence or absence of inflammatory lesions in the sacro-iliac area on the MRI scan at the start of the study.

3. STUDY DESIGN

3.1 Study type

National, multicentre, prospective, non-comparative, non-randomised cohort study

3.2 Schedule

Visits' schedule

Variables	Collection time (Months)							
	0	6	12	18	24	36	48	60
Patient self-questionnaire:								
○ Medico-economic	X	X	X	X	X	X	X	X
○ BASG	X	X	X	X	X	X	X	X
○ BASDAI	X	X	X	X	X	X	X	X
○ BASFI	X	X	X	X	X	X	X	X
○ HAQ-AS	X	X	X	X	X	X	X	X
○ SF36	X	X	X	X	X	X	X	X
○ ASQoL	X	X	X	X	X	X	X	X
Physical examination:								
○ Weight	X	X	X	X	X	X	X	X
○ Height	X	X	X	X	X	X	X	X
○ Blood pressure	X	X	X	X	X	X	X	X
○ Schober	X	X	X	X	X	X	X	X
○ Chest expansion	X	X	X	X	X	X	X	X
○ Occiput-to-wall distance	X	X	X	X	X	X	X	X
○ Tragus-to-wall distance	X	X	X	X	X	X	X	X
○ Fingers-to-floor distance	X	X	X	X	X	X	X	X
○ Lateral spinal flexion	X	X	X	X	X	X	X	X
○ Spinal rotation	X	X	X	X	X	X	X	X
○ Intermalleolar distance	X	X	X	X	X	X	X	X
Treatments/comorbidity	X	X	X	X	X	X	X	X
Doctor's overall assessment (spondyloarthritis dg)	X	X	X	X	X	X	X	X
Biological examinations:								
○ CRP	X	X	X	X	X	X	X	X
○ Cholesterol (HDL, LDL), TG, NFS, ESR, glycaemia	X				X			X
○ HLA B27	X							
○ DNA	X							
○ RNA	X*							
○ Serum bank	X	X	X		X			X
○ Urine bank	X				X			X
Radiological examinations:								
○ Standard x-rays	X		X		X			X
○ MRI	X		X*		X*			X*
Enthesis ultrasound	X**		X**		X**			X**
Bone densitometry	X**		X**		X**			X**

* AP-HP investigation centres only;

** Investigation centres with DEXA and/or ultrasound only.

Visit frequency

Patients will be seen 6 months after inclusion, then after 12 months, 18 months and 24 months.

Patients are monitored in investigation centres only in principle. All patients included in the study will be monitored for at least two years.

Follow-up will be interrupted at the end of the 2 years at the latest for patients diagnosed with a disorder other than spondyloarthritis, both according to the investigator's opinion (with a certainty factor higher than 7/10) and according to the disease criteria selected.

Patients that become asymptomatic but for whom spondyloarthritis diagnosis is confirmed, will continue the follow-up visits as required by the protocol. To ensure monitoring of patients no longer consulting in the investigation centres, the coordination centre shall have access to the postal address and telephone number of the patient, general practitioner or rheumatologist. Self-questionnaires will be sent to these patients by post and telephone numbers will be collected.

3.3 Visit procedures:

3.3.1- Acceptable authorised interval for visits after inclusion

Patients will be seen every 6 months for two years, then every year. Regardless of the date of a visit, the subsequent visit must be set taking the date of inclusion as basis (e.g. a patient seen again after 7 months instead of 6 months will be called back after 5 months instead of 6 months). In the first year, a 2-week discrepancy from the theoretical date is acceptable. After the two years' follow-up, the visits can take place at the theoretical date give or take 1 month.

3.3.2- Tests and management of data measured or generated

Three categories of data will be collected in this cohort (clinical, biological and radiological). For each of these categories, we will look at the exact type of data to be collected and the time it takes to collect it.

3.3.2.a- Physical examinations

Personal and family history and principal demographic data will be collected from patients on inclusion. The same information will also be collected in M6, M12, M18 and M24 in the first two years of the study, then every year for patients continuing cohort follow-up.

The following will take place at the various visits:

- General physical examination, notably weight and blood pressure measurement
- Any treatment taken the last 6 months will be noted
- Current treatment will be noted
- Self-questionnaires for evaluating the activity and the impact of the disease will be administered to assess the following:
 - o Overall assessment of the disease by the patient: BASG (appendix 8)
 - o Assessment of disease activity: BASDAI (appendix 9)
 - o Assessment of the patient's functional impairment: BASFI (appendix 10)
 - o Assessment of the patient's functional impairment: HAQ-AS (appendix 11)
 - o Quality of life assessment: SF36 (appendix 12)
 - o Quality of life assessment: ASQoL (appendix 13)
 - o Medical and economic questionnaire (appendix 14)

- Metrological examination, notably:
 - o Height measurement
 - o Amended Schober scale (appendix 15)
 - o Chest expansion (appendix 16)
 - o Occiput-to-wall distance (appendix 17)
 - o Tragus-to-wall distance (appendix 18)
 - o Fingers-to-floor distance (appendix 19)
 - o Lateral spinal flexion (appendix 20)
 - o Cervical spine rotation (appendix 21)
 - o Intermalleolar distance (appendix 22)
 - o Patient mobility assessment: BASMI (appendix 23)
- Doctor's appraisal using a numeric scale on a score of 0 to 10, as to whether the patient is likely to suffer from spondyloarthritis, where 0 signifies "I am sure that the patient's inflammatory rachialgia is not related to spondyloarthritis" and 10 "I am sure that the patient's inflammatory rachialgia is related to spondyloarthritis".

3.3.2.b- Biological examinations

Will include two types: Those conducted by the investigation centre and noted in the case report form and those centralised at the biological resources centre.

Non-centralised biological data

Includes:

- HLA B27
- C reactive protein
- Erythrocyte sedimentation rate
- Creatininemia
- Haemoglobin
- Leukocytes
- Platelets
- Total cholesterol, HDL, LDL, Triglycerides
- Glycaemia

The notion of the presence of the HLA B27 antigen will be noted at the inclusion visit if it was not done before.

C reactive protein will be assessed at each visit, in M0, M6, M12, M18 and M24 for the first two years, then every year for those patients continuing in the cohort.

Other biological data will be collected in M0, M24, and M60 only.

The results will be reported in the case report form.

Centralised biological data

They include serum, urine, DNA and RNA.

Description:

DNA will be collected at the first visit (M0) by all participating centres.

RNA will be collected at the inclusion visit in AP-HP centres only.

Serum will be collected by all centres at the initial visit, then in M6, M12 and M24 for the first two years of the study, then in M60.

Urine will be collected by all centres at the initial visit, then in M24 for the first two years of the study, then in M60.

Data transmission and verification methods are described in section 3.3.3

3.3.2.c- Radiological examinations

Standard x-rays

Standard x-rays will be used to calculate the mSASSS radiographic score (appendix 25) and the BASRI score (appendix 26), and to evaluate kyphosis or vertebral collapse where applicable.

They include an x-ray of the cervical spine (side-on), of the thoracic spine (side-on), of the lumbar spine (side-on), of the lumbar spine from the front and an x-ray of the pelvis from the front. The technique is described in appendix 24.

Schedule: The x-rays will be taken at the inclusion visit, in M12, and in M24 in the first 2 years and then in M60.

Each investigation centre will be asked to evaluate the sacroiliac joint (modified New York criteria in appendix 27), the mSASSS score and BASRI for hips, and to record the results on the case report form (appendix 24).

The x-rays will also be submitted for centralized reading:

Methods for the analysis of centralised radiological data

The clinical investigation centre will provide the radiology team with a CD for each patient, in

DICOM format, on which features:

- The number of the centre,

- The name of the investigator,
- The patient number,
- The patient's initials,
- The date of the examination.

The radiology team will write the patient's radiological data to the CD and will send it to the investigation centre. The required timeframe (immediate or deferred) for writing to CD and transfer to the investigation centre (by internal or external mail, submitted with the images ...) will be described in detail when the centre is opened (local procedure to be established before that time by the centre's principal investigator).

The clinical investigation centre must:

- Check that the CDs are received in due time
- Send the CDs to the national imaging collection centre (Prof. Daurès) within 5 days of receipt, where they will be made anonymous.

Transfer of x-rays for centralised reading:

Centralised data will be checked on the CDs collected at the national imaging collection centre (Prof. Jean-Pierre Daurès).

The first radiological CD for the first 2 patients included in each centre will be subjected to quality controls. The controls will be conducted by a trained operator. The operator will inform the correspondent radiologist in the event of discrepancy with respect to the protocol. The radiologist will then contact the relevant radiology department in order to request the necessary technical modifications.

MRI scans

MRI scans are taken of the cervical, thoracic and lumbar spine and sacroiliac joints, of which a detailed description can be found in appendix 28.

All of the centres will collect this information in M0. AP-HP centres only will also collect this information in M12, M24 and M60.

Transfer of non-centralised data:

Each centre will be asked to evaluate the MRI scans according to the scoring system described in detail in appendix 28, and to record the results on the case report form.

Transfer of images for centralised reading:

The clinical investigation centre will provide the MRI team with a CD for each patient, in DICOM format, featuring:

- The number of the centre,
- The name of the investigator,
- The patient number,
- The patient's initials,
- The date of the examination.

The MRI team will write the patient's MRI scan results to the CD provided, before sending it to the investigation centre, which will then transfer it to the national imaging coordination centre.

The required timeframe (immediate or deferred) for writing to CD and transfer to the investigation centre (by internal or external mail, submitted with the images, etc.) will be described in detail when the centre is opened (local procedure to be established before that time by the centre's principal investigator).

The clinical investigation centre must:

- Check that the CDs are received in due time
- Send the CDs to the national imaging collection centre (Prof. Daurès) within 5 days of receipt, where they will be made anonymous.

Data quality checks

For the centralised data, the first MRI images CD for the first 2 patients included in each centre will be subjected to quality controls. The controls will be conducted by a trained operator. The operator will inform the correspondent radiologist in the event of discrepancy with respect to the protocol. The radiologist will then contact the relevant radiology department in order to request the necessary technical modifications.

Procedure creation in centres – Overview of the tasks of each investigation centre for x-rays and MRI scans

- Each centre should draw up a procedure in conjunction with the imaging department before it opens, in order to streamline the stages of the image processing system, from the patient's appointment through to transfer of the CD,
- Preparation of a marked x-ray CD for each patient, and if required a marked MRI scan CD along with an MRI case report form page
- Transfer of items to the imaging centre at the same time as the patient
- Verification that the items are collected within the allotted timeframe
- Copy standard x-ray and MRI data in the case report form once again
- Send the CDs to the national imaging collection centre (Prof. Daurès) within the required timeframe

3.3.2.d- Bone densitometry

This will include evaluation of bone densitometry of the lumbar spine and femoral neck. A detailed description can be found in appendix 29.

Schedule: Only those centres equipped with the appropriate devices will collect such data. This data will be collected in M0, M12 and M24 in the first two years of the study, then in M60.

The investigation centre must keep the paper print-out of the densitometry examination in the insert of the corresponding visit in the case report form. This will help the clinical research associate to check bone densitometry and body composition results entered in the case report form.

3.3.2.e- Enthesis ultrasound

This will include a bilateral evaluation of enthesal insertions for the Achilles tendon, patella tendons and epicondyle tendons. A detailed description can be found in appendix 30.

Schedule: Only those centres equipped with the appropriate devices will collect such data. This data will be collected in M0, M12 and M24 in the first two years of the study, then in M60.

The investigation centre must keep the paper print-out of the examination in the insert of the corresponding visit in the case report form.

The investigation centre must record the data collected on a diskette specific to the study. The diskette must be kept by the centre in the event of inspection and/or future studies requiring centralised analysis of data.

3.3.3 Biological procedures and collections

Serum, urine and nucleic acid (DNA and RNA) samples extracted from whole blood will be collected and stored in the laboratory at the Biological Resources Centre at hôpital Bichat (CRB), under the supervision of Dr Joëlle BENESSIANO, until all the samples have been used. Samples will be taken at patient inclusion and at the follow-up visits, according to biological procedures specifying each of the steps to be undertaken by the investigation centre.

The CRB will send individual patient sampling kits to each investigation centre before inclusion, with pre-printed labels bearing the patient number. *A single number will be allocated to each sample*, the numbers will never be re-used, even in the event of withdrawal or destruction of the sample. Samples centrifuged and aliquoted by the centre will be stored at -80°C then sent to the CRB in carboglance, according to a timeframe to be defined according to freezer capacity.

Collection storage methods

Biological samples are stored in freezers at -80°C , (large capacity 700 litres) with back-up CO_2 injections to compensate for brief temperature variations. The freezers are equipped with a temperature recording and monitoring system. An alarms report (audible, telephone and fax) enables monitoring 24 hours a day, seven days a week. A fail-soft procedure has been drawn up to define the methods of intervention (refrigerator technician, on-call duty electrician or biologist in charge of the CRB) in the event of breakdown of a freezer. A back-up freezer is kept empty to enable rapid transfer of samples in the event of prolonged breakdown of one of the storage chambers.

Ambient temperature and temperature of storage chambers is traced by network monitoring software on the two storage sites. The hospital refrigerator technician must edit the temperature readings and fault reports. The documents are then archived at the CRB. Technicians must also ensure preventive maintenance of freezers along with traceability of maintenance.

Computerized sample management

The computerized management of human biological samples stored at the CRB requires special equipment. The computer system for this purpose is installed in a network in the hospital (reception, laboratory, offices, storage room etc.) and is linked to a server, supervised by the hospital computer department, which ensures daily data back-up.

CRB's commitments:

The CRB undertakes to ensure the following:

- Receipt of samples and verification of their integrity
- Due regard for confidentiality: The CRB undertakes to keep all information entrusted to it confidential, and to ensure that it is not disclosed to third parties, without written authorisation from the principal investigator or co-investigator.
- Registration and storage of samples in the storage rooms (-80°C and -20°C) with a security and surveillance system. The CRB may provide a procedure for regular verification of defrosting procedures, of the temperatures displayed; for ensuring the proper working order of temperature readings and the alarm, along with procedures describing the action taken in the event of freezer breakdown.
- Extraction of nucleic acid (DNA and RNA) in a molecular biology laboratory, in observance of the instructions for the proper conduct of the analyses.

Quality control

Nucleic acid extracted from whole blood (fresh or frozen) will be submitted to two types of validation: quantitative and qualitative.

Quantitative validation: Extracted nucleic acid concentration is measured using fluorimetry techniques. This type of technique uses fluorophore which binds to nucleic acid and which, when excited in a specific wavelength, emits a quantity of fluorescence proportional to the quantity of nucleic acid. Concentration is then calculated by comparison to a known concentration range. For DNA assay, a fluorophore binding specifically to DNA is used (excitation peak: 365 nm and emission peak: 450 nm). Another fluorophore is used for RNA assay (excitation peaks: 470 and 500 nm and emission peak: 525 nm); it can also bind to DNA. There is however, no interference with proteins.

Qualitative validation: Spectrophotometry is used to determine the purity of a nucleic acid. A sample is usually characterised by an A260/A280 ratio of >2 for RNA and >1.8 for DNA. Microfluidic capillary electrophoresis (Agilent) will be used for total RNA assay. This technology consists of using gel miniaturisation to produce migration patterns, making it possible to work with 1 µl sample at a very low concentration.

3.4 Patient inclusion procedure

Information meetings with private practice rheumatologists, general practitioners and the general public will be organized in order to establish a study population the most representative as possible of patients suffering from this disease. The doctors will be asked to refer patients meeting the study eligibility criteria to the regional centre.

An inclusion page from the case report form will be faxed to the URC on 01.58.41.11.83 by the centre's investigator as each new patient is included.

3.5 Patient participation and follow-up methods

Patients will take part in the cohort for 10 years, thus a total study period of 12 years (2 years' inclusion + 10 years' follow-up).

Monitoring of patients for whom diagnosis of a disorder other than spondyloarthritis is made by the investigator will be interrupted 2 years after their inclusion. Minimum participation in the cohort for these patients will therefore be 2 years. If a disorder other than spondyloarthritis is diagnosed after the minimum 2 years' monitoring, the patient will leave the study.

Monitoring procedures

Patients are monitored in investigation centres only in principle. All patients included in the study will be monitored for at least two years.

Follow-up will be interrupted at the end of the 2 years at the latest for patients diagnosed with a disorder other than spondyloarthritis, both according to the investigator's opinion (with a certainty factor higher than 7/10) and according to the disease criteria selected.

To ensure monitoring of patients no longer consulting in the investigation centres, the coordination centre shall have access to the postal address and telephone number of the patient, general practitioner or rheumatologist. Self-questionnaires will be sent to these patients by post and telephone numbers will be collected.

Minimizing patients lost from sight

To reduce as far as possible the number of patients lost from site, the following actions will be taken to maintain contact with patients and general practitioners or private practice rheumatologists:

- Publication of the DESIR cohort journal presenting the results and the research projects
- Issue of a liaison form enabling patients to notify their change of address
- A card will be sent to patients each year on their birthday

4. EARLY TERMINATION OF THE TRIAL

4.1 Reasons and description

Rules governing permanent or temporary interruption:

- of participation of subjects in the research

Patients may leave the study if they so wish, at any time and for any reason. The investigator and/or the sponsor may also ask terminate patient participation in the trial. Early termination of patients must be recorded and the investigator must state the reason (e.g. non-attendance of the patient at visits following reminders, absence of patient cooperation, treatment ineffectiveness, etc.).

Follow-up will be interrupted at the end of the 2 years at the latest for patients diagnosed with a disorder other than spondyloarthritis, both according to the investigator's opinion (with a certainty factor higher than 7/10) and according to the disease criteria selected.

- of participation in part of the research or the research as a whole. The sponsor and/or the competent authorities are also within their rights to suspend the study.

4.2 Procedures

Early termination of the study means interruption of follow-up of a subject as part of the research

- Patients leaving the research study are not expected to be replaced

The case report form must be completed for subjects lost from site, up to the last visit. The investigator and their associates will make every effort to provide reasons for non-attendance of patients at visits and information about their state of health.

4.3 Consequences

Patients leaving the trial cannot be included in the study again. Their inclusion and treatment numbers must not be used again.

5. POPULATION SELECTION AND TERMINATION OF THE STUDY

5.1 Number of patients (or volunteers)

The number of patients to be included, taking into account the probability of patients lost from sight (15 to 20 %) and the various hypotheses, varies from 685 to 768 patients. 700 patients were therefore selected (see section 7.2).

5.2 Inclusion criteria

The subjects must meet all of the following conditions or characteristics to be able to be included in the study:

- 1) Men or women aged over 18 years and under 50 years with
- 2) Recent onset inflammatory rachialgia defined by:
 - Pain in the lumbar spine or thoracic spine or buttock
 - Meeting the Calin or Berlin criteria or both

Calin criteria (at least 4 of the 5 following criteria must be met) (ref. 25)

- Insidious onset
- Onset before the age of 40
- Persistence for at least three months
- Morning stiffness lasting \geq 30 minutes
- Improves with exercise

Berlin criteria (at least 2 of the 4 following criteria must be met) (ref. 26)

- Morning stiffness lasting \geq 30 minutes
- Improvement with exercise and absence of improvement at rest
- Pain in the second part of the night
- Buttock pain upon pelvic rocking

- 3) Symptoms lasting longer than 3 months and less than 3 years

- 4) Symptoms likely to be related to spondyloarthropathy according to the doctor (≥ 5 on a visual numerical scale of 0 to 10)
- 5) Initial medical examination (*results to be sent to the patient*)
- 6) Informed and free consent given and form signed and dated

5.3 Non-inclusion criteria

Subjects with the following characteristics or conditions cannot be included in the study.

- 1) Patients with formally diagnosed painful spine disorder, other than spondyloarthropathy (e.g.: Symptomatic mechanical discopathy)
- 2) Pregnant women (Any method of contraception can be accepted (oral contraception, coil, etc.))
- 3) History of alcoholism, drug abuse, psychological disorders, severe co-morbidity which may invalidate informed consent or limit patient compliance with the study protocol
- 4) History of treatment with biotherapy and notably anti-TNF therapy. Patients having received or receiving maintenance treatment such as Salazopyrine, Methotrexate or Imurel can however be included.
- 5) Contra-indication to MRI scans (ferromagnetic surgical clips, ocular implants, intraocular metallic foreign body or in the nervous system, implants or metallic objects likely to concentrate the radiofrequency magnetic field, cochlear implants, brain or heart stimulator)
- 6) Patients having received or receiving corticotherapy can be included on the conditions that it is
 - Stable for at least 4 weeks at the time of inclusion.
 - Administered at a daily dose lower than 10 mg prednisone.
- 7) Non registration with a social security scheme (holder or beneficiary)

5.4 Study termination criteria

- 1) Patient's decision to no longer be monitored in the cohort is a termination criterion if declared in the first two years.
- 2) Diagnosis other than spondyloarthropathy gives rise to termination after at least 2 years follow-up in the trial. After this date, only those patients formally meeting the criteria for disorders other than spondyloarthropathy, even possible, will no longer be monitored.
- 3) Patients mistakenly included (inclusion and non-inclusion criteria not met) may be withdrawn early from the research on the decision of the coordination committee.

Pregnancy occurring during the study will not be considered to be an exclusion criterion. The patient will continue to be monitored in the cohort but will not undergo the x-ray and MRI examinations while pregnant.

6 SAFETY EVALUATION

6.1 Description of safety evaluation parameters

- Adverse events (AE): Adverse events are any undesirable harmful effects or aggravation of an existing condition, occurring in persons taking part in biomedical research, whether considered or not to be related to exposure to the investigational treatment.

- Adverse drug reaction: Any harmful and undesirable reaction to an investigational drug regardless of the dose administered

- Serious adverse event or effect (SAE): Any undesirable event or effect leading to death, endangering a research participant's life, entailing extended stay in hospital, or leading to significant or lasting disability or handicap, or causing a congenital anomaly or malformation, and where it is a drug, regardless of the dose administered.

Cancer, pregnancy, overdose or drug abuse shall be declared as serious events.

A hospital stay scheduled before the start of the study shall not be considered as a serious adverse event.

- Unexpected adverse drug reaction: Any adverse effect of which the nature, severity or outcome is not in keeping with the information featuring in the product summary of characteristics, where the medicinal product is authorised, and in the investigator brochure where it is not authorised.

- New information: Any new safety data, possibly giving rise to re-evaluation of the benefit/risk ratio of the research or investigational medicinal product, or which may be sufficient to foresee modifications in administration of the investigational medicinal product, in the conduct of the research.

6.2 Methods and schedule

Methods and schedule for measuring, collecting and analysing safety evaluation parameters. In addition to the initiation and information meetings held with the medical community for this cohort, a yearly meeting with the scientific committee and at least half-yearly meeting with the coordination committee is planned. Other meetings will be organised depending on the questions raised. Weekly discussion will be ensured between the principal investigator and the clinical research associate in charge of coordinating this cohort.

6.2.1 Founding members' committee

The committee will be made up of the project founders:

- SFR (French society for rheumatology) representative: Maxime Dougados
- INSERM representative: Francis Berenbaum.
- Wyeth representative: Claude Griscelli
- AP-HP representative: Jean-Marc Treluyer

It will define the general organisation (respective roles of the coordination committee and the scientific committee) and research procedures and will coordinate the information.

It will initially determine methodology, and during the research, will decide on the procedures to be followed in the case of unexpected developments. It will also monitor the research procedures.

The members of the committee shall sign an agreement specifying the method of operation (e.g. organization of investigator meetings), financing and duration of commitment to the cohort. The content of the agreement will also be set out by the committee: role of the various partners, use of data, conditions of publication

Renewal of the members of the committee shall be discussed at the end of each term.

6.2.2 Independent monitoring committee

An independent committee is not necessary as this study does not carry any specific risk for volunteers.

6.2.3. Coordination committee

The Coordination committee is made up of:

Doctor Joëlle Benessiano, Hôpital Bichat, Paris
Professor Francis Berenbaum, Hôpital Saint-Antoine, Paris
Professor Pascal Claudepierre, Hôpital Henri-Mondor, Créteil
Professor Bernard Combe, CHU Lapeyronnie, Montpellier
Doctor Patricia Dargent, INSERM U-149, Villejuif
Professor Jean-Pierre Daures, IURC-INSERM, Montpellier
Professor Maxime Dougados, Hôpital Cochin, Paris
Professor Philippe Goupille, CHU Bretonneau, Tours
Professor Alain Saraux, CHU La Cavale Blanche, Brest
Professor Jean-Marc Treluyer, URC Paris Centre
Professor Daniel Wendling, CHU Jean Minjot, Besançon

Guest shall also taking part in the coordination committee meetings according to the items on the agenda.

Role

Ensure the proper function of the cohort (inclusions, monitoring)

Manage logistics, administrative and financial aspects

Develop the protocol, case report form and budget

Create procedural manuals

6.2.4 Scientific committee

The scientific committee is made up of:

- Members of the Strategic Orientation Committee
- Members of the Coordination Committee
- French or foreign personalities
 - Doctor Maria-Antonietta d'Agostino, Hôpital Ambroise Paré, Boulogne sur Seine
 - Doctor Joëlle Benessiano, Hôpital Bichat, Paris
 - Professor Francis Berenbaum, Hôpital Saint-Antoine, Paris
 - Professor Maxime Breban, Hôpital Ambroise Paré, Boulogne sur Seine
 - Professor Alain Cantagrel, Hôpital de Rangueil, Toulouse
 - Professor Pascal Claudepierre, Hôpital Henri-Mondor, Créteil
 - Professor Bernard Combe, CHU Lapeyronnie, Montpellier
 - Professor Anne Cotten, CHU Roger Salengro, Lille
 - Doctor Patricia Dargent, INSERM U149, Villejuif
 - Professor Jean-Pierre Daures, IURC-INSERM, Montpellier
 - Professor Maxime Dougados, CHU Cochin
 - Professor Bruno Fautrel, Hôpital La Pitié-Salpêtrière, Paris
 - Doctor Antoine Feydy, Hôpital Cochin, Paris
 - Professor Philippe Goupille, CHU Tours
 - Professor Désirée van der Heijde, Maastricht
 - Doctor Corinne Miceli, Hôpital Bicêtre, Le Kremlin Bicêtre
 - Doctor Pascal Richette, Hôpital Lariboisière, Paris
 - Doctor Thao Pham, CHU La Conception, Marseille
 - Professor Christian Roux, Hôpital Cochin, Paris
 - Doctor Martin Rudwaleit, Berlin
 - Professor Alain Saraux, CHU La Cavale Blanche, Brest
 - Professor Daniel Wendling
- Representatives of Wyeth to take part in the Scientific Committee:
 - Doctor Danièle Girault
 - Doctor Isabelle Logeart

The two international experts will make coordination with other spondyloarthritis cohorts possible.

The scientific committee will be renewed, as will the committee of founder members, at the end of each term.

Role

The scientific committee is in charge of:

1. Contributing to creation of the protocol
2. Evaluating and selecting scientifically relevant projects by teams the most apt to carry out the work. The scientific committee will propose partnerships for similar projects conducted by different teams. The strategic committee shall approval the Scientific Committee's proposals.
3. Monitor the progress of work undertaken by analysis of a yearly activity report in French, a short report in English and publications' collection.

6.3 Procedures for registration and notification of adverse events

6.3.1 Non-serious adverse events:

Any non-serious adverse event matching the aforementioned definition, observed during the research or after, must be reported in the case report form in the appropriate section.

A single event must be recorded per item. The event may be a symptom, diagnosis or additional test result considered to be significant. All clinical or paraclinical elements used to describe the event in the most appropriate terms must be reported.

6.3.2 Serious Adverse Events (SAE):

Investigators must notify the sponsor (AP-HP) **immediately** of any serious adverse events as defined in appendix 5.

The investigator shall complete the serious adverse event forms (in the research case report form) and shall send them to the DRCD (AP-HP Clinical Research and Development Division) by fax on 01 44 84 17 99 immediately (after calling 01 44 84 17 23 first where possible, in the event of death or unexpected vital threat).

The investigator must also inform the CRA in charge of the research of the occurrence of the SAE.

For each serious adverse event, the **investigator must issue an opinion on the causal relationship of the event with each investigational product and any other treatments.**

Collection of information in order to describe and evaluate an adverse event may not be possible within the timeframe allocated for initial declaration.

Therefore the clinical outcome and results of any clinical tests and diagnostic and/or laboratory tests, or any other information making it possible to appropriately analyse the causal relationship shall be reported:

- **Either on the initial SAE declaration if immediately available,**
- **Or later and as soon as possible, by sending a new SAE declaration completed by fax (and by specifying that it follows on from a declared SAE and stating the tracking number).**

All declarations made by the investigators should identify each subject taking part in the research by a **single code number** allocated to each of them.

Where death is notified for a research participant, the investigator will send any additional information requested to the sponsor (hospital report, autopsy results, etc.).

Any new information coming to light during the research or in the context of the research, deriving from data in literature or research underway, must be notified to the sponsor.

- Declaration of serious adverse events to health authorities

This shall be ensured by the DRCD drug monitoring unit, further to evaluation of the severity of the adverse event, of the causal relationship with each investigational medicinal product and of other treatment, along with evaluation of the unexpected nature of the adverse effects. All suspected unexpected serious adverse effects shall be declared by the sponsor to the competent authorities within the timeframe set out by law.

The competent authorities, ethics committee and research investigators must be informed in the event of unexpected adverse events due to one of the research treatments or the research per se.

6.4 Pre- and post study procedures

Monitoring methods and times further to the occurrence of adverse events

Patients presenting with an adverse event must be monitored until the event is resolved or stabilised.

- If the event is not serious, the outcome shall be noted on the relevant page in the case report form, in the appropriate section.

- If the event is serious, SAE follow-up will be sent to the DRCD.

7. STATISTICAL ANALYSIS

7.1 Strategy for the analysis of data and statistical analysis methods

This cohort will be subject to descriptive analysis while taking the time factor into account. Conventional tests will be conducted for the descriptive analysis.

For the temporal analysis, we will use the Kaplan Meier estimate or Nelson Aalen estimate for assessing survival, and we will then compare survival between groups using the log rank test. For the multivarious analysis, we will use the Cox model, after having checked the time-dependent hypotheses. To do this, we will use repeated measures analysis of variance, with or without group effect, mixed models, GEE models and multi-state models, by identifying the various states used with professionals, and by estimating the force of passage from one state to another with return. Markov or semi-Markov models will be used.

We will also seek factors to explain sacroiliitis on the standard x-ray after 5 years or using an ROC curve with multivariate model. If possible we will construct a score with a predictability limit. The overall test limit will be 5% and the SAS software version 8 will be used.

7.2 Number of patients / subjects required

The number of subjects required was calculated according to the primary objective of this study, namely the ability to demonstrate the usefulness of certain investigations such as the MRI scan in patients with inflammatory rachialgia for predicting occurrence of ankylosing spondylitis. At this time, a number of studies highlight the probability of observing MRI lesions suggesting inflammation of the sacroiliac region in patients suffering from inflammatory rachialgia and/or undifferentiated spondyloarthropathy, without radiological evidence of sacroiliitis. We are not, however, aware of the validity of these MRI anomalies for predicting the occurrence of ankylosing spondylitis, defined by radiological evidence of sacroiliitis (modified New York criteria).

Calculation of the number of subjects necessary took the following elements into account:

The probability of patients included meeting modified New York criteria for the diagnosis of ankylosing spondylitis after 5 years' follow-up is estimated at 70 to 90%.

Data recently obtained from German and Dutch cohorts suggests that such MRI anomalies suggesting inflammation in the sacro-iliac region are around 30 to 50% (ref. Heuft Dorenbosde *et al.* Ann Rheum Dis, 2006, published on line 22 Oct 2005).

The number of patients was calculated by estimating a relative clinically relevant risk of 2 or 3 with a power of 90%.

For a) each of the relative risks (2 or 3), b) three different percentages of patients with an MRI lesion at the start of the study (30, 40, 50%) and finally c) three different percentages of patients with radiological sacroiliitis after 5 years in patients with an MRI lesion at the start of the study (70%, 80% and 90%), the number of patients was calculated for a 5% bilateral risk and 90% power.

1. *First hypothesis*: Percentage of patients at the start of the study with an MRI lesion in the sacroiliac region: 30%

Relative risk	Probability of sacroiliitis after 5 years in patients with an MRI lesion at the start of the study	Number of patients with an MRI lesion at the start of the study	Number of patients without an MRI lesion at the start of the study
2	90%	186	428
	80%	77	178
	70%	40	92
3	90%	186	428
	80%	77	178
	70%	40	92

2. *Second hypothesis*: Percentage of patients at the start of the study with an MRI lesion in the sacroiliac region: 40%

Relative risk	Probability of sacroiliitis after 5 years in patients without an MRI lesion at the start of the study	Number of patients with an MRI lesion at the start of the study	Number of patients without an MRI lesion at the start of the study
2	90%	219	329
	80%	90	135
	70%	47	71
3	90%	68	102
	80%	25	38
	70%	10	15

3. *Third hypothesis*: Percentage of patients at the start of the study with an MRI lesion in the sacroiliac region: 50%

Relative risk	Probability of sacroiliitis after 5 years in patients without an MRI lesion at the start of the study	Number of patients with an MRI lesion at the start of the study	Number of patients without an MRI lesion at the start of the study
2	90%	266	266
	80%	109	109
	70%	56	56
3	90%	82	82
	80%	30	30
	70%	12	12

The number of patients to be included, taking into account the probability of patients lost from sight (15 to 20%) and the various hypotheses, varies from 685 to 768 patients. 700 was therefore decided.

8. RIGHT OF ACCESS TO DATA AND SOURCE DOCUMENTS

Persons with direct access to data, in accordance with applicable legal and regulatory provisions, notably sections L.1121-3 and R.5121-13 of the French Code of Public Health (investigators, quality control managers, investigators, clinical research assistants, auditors and any other people working on trials) shall take all the necessary precautions in order to ensure the confidentiality of information relating to the investigational medicinal products, to the trials, to persons taking part and notably concerning their identity and the results. The data collected by these persons during quality controls or audits shall be made anonymous.

Transmission of data from the case report form to service providers

After each visit, the investigators shall send the pages of the case report form completed during the visit to the service provider, in a postage-paid envelope.

The data shall be entered in a computer system by the third party in question. The data will then be consultable on a secure internet site accessible by the coordination centre only. This will enable centralised monitoring and amendments, tracked in the database directly.

9. QUALITY CONTROL AND ASSURANCE

The research will be supervised according to the sponsor's standard procedures

The research shall be conducted and subjects managed in the centres in accordance with the declaration of Helsinki and applicable good practice.

9.1 Monitoring procedures

This study has been evaluated at risk level A. The level of monitoring shall be determined in a separate document (monitoring plan and guide)

The CRAs representing the sponsor shall visit the investigation centres according to the patient monitoring schedule in the protocol, the inclusions in the various centres and the level of risk allocated to the research.

- Centre initiation visits: Before inclusion, for implementation of the protocol and familiarisation with the various participants of the biomedical research.

- The case report forms will be reviewed the CRAs at the following visits, as the research progresses. The principal investigator of each centre and the other investigators which include or regularly monitor persons taking part in the research, undertake to receive the CRAs at set intervals.

During the on-site visits, the following elements will be reviewed in accordance with Good Clinical Practice:

Observance of the protocol and the procedures defined for the research,

Verification of patient informed consent forms

Examination of source documents and comparison with the data recorded in the case report form as to accuracy, missing data and consistency of data, according to the rules set out by the DRCD.

- Site closure visit: Collection of case report forms, pharmacy audit, biomedical research document collection and archiving.

9.2 Transcription of data in the case report form

All information required by the protocol must be provided in the case report forms. The investigator must provide an explanation in the case of missing data.

The data must be transferred to the case report forms as it is collected, whether it is clinical or paraclinical data. The data should be copied in a clear and legible way in black ink (to enable duplication and computer entry).

Erroneous data detected on case report forms shall be clearly crossed out, and the new data added to the form. The member of the investigator's team having made the correction shall initial and date the form.

Anonymity of patients shall be ensured using a code number and the initials of the person taking part in the research, which will feature on the research documents. Patients' names shall also be erased from copies of source documents used for documenting the research, in the appropriate manner.

Computerised data on file shall be declared to the CNIL, the French data protection authority, according to the relevant procedure.

9.3 Quality control by an audit team

Studies may be audited by the sponsor at any time. During the auditor's visit, the investigator and their team shall make themselves available, and shall authorize access to auditors to the technical platform, the study equipment and to patient records.

Patient anonymity must be respected and the information checked during the audit must remain confidential.

9.4 Quality control by Health Authorities

The following points may be checked during inspection by the French Health Authorities:

- general study organisation,
- qualification of the staff in charge of conducting the study,
- equipment quality,
- informed consent forms,
- ethics committee opinion,
- methods for dispensing and storing products,
- study procedure,
- archiving of study documents.

The investigator will inform the sponsor as soon as the request has been made by the health authorities to conduct the audit.

10. ETHICAL CONSIDERATIONS

The term sponsor is defined by law 2004-806 of 9 August 2004. In this research, AP-HP is the sponsor and the Clinical Research and Development Division (DRCD) manages all regulatory aspects.

10.1 Applicable texts

The study will be conducted in accordance with:

- the updated version of the Declaration of Helsinki
- French Good Clinical Practice guidelines, version dated 30 November 2006

10.2 Investigation centre selection

Patients will be recruited in 26 volunteer rheumatology departments (see appendix 1) meeting the predefined quality criteria. The centres are teaching or general hospital wards invited by the Société Française de Rhumatologie (French society of rheumatology) to take part in the study. The volunteer centres have undertaken to respect the charter in appendix 2.

10.3 Authorisation request to the DGS (French health ministry)

To start the research, the AP-HP, as sponsor, must submit an authorisation application to the DGS. The competent authority, defined in section L. 1123-12, sets out rules for the safety of persons taking part in biomedical research, notably considering the safety and quality of products used during the research, in accordance with applicable guidelines, their conditions of use and the safety of persons with regard to procedures and methods used, and the procedures for monitoring patients.

10.4 Request for opinion from the French ethics committees

In accordance with section L.1123-6 of the French Code of Public Health, the research protocol must be submitted to an ethics committee by the sponsor. The opinion of this committee is notified to the competent authority by the sponsor before the research starts.

10.5 Amendments

The coordinating investigator must inform the DRCD of intentions to amend the protocol. The amendments must be qualified as substantial or not.

A substantial amendment is an amendment likely, in one way or another, to affect the guarantees of persons taking part in the biomedical research (amendment of an inclusion criterion, extension of inclusion, participation of new centres etc.).

After the research has begun, a favourable opinion from the ethics committee must be issued for substantial amendments made to the protocol after this date, and authorization must be granted by the competent authority before the amendments are implemented. In this case, if it is necessary, the committee shall ensure that consent is collected from the persons taking part in the research once again.

Extension of the research (substantial amendment to therapeutic regimen or populations included, extension of treatment and or procedures not initially provided for in the protocol) should be considered to be a new research project.

Substantial amendments must be submitted for authorisation to the DGS and/or opinion from the ethics committee **after payment of a tax by the sponsor**.

10.6 Data confidentiality and declaration to the CNIL

The investigator must keep the list of patients screened / included in the study up to date, by an initials system, in the same way as in the case report form.

In order to respect patient anonymity, an anonymous code, made up of the number of the investigation centre and the patient's study entry number, will be allocated to patients per centre, according to their order of inclusion in the protocol. Only the first letter of the patient's last name and the initial of the first name will feature on the case report form.

10.6.1 Computerised data file

The computer file containing the personal data collected for the research must be declared before the effective start date of the research, according to law.

A **specific reference method for personal data processing in biomedical research studies, set out by law 2004-806 of 9 August 2004**, as entering into the scope of sections L.1121-1 and following of the French Code of Public Health, was established by the CNIL in January 2006.

This method provides for a **simplified declaration procedure** where the type of data collected in the research is compatible with the list in the CNIL's reference document.

Where the protocol is subject to quality control of data by a CRA representing the sponsor, and where it enters into the scope of application of the CNIL's simplified procedure, the DRCD as sponsor shall request a written undertaking from the computer file manager concerning observance of the simplified MR06001 reference methodology.

10.6.2 Non-anonymous file

The computer file featuring the full names and addresses of the patients included in the study will be stored at the URC Paris-Centre only. An authorisation application shall be submitted to the CNIL for the file as a whole and single entity.

10.7 Information leaflet and informed consent form

Written consent must be collected from persons taking part in the research before any biomedical research procedures are performed.

Informed consent will be collected either at the screening visit or on the date of inclusion, according to the internal administrative system in each centre

Patients must read and examine the content of the form before signing and dating it. A signed copy will also be given to them for them to keep. Patients cannot take part in the study without having given their informed consent.

Patients may withdraw their consent at any time, without this having an effect on the quality of their treatment.

Participation in the study is voluntary. Patients may only take part in the study if they have given their free and informed written consent.

Patient anonymity shall be observed during the study and in publications where applicable.

Three copies of the consent form shall be initialled and signed by the patients and the investigator. A copy of the document will be given the patient; the investigator shall keep the second copy in their archives for at least 15 years; the third copy will be submitted to the sponsor in a sealed envelope at the end of the study.

All data collected will be processed so as to guarantee the highest level of confidentiality. Patients will be informed that the data collected during the study will be archived and computer processed in accordance with law 78-17 of 6 January 1978 (French data protection law, amended by law 94-548 of 1 July 1994).

Patients will also be informed that the clinical research assistants designated by the Paris Centre Clinical Research Centre, health authority inspectors and members of the ethics committee, may request access to source clinical data in order to verify the data in the case report form. The informed consent form should specify this point in an explicit manner.

10.8 Final research report

The final research report will be written in by the coordinator and biostatistician for this study. The report will be submitted to each of the investigators for opinion. Once a consensus has been obtained, the final version must be approved and signed by each of the investigators, and sent to the sponsor as soon as possible at the end of the research. A report drawn up according to the competent authority's template must be sent to the competent authority and to the ethics committee within one year after the end of the research, this being the last follow-up visit of the last subject included. The deadline is brought up to 90 days where the research is terminated early. 11. Data processing and archiving of research documents and data

Research documents subject to the law on biomedical research, must be archived by all parties for 15 years after the end of the research.

(see GCP, chapter 8: Essential documents)

The following will be archived:

- Copies of the letter of authorisation from the DGS and compulsory ethics committee opinion
- Successive protocol versions (identified by the version no. and date),
- Correspondence with the sponsor,
- Patients' signed consent forms in a sealed envelope (in the case of forms for minors signed by holders of parental authority) with the matching inclusion list or register,
- The case report form for each subject included, completed and approved,
- All appendices specific to the study,
- The final study report resulting from the study statistical analysis and quality control (duplicate sent to the sponsor)
- Any audit certificates issued during the research

The database resulting from the statistical analysis must also be archived by the person in charge of the analysis (paper or computer format)

12. FINANCING AND INSURANCE

12.1 Insurance

Assistance Publique- Hôpitaux de Paris is the sponsor of the research. In accordance with biomedical research law, the sponsor has taken out an insurance policy with GERLING KONZERN insurance company for the duration of the research, covering their legal liability and that of all participants (doctors or personnel involved in conducting the research) (law 2004-806, sect L.1121-10 of the French Code of Public Health).

Assistance Publique - Hôpitaux de Paris reserves the right to interrupt the research at any time for medical or administrative. The investigator will be notified, where this happens.

12.2 Scientific commitment

Each investigator shall undertake to observe their legal obligations and to conduct the research according to GCP, in accordance with the terms and conditions of the applicable declaration of Helsinki. A copy of the **scientific commitment (DRCD template document)** dated and signed by **each investigator** from each clinical department in participating centres, will be submitted to the sponsor's representative.

12.3 Financing

A tripartite agreement shall be established between AP-HP, Wyeth and the SFR in order to effectively conduct the study.

13. PUBLICATION RULES

AP-HP is owner of the data mentioned herein. The data cannot be transferred to third parties without the sponsor's prior agreement and agreement of the coordination committee.

Persons having actually taken part in elaboration of the protocol and its implementation and in compiling the results shall be eligible to sign any resulting publications.

Assistance Publique-Hôpitaux de Paris must feature as sponsor of the biomedical research and financial backer where applicable. The terms 'Assistance Publique-Hôpitaux de Paris' must appear in the address of the authors.

The publication shall mention the Biological Resources Centre at the Bichat-Claude Bernard hospital in the methods section.

Publications must feature the following: "This research has been conducted with the institutional support of Wyeth Pharmaceuticals France".

14. LIST OF APPENDICES

1. List of centres and investigators
2. Investigation centres charter
3. Scientific commitment
4. SAE declaration form
5. SAE table
6. Cohort organisation
7. Validation of requests to access the cohort
8. BASG scale
9. BASDAI scale
10. BASFI scale
11. HAQ scale
12. SF36 scale
13. ASQol scale
14. Medical and economic questionnaire
15. Modified Schober test
16. Chest expansion
17. Occiput-to-wall distance
18. Tragus-to-wall distance
19. Finger-to-floor distance
20. Lateral spinal flexion
21. Cervical spinal rotation
22. Intermalleolar distance
23. BASMI scale
24. Method of acquisition of radiological data
25. mSASSS radiological score
26. BASRI radiological score
27. Ankylosing spondylitis classification criteria: Modified New York criteria
28. Spondyloarthritis lesions MRI scan
29. Bone density acquisition methods and evaluation
30. Enthesis ultrasound acquisition methods and evaluation
31. General bibliography

Appendix 1: List of centres and investigators

Centre no.	Hospital	Centre investigators	Telephone numbers
1	CHU Cochin Service de Rhumatologie B 27 bd du Fbg St-Jacques 75014 Paris	Prof. Maxime Dougados	+33 (0)1 58 41 25 62
2	CHU Cochin Service de Rhumatologie A 27 bd du Fbg St-Jacques 75014 Paris	Prof. André Kahan	+33 (0)1 58 41 25 50
3	CHU Bichat Service de rhumatologie 46 rue Henri Huchard 75018 Paris	Prof. Olivier Meyer	+33 (0)1 40 25 74 03
4	GHU La Pitié-Salpêtrière Service de rhumatologie 47-83 boulevard de l'hôpital 75651 Paris cedex 13	Prof. Pierre Bourgeois	+33 (0)1 42 17 78 01
5	CHU Saint Antoine Service de rhumatologie 184 rue du faubourg St Antoine 75012 Paris	Prof. Francis Berenbaum	+33 (0)1 49 28 25 20
6	CHU Henri Mondor Service de rhumatologie 51 avenue du Maréchal De Lattre de Tassigny 94010 Créteil	Prof. Pascal Claudepierre	+33 (0)1 49 81 47 04
7	CHU Ambroise Paré Service de rhumatologie 9 avenue Charles de Gaulle 92100 Boulogne Billancourt	Prof. Maxime Breban	+33 (0)1 49 09 56 74
8	Hôpital Robert Ballanger Boulevard Robert Ballanger 93602 Aulnay sous Bois cedex	Dr Bernadette Saint-Marcoux	+33 (0)1 49 36 71 38
9	Hôpital René Dubos Service de rhumatologie 6 avenue de l'Île de France 95300 Pontoise	Prof. Edouard Pertuiset	+33 (0)1 30 75 43 90
10	CHU Trousseau Service de rhumatologie Avenue de la République 37044 Chambray les Tours cedex	Prof. Philippe Goupille	+33 (0)2 47 47 59 17
11	Hôpital Général Service de rhumatologie 3 rue du faubourg Raines 21000 Dijon	Prof. Jean-François Maillefert	+33 (0)3 80 29 37 45
12	CH Le Mans Service de rhumatologie 194 avenue Rubillard 72037 Le Mans cedex	Dr Xavier Puechal	+33 (0)2 43 43 26 56

13	Hôpital Jean Minjot Service de rhumatologie Boulevard Fleming 25030 Besançon	Prof. Daniel Wendling	+33 (0)3 81 66 82 41
14	Hôpital Lapeyronie Service de rhumatologie 371 Avenue du Doyen Gaston Girard 34295 Montpellier cedex 5	Prof. Bernard Combe	+33 (0)4 67 33 87 10
15	CHU Nice Hôpital Archet 151 route Saint-Antoine de Ginestière 06200 Nice	Prof. Liana Euller-Ziegler	+33 (0)4 92 03 55 12
16	Hôpital Lariboisière Service de rhumatologie 2 rue Ambroise Paré 75475 Paris cedex 10	Dr Pascal Richette	+33 (0)1 49 95 88 25
17	Hôpital de la Conception 147 boulevard Baille 13385 Marseille cedex 5	Prof. Pierre Lafforgue	+33 (0)4 91 38 38 12
18	CHU Amiens Service de rhumatologie 2 place Victor Pauchet 80001 Amiens Cedex 1	Dr Patrick Boumier	+33 (0)3 22 66 82 50
19	Hôpital Gabriel Montpied Service de rhumatologie Place Henri Dunant 63003 Clermont-Ferrand Cedex	Prof. Jean-Michel Ristori	+33 (0)4 73 75 14 88
20	Hôpital Pellegrin Service de rhumatologie place Amélie Raba Léon 33076 Bordeaux	Dr Nadia Mehzen	+33 (0)5 56 79 55 56
21	Hôpital Brabois Service de rhumatologie Rue Morvan Vandoeuvre les Nancy	Dr Damien Loeuille	+33 (0)3 83 15 32 03
22	Hôpital Roger Salengro Service de rhumatologie Rue du Professeur Emile Laine 59037 Lille cedex	Prof. René-Marc Flipo	+33 (0)3 20 44 60 62
23	Hôpital Cavale Blanche Service de rhumatologie Boulevard Tanguy Prigent 29609 Brest cedex	Prof. Alain Saraux	
24	Hôpital Bicêtre Service de rhumatologie 78 rue du Général Leclerc 94276 Le Kremlin Bicêtre	Dr Corinne Miceli	+33 (0)1 45 21 37 61
25	Hôpital Purpan Place du docteur Baylac TSA 40031 31059 Toulouse cedex 9	Prof. Alain Cantagrel	+33 (0)5 67 77 15 58
26	CHU Bois-Guillaume Service de Rhumatologie 1 rue de Germont 76230 Rouen cedex	Prof. Olivier Vittecoq	+33 (0)2 32 88 90 19

Appendix 2: Investigation centres charter

The hospital department _____, taking part in the study (herein named the investigation centre), hereby undertakes to:

These commitments will be set out in a contract signed between the study coordinator and the investigation centre.


Commitments	Yes	No
1. Demonstrate strong and recognised involvement in management of ankylosing spondylitis and spondyloarthropathies, and recruit a large number of patients with spondyloarthropathy. Patients with a stable geographical situation must be recruited to minimize the number of patients lost from sight.		
2. Be able to include at least 35 patients in the DESIR cohort over a 2-year period. Otherwise, please state the number of inclusions expected.		Please specify...
3. Have confirmed experience in long-term clinical research (several years), whether in therapeutic trials, epidemiological studies or cohort monitoring.		
4. Have the ability to implement the necessary means at local level (networking, media campaigns, etc.), in order to ensure good representativeness of the sample of patients recruited.		
5. Have the ability to maintain and implement human and material resources (temporary storage of serum, urine, DNA, RNA) necessary to the proper conduct of the study, throughout the study, for a minimum 5-year period.		
6. Immediately inform the Coordination Committee if difficulties arise, regardless of the nature, in order to identify a solution rapidly.		
7. Have clinical research personnel (nurse and/or clinical research assistant) for whom all or part of their work time is devoted to the study only, and to appoint an investigator for the study in the department that will be in direct contact with the trial coordinators.		
8. Have premises suitable for conducting the study, in accordance with Good Clinical Practice, notably specific consultation times, specific storage area for case report forms.		
9. Have access to a secure –80°C freezer and to be able to immediately centrifuge samples either on-site or by an external laboratory nearby (specify the procedure selected before the centre opens)		
10. Call back patients 2 to 4 weeks before the next consultation, in order to minimize the risk of patients lost from sight		
11. Organise a meeting with the local radiologist before the centre opens, in order to explain the procedures for taking standard digital x-rays, MRI scans, writing reports and copying radiographic and MRI images to CD, according to the protocol		
12. Collect radiographic data (standard x-rays, MRI scans in digital format using CDs specifically allocated for the study.		
13. Agree to receive the coordination centre representative at the site, before the centre opens, and at least once per year thereafter.		
14. Agree to the investigator at the centre having regular telephone interviews (at least three times per quarter) with the clinical research associate coordinating the study, to satisfy requests for additional information and/or clarification (queries).		
15. Agree to a site visit at any time during the study, and to provide the		

case report forms and any other study-related data or information, in accordance with Good Clinical Practice.		
16. Agree to at least one member of the centre (doctor, nurse, clinical research associate) taking part in the project initiation meeting and monitoring meetings (around twice yearly).		
17. Agree to the contact details of the patients and general practitioners being transferred to the coordination centre, which will be authorised to contact them if necessary.		
18. Cooperate with private practice rheumatologists not only to make recruitment easier but also patient adherence to the cohort.		
19. Remain available to recruit patients meeting the pre-screening criteria, referred by private practice rheumatologists, within under two weeks.		
20. Submit the clinical, biological and radiological results for the cohort to the referring rheumatologist as soon as possible.		
21. Not to influence patient treatment management if the patient is followed by a rheumatologist, unless otherwise explicitly agreed by the doctor in question.		

In witness whereof date

Name and Signature
Of the investigation centre manager

Appendix 3: Scientific commitment

<i>SCIENTIFIC COMMITMENT</i>	ASSISTANCE PUBLIQUE  HÔPITAUX DE PARIS
------------------------------	--

Biomedical research code: P

Without monitoring

Title of the research

Protocol version number and date:

1. The principal investigator and physician colleagues are qualified by their specific training and work experience to conduct the biomedical research in the stated indication. This is **confirmed in their dated and signed curriculum vitae (as is their National Medical Council registration number)** submitted to the sponsor.
2. The principal investigator and physician colleagues certify that they undertake to conduct this research in accordance with Good Clinical Practice, and in accordance with the law of 20 December 1988, amended by law 2004-806 on biomedical research, along with its orders and implementing laws.
3. The principal investigator and physician colleagues undertake to observe the medical ethics considerations defined by the World Medical Association in the Declaration of Helsinki, enclosed in its Somerset West amended version (October 1996) and to observe rules of confidentiality.
4. The principal investigator and physician colleagues have acknowledged the prerequisites of the research and the protocol and its appendices. They undertake to observe the protocol during the research and to ensure the quality of data collection in the case report forms.
5. The principal investigator hereby certifies that they have the resources to conduct the research concerned properly, in terms of availability, personnel, subject recruitment, technical platform and environment.
6. The principal investigator and physician colleagues, undertake to collect the free and informed consent from persons likely to take part in the biomedical research, or from their legal representative where applicable. Consent shall be collected when subjects have been duly informed of the trial procedures in the information leaflet submitted to them, and will be given in writing, if possible after a cooling off period. At the end of the research, the **original** consent forms will be archived by the centre, and copies shall be given to the sponsor in a sealed envelope.
7. The principal investigator undertakes to file the case report forms of subjects taking part in the research, along with all source documents relevant to the biomedical research. The principal investigator undertakes to inform the sponsor of the number of inclusions being made, on a regular basis.
8. The principal investigator or physician colleagues shall inform the sponsor of any serious adverse events, or new information coming to light during the research, within 48 hours using the DIRC template document.
9. The principal investigator agrees to controls being carried out via an audit by the sponsor and/or inspection by the health authorities. They also agree to answer to any requests for information or data from the sponsor, as soon as possible.
10. The principal investigator undertakes to inform AP-HP of any publications mentioning this research and to cite AP-HP as sponsor of the research, in them. They also undertake, where applicable, to contribute to drawing up the final report with the research coordinator.
11. The principal investigator hereby declares that this biomedical research will be conducted under their personal responsibility.
12. The principal investigator is the sponsor's correspondent in each centre. They agree to train the local team in the protocol and to supervise the team, the names of the members of which they shall have submitted to the sponsor.

Name and signature of the principal investigator:

Centre partner physicians:

Name(s):

Position(s):

Signature(s)

Date...../...../.....

department stamp

Appendix 5: SAE table**Table for the Classification of Adverse Events for Biomedical research not concerning medicinal products or similar products**

Research risk: IAI

Independent Monitoring Committee: No

Biomedical Research SAE table (Art. R. 1123-54 of the French Code of Public Health)

DO NOT NOTIFY THE SPONSOR BY FAX (do not complete the SAE declaration form) but note on the CRF adverse effects page		TO BE NOTIFIED IMMEDIATELY by the investigator to the sponsor (SAE declaration form to be returned by fax on 01 44 84 17 99) and to be recorded on the CRF adverse event pages	
Other events	Expected non-serious adverse effects Directly related to the explorations carried out for the research in addition to routine monitoring	Expected serious adverse events Directly related to the explorations carried out for the research in addition to routine monitoring	Unexpected serious adverse events
<p>POTENTIALLY SERIOUS EVENTS But not relating to research procedures:</p> <p>Reminder: Only SAEs directly relating to additional examinations conducted for the research, in addition to routine monitoring, are to be declared to the DRCD.</p> <p>Serious adverse effects likely to be caused by a given medicinal product during monitoring, are to be reported to the regional drug monitoring centre.</p> <p>Even deaths (except those directly related to the examinations: anaphylactic shock during an examination using contrast products for example) are not to be notified to the DRCD.</p>	<p>Description:</p> <p>Relating to additional examinations conducted for the research.</p> <p>Bruising during vein puncture, patient falling from the examination table</p>	<p>Description:</p> <p>Relating to additional examinations carried out that would not have been conducted outside routine monitoring and meeting one of the severity criteria*</p> <p>NONE</p>	<p>This column shall be completed as notifications are submitted by the investigators.</p> <p>All adverse events meeting one of the severity* criteria below should be noted, except for those stated in the other columns</p> <p>*Severity criteria: 1- Death 2- Threat to vital prognosis 3- Admission to hospital or extended hospital stay required 4- Lasting sequelae 5- Congenital defect or malformation 6- Event considered to be serious by the investigator (reason to be specified)</p>
Last name, first name and signature of the coordinating investigator:	Last name, first name and signature of the URC manager:	Last name, first name and signature of the project referent:	Last name, first name and signature of the drug monitoring manager:
		Last name, first name and signature of the medical coordinator	

Appendix 6: Cohort organisation

1- Coordination centres

The coordination centre is located at the Paris-Centre Clinical Research Unit. This centre works with the EA 2415 Epidemiology and Biostatistics clinical epidemiology unit directed by Jean-Pierre Daurès.

The coordination centre shall ensure the following:

- personnel training
- organisation of clinical information and radiological networks
- creation of a database for all clinical, biological and radiological data.
- compilation of a descriptive analysis at regular intervals for the coordination committee and the scientific committee
- quality controls and audits on site
- logical data checks
- organisation of the receipt and storage of radiological documents
- transfer of all or part of the database in accordance with the procedures
- submission and tracking of correction/approval requests
- contacts with patients and/or general practitioners for patients no longer agreeing to be monitored at the centre

2- Biological resources centre

2.1. Structure

The Biological Resources Centre at Hôpital Bichat (CRBHB) is a cross-functional clinical research structure at the Bichat - Claude Bernard hospital centre. Its principal mission is to assist biomedical research project instigators in compiling human biological sample collections. Since its creation in January 2002, the CRBHB created a structure for the receipt, processing, storage and transfer of human biological samples for research purposes, according to quality assurance rules.

2.2. Premises

The premises used by the CRB are located within the hospital's technical platform. An air-conditioned room houses around twenty secure storage chambers, and was recently fitted out according to CRB specifications; it will enable the centre to considerably increase its storage capacity over the next few years. Located in an INSERM building, for which the refurbishments were funded entirely by the organisation, the room must be made the subject of a specific contract between the two bodies.

Access to storage sites is regulated: Only CRB personnel are authorised to enter. Surveillance and traceability of access to the room are under the supervision of the hospital's central security unit. Named chip cards contain the times of authorised access. The room is managed by the hospital's technical departments which have unrestricted access.

2.3. CRB personnel

The CRB's personnel is hired according to the qualifications required for projects undertaken (design engineers, laboratory technicians etc.). Hired on fixed term contracts, the personnel is remunerated by research credit; between four and seven members of staff are hired depending on the needs of the centre. The CRB personnel, having the necessary technical skills, are often involved in the transfer and/or conduct of laboratory tests, in order to effectively optimize the use of samples managed by the centre. A designated laboratory technician, shall be directly in charge of the samples for the DESIR cohort.

3- Investigation centres

26 investigation centres have been selected. The detailed list can be found in appendix 1.

Appendix 7: Validation of requests to access the cohort

1. General information

Access to clinical data, biological sample, and radiological and imaging data collections is open to teams having taken part in constituting these collections and to external French or foreign teams. Requests for the transfer of data (clinical or imaging) and for the transfer of biological samples shall be approved by the study's scientific committee, which will take the following into account in its decision:

- Scientific relevance of the proposed study
- Non-competition with research projects started by teams having contributed to constituting collections
- Sample availability

In this context, the requirements for acquiring biological samples, which are naturally few, shall differ from those for acquiring clinical and imaging data.

Ownership of the results shall be specified in an agreement, which will also feature the terms and conditions of transfer (prices, publications etc.)

2. Access to clinical data

Clinical data will be made available further to approval from the scientific council. The elements requested will be transferred as a database.

3. Access to biological material

Human biological material stored at the CRBHB for the DESIR cohort, shall be made available according to the provisions of the **Research Contract**, drawn up between the AP-HP and the centre manager. The agreement features the study start and end dates, the CRBHB's undertakings with respect to expected services, insurance of the quality and safety of the samples stored (protection of patient identity, temperature monitoring etc.); it also recalls the terms and conditions of the financial commitment. During the study, the samples will be provided upon written request only (**Transfer Agreement**). The Transfer Agreement authorises transfer of certain samples, according to specific terms and conditions (recipient, transport costs, return of unused samples, conditions of publication etc.). Requests are approved by the Scientific Council supervising the collection, of which the CRBHB manager is a member.

Use of a biological sample for research other than that initially provided for is only permitted if the consent form states this, further to agreement by the CRBHB Scientific Committee and establishment of a Transfer Agreement.

For biomedical research organised by a public institution other than AP-HP, or by a private company, the use of human biological samples for research purposes necessarily requires that a **Material Transfer Agreement (MTA)** be drawn up. This is a contract which ensures intellectual protection of AP-HP in the event of development of the research and patent applications.

The templates for the various contracts are available at the AP-HP DRCR and are approved by legal advisors. Agreements established between institutional partners should make it possible to clarify and facilitate exchange between researchers.

4. Access to radiological examinations

Radiological material (standard x-rays, MRI scans) stored at the coordination centre can be provided further to approval by the cohort scientific committee. The elements will be copied to hard drive and send to the research team requesting them.

Appendix 8: BASG Scale

Bath Ankylosing Spondylitis – Global Score (BAS-G)

Reference:

Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). Br J Rheumatol. 1996 Jan;35(1):66-71.

Two questions:

1. How do you evaluate the effect of your disease on your well-being over the last week?

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

none very severe

2. How do you evaluate the effect of your disease on your well-being over the last 6 months?

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

none very severe

Appendix 9: BASDAI Scale**Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)****Reference:**

Garrett S, Jenkinson T et al. A new approach to defining disease status in ankylosing spondylitis: The Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol.* 1994; 21: 2286-2291.

Please cross the responses to each question, relating to the last 48 hours.

1) How would you describe the overall level of fatigue/tiredness you have experienced?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

2) How would you describe the overall level of AS neck, back or hip pain you have had?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

3) How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

4) How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

5) How would you describe the overall level of morning stiffness you have had from the time you wake up?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

6) How long does your morning stiffness last from the time you wake up?

0 hrs	1/2	1	1 1/2	2 or more hrs

Calculation of BASDAI:

- Compute the mean questions 5 and 6
- Calculate the sum of the values of question 1-4 and add the result to the mean of questions 5 and 6.
- Divide the result by 5.

The score should be 0 to 100.

Appendix 10: BASFI Scale**Bath Ankylosing Spondylitis Functional Index (BASFI)**REFERENCE:

Calin A, Garrett S, et al. A new approach to defining functional ability in ankylosing spondylitis: The development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol.* 1994; 21: 2281-2285.

Please cross the responses to each question, relating to the last 48 hours.

- 1) Putting on your socks or tights without help or aids (e.g. sock aid)

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10
 easy impossible

- 2) Bending forward from the waist to pick up a pen from the floor without an aid

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10
 easy impossible

- 3) Reaching up to a high shelf without help or aids (e.g. helping hand)

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10
 easy impossible

- 4) Getting up out of an armless dining room chair without using your hands or any other help

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10
 easy impossible

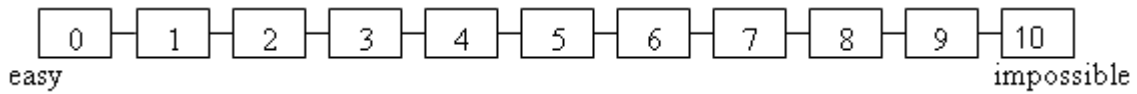
- 5) Getting up off the floor without help from lying in your back

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10
 easy impossible

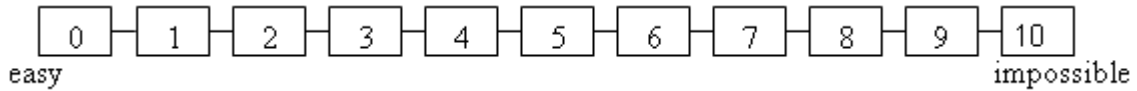
- 6) Standing unsupported for 10 minutes without discomfort

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10
 easy impossible

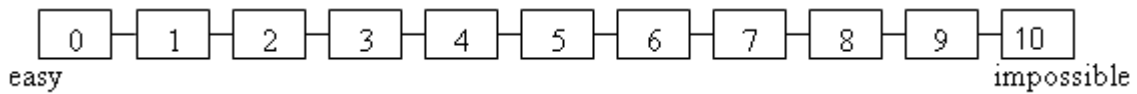
7) Climbing 12-15 steps without using a handrail or walking aid. One foot on each step



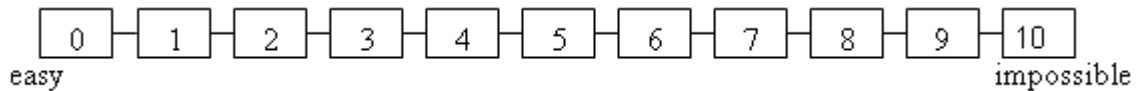
8) Looking over your shoulder without turning your body



9) Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports)



10) Doing a full days activities whether it be at home or at work



Calculation of BASFI

- The BASFI is the mean of 10 item-scores completed on a NRS. The score should be 0 to 100.

Appendix 11: HAQ Scale

Sample Health Assessment Questionnaire (Disability and Discomfort Scales)

HEALTH ASSESSMENT QUESTIONNAIRE					PATKEY# _____
Name _____	Date _____				QUESTDAT _____
In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.					HAQADMIN _____
Please tick the response which best describes your usual abilities OVER THE LAST WEEK:					QUESTYPE _____
	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	RMSVS _____ 1
DRESSING & GROOMING					RSTUDY _____
Were you able to:					QUESTNUM _____
- Dress yourself, including tying shoelaces and doing up buttons?	_____	_____	_____	_____	DRESSNEW _____
- Wash your hair?	_____	_____	_____	_____	
GETTING UP					RISENEW _____
Were you able to:					
- Stand up from a chair without armrests?	_____	_____	_____	_____	
- Get in and out of bed?	_____	_____	_____	_____	
EATING					EATNEW _____
Were you able to:					
- Cut a piece of meat on a plate?	_____	_____	_____	_____	
- Lift a full cup or glass to your mouth?	_____	_____	_____	_____	
- Open a new milk carton?	_____	_____	_____	_____	
WALKING					WALKNEW _____
Were you able to:					
- Walk outdoors on flat ground?	_____	_____	_____	_____	
- Walk up five steps?	_____	_____	_____	_____	
Please tick any AIDS OR EQUIPMENT that you usually use for any of the activities mentioned above:					DRSGASST _____
<input type="checkbox"/> Walking stick				<input type="checkbox"/> Aids used for dressing (button hook, zip-puller, long-handled shoe horn, etc)	RISEASST _____
<input type="checkbox"/> Walking frame				<input type="checkbox"/> Specially adapted utensils (such as for cooking and/or eating)	
<input type="checkbox"/> Crutches				<input type="checkbox"/> Specially adapted chair	
<input type="checkbox"/> Wheelchair				<input type="checkbox"/> Other aids or equipment (Please specify: _____)	EATASST _____
Please tick any categories for which you usually need HELP FROM ANOTHER PERSON:					WALKASST _____
<input type="checkbox"/> Dressing and Grooming				<input type="checkbox"/> Eating	
<input type="checkbox"/> Getting up				<input type="checkbox"/> Walking	

Please tick the response which best describes your usual abilities OVER THE LAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do		
PERSONAL CARE						
Were you able to:						
- Wash and dry your body?	_____	_____	_____	_____	HYGNNEW _____	
- Have a bath?	_____	_____	_____	_____		
- Get on and off the toilet?	_____	_____	_____	_____		
REACHING						
Were you able to:						
- Reach up for and take down a 2 kg (4½ lb) object (e.g. a bag of sugar) from just above your head?	_____	_____	_____	_____	REACHNEW _____	
- Bend down to pick up clothing from the floor?	_____	_____	_____	_____		
GRIPPING						
Were you able to:						
- Open car doors?	_____	_____	_____	_____	GRIPNEW _____	
- Open jars which have been previously opened?	_____	_____	_____	_____		
- Turn taps on and off?	_____	_____	_____	_____		
ACTIVITIES						
Were you able to:						
- Go shopping (supermarket, post office, bank, etc)?	_____	_____	_____	_____	ACTIVNEW _____	
- Get in and out of a car?	_____	_____	_____	_____		
- Do chores such as vacuuming or gardening?	_____	_____	_____	_____		
Please tick any AIDS OR EQUIPMENT that you usually use for any of the activities mentioned above:						
<input type="checkbox"/> Raised toilet seat		<input type="checkbox"/> Bath rail				
<input type="checkbox"/> Bath seat		<input type="checkbox"/> Long-handled appliances for reaching things				
<input type="checkbox"/> Jar opener (for jars previously opened)		<input type="checkbox"/> Long-handled appliances in the bathroom (e.g. a long-handled brush for the body)				
		<input type="checkbox"/> Other aids or equipment (Please specify: _____)				
Please tick any categories for which you usually need HELP FROM ANOTHER PERSON:						
<input type="checkbox"/> Personal Care		<input type="checkbox"/> Gripping and opening things			HYGNASST _____	
<input type="checkbox"/> Reaching		<input type="checkbox"/> Shopping and chores			RCHASST _____	
					GRIPASST _____	
					ACTVASST _____	
We are also interested in learning whether or not you are affected by pain because of your illness.						
How much pain have you had because of your illness OVER THE LAST WEEK:						
PLACE A <u>VERTICAL</u> () MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN:						
NO PAIN 0	_____				SEVERE PAIN 100	PAINSCALE _____

Appendix 12: Sample SF-36 Health Survey Questionnaire

SF36 Health Survey

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.			
1.	In general, would you say your health is: (Please tick one box.)		
	Excellent	<input type="checkbox"/>	
	Very Good	<input type="checkbox"/>	
	Good	<input type="checkbox"/>	
	Fair	<input type="checkbox"/>	
	Poor	<input type="checkbox"/>	
2.	<u>Compared to one year ago</u> , how would you rate your health in general <u>now</u> ? (Please tick one box.)		
	Much better than one year ago	<input type="checkbox"/>	
	Somewhat better now than one year ago	<input type="checkbox"/>	
	About the same as one year ago	<input type="checkbox"/>	
	Somewhat worse now than one year ago	<input type="checkbox"/>	
	Much worse now than one year ago	<input type="checkbox"/>	
3.	The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much? (Please circle one number on each line.)		
	Activities	Yes, Limited A Lot	Yes, Limited A Little
	Not Limited At All		
3(a)	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2
3(b)	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2
3(c)	Lifting or carrying groceries	1	2
3(d)	Climbing several flights of stairs	1	2
3(e)	Climbing one flight of stairs	1	2
3(f)	Bending, kneeling, or stooping	1	2
3(g)	Walking more than a mile	1	2
3(h)	Walking several blocks	1	2
3(i)	Walking one block	1	2
3(j)	Bathing or dressing yourself	1	2
4.	During the <u>past 4 weeks</u> , have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u> ? (Please circle one number on each line.)		
		Yes	No
4(a)	Cut down on the amount of time you spent on work or other activities	1	2
4(b)	Accomplished less than you would like	1	2
4(c)	Were limited in the kind of work or other activities	1	2
4(d)	Had difficulty performing the work or other activities (for example, it took extra effort)	1	2
5.	During the <u>past 4 weeks</u> , have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (e.g. feeling depressed or anxious)? (Please circle one number on each line.)		
		Yes	No
5(a)	Cut down on the amount of time you spent on work or other activities	1	2
5(b)	Accomplished less than you would like	1	2
5(c)	Didn't do work or other activities as carefully as usual	1	2

6. During the <u>past 4 weeks</u> , to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick one box.)									
Not at all <input type="checkbox"/>									
Slightly <input type="checkbox"/>									
Moderately <input type="checkbox"/>									
Quite a bit <input type="checkbox"/>									
Extremely <input type="checkbox"/>									
7. How much <u>physical</u> pain have you had during the <u>past 4 weeks</u> ? (Please tick one box.)									
None <input type="checkbox"/>									
Very mild <input type="checkbox"/>									
Mild <input type="checkbox"/>									
Moderate <input type="checkbox"/>									
Severe <input type="checkbox"/>									
Very Severe <input type="checkbox"/>									
8. During the <u>past 4 weeks</u> , how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)? (Please tick one box.)									
Not at all <input type="checkbox"/>									
A little bit <input type="checkbox"/>									
Moderately <input type="checkbox"/>									
Quite a bit <input type="checkbox"/>									
Extremely <input type="checkbox"/>									
9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u> . Please give the one answer that is closest to the way you have been feeling for each item.									
(Please circle one number on each line.)				All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
9(a)	Did you feel full of life?	1	2	3	4	5	6		
9(b)	Have you been a very nervous person?	1	2	3	4	5	6		
9(c)	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6		
9(d)	Have you felt calm and peaceful?	1	2	3	4	5	6		
9(e)	Did you have a lot of energy?	1	2	3	4	5	6		
9(f)	Have you felt downhearted and blue?	1	2	3	4	5	6		
9(g)	Did you feel worn out?	1	2	3	4	5	6		
9(h)	Have you been a happy person?	1	2	3	4	5	6		
9(i)	Did you feel tired?	1	2	3	4	5	6		
10. During the <u>past 4 weeks</u> , how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives etc.) (Please tick one box.)									
All of the time <input type="checkbox"/>									
Most of the time <input type="checkbox"/>									
Some of the time <input type="checkbox"/>									
A little of the time <input type="checkbox"/>									
None of the time <input type="checkbox"/>									
11. How TRUE or FALSE is <u>each</u> of the following statements for you?									
(Please circle one number on each line.)				Definitely True	Mostly True	Don't Know	Mostly False	Definitely False	
11(a)	I seem to get sick a little easier than other people	1	2	3	4	5			
11(b)	I am as healthy as anybody I know	1	2	3	4	5			
11(c)	I expect my health to get worse	1	2	3	4	5			
11(d)	My health is excellent	1	2	3	4	5			

Thank You!

Appendix 13: ASQOL Scale

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

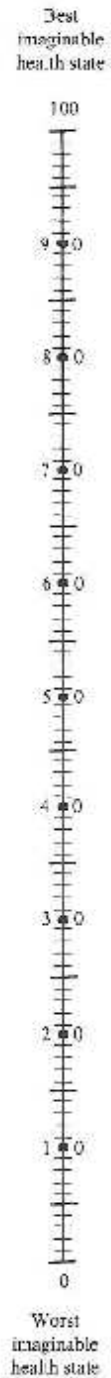
Compared to your general health during the last 12 months, today my health is :

- Improved
- Not changed
- Worse

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is 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 health state is today.

**Your own
health state
today**



Appendix 14: Medical and economic questionnaire

Medical and economic questionnaire

Before continuing, we would like to specify a few points in order to help you complete the questionnaire.

We have asked you to take part in the DESIR cohort as you are suffering from inflammatory back pain.

We wish to collect information about your “disease”, its management and its effect on your occupational activity.

Referred to as “your disease”, we will include all types of pain affecting your back or joints, along with other symptoms relating to:

- ophthalmological disorders if you have already had uveitis (red and painful eyes),
- digestive disorders if you have been diagnosed with ulcerative colitis or Crohn’s disease,
- cutaneous psoriasis.

Please read the questions carefully be answering.

Demographic, medical and economic data

1. Highest level of education reached:

Primary

Secondary

o year 8-11

o year 12-13

Higher education

o ≤ 3 years

o > 3 years

2. Social characteristics:

- Marital status
Married/Living maritally
Single / Divorced / Widowed
- Parental status: Please state number of children |__|__|

3. Occupational category in the last year of work:

Farm owner

Tradesman, shop owner or business owner

Management and senior positions

Middle-level positions

Employee

Worker

Retired

If yes, what was your main social and occupational category?

Unemployed

4. If you have worked during the last 6 months, that is to say you have undertaken paid work:

- a. Which occupation did you undertake for the longest period over the **last 6 months** (only 1 response possible):
- b. How many days off work did you need to take due to **your disease** over the **last 6 months**? / / /
- c. Did onset of **your disease** (or its aggravation) have effects on your occupational status over the **last 6 months** (only one response possible):
 - No, no effect
 - Yes, I had to change jobs without necessarily having to change occupation
 - Yes, I had to change occupation
 - Yes, I was made redundant and I am now unemployed
 - Yes, I was made redundant but I managed to find a similar job
 - Yes, I was made redundant but I managed to find a different job in another sector of activity
 - Yes, I was put on disability leave(is yes, which category?)
 - Yes, I was put on early retirement
 - Other (please specify):
 - No, no effect

4a. If you have not worked during the last 6 months, that is to say you have not undertaken paid work, are you on:

- Long-term sick leave? Start date: _____
Is the cause of this **your disease**? Yes No
- Disability leave? Disability leave start date: _____
Is the cause of this **your disease**? Yes No
- Unemployed What was your last job?
- Retired
- Housewife or husband
- Other (please specify):

5. During the last 6 months, have you consulted doctors or other health professionals for your disease? Yes No

If YES, please indicate the number of visits to each in the table below. Please state **all visits**, except those taking place during hospital stays.

Remark: The examinations carried out during participation in the cohort must not be included

Physician category	Number of visits (or sessions where applicable) over the last 6 months
General practitioner	
Rheumatologist	
Gastroenterologist	
Dermatologist	
Ophthalmologist	
Other specialist:	
Other specialist:	
Other specialist:	
Nurse: Reason for treatment:	
Physiotherapist: Reason for treatment:	
Osteopath:	
Other:	
Other:	

6. Over the last 6 months,

How many blood tests have you had for ***your disease***:

How many urine tests have you had for ***your disease***:

7. Over the last 6 months, have you had any other medical examinations for *your disease* such as those listed below? Yes No

- If **YES**, please state which in the table below:

Examination	YES	NO	Please state type
X-ray	<input type="checkbox"/>	<input type="checkbox"/>	
Ultrasound	<input type="checkbox"/>	<input type="checkbox"/>	
CT-scan	<input type="checkbox"/>	<input type="checkbox"/>	
MRI scan	<input type="checkbox"/>	<input type="checkbox"/>	
Gastrofiberscopy	<input type="checkbox"/>	<input type="checkbox"/>	
Colonoscopy	<input type="checkbox"/>	<input type="checkbox"/>	
Functional respiratory tests	<input type="checkbox"/>	<input type="checkbox"/>	
Bone densitometry	<input type="checkbox"/>	<input type="checkbox"/>	
Bone scintigraphy	<input type="checkbox"/>	<input type="checkbox"/>	
Others:	<input type="checkbox"/>	<input type="checkbox"/>	

8. Have you been admitted to a hospital casualty department over the last 6 months? Yes No

If **YES**, please specify the circumstances in the table below:

	Reason	Date	Place (hospital name, town)	Admission to hospital
1				Yes No
2				Yes No
3				Yes No
4				Yes No

9. Have you been admitted to hospital over the last 6 months? Yes No

If **YES**, please list the dates and times of admission to **hospital** over the year, including admission to rehabilitation centres, medium stay clinics or convalescence homes.

	Reason	Date of admission	Place (hospital name, town)	Number of days
1				
2				
3				
4				
5				

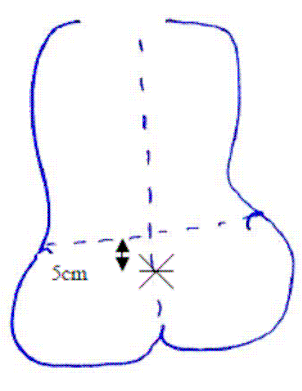
Appendix 15: Modified Schober test**Modified Schober test**

- **Bibliographic references:**

Miller M, Lee P, Smythe HA, Goldsmith CH. Measurement of spinal mobility in the sagittal plane: a new skin contraction technique compared with established methods. *J Rheumatol* 1984;411:507-11. Moll JMH, Wright V. Normal range of spinal mobility. An objective clinical study. *Ann Rheum Dis* 1971;30:381-6.

- **Modified Schober test.**

The patient must be standing. The test consists of first of all marking a point, 5cm below the posterior iliac spines (see drawing below). The second point is measured 10 cm directly above the first, with the patient upright (with no hyper extension or flexion). The patient is the asked to lean forward as far as possible without bending the knees. The distance between the two points is measured. Usually, the initial 10 cm distance increases to 16 or more. The difference is noted in the case report form.



Appendix 16: Chest expansion

Chest expansion

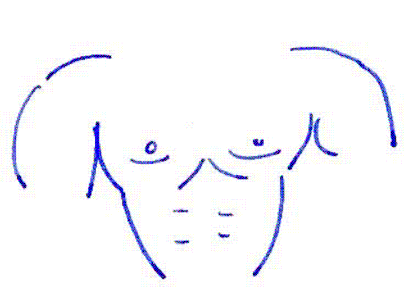
- **Bibliographic references:**

Moll JMH, Wright V. An objective clinical study of chest expansion. Ann Rheum Dis 1972;31:1-8.

- **Chest expansion**

The patient is standing with the arms alongside the body and chest perimeter is measured at xiphoid process level (see drawing below)

Chest expansion is measured as being the difference in centimetres between maximum exhalation to maximum inspiration. The best score of the two tests is retained.



Appendix 17: Occiput-to-wall distance

<u>Occiput-to-wall distance</u>
--

- **Occiput-to-wall distance**

While standing, the patient is asked to try to touch the wall with their neck, while looking straight ahead (without hyper extension of the cervical spine).

The distance from the wall to the occiput (generally non-existent) is noted.

Appendix 18: Tragus-to-wall distance

Tragus-to-wall distance

- **Tragus-to-wall distance**

The patients must stand with their heels and back, where possible, against the wall. The patients is asked to try and touch the wall with their head. The tragus-to-wall distance is measured on the left and on the right. The average of the right and left measurements is retained.



Appendix 19: Fingers-to-floor distance

Fingers-to-floor distance

- **Bibliographic references:**

Miller M, Lee P, Smythe HA, Goldsmith CH. Measurement of spinal mobility in the sagittal plane: a new skin contraction technique compared with established methods. J Rheumatol 1984;411:507-11.

- **Fingers-to-floor distance.**

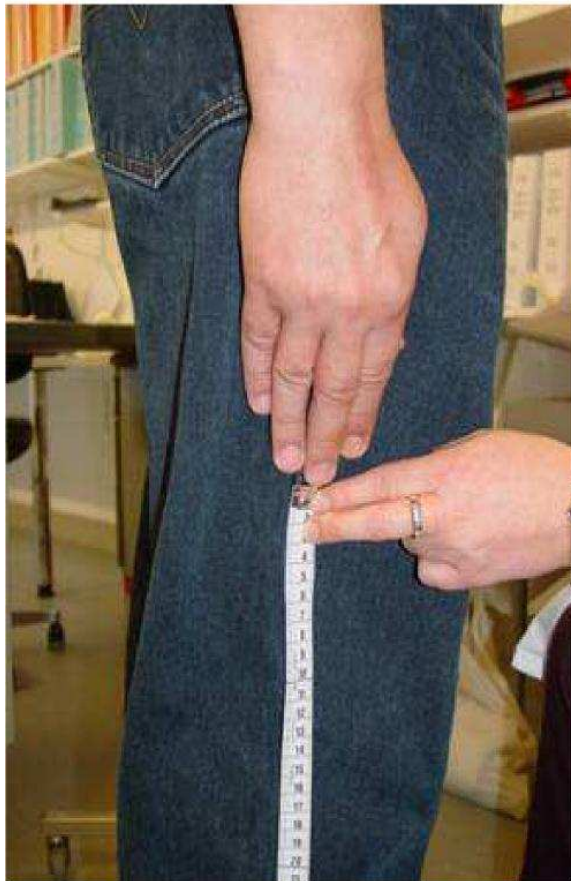
The subject must be standing barefoot, feet together. They are asked to lean forward as far as possible to try and touch the floor with their fingers, without bending the knees. The distance between the tip of the right index finger is measured with a tape measure with 0.1 cm increments.

Appendix 20: Lateral spinal flexion

Lateral spinal flexion

- **Lateral spinal flexion**

This is evaluated by measuring the distance between the fingers and the floor, when bending to the side, without leaning forwards or bending the knees. The patient must therefore be as close to the wall as possible, with shoulders at even height. The investigator asks the patient to lean to the right side, then the left side, while keeping the shoulders against the wall as far as possible. The ankles and knees must also remain in the same position. The best result of the two tests is retained for each side (right and left). The average of the best results for the right and left sides produces a result for lateral spinal flexion (measured using a measuring tape with 0.1 cm increments).

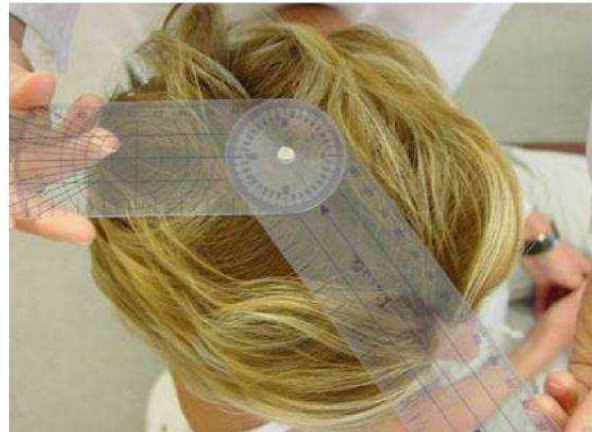


Appendix 21: Cervical spinal rotation

Cervical spinal rotation

- **Cervical spinal rotation**

Cervical rotation is measured using a goniometer. The patient is lying down straight. The goniometer is placed on the forehead. The patient is then asked to turn their head as far as possible to the right and then to the left. The best of the two results is retained for each measurement (right and left). The average of the right and left measurements gives the final result in degrees' cervical rotation.

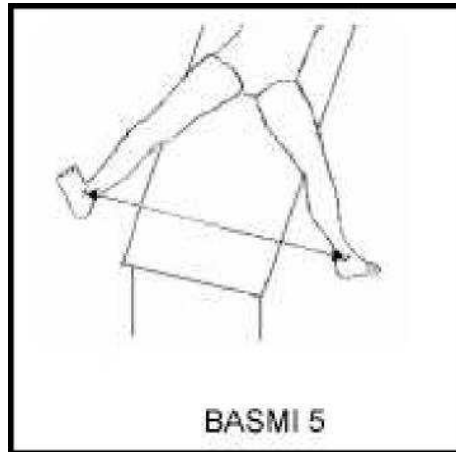


Appendix 22: Intermalleolar distance

Intermalleolar distance

- **Intermalleolar distance**

Intermalleolar distance is measured on a patient lying down, the knees apart and feet straight. The patient is asked to move the legs as far apart as possible, and the distance between the two ankle bones is measured. The best score of the two tests is retained.



Appendix 23: BASMI scale**Patient mobility assessment: BASMI**

- **Bibliographic reference**

Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Harrett SL, Calin A. Defining spinal mobility in ankylosingspondylitis (AS). The Bath AS Metrology Index (BASMI). J Rheumatol 1994;21:1694-8.

- **Composite index**

Criterion	Score		
	0	1	2
Cervical rotation (°)	> 70	20-70	< 20
Tragus-to-wall distance (cm)	< 75	15-30	> 30
Lateral spinal flexion	> 10	5-10	< 5
Lumbar flexion	> 4	2-4	< 2
Intermalleolar distance	> 120	70-100	< 70

- **BASMI score:** This is the sum of the scores obtained for each of the 5 measurements. It is therefore between 0 and 10.

Appendix 24: Methods for the acquisition of radiological data

Methods for the acquisition of radiological data, and for transmission and verification of the quality of centralised data, and for analysis of non-centralised data

1. Acquisition methods

Thoracic spine, side-on

- 35 x 43 cm x-ray film.
- The x-ray film is centred on the 7th thoracic vertebra.
- As landmark, the upper part of the film must be 4 to 6 cm above the upper part of the shoulders.
- The subject identification number must feature at the bottom of the film.
- The patient is placed lying down on their left side, with the coronal plane of the spine in line with the middle of the table (if for any reason this image must be taken with the patient lying on their right side, please explain why on the data transfer form, and use the same position for all images).
- The patient's arm must be placed at a right angle to the body (in order to avoid superimposition with the vertebrae).
- The knees and hips must be bent (to avoid rotation of the pelvis, and the spine must be kept as straight as possible).
- Adjust focal-film distance (FFD) to 100 - 120 cm.
- Direct the central ray to the spine, for beam to penetrate approximately 4 to 6 cm below T7.
- Right or left markers should be used while avoiding superimposition with relevant anatomical elements.
- Bone structures should be visible from at least T3 to L2, and T3 and L2 vertebral bodies should be visible
- The patient must breathe in to maximum inhalation and must not move. 4.

Lumbar spine, side-on

- The patient is placed in the same position as for the thoracic spine side-on
- The x-ray beam must penetrate at iliac crest level (L4)
- A 35 x 43 cm film must be used and placed lengthwise, at iliac crest level, label facing downwards
- The focus-film distance is the same as for the thoracic spine side-on
- Breathing must be blocked at maximum exhalation.
- Bone structures must be visible from T12 to the lumbosacral junction, including the upper third of the sacrum, on a single image. Images centred on L5-S1 should not be used.

Lumbar spine, from front, anterior posterior

- The patient must be placed in anterior posterior supine position with the median line of the body in the sagittal plane, aligned with the middle of the x-ray table.
- The patient's arms should be placed either side of the body or resting on the chest, so as not to appear in the image.
- Bend the knees so as to place the lumbar spine flat against the table, thus reducing lumbar lordosis.
- Direct the central ray perpendicularly to the spine. The beam must penetrate at the median line at L3 (usually the lower part of the costal margins).
- A 35 x 43 cm film must be used and placed lengthwise, label facing downwards.
- Focal distance must be 100 to 120 cm.

- Breathing must be blocked at maximum exhalation.
- Bone structures must be visible from T11 to the lumbosacral junction, including the upper third part of the sacrum.

Cervical spine, side-on

- The patient is placed side-on to the left, either sitting or standing, with the shoulders in contact with the film, to prevent rotation. The same profile must be used for all images taken during monitoring (if images side-on from the right must be used).
- Ask the patient to relax and to relax the shoulders as much as possible (it must be noted that C1 to T1 must be visible to be able to allocate a score to the images, and it may be necessary to ask the subject to hold weights to view T1).
- Slightly raise the chin so as to avoid superimposition of the mandible and the upper cervical spine.
- Align the central ray perpendicularly to the film, with the beam directed horizontally to C4-C5.
- A 24 x 30 cm film must be used and placed lengthwise, landmarks being placed at the anterior and superior parts of the cervical spine and centred with respect to the beam.
- Focal distance must be 183 cm.
- The entire cervical spine must be visible from C1 to T1, without rotation. The mandibular nerves must not be seen over the upper cervical spine. Optimal exposure is achieved when the soft parts and margins of the upper spine are visible along with the bone framework of the entire cervical spine.

Pelvic x-ray, from front

- The patient must be placed in supine position, with the median line of the body in line with the middle of the x-ray table. Pelvic rotation should be avoided.
- The patient's arms should be placed either side of the body or resting on the chest, so as not to appear in the image.
- The knees and hips must be bent (to avoid rotation of the pelvis, and the spine must be kept as straight as possible).
- Direct the central ray to a point on the median line and at an equal distance from the anterior superior iliac spines and symphysis pubis.
- A 35 x 40 cm film must be used and placed width wise, with the identification label facing downwards and centred with respect to the median ray.
- Focal distance must be 100 to 120 cm.
- The film must include the soft parts at the sides.
- Breathing must be blocked at maximum inhalation.
- The entire pelvis and proximal part of the femurs must be included in the image. Optimal exposure is achieved where the margins of the sacroiliac joint and the entire lumbosacral pelvic junction are visible.

2. Methods for the collection and transfer of non-centralised radiological data

The sacroiliac joints, hips and spine will be evaluated and noted directly in the case report form by the investigator, according to New York, BASRI and mSASSS scores respectively.

a. Sacroiliac joint assessment

- 1.
- ii. Film: Pelvis, from front
- iii. Score: The following elements will be noted:
Date of x-ray /__/__/ /__/__/ /_2_/0_/__/__/
- iv. Right /__/* left /__/*sacroiliac
*Enter: 0 if normal
1 uncertain sacroiliitis

- 2 possible sacroiliitis
- 3 sacroiliac joint fusion

v.

b. Hip assessment

- i. System: Bath Ankylosing Spondylitis Radiological Index (BASRI)
- ii. Reference: Kennedy LG, Jenkinson TR, Mallorie PA, Whitelock HC, Barrett SL, Calin A. The correlation between a new metrology score and radiology. Br J Rheumatol 1995;34:767-71
- iii. Film: Pelvis, from front
- iv. Score: The following elements will be noted:
 Date of x-ray /__/__/ /__/__/ / 2_/0_/__/__/
 Hip right /__/* left /__/*
 *Enter 0 if normal appearance
 1 if suspected lesion
 2 if certain lesions but mild
 3 if certain lesions but still moderate
 4 if severe lesions
 If in doubt, a more accurate definition of these stages is provided in appendix 25

c. Spine assessment

- i. System: Modified Stoke Ankylosing Spondylitis Spinal Score.
- ii. Reference: Creemers MC, Franssen MJ, van Hof MA, Gribnau FW, van de Putte LB, van Riel PL. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis 2005;64:127-9
- iii. Films: Side-on images of the lumbar and cervical spine
- iv. Score: The following elements will be noted:
 1. Date of x-ray /__/__/ /__/__/ / 2_/0_/__/__/
 2. Anterior part of the C2 inferior vertebral body /__/*
 3. Anterior part of the C3 superior vertebral body /__/*
 4. Anterior part of the C3 inferior vertebral body /__/*
 5. Anterior part of the C4 superior vertebral body /__/*
 6. Anterior part of the C4 inferior vertebral body /__/*
 7. Anterior part of the C5 superior vertebral body /__/*
 8. Anterior part of the C5 inferior vertebral body /__/*
 9. Anterior part of the C6 superior vertebral body /__/*
 10. Anterior part of the C6 inferior vertebral body /__/*
 11. Anterior part of the C7 superior vertebral body /__/*
 12. Anterior part of the C7 inferior vertebral body /__/*
 13. Anterior part of the T1 superior vertebral body /__/*
 14. Anterior part of the T12 inferior vertebral body /__/*
 15. Anterior part of the L1 superior vertebral body /__/*
 16. Anterior part of the L1 inferior vertebral body /__/*

- 17. Anterior part of the L2 superior vertebral body /___/*
- 18. Anterior part of the L2 inferior vertebral body /___/*
- 19. Anterior part of the L3 superior vertebral body /___/*
- 20. Anterior part of the L3 inferior vertebral body /___/*
- 21. Anterior part of the L4 superior vertebral body /___/*
- 22. Anterior part of the L4 inferior vertebral body /___/*
- 23. Anterior part of the L5 superior vertebral body /___/*
- 24. Anterior part of the L5 inferior vertebral body /___/*
- 25. Anterior part of the S1 superior vertebral body /___/*

*Enter 0 if normal

1 if erosion, sclerosis or squaring

2 if syndesmophyte

3 If intervertebral bone bridge

v. **Score**

The sum of the scores for each level is presented (0 to 72)

Score =

Appendix 25: mSASS radiological score

mSASSS radiological score

- **Bibliographic reference**

Creemers G. Medical Thesis 1993, Nijmegen University, Holland.

Averns HL, Oxtoby J, Taylor HG, Jones PW, Dziedzic K, Dawes PT. Radiological outcome in ankylosing spondylitis: use of the Stoke Ankylosing Spondylitis Spine Score (SASSS). Br J Rheumatol 1996;35:373-6.

- **Calculation method**

The modified SASSS (mSASSS) is derived from the initial SASSS score. The cervical spine is examined side-on in addition to the lumbar spine. The sites examined are the anterior margins of each vertebral body, from the C2 inferior vertebral body to the T1 superior vertebral body, and from the T12 inferior body to the S1 superior vertebral body. The following scoring system is thus applied to each vertebral body corner concerned:

0 = normal

1 = erosion, sclerosis or squaring (squaring is considered to be present if the anterior surface of the vertebra is not concave)

2 = syndesmophyte

3 = bone bridge

The 3rd cervical vertebra is not evaluated for squaring. Sclerosis and erosion are evaluated however. Lesions not relating to spondylitis, such as osteophytes, are not evaluated. Sites not clearly visible on the x-ray are not taken into account in the system. If more than 3 sites are missing, the x-rays are not taken into account.

The total score may range from 0 to 72.

Appendix 26: BASRI radiological score

BASRI radiological score

- **Bibliographic reference**

Kennedy LG, Jenkinson TR, Mallorie PA, Whitelock HC, Barrett SL, Calin A. Ankylosing spondylitis: the correlation between a new metrology score and radiology. Br J Rheumatol 1995;34:767-71.

- **X-rays to be considered:**

- Pelvis, from front
- Lumbar spine, from front
- Lumbar spine, side-on
- Cervical spine, side-on

- **Calculation method**

A global scoring system for the lumbar spine side-on, the lumbar spine from front and the cervical spine side-on, define the BASRI. Each x-ray is evaluated according to the following method:

0 = normal

1 = suspect

2 = mild stage: erosion, obvious squaring, or sclerosis, on at least 3 vertebrae

3 = moderate stage: syndesmophytes on at least 3 vertebrae, incomplete or with fusion, not exceeding 2 vertebrae

4 = severe stage: fusion affecting at least 3 vertebrae

The hips are evaluated on an x-ray of the pelvis from front, where:

0 = normal

1 = suspect

2 = mild stage: joint space pinched in circumferential pattern, residual of more than 2 mm

3 = moderate stage: joint space pinched, less than or equal to 2 mm, or bone production of less than 2 cm)

4 = severe stage (deformation of the head or bone production of more than 2 cm)

The score will be increased by one point where there are at least 2 of the following: erosion, osteophytes, protrusion.

Appendix 27: Ankylosing spondylitis classification criteria: Modified New York criteria

- **Bibliographic reference:**

van der Linden S, Walkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8

- **Criteria**

- o **Collection method**

1. Radiological criterion
 - Unilateral, grade III or bilateral grade II sacroiliitis
2. Clinical criteria
 - Lower back pain for at least 3 months, improved by physical activity and not relieved by resting,
 - Limited mobility of the lumbar spine in the sagittal and frontal planes,
 - Chest expansion reduced compared to the values of subjects of the same age and sex

This criterion is often unrecognized. To make collection easier, the table below specifies the lower limits of normal for chest expansion (courtesy of: Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS): The Bath AS Metrology Index (BASMI). *J Rheumatol* 1994;21:1694-8.

Age (years)	15-24		25-34		35-44		45-54		55-64		65-74		75=	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Lower limit	4.0	3.6	4.3	3.0	3.4	2.7	2.7	2.6	1.7	1.0	2.0	1.1	2.0	1.1

- o **Analysis method**

Ankylosing spondylitis diagnosis is confirmed if one of the radiological criteria and at least one of the three clinical criteria are met

Is an MRI scan of the spine available (optional)? yes no

If yes, are there characteristic

acute/active* inflammatory lesions in the spine? yes no suspect

If yes, at which level?

- Lumbar yes no
- Thoracic yes no
- Cervical yes no

If yes, are there characteristic

chronic* inflammatory lesions in the spine? yes no suspect

If yes, at which level?

- Lumbar yes no
- Thoracic yes no
- Cervical yes no

***Acute/active** inflammatory lesions include bone oedema/contrast product uptake in or adjacent to the sacroiliac joints or entheses at the margins of the vertebrae or whole vertebra (with or without disc involvement, compatible with active lesions observed in cases of ankylosing spondylitis/axial spondyloarthritis; STIR and/or T1 sequences with gadolinium injection are required).

****Chronic** lesions are clear characteristic lesions such as sclerosis, erosion, bone bridges or ankylosis or sclerosis, erosion, or syndesmophytes on the vertebrae.

Appendix 29: Bone density acquisition methods and evaluation**Bone density acquisition methods and evaluation****Participating centres**

Rheumatology Department B, Hôpital Cochin, Paris
 Rheumatology Department A, Hôpital Cochin, Paris
 Rheumatology Department, Hôpital Bichat, Paris
 Rheumatology Department, Hôpital Pitié Salpêtrière, Paris
 Rheumatology Department, Hôpital Ambroise Paré, Boulogne-Billancourt
 Rheumatology Department, Hôpital Robert Ballanger, Aulnay-sous-Bois
 Rheumatology Department, Hôpital Trousseau, Tours
 Rheumatology Department, Centre Hospitalier du Mans
 Rheumatology Department, Hôpital Jean Minjoz, Besançon
 Rheumatology Department, Hôpital Lapeyronie, Montpellier
 Rheumatology Department, Hôpital de la Conception, Marseille
 Rheumatology Department, Hôpital Gabriel Montpied, Clermont-Ferrand

The following elements will be noted:

Bone densitometry done Yes No

If yes, date: /__/__/__/__/__/__/__/__/__/

Device type:

Hologic Lunar Norland DMS

Model:

Results:**Lumbar spine:**

Done Yes No

L1 – L4 BMD = g/cm²

T score = /__/__, /__/

Z score = /__/__, /__/ (the non-adjusted Z score should be used for Lunar devices)

Curve:

Hip:

Done Yes No

Femoral neck BMD = g/cm²

Z score = /__/__, /__/

Z score = /__/__, /__/ (the non-adjusted Z score should be used for Lunar devices)

Total Femur BMD = g/cm²

Z score = /__/__, /__/

Z score = /__/__, /__/ (the non-adjusted Z score should be used for Lunar devices)

Curve:

Full body:

Done Yes No

Full body BMD = g/cm²

T score = / / , /

Z score = / / , / (the non-adjusted Z score should be used for Lunar devices)

Curve:

Body composition:

Left arm:

Body fat mass (g) = / / / / , /

Lean body mass (g) = / / / / / , /

Body fat percentage (%) = / / , /

Right arm:

Body fat mass (g) = / / / / / , /

Lean body mass (g) = / / / / / , /

Body fat percentage (%) = / / , /

Left leg:

Body fat mass (g) = / / / / / , /

Lean body mass (g) = / / / / / , /

Body fat percentage (%) = / / , /

Right leg:

Body fat mass (g) = / / / / / , /

Lean body mass (g) = / / / / / , /

Body fat percentage (%) = / / , /

Trunk:

Body fat mass (g) = / / / / / / / , /

Lean body mass (g) = / / / / / / / , /

Body fat percentage (%) = / / , /

Total:

Body fat mass (g) = / / / / / / / , /

Lean body mass (g) = / / / / / / / , /

Body fat percentage (%) = / / , /

NB: For HOLOGIC devices, if the lean body fat results are only available in the form 'Lean + BMC', then the BMC for the following areas must be entered:

L Arm BMC = / / / / / , / / / /

R Arm BMC = /___/___/___/, /___/___/

L Ribs BMC = /___/___/___/, /___/___/

R Ribs BMC = /___/___/___/, /___/___/

T spine BMC = /___/___/___/, /___/___/

L spine BMC = /___/___/___/, /___/___/

L Leg BMC = /___/___/___/, /___/___/

R Leg BMC = /___/___/___/, /___/___/

TOTAL BMC = /___/___/___/___/, /___/___/

Appendix 30: Enthesis ultrasound acquisition methods and evaluation

Enthesis ultrasound acquisition methods and evaluation

Clinical examination

	History		Symptoms		Physical examination	
	right	left	right	left	right	left
Inferior heel pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Posterior heel pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Patella tendon pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Epicondyle pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

B-mode ultrasound, 12-16 MHz high-frequency probe, Doppler with PRF 500-800 HZ or set according to the device's technical specifications.

2 sagittal slices and coronal slice on each insertion.

	right	left
Achilles tendon		
Tendon thickness	/___/mm	/___/mm
Thickness increase	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Calcifications	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Bone erosion	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Enthesophytes	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Vascularisation (Doppler)		
Tendon	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Bone-enthesis junction	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Sub-Achilles bursa		
Bursa abnormal in B-mode	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Hypervascularisation (Doppler)	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Patella tendon (proximal and distal insertions)		
Thickness increase (prox)	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Calcifications (prox)	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Bone erosion (prox)	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Enthesophytes (prox)	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Thickness increase (dist)	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Calcifications (dist)	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Bone erosion (dist)	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Enthesophytes (dist)	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Vascularisation (Doppler)	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Proximal bone-enthesis junction	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No
Distal bone-enthesis junction	<input type="checkbox"/> yes <input type="checkbox"/> No	<input type="checkbox"/> yes <input type="checkbox"/> No

Epicondyle tendons

Thickness increase

yes No

yes No

Calcifications

yes No

yes No

Bone erosion

yes No

yes No

Enthesophytes

yes No

yes No

Vascularisation (Doppler)

yes No

yes No

 Tendon

yes No

yes No

 Bone-enthesis junction

yes No

yes No

Appendix 31: General bibliography

1. Dougados M, Hochberg MC. Why is the concept of spondyloarthropathies important? *Best Pract Res Clin Rheumatol* 2002;16:495-505.
2. Braun J, Bollow M, Remlinger G, Eggens U, Rudwaleit M, Distler A, *et al.* Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. *Arthritis Rheum* 1998;41:58-67.
3. Gran JT. An epidemiological survey of the signs and symptoms of ankylosing spondylitis. *Clin Rheumatol* 1985;4:161-9.
4. Guillemin F, Saraux A, Guggenbuhl P, Fardellone P, Fautrel B, Masson C, *et al.* Prevalence of rheumatoid arthritis in France - 2001. *Ann Rheum Dis* 2003;63(suppl 1):75.
5. Wendling D, Toussiroit E. Spondylarthropathies: critères et indices. *Rhumatologie* 1997;49:199-306.
6. Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, *et al.* The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991;34:1218-27.
7. Amor B, Dougados M, Mijiyawa M. Criteria of the classification of spondylarthropathies. *Rev Rhum Mal Osteoartic* 1990;57:85-9.
8. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.
9. Kidd BL, Cawley MI. Delay in diagnosis of spondylarthritis. *Br J Rheumatol* 1988;27:230-2.
10. Mau W, Zeidler H, Mau R, Majewski A, Freyschmidt J, Stangel W, *et al.* Clinical features and prognosis of patients with possible ankylosing spondylitis. Results of a 10-year followup. *J Rheumatol* 1988;15:1109-14.
11. Wendling D. Spondylarthrite ankylosante; 1998.
12. Zochling J, van der Heijde D, Burgos-Vargas R, Collantes E, Davis JC Jr., Dijkmans B, *et al.* ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2006;65:442-52.
13. Toussiroit E, Wendling D. Current guidelines for the drug treatment of ankylosing spondylitis. *Drugs* 1998;56:225-40.
14. Wendling D, Toussiroit E. Anti-TNF-alpha therapy in ankylosing spondylitis. *Expert Opin Pharmacother* 2004;5:1497-507.
15. Braun J, Pham T, Sieper J, Davis J, van der Linden S, Dougados M, *et al.* International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2003;62:817-24.
16. Pham T, van der Heijde D, Calin A, Khan MA, van der Linden S, Bellamy N, *et al.* Initiation of biological agents in patients with ankylosing spondylitis: results of a Delphi study by the ASAS Group. *Ann Rheum Dis* 2003;62:812-6.
17. Pham T, Guillemin F, Claudepierre P, Luc M, Miceli-Richard C, Fautrel B, *et al.* Élaboration de recommandations pour la pratique clinique pour l'utilisation des biothérapies dans la spondylarthrite ankylosante. *Rev Rhum* 2006 (sous presse).
18. Boonen A, Chorus A, Miedema H, van der Heijde D, van der Tempel H, van der Linden S. Employment, work disability, and work days lost in patients with ankylosing spondylitis: a cross sectional study of Dutch patients. *Ann Rheum Dis* 2001;60:353-8.
19. Khan MA, Khan MK, Kushner I. Survival among patients with ankylosing spondylitis: a life-table analysis. *J Rheumatol* 1981;8:86-90.
20. Boonen A. Socioeconomic consequences of ankylosing spondylitis. *Clin Exp Rheumatol* 2002;20(Suppl 28):S23-6.
21. Ward MM. Functional disability predicts total costs in patients with ankylosing spondylitis. *Arthritis Rheum* 2002;46:223-31.

22. Amor B, Santos RS, Nahal R, Listrat V, Dougados M. Predictive factors for the long term outcome of spondyloarthropathies. *J Rheumatol* 1994;21:1883-7.
23. Hajjaj-Hassouni N, Maetzel A, Dougados M, Amor B. Comparison of patients evaluated for spondylarthropathy in France and Morocco. *Rev Rhum Ed Fr* 1993;60:420-5.
24. Claudepierre P, Gueguen A, Ladjouze A, Hajjaj-Hassouni N, Sellami S, Amor B, Dougados M. Predictive factors of severity of spondyloarthropathy in North Africa. *Br J Rheumatol* 1995;34:1139-45.
25. Calin A, Porta J, Fries JF, Schurman DJ. Clinical history as a screening test for ankylosing spondylitis. *JAMA* 1977;237:2613-4.
26. Rudwaleit M, Metter A, Listing J, Sieper J, Braun J. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. *Arthritis Rheum* 2006;54:569-78.