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## **Data to be collected for an optimal management of axial spondyloarthritis in daily practice: Proposal from evidence-based and consensual approaches**

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## **ABSTRACT (249 words)**

**Objective:** To propose a list of variables to be collected right after the diagnosis has been made and during the follow-up of patients with axial spondyloarthritis (ax-SpA) for an optimal management in daily practice.

**Methods:** The process comprised (1) the evaluation of the interest of 51 variables proposed for the assessment of ax-SpA by means of a systematic literature research (2) a consensus process involving 78 hospital-based or office-based rheumatologists ,considering the collection of each variable in a 4 grade scale from "not very useful/useless" to "mandatory", (3) a consensus on the minimum interval of time for periodic assessment of the selected variables on a 5 grade scale from "at each visit" to "never to be re-collected".

**Results:** The systematic literature research retrieved a total of 14,133 abstracts, of which 213 were included in the final qualitative synthesis. Data to be collected at the initial systematic review comprised 5 patient's self-administered questionnaires, 3 variables of the physician's interview, 2 variables of the physical examination, 2 variables of the specific ax-SpA imaging and 2 other investigations. Two variables were recommended to be systematically collected at each visit, 1 variable twice a year, 6 variables yearly and 1 variable every 2 years.

**Conclusions:** Using an evidence-based and an expert consensus approaches, this initiative defined a core set of variables to be collected and reported right after the diagnosis and during follow-up of patients with ax-SpA in daily practice.

Key words: comorbidities, physical examination, spondyloarthritis, management

## Introduction

Axial spondyloarthritis (ax-SpA) is one of the most common chronic inflammatory rheumatic diseases [1], which mainly affects young adults. The functional consequences of inadequately controlled disease alter both patient's quality of life and professional capacities with direct impact on healthcare costs [2]. In addition to the disabling joint manifestations, some ax-SpA patients develop extra-rheumatological manifestations such as inflammatory bowel disease, uveitis and psoriasis. The prognosis of both rheumatological features (*e.g.* axial disease, peripheral synovitis/enthesitis/dactylitis) and extra-rheumatological manifestations of ax-SpA have dramatically improved during the last decades, especially with regard to new treatments [3], earlier diagnosis [4] and imaging investigations [5].

The potential number of variables proposed to evaluate an ax-SpA patient (*e.g.* patient's self-administered questionnaires, physician's interview, physical exam, specific ax-SpA imaging modalities ...) is huge. Therefore, a selection of the number of these variables would facilitate the daily task of the rheumatologists [6]. Moreover, discrepancies in collecting and reporting these outcome measures have been observed between rheumatology teams as well as between health professionals who manage ax-SpA patients. For instance, substantial differences were observed in the tools used to perform a physical examination of spinal mobilities between physiotherapists and physicians [7] or between physicians.

In order to standardize the collection of variables in both clinical trials and daily practice, two decades ago, the Assessment of SpondyloArthritis International Society (ASAS) developed and reviewed SpA-specific instruments which were analyzed through the Outcome Measures in Rheumatology (OMERACT) filter for relevance and feasibility [8, 9] by means of Delphi method and with a consensus meeting of the working group. ASAS endorsed core-sets of domains were Physical Function, Spinal Stiffness, Spinal Mobility Measurement and Patient Global Assessment of disease and endorsed also instruments to measure these domains. More recently, ASAS has detailed in a handbook the best way to collect outcome measures [8] and also the way of collection of outcome measures in clinical trials [10].

The optimal management of patients includes an holistic approach which usually requires the collaboration of different health professionals (*e.g.* rheumatologists, nurses, physiotherapists...). This approach has been recognized by international scientific societies

[11] and health care providers [12]. The current recommendation is to provide the opportunity to a recently diagnosed patient with chronic inflammatory rheumatic disease to take benefit of the so-called “systematic initial review”.

This initial review has to be performed right after the diagnosis has been made and includes (besides the educational self-assessment and self-management activities) the review permitting a precise phenotype of the patient, a precise evaluation of the activity (inflammatory part of the disease) and the severity or the potential severity (irreversible structural damage) of the disease.

This part of the review is far to be implemented in practice. For example, in order to check whether a patient suffering from ax-SpA has concomitant skin psoriasis, should this information be collected only by interviewing the patient or by performing a physical exam or by systematically referring the patient to a dermatologist? Another example could be given for the laboratory tests or imaging modalities : in case diagnosis of definite ax-SpA, based on the information collected by interviewing the patient and by the presence of an obvious inflammation at the MRI of the sacroiliac joints, is there any interest to check for HLAB27 typing or pelvis conventional radiographies?

Besides from the importance of this initial systematic review, the international scientific societies (*e.g.* ASAS for spondyloarthritis [13]) and health care providers (*e.g.* National Institute for Health and Care Excellence (NICE) recommendations in the United KingdomUK [12]) have also recognized the importance of the so-called “periodic systematic review” . This periodic review usually includes educational programs, evaluation of adherence to treatment and comorbidities but also the list of variables to be periodically collected. For example, what is the minimum interval of time of a systematic repetition of a physical examination or imaging modalities?

Here, by “systematic”, we mean that this investigation has to be performed even in the absence of symptoms or alarm signal. For example, should we repeat a physical examination of the hip even in the absence of groin pain and/or walking lameness?

The standardization of the exact content of these initial and periodic reviews with regard to the variables to be collected and reported in the medical records will facilitate but also improve the management of these patients. Indeed, standardization of management of diseases and in particular chronic diseases has been proven to be effective [11].

These preliminary remarks prompted us to run an initiative aimed at proposing a list of variables to be systematically collected and reported in patients suffering from ax-SpA in daily practice differentiating the variables to be collected right after the diagnosis and during follow-up.

## Methods

This process included systematic literature review and a consensus process, in accordance with a methodology adopted in previous similar initiatives (e.g. Rencontres d'Experts en Rhumatologie (RER) and 3E (Evidence, Expertise, Exchange) [14, 15].

### *Definition of the scope of this initiative*

During the first meeting of the steering committee of this initiative (a convenor (MD), a facilitator (AB), 3 rheumatology fellows (XR, AP, MD), 13 rheumatologists all experts in the field of SpA and 2 rheumatology nurses (FF and JS)), the following tasks were proposed:

- To exclude from this initiative the investigations aimed at making a diagnosis. The postulate was the following: “Considering that the diagnosis of ax-SpA is confirmed which are in your opinion, the information you need to collect and report in order to optimally monitor/manage the patients?”
- To consider not only the list for variables to collect at the time of the diagnosis but also for the selected variables the minimum interval of time these variables have to be collected again.
- To exclude from this initiative the data to be collected in order to detect and/or prevent comorbidities. In this area, the steering committee proposed to strictly follow the recommendations issued from a similar (RER) initiative [14, 16].
- To exclude from this initiative the variables permitting to check the treatment adherence by the patient. Here again, in this area, the steering committee proposed to strictly follow the recommendations issued from a similar (RER) initiative [15].
- To propose a list of potential variables which will be in the scope of the systematic literature research. The list of these variables explored by the systematic literature review comprised “conventional” outcome measures of ax-SpA disease activity and severity (e.g. BASDAI, BASFI, ASDAS...). However, in order to be in a position to check whether these

variables have been not only collected but also reported in the patient's medical file (usually an Electronic Medical Record), some variables were split—into different categories. For example, we proposed to check the interest of reporting the total score of the BASDAI versus the interest of reporting the score of each individual question of the BASDAI. Moreover, we proposed also to check the interest of reporting extra-rheumatological manifestations considering not only the most frequent ones (e.g. uveitis, psoriasis, inflammatory bowel diseases) but also more rare events such as cardiovascular manifestations (e.g. aortic regurgitation [17, 18], atrioventricular conduction disturbances [19, 20] and urolithiasis [21]). For each variable we tried to be as closer as possible from the daily practice. For example in order to check cardiovascular manifestations, we proposed to check the interest of the physician's interview versus the systematic prescription of an electrocardiogram and/or an echocardiogram.

To anticipate the presentation of the results in a chronological order reflecting the daily practice (*i.e.* patient's self-administered questionnaire followed by the physician's interview, the physical examination and finally prescription of laboratory tests and/or imaging modalities). Using this procedure, a specific question could be included at different stages. For example, the question related to psoriasis occurred in the section "physician's interview" but also in the section "physical examination" and in the "other investigations" (e.g. systematic referral to a dermatologist). The section related to imaging modalities was split into two sub-sections: one focused on the ax-SpA-specific imaging modalities of and one focused other investigations because of the importance of the imaging modalities (*e.g.* spine or sacro-iliac joint radiographs and MRI) evaluating the activity or the severity of ax-SpA (*e.g.* chest CT-scan or echocardiography).

#### *Hierarchical systematic literature reviews*

The systematic literature review was performed by 3 fellows (MD, XR, AP) from December 2018 to April 2019, in order to search for evidence of the usefulness and relevance of each variable in the context of a systematic review in ax-SpA.

The first step of the hierarchical systematic literature reviews consisted of checking whether there were data available in international European League Against Rheumatism (EULAR) or ACR American College of Rheumatology (ACR) recommendations for SpA management. If none were available, the second step retrieved data in systematic literature reviews or

meta-analysis. If these were not available, the third step focused on clinical trials and ax-SpA cohorts. As the search was hierarchical, when data was found at a specific step, the next steps were not applied. We used a sensitive search of Medline via PubMed. The combination of key words used for this search and the flow charts are detailed in Appendix A [fig. S1; See the supplementary material associated with this article online]. This search was completed by a hand search of references from relevant articles, or reviews. From each selected article, the following information was extracted: definition of the variable, measurement properties according to the OMERACT filter (Truth, Discrimination and Feasibility) [22], how to report its occurrence, prevalence and incidence of abnormalities of each variable in ax-SpA and the general population and proposed a minimum interval of time between two collections/reports. All collected data were compiled in tables and graphs to facilitate appraisal.

#### *Consensus process and votes for agreement*

During a two-day physical meeting in October 2019, the literature review was presented to and discussed with an expert panel of 83 rheumatologist experts. Amongst them 53% were female; 44% had office- based activities.

The literature review was split into 3 workshops, each repeated 3 times. Every attendee participated at each workshop once. During these workshops, one fellow presented the information issued from the literature search and one convenor (member of the steering committee) managed the discussion between the participants. Right after the presentation and discussion, members of the expert panel were asked to state their level of agreement concerning the collection and the report of the different variables based on a 4 grade scale: (i) not very useful/useless, (ii) potentially useful, (iii) very useful, (iv) mandatory). Consensus for usefulness of a specific variable was retained if at least 66% of the panel voted for the same grade. If not, the two grades with the higher percentages were selected and the expert panel were asked to vote again on the next day. The final selected grade was the one obtaining at least 50% of the votes during this second round (**appendix A, figure S2**).

The next day, for the variables which have been considered as very useful or mandatory, the expert panel was asked to define the minimum interval of time between two collections they considered optimal using a 5 grade scale: ((i) at each visit, (ii) every 6 months, (iii) every year, (iv) every other year or more or (v) never to be re-collected systemically) For variables



related to structural evaluation the following grade scale was proposed ((i) every other year, (ii) every 5 years, (iii) more than 5 years apart or iv) never to be re-collected systemically).

## **Results**

### ***Hierarchical systematic literature reviews***

A total of 14,133 abstracts were retrieved by the searches, of which 213 were included in the final qualitative synthesis (Appendix, Fig. S1).

### ***Core set-of variables to collect and report during the initial systematic review in ax-SpA***

The list of the 51 evaluated variables and the results of the votes of the expert panel are summarized in table 1. The proposed core set of variables to collect and report in the initial systematic review in axial spondyloarthritis based on this initiative is presented in figure 1.

#### ***1. Patient reported outcomes***

Despite literature concerning nocturnal pain and morning stiffness was scarce [23], these two variables were the only patient's reported outcome that were considered as mandatory to be collected. Patient global visual analogue scale (VAS), BASDAI and ASDAS global scores were considered very useful, whereas the reporting of the 6 questions of the BASDAI score and physician global or fatigue VAS were considered potentially useful. Fibromyalgia Rapid Screening Tool (FIRST) and BASFI questionnaires were considered not very useful/useless.

#### ***2. Physician's interview***

The expert panel considered mandatory collecting and reporting history of uveitis, psoriasis and inflammatory bowel disease in the initial systematic review in ax-SpA patients. Signs of heart failure (dyspnoea and malaise) were considered very useful, whereas collecting and reporting the history of kidney involvement was only considered potentially useful and history of amyloidosis not very useful/useless.

#### ***3. Physical examination of ax-SpA***

None of the variables were considered mandatory. Modified Schöber test, coxo-femoral rotations and swollen joint count were considered very useful. Indeed other variables of the physical examination were only considered potentially useful or not very useful.

#### ***4. Specific ax–SpA imaging modalities***

Pelvis conventional radiographs were the only variable that was considered mandatory in the systematic review. Spine radiographs were considered very useful. Other variables related to structural damage were considered not very useful/useless. It must be noticed that the investigation by magnetic resonance imaging (MRI) in order to check for either inflammation or structural damage was only considered as potentially useful.

#### ***5. Non-specific-ax-SpA imaging modalities and laboratory tests***

C-reactive protein (CRP) was the only variable that was considered mandatory in the systematic review. Urine strip test was considered very useful. Of note, the panel considered the HLA B27 typing not very useful/useless in case of a patient with a definite diagnosis of ax-SpA.

#### ***6. Periodic systematic review in ax-SpA***

The minimum interval of time for repetition of the variables which have been considered as either “mandatory” or “very useful” is presented in table 1 and figure 2. A systematic evaluation at each visit was only proposed for morning stiffness and nocturnal pain whereas ASDAS and BASDAI were proposed to be systematically collected at least yearly. Moreover, search for both extra-rheumatological manifestations (*e.g.* uveitis, psoriasis, IBD) and hip involvement was also proposed to be systematically checked at least yearly. A systematic repetition of imaging modalities was not considered as of great interest. The panel considered that sacro-iliac joints and spine radiographs will never to be systematically repeated.

## **Discussion**

This initiative permitted to propose a list of variables to be collected in a patient with a definite diagnosis of ax-SpA, right after the diagnosis is confirmed, in order to facilitate an optimal management in daily practice. The methodology used for this initiative has some strengths and weaknesses. Moreover the obtained results might be considered as intriguing in particular in comparison to the scientific literature in this area [24, 25].

One of the main strengths of the methodology used for this initiative is the combination of an evidence-based and a consensus approach with a representative panel of rheumatologists.

However, the fact that we have excluded some outcome measures out of the list of variables considered for systematic review could be considered as a weakness. For example, smoking habits is a well-known parameter responsible for some comorbidities such as cardiovascular diseases [26] or lung cancer [27]. Moreover, smoking habits has been recognized as a predisposing factor of the occurrence of ax-SpA and as a predisposing factor of structural damage in ax-SpA [28]. Because this variable has been included in the list of variables to be checked in the previous task force which was focused on comorbidities in chronic inflammatory rheumatic diseases [29, 30], we have not considered this variable in this current initiative. The same criticism could be done with regard to the height of the patient. One could consider this variable as crucial in the physical examination of a patient with ax-SpA as a good proxy of the severity of the axial involvement (height loss in case of loss of lumbar lordosis and /or thoracic kyphosis). Because this variable has to be collected in order to calculate the body mass index and because the collection of body mass index has been strongly recommended to check for comorbidities [29, 30] this variable has not been included in this current initiative.

Some results can be considered as intriguing in comparison to the information provided in the literature. This can be the case for some variables which have not been considered as very useful such as the HLA B27 typing or the MRI investigations. In these areas there are an important number of publications and recommendations emphasizing the importance of these variables in the field of ax-SpA[25]. This importance is usually considered at two levels: either for diagnostic or for prognostic purpose. Here we would like to emphasize that the postulate of this current initiative was to focus on the variables to be collected in patients who have already a definite diagnosis. We took this decision in order to be in accordance with the current ASAS quality standards [13] proposing that a patient should benefit from a

comprehensive/holistic review within 2 months after the diagnosis has been made (initial systematic review) and also should benefit from this review periodically (periodic systematic review). This approach permitted us to detail the content of the recommended initial and periodic systematic reviews.

Concerning the prognostic value of variables, the discrepancies existing between the literature and the variables proposed by this initiative might be explained by the fact that, despite a relevant odds-ratio observed in clinical epidemiological studies, the implementation in daily practice might have been considered as questionable by the expert panel of this initiative. For example, MRI inflammation on sacro-iliac joint [31] and/or vertebra corner [25] are strong and independent predisposing factors of structural progression such as syndesmophyte formation or growth. One would expect that MRI would have been included by the panel of rheumatologists in this reported initiative. This non-selection is probably explained by the lack of clinical relevance at the individual level of data observed in epidemiological studies. Indeed, most of new bone formation still develops without previous MRI inflammation [25]. Hence at the patient level, MRI inflammation only marginally predicts new syndesmophyte formation [32] explaining why this imaging modality is not recommended in daily practice [3, 33]. Furthermore, in the German Spondyloarthritis Inception Cohort (GESPIC) and the Outcome in Ankylosing Spondylitis International Study (OASIS) cohorts an increase of modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) score of 2 units, corresponding to the formation of a new syndesmophyte (increase of 3 mSASSS units in case of bridging syndesmophyte), was only associated with a limited alteration of function scores [34, 35]. These data might explain why variables predicting structural progression were not included in the core set of variables to be collected in our initiative and were discarded from the repetition of these investigations. Finally, another potential explanation of some intriguing results of this initiative might be the lack of interest (or even the potential deleterious effect [36]) of a systematic screening of a rare event. For instance, low grade aortic regurgitation [17, 18] and/or atrioventricular conduction disturbances [19, 20] may be often found by systematic electrocardiogram and echocardiogram examinations in ax-SpA patients despite the absence of clinical manifestation. However systematic electrocardiogram and echocardiogram were not proposed to be included in the core set of variables to collect in our initiative as clinical relevance of these abnormalities are not clear.

In summary, to our knowledge, for the first time this initiative permitted to propose a list of variables to be collected during initial and periodic systematic reviews of a patient suffering from ax-SpA. This initiative should facilitate the implementation in daily practice of the recently published quality standards [13]. Obviously similar initiatives conducted in other parts of the world might be of interest to check the inter- country variability of the results. Finally, this initiative will necessitate regular updates as some new outcome measures may emerge or change over time.

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**Table 1. Variables to collect and report for initial and periodic systematic review of axial spondyloarthritisax-SpA**

VARIABLES TO COLLECT AND REPORT	RELEVANCE		INTERVAL OF TIME BETWEEN 2		
		Votes	%	Votes	%
<b>1.Patient's self-administered questionnaires</b>					
patient global VAS *	very useful	40/71	53	6 months	41/71 58
nocturnal back pain and/or morning stiffness **	mandatory	39/71	55	each visit	46/71 65
BASDAI (global score)	very useful	55/71	76	yearly	53/71 75
BASDAI (6 questions reported)	potentially	52/71	73	-	
ASDAS	very useful	56/71	79	yearly	52/71 73
FIRST	not very useful	45/71	63	-	
Fatigue VAS *	potentially	52/71	73	never systematically	52/71 73
BASFI	not very useful	39/71	55	never systematically	61/79 77
<b>2.Physician's interview</b>					
history of uveitis **	mandatory	59/78	76	yearly	47/71 66
history of psoriasis **	mandatory	58/80	72	yearly	36/71 51
history of Inflammatory bowel diseases **	mandatory	66/8	82	yearly	43/71 43
signs of heart failure (dyspnea, malaise)	very useful	69/71	97	never systematically	46/71 65
history of kidney involvement	potentially	65/71	91	-	
history of amyloidosis	not very useful	69/77	89	-	
physician global VAS *	potentially	37/71	52	never systematically	69/83 83
<b>3.Physical exam</b>					
anterior chest wall pain **	potentially	49/71	59	never systematically	52/78 66
occiput – wall distance #	potentially	44/71	61	every 2 years or more¥	47/71 66
modified Schober (cm)	very useful	43/71	61	every 2 years or more¥	47/71 66
lumbar lateral flexion (cm)	potentially	56/71	79	every 2 years or more¥	47/71 66
chest expansion (cm)	not very useful	40/71	56	every 2 years or more¥	47/71 66
finger-floor distance (cm)	not very useful	39/71	55	every 2 years or more¥	47/71 66
chin-manubrium distance (cm)	not very useful	47/71	66	every 2 years or more¥	47/71 66
cervical rotation (degrees)	potentially	52/71	73	every 2 years or more¥	47/71 66
coxo-femoral rotations **	very useful	44/71	62	yearly	53/71 75
swollen joint count	very useful	40/71	56	yearly	40/71 56
enthesitis	potentially	50/71	70	never systematically	45/71 63
BASMI (total score)	not very useful	58/71	82	never systematically	69/77 89
physical examination of psoriasis	potentially	44/71	62	never systematically	50/71 70
heart auscultation	potentially	55/71	78	never systematically	47/71 66
<b>4.Extra-rheumatological manifestations</b>					
systematic visit to the ophthalmologist **	not very useful	63/79	79	-	
systematic visit to the dermatologist **	not very useful	70/81	86	-	
systematic visit to the gastroenterologist **	not very useful	71/88	88	-	
calprotectin in faeces ##	not very useful	66/81	82	-	
electrocardiogram	not very useful	54/80	68	-	
echocardiography	not very useful	72/80	90	-	
spirometry	not very useful	60/79	74	-	
chest CT-scan	not very useful	64/80	81	-	
urine test strip	very useful	70/21	99	never systematically	55/78 71
kidney ultrasound	not very useful	73/81	93	-	
blood calcium and phosphate	not very useful	50/70	71	-	
HLA B27	not very useful	36/71	51	-	
CRP	mandatory	53/74	72	yearly	41/71 58
<b>5.Other investigations</b>					
pelvis conventional radiographs	mandatory	40/71	56	never systematically	45/71 63
spine conventional radiographs	very useful	44/71	62	never systematically	49/71 69
sacro-iliac joints MRI	not very useful	48/71	68	-	
spine MRI	not very useful	52/73	72	-	
spine CT-scan	not very useful	72/74	94	-	
bone scintigraphy	not very useful	72/73	98	-	
sacro-iliac joint PET scan	not very useful	73/73	100	-	
spine PET scan	not very useful	74/74	100	-	
Enthesis ultrasound	not very useful	57/73	78	-	

ASDAS=Ankylosing Spondylitis Disease Activity Score, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI=Bath Ankylosing Spondylitis Functionnal Index, BASMI=Bath Ankylosing Spondylitis Metrology Index, CRP=C Reactive Protein, CT=computerized tomography, FIRST=Fibromyalgia Rapid Screening Tool, HLA=Human Leukocyte Antigen, MRI=Magnetic resonance imaging, PET=positron emission tomography .

\* on Visual Analogic Scale (VAS) a 0 to 10 scale, \*\* a YES or NO answer, # in cm, ## in mmol/mg feces, ¥=Time lime for spinal mobility was consider at once

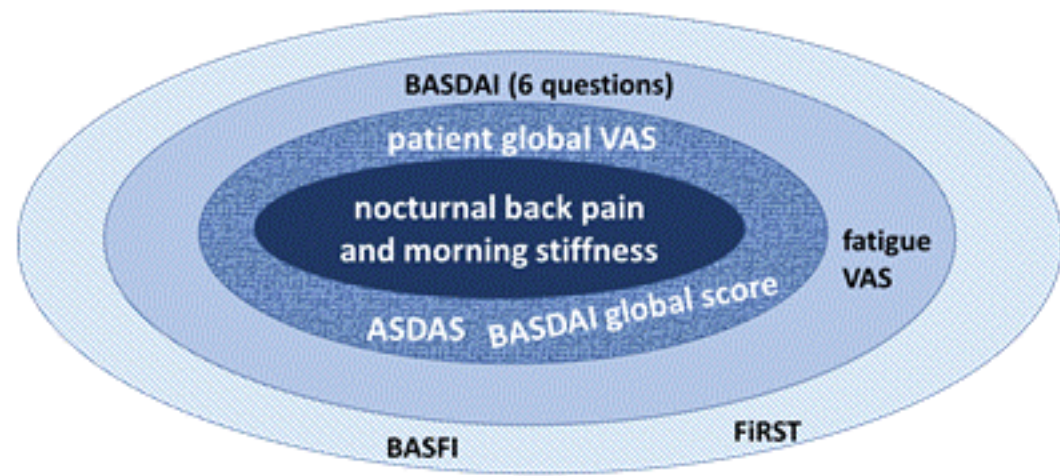
**Figure 1.** Proposed core sets of variables to collect and report during the initial systematic review in axial spondyloarthritis

ASDAS=Ankylosing Spondylitis Disease Activity Score, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI=Bath Ankylosing Spondylitis Functionnal Index, BASMI=Bath Ankylosing Spondylitis Metrology Index, CRP=C Reactive Protein, CT=computerized tomography, FIRST=Fibromyalgia Rapid Screening Tool, HLA=Human Leukocyte Antigen, MRI=Magnetic resonance imaging, PET=positron emission tomography.

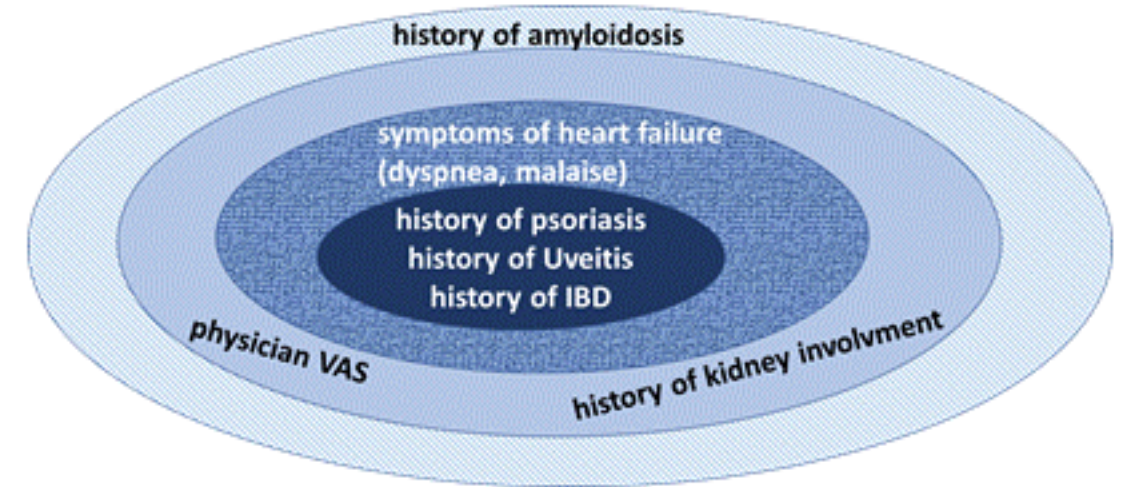
**Figure 2.** Proposed interval of time between two systematic collections and reports of variables considered as “mandatory” or “very useful” by the panel of rheumatologists

ASDAS=Ankylosing Spondylitis Disease Activity Score, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, Spondylitis Metrology Index, CRP=C Reactive Protein, IBD = inflammatory bowel diseases, PRO = Patient Reported Outcomes *i.e. patient's self-administered questionnaire*

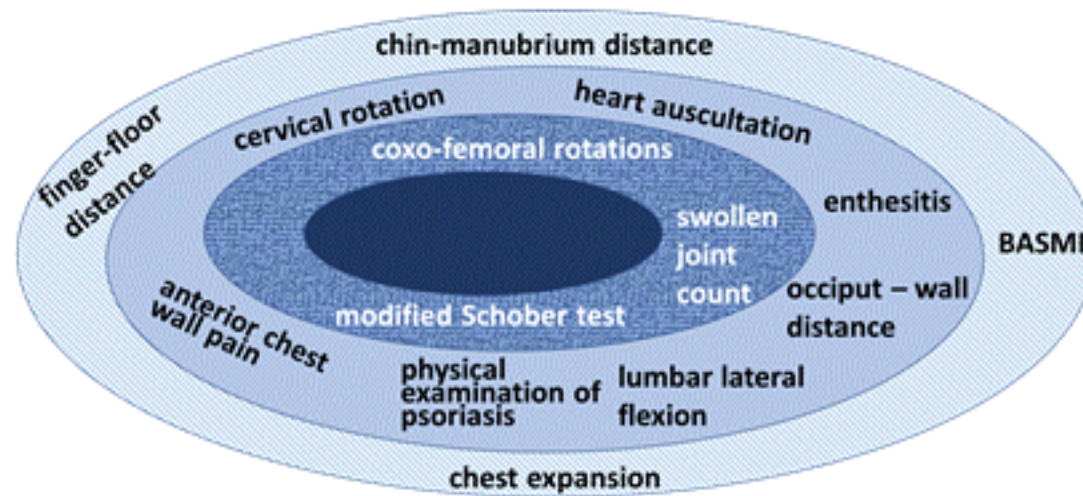
### Patient's self administered questionnaires



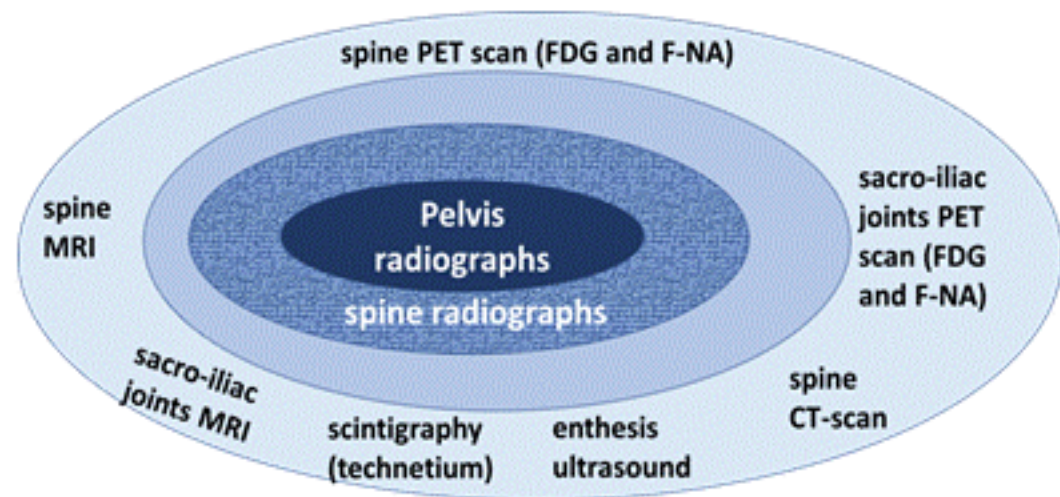
### Physician's interview



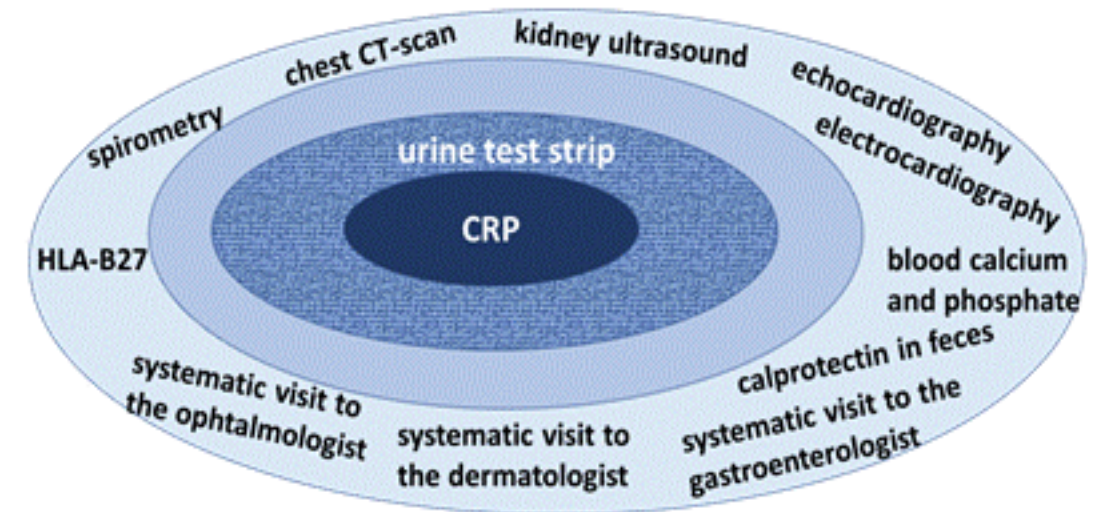
### Physical exam



### Specific axSpA imaging modalities



### Other investigations



Mandatory
  Very useful
  Potentially useful
  Not very useful/useless

