



DCVAS

ACR/EULAR endorsed study to develop classification and diagnostic criteria for primary systemic vasculitis

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Short study title: ACR/EULAR diagnostic and classification criteria for vasculitis

Estimated number of centres: 40

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All applicants have been engaged in the design of this protocol, agreed to the proposal and expressed their consent and willingness to act as committee members for this project on the basis of their interest and expertise.

Abstract

The systemic vasculitides are a group of uncommon but important diseases whose prognosis has improved dramatically with the use of immunosuppressive therapy. However, long-term morbidity from recurrent disease flares, low-grade grumbling disease and/or accumulating damage from previous disease activity or drug therapy now characterise the long-term outlook for patients with vasculitis. There remains major controversy, and incompatibility between the ANCA-associated vasculitides (AAV): Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and Churg Straus Syndrome (CSS), as well as polyarteritis nodosa (PAN) in the current classification criteria and disease definitions. In addition, the classification criteria for the large vessel vasculitides (giant cell arteritis (GCA) and Takayasu's arteritis (TAK)) are dated and considered not fit for purpose by experts in the field. There are currently no diagnostic criteria for primary systemic vasculitis.

We propose to improve existing classification criteria for the primary systemic vasculitides and develop diagnostic criteria for these diseases. As a starting point we have used existing classification terms and vessel size discrimination to help identify patients with systemic vasculitis that we will study, but we will include all forms of primary vasculitis for data collection to help avoid circularity. This will enable more accurate disease definitions for use in clinical practice and in clinical studies of systemic vasculitis. This project would produce the following deliverables:

- 1) A new validated set of *classification* criteria for the primary systemic vasculitides.
- 2) A validated set of *diagnostic* criteria for the primary systemic vasculitides.

Current classification criteria for systemic vasculitis are widely used in clinical trials but there are considerable limitations to their application to research. Similarly, while these criteria are often applied in clinical practice as *diagnostic* criteria, they were not designed or validated for use as diagnostic tools. The current proposal aims to improve existing standards for international research studies and for management of individual patients. The application of valid criteria would ensure that all clinicians who manage patients with these vasculitides use a standardised approach.

We plan to recruit patients with vasculitis and a comparator cohort with other autoimmune diseases/mimics of vasculitis and analyse the clinical, serological, pathological, and radiological parameters used to make a diagnosis of vasculitis, and develop a multivariate analysis model of key factors which discriminate between conditions. As part of this process, we will create a series of vignettes based on the cases acquired to identify important discriminating variables that group patients into a specific type of vasculitis in the opinion of an expert panel. By this process we may identify new classifications of vasculitis and a method by which a reference diagnosis can be made on each patient with vasculitis. In addition, we will create criteria which distinguish patients with vasculitis from those with a similar presentation (context-specific diagnostic criteria). We anticipate that we will recruit 2028 patients with primary systemic vasculitis and 1560 patients with conditions that mimic vasculitis (total of 3588 patients).

Background

The systemic vasculitides are an important cause of mortality and morbidity with a combined annual incidence greater than 100 new cases per million persons.[1] Classification criteria are useful to confirm for research purposes that a group of patients with a clinical diagnosis have a similar or identical condition. However, in order to discriminate between patients with or without a specific disease in clinical settings, diagnostic criteria are required. There are currently no validated diagnostic criteria for systemic vasculitis. The existing American College of Rheumatology (ACR) classification criteria [2-8] and Chapel Hill Consensus Conference (CHCC) disease definitions,[9] supplemented with surrogate clinical and laboratory parameters, failed to act as diagnostic criteria.[10,11]

Problems with the current ACR classification criteria and CHCC disease definitions

The current ACR classification criteria for systemic vasculitis were developed 20 years ago from large retrospective cohorts of patients with 7 forms of vasculitis: Giant cell arteritis (GCA), Takayasu's arteritis (TAK), Wegener's granulomatosis (WG), Churg Strauss syndrome (CSS), polyarteritis nodosa (PAN), Henoch Schönlein purpura (HSP), and hypersensitivity vasculitis (HSV)) plus a separate classification of unspecified vasculitis. The goal of the ACR was to establish criteria to distinguish individual types of vasculitis from the others for inclusion in clinical trials. The sensitivity and specificity of these criteria vary between 71.0-93.5% and 83.9-99.7% respectively. [12] However, the criteria have not been widely validated in a prospective cohort. The criteria were also developed before the wide spread introduction of ANCA testing which now plays an important role in the diagnosis and classification of vasculitis.

The CHCC 1994 definitions were developed by a group of international experts in vasculitis who met at Chapel Hill to clarify and standardise terms.[9] The goal was to produce a list of names and definitions for the most important vasculitic conditions. The definitions were supported unanimously by the expert group, and have been important in encouraging standardisation. One of the important points made was the restriction of PAN to a medium vessel disease, with the subsequent recognition of MPA as a discrete condition. As a result, the ACR criteria and the Chapel Hill definitions for AAV and PAN are incompatible. The absence of MPA from the ACR criteria has led to attempts to use both the ACR criteria and the Chapel Hill definitions in parallel. However, this results in considerable overlap. The major recently conducted or ongoing clinical trials in vasculitis routinely found it necessary to use "modified" ACR criteria for study entry, illustrating the weaknesses of the current classification system for modern clinical trials.[9,13-16]

Pilot study

We have conducted a pilot study using the Birmingham Vasculitis Activity Score (BVAS) as a screening tool for the diagnosis of vasculitis (Mukhtyar et al, unpublished data). Additional laboratory parameters pertinent to systemic vasculitis and its mimics were also recorded. BVAS comprises 59 clinical items grouped in 9 organ systems. Each item is scored if the abnormality is attributed to active vasculitis by the trained observer. In developing diagnostic criteria, the BVAS item list was used as a checklist of clinical features for patients with suspected systemic vasculitis. The items were recorded without attribution to disease activity. We recruited 74 patients into the study over a 12 month period. 55 patients had a respiratory presentation, 13 a renal presentation and 6 patients had pulmonary-renal syndrome. A total of 7 patients had a primary systemic vasculitis. Other diagnoses included infection, malignancy, pulmonary embolism, and acute tubular necrosis, amongst others. Using the preliminary dataset of the first 264 new patients entered into EUVAS studies [13,15,17] we calculated that a cut-off value of 5 or more BVAS items at presentation would include 90% of patients with primary AAV. The median BVAS values for the vasculitis and non vasculitis groups were: 8 (5-14) vs. 5 (2-12) $P=0.008$. Applying a cut off of 5 or more BVAS items would result in a sensitivity of 86% and specificity of 63% for the new dataset (positive predictive value 70%, negative predictive value 82%). We have also recorded ANCA values in a standard assay for all patients and are currently analysing the data. We suggest that on the basis of the pilot study, a few carefully defined clinical items, together with the results of ANCA testing, would provide strongly predictive diagnostic criteria in the appropriate clinical settings.

Summary of our proposal

We propose to develop classification and diagnostic criteria for primary systemic vasculitis. As a starting point we will use the current concepts of ANCA-associated vasculitides, polyarteritis nodosa, GCA, and Takayasu's arteritis, to identify and recruit patients with systemic vasculitis; however we will try and be as all inclusive of primary systemic vasculitis. We will do this by studying new and current cases of vasculitis by utilizing data collected from prospectively-assembled cohorts that takes into consideration current diagnostic testing. We will incorporate clinical phenotypes not included in the ACR (1990) criteria such as MPA and produce internationally accepted criteria for use in clinical research and daily medical practice. This study will build on the work started by the collaborative EULAR/ACR taskforce considering "EULAR/ACR endorsed points to consider in the diagnosis of the systemic vasculitides". This group met in December 2008 and developed a classification framework (Figure 1) together with recommendations on how definitions for the systemic vasculitides could be improved (Basu et al unpublished data).

Justification of need for project

Preliminary data from a survey of the members of this group (21 international experts in the field of vasculitis) who were asked "are the current ACR criteria fit for purpose?" shows that 85% reported that the criteria for WG and HSP were currently not fit for purpose, and 76% felt the criteria for CSS, PAN, and HSV were unfit. The criteria for GCA and TAK were felt to be unfit by 38% and 43% respectively (Basu, Watts, and Luqmani unpublished data). Content validity was felt to be poor particularly due to the lack of inclusion of ANCA. New criteria were recommended for consistency with the CHCC definitions and the division of PAN into MPA and classical PAN as suggested by the CHCC. Furthermore there are no validated diagnostic criteria for the systemic vasculitides. The ACR (1990) criteria are often used incorrectly as diagnostic criteria and they have been shown to perform badly when used for that purpose.[10] There was unanimous opinion that validated diagnostic criteria in vasculitis are needed.

How will the final revisions differ from the current ACR criteria?

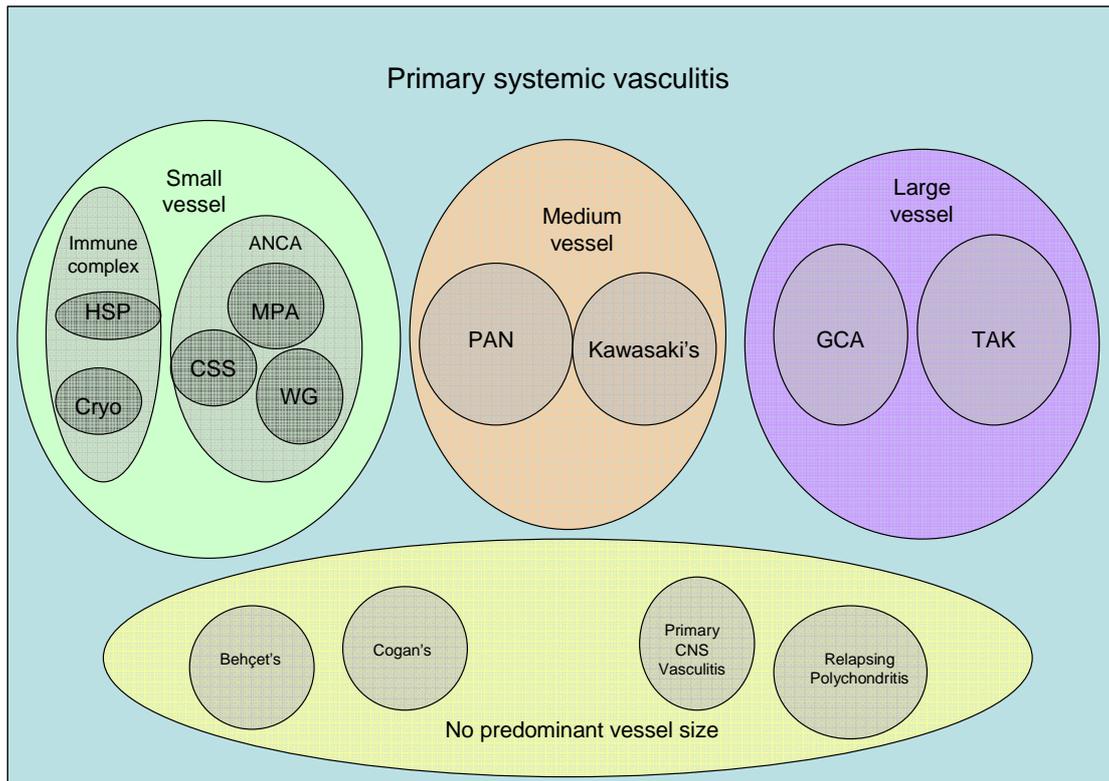
The main differences are:

- a) We will improve on the existing classification criteria for use in clinical trials by introducing the concept of MPA as a separate entity to PAN. In addition we will potentially create new classifications of vasculitis.
- b) We will use modern diagnostic tests (e.g. ANCA, use of diagnostic ultrasound for GCA), new tools of disease activity (BVAS) and tools measuring vasculitis damage (VDI) to further refine the criteria.
- c) We will develop a reference standard by using clustering of clinical features, from real and hypothetical cases so that an expert panel may define a boundary around these clinical features to define each disease. The expert panel will then use this experience and boundaries they create around each disease to make a consensus diagnosis on each individual patient. This is to minimize the inherent circularity when developing criteria sets.
 - The 1990 ACR classification criteria used submitting physician diagnosis to define the type of vasculitis a patient had. This leads to circularity: if the criteria the submitting physician used to classify a patient, is then selected as potential predictor variables for the classification model. So it is no surprise we then identify them as predictors. The difficulty with criteria for diseases such as vasculitis is that these are in fact no more than syndromes, i.e. a collection of symptoms, signs and a clinical course

that sets them apart from other syndromes. The utility of any syndrome definition is limited in time, and the definition is replaced by one or more new definitions as pathophysiologic understanding evolves. There is inherent circularity in trying to define a syndrome through its observed features when the same features are used to select patients with the syndrome. The classic way to select patients with and without the disease is to ask the physician to submit certain cases and non-cases (as in the current ACR criteria). The physician is then the 'gold' standard, but circularity is present as the physician's mindset is formed by the syndrome definition he or she is familiar with (usually informed by criteria already in place). We will try and improve on this situation by using clustering of clinical features, from real and hypothetical cases to define a reference standard. In this way, a standard comprising the opinion of one physician on a group of submitted patients, followed by the opinion of another physician on the next group of submitted patients is replaced by a standard comprising the opinion of a group of experts on all submitted patients, enhanced by an exercise exploring the borders of the syndrome.

- d) We will consider Hepatitis B related PAN as an infectious disease, and only include non Hepatitis B related PAN as a primary systemic vasculitis.
- e) Additionally, we will develop diagnostic criteria which can be used in daily clinical practice. The current ACR criterion was never intended for, and does not function well for this purpose.[10]

Figure 1: ACR/EULAR proposed schema for primary systemic vasculitis



Abbreviations:

HSP = Henoch Schönlein purpura

Cryo = cryoglobulinaemia

MPA = microscopic polyangiitis

CSS = Churg-Strauss syndrome

WG = Wegener's granulomatosis

PAN = non infectious polyarteritis nodosa

GCA = giant cell arteritis

TAK = Takayasu's arteritis

CNS = central nervous system.

Specific Aims

1. To establish and validate classification criteria for primary systemic vasculitis.
2. To establish and validate diagnostic criteria for primary systemic vasculitis.

Methods

We propose to develop and validate classification and diagnostic criteria for the primary systemic vasculitides. As a starting point we will include patients that fall into the current concepts of AAV, PAN, GCA, TAK, and other large vessel vasculitis. Vessel size may or may not remain an organising feature of the new criteria. We will follow the guidelines suggested by the Classification and Response Criteria Subcommittee of the American College of Rheumatology Committee on Quality Measures. [18] To be consistent with these guidelines the following 6 diseases (using existing concepts of classification for vasculitis) have been chosen as our starting point by which our methodology and the estimated numbers required for this project are based: WG, MPA, CSS, PAN, GCA and TAK.

We will use new methodology to try and reduce the inherent circularity when developing new classification criteria. We will use a clustering of clinical features, from real and hypothetical cases to define boundaries around each disease. As part of this process we may create new disease categories, and/or modify existing concepts about disease categories. A reference diagnosis will be made on each patient by consensus expert opinion using the new concepts/categories of disease that were developed in the previous exercise. This differs from the methodology used for the 1990 ACR criteria; the differences are described in the section: '**How will the final revisions differ from the current ACR criteria?**' Specifics about exactly how this will be done are described in detail below.

This project will require an extensive planning phase involving all participants in a series of Delphi exercises which are described in detail below. This consultation process will be integral to the project to ensure the comprehensiveness of the project and to engage all participants.

Classification criteria for AAV and PAN

We will study a minimum of 100 patients (new and existing patients) prospectively within each currently defined disease category (WG, CSS, MPA, PAN, GCA, TAK) for the development of the classification criteria. **We anticipate the need to recruit 130 patients to account for misdiagnosis and dropout to achieve the target of 100 with the confirmed reference diagnosis.** This will include patients that have vasculitis which are assumed to be related to ANCA but do not fulfil the current definitions of any of the diseases, and patients with large vessel vasculitis which do not fulfil current definition for GCA or TAK. Therefore new categories of disease may be created as part of this process and some of the current disease categories may be changed to include or exclude certain patients.

The other diseases will be the controls. The same minimum number of patients will be used to validate the criteria. The 1st 100 patients with a formal reference diagnosis that are recruited for each disease will be used for development of the classification criteria; the next 100 consecutive patients recruited with a confirmed reference diagnosis for each disease will be used to validate the criteria. Again we anticipate the need to recruit 130 patients to account for misdiagnosis and dropout to achieve

the 100 target. The majority of cases included will be the same as that used for the development of the diagnostic criteria.

An overview of the methodology for developing and validating the classification criteria is presented in Figure 2.

Phase 1a: Development of classification criteria

1. Establish a list of potential criteria (i.e. clinical features) to be studied. We will use a Delphi approach with nominal group technique to get a wide representation of views from all participating centres as to what predictors we should include. The categories of data collection used for the development of the ACR 1990 classification criteria for vasculitis will be included, but we will not be limited to these categories.[19] Examples of the broad categories to be studied are listed below:
 - i. Patient demographics
 - ii. Medical history
 - iii. Physical examination findings (encompassing all items on the Birmingham Vasculitis Activity Score and Vasculitis Damage Index)
 - iv. Laboratory tests (blood and urine, including ANCA testing)
 - v. Diagnostic radiology findings (angiograms, CTs, MRIs, etc.)
 - vi. Biopsy results
 - vii. Treatment
 - viii. Response to treatment
 - ix. Any new biomarkers or genetic testing that becomes available for routine clinical use
 - x. Any other investigation that may help include or exclude vasculitis
2. The full list of criteria will be circulated to the expert panel for feedback regarding any potential omissions or redundancy in the list, and appropriate revisions made.
3. A paper-based data collection form and an online web based database will be designed. (The electronic database will be similar to that used successfully by the PReS/EULAR group to develop classification criteria for paediatric vasculitis).
4. Each participating centre will be asked to enter data on prospective patients with a current working diagnosis of WG, MPA, CSS, PAN, GCA, TAK or other AAV or large vessel vasculitis onto the data collection form. This may include some mandatory investigations for each patient (e.g. CBC, ANCA, Urine analysis, etc)
5. Each participating centre will have the opportunity to enter the information collected on the form onto the on-line web-based database. Extra payment would be made to the site for completing the online form(s).
6. Centres that are unable to complete the online forms will submit anonymised paper forms to the Oxford site for transfer into electronic format.
7. In the absence of an established gold standard, we propose to develop a reference standard. Patients that are submitted to this study will by default have had a diagnosis made by the submitting physician. Historically this has been used as the 'gold' standard when developing criteria sets (including in the current ACR classification criteria for vasculitis). This methodology results in circularity, and therefore we intend on minimize this circularity in the following way:
 - Members of the steering committee will create clinical vignettes for each disease category using a clustering of clinical features and investigations from actual cases. An expert panel will then be asked

to classify each vignette. This classification will include the potential for other new disease categories not currently defined. Hypothetical changes will then be made to components of each clinical vignette and the expert panel will be asked to re classify the case. Based on that change the patient may or may not be re-classified as having a different type of vasculitis. This process will be repeated multiple times in an attempt to determine the key clinical features that influence that expert panel to change the diagnosis.

- This exercise will:
 - Help identify key elements that constitute each disease in the opinion of an expert panel.
 - Identify areas that are poor discriminators.
 - Enable us to form a boundary around clustering of clinical features to help determine what constitutes each separate type of vasculitis. These boundaries will be defined by consensus opinion of the expert panel using a Nominal Group Technique. This new 'boundary' or cluster of key clinical features would then serve as a guide by which a reference diagnosis is made for each real patient.
 - Develop a short list of items that would provide face, content and criterion validity when constructing the final classification criteria.
 - Potentially create new categories and modify or combine existing categories of vasculitis.
- 8. The expert panel, by consensus opinion will then re classify each patient to a specific type of vasculitis. This will be the **reference diagnosis** for that patient. Any patient that is not thought to have vasculitis or there is insufficient clinical information to make a diagnosis in the opinion of the expert panel, will be excluded from further analysis for classification criteria. Patients excluded on the basis of not having vasculitis may be considered for inclusion as a control patient for the development or validation of diagnostic criteria if they were a new presentation.
- 9. The 1st 100 patients with a formal **reference diagnosis** for each of the types of vasculitis being studied will be used to develop the classification criteria. (We estimate 130 patients will need to be recruited to allow for misdiagnosis and dropout to achieve this target of 100 patients with a confirmed **reference diagnosis** for each disease category). All subsequent patients recruited above this number will be used to validate the new criteria.
- 10. **Statistical methods:** A number of statistical methods have been proposed for disease classification.[19-21]. We intend to use three approaches: the 'number of criteria' rule, logistic regression, and Classification and Regression Tree analysis.

From the clinical vignettes exercise, we will have created a list of criteria that can be used to define the type of vasculitis a patient has. This is the 'reference standard' based on group consensus of what the important attributes and criteria are for a patient to have a specific type of vasculitis. All patients recruited to the study have since been reclassified according to this reference standard. For each type of vasculitis we will use the 'number of criteria' rule. This involves identifying the minimum number of criteria that must be present to correctly classify patients as having a specific type of vasculitis. This can be done through a receiver operating characteristic (ROC) curve analysis plotting sensitivity (the proportion of positive

outcomes correctly classified) against specificity (the proportion of negative outcomes correctly classified). The 'gold standard' is whether the patient is classified as having vasculitis according to the reference standard. The alternative is whether someone is classified with disease if only a certain number of criteria are present. We will repeat the analysis, varying the number of criteria required, to identify the optimal cut-point that maximises the area under the curve and correctly classifies the greatest number of patients.

We will then use logistic regression modelling. Separate models are to be fitted for each type of vasculitis (i.e. WG, CSS, MPA, PAN, GCA, TAK and other new categories) where the outcome is whether or not a patient has a specific type of vasculitis. Because ANCA-related and large vessel vasculitis are different, we will restrict the control sample for these groups. e.g. WG (case) versus other AAV (controls), and GCA (case) versus other large vessel vasculitis (controls). Allowing for 30% loss to follow-up and misclassification we should have a minimum of 100 cases and between 100-300 controls. A provisional list of predictor variables has been suggested earlier in the proposal and subject to change following an exhaustive search of all possible predictors using Delphi techniques. A full multivariable logistic regression model is then fitted including all possible predictors. However we need to consider the possibility of model over fitting. A general rule is that we need 10 times as many observations as predictor variables, and in the specific case of logistic regression this relates to the number of observations in the outcome group (the smaller of cases or controls). If a model is fitted that is too complex, having too many variables to estimate for the amount of information in the data, the worth of the model (e.g. R^2) will be exaggerated and future observed values not agree with predicted ones. Hence as we have 100 cases (assuming no missing data on predictor variables which would reduce the number of cases included in analysis) we can include a maximum of 10 predictor variables in the full model. In order to decide which 10 variables to select from the initial exhaustive search of all possible predictors, we would have to come to some group consensus based on pre-specified a-priori predictors of importance.

One of the assumptions of a logistic regression model is that for continuous variables the log-odds of outcome increase in a linear manner. It is therefore important to check for departure from linearity in logistic models. We use likelihood ratio tests to examine evidence of non-linearity by comparing a model with a categorical variable to a model with the variable as a score. If there is evidence of a non-linear association one approach is to categorise the data (e.g. create age-groups) with the assumption that the odds of outcome will not change greatly within each group. However, for predictive modelling it is preferable to keep variables continuous to retain more predictive power, so fractional polynomial regression modelling is used to model non-linear relationships for continuous variables.

However the results of complete case analyses can be biased. The cumulative effect of missing data in several variables often leads to exclusion of a substantial proportion of the original sample, causing a loss of precision and power. Multiple imputation methods can be used to handle datasets with missing values, which allows for the uncertainty about missing data by creating several plausible imputed datasets and appropriately combining their results. We will do this using the ICE procedure in Stata. The first stage is to create multiple copies of the dataset with missing values replaced by imputed ones. Missing values are sampled from their predictive distribution based on the observed data. The imputation procedure accounts for uncertainty in predicting missing values by injecting appropriate variability into the multiple imputed values. In the second stage regression models

are fitted to each of the imputed datasets and averaged together to give overall estimated associations. Standard errors are calculated using Rubin's Rules. We include all predictor variables in the multiple imputation process, together with the outcome variable as this carries information about missing values of the predictors.

Having fitted the full multivariable model, a backwards selection process is used to exclude variables that do not improve model fit. Likelihood ratio tests are used to compare model fit and a nominal significance level of 5% is pre-specified. The final model then provides an equation from which we can calculate the probability of having a specific type of vasculitis based on the patient's clinical characteristics.

The performance of the predictive model is then assessed in terms of calibration and discrimination. Calibration measures how closely predicted risk agrees with observed risk. This is assessed for each tenth of predicted risk ensuring 10 equally sized groups, and a Hosmer-Lemeshow goodness of fit test performed. The idea behind Hosmer and Lemeshow's goodness-of-fit test is that the predicted frequency and observed frequency should match closely, and that the more closely they match, the better the fit. Discrimination is the ability of the model to differentiate between cases and controls. This can be assessed by calculating the area under the ROC curve. A model with no predictive power would have a 45 degree line corresponding to an AUC of 0.5, a perfect model would have area 1. Another measure is R^2 , which for logistic regression assesses the explained variation in risk and is the square of the correlation between the observed outcome (0 or 1) and the predicted risk. Finally we perform regression diagnostics to ensure the assumptions underlying the logistic regression model are met.

A complimentary approach to logistic regression model when developing classification criteria is the use of Classification and Regression Tree (CART) analyses, which are said to be ideally suited to the generation of clinical decision rules. CART has a number of advantages over traditional methods of analysis. Firstly, when generating clinical decision rules, there may be many possible predictor variables. This limits the usefulness of logistic regression methods where we need to consider issues of model over fitting so only a limited number of predictor variables can be included in the multivariable model. Since efficient algorithms are used, CART is able to search all possible variables as splitters, even in problems with many hundreds of possible predictors. Secondly parametric statistical methods such as logistic regression have a number of underlying model assumptions where predictors must have a linear association with the outcome, usually requiring the variable to be normally distributed. There are methods to overcome this problem when the assumptions are not satisfied, but an advantage of CART is that it is non-parametric, so no assumptions are made regarding the underlying distribution of predictor variables. Thirdly, complex interactions may exist in the data. Using traditional methods, tests for interaction are low powered, and we generally pre-specify a-priori interactions of importance. CART is often able to uncover complex interactions between predictors which may be difficult or impossible to uncover using traditional multivariable techniques. Fourthly, missing data causes problems when fitting regression models, although this can be overcome using multiple imputation techniques. CART also has sophisticated methods for dealing with missing variables. Finally, the output of logistic regression models will estimate the proportion of patients with disease based on a number of predictor variables (patient characteristics). But clinicians tend not to think in terms of probability, and prefer to classify patients as 'low' or 'high' risk, so such models tend not to be used in clinical practice. The CART tree is much simpler to interpret than the multivariable logistic regression model, making it more likely to be practical in a clinical setting and make

sense to clinicians. Clinical decision rules which make sense to clinicians are more likely to be followed in clinical practice than rules in which the reasoning is not apparent. However a disadvantage of CART is that power is lost during the partitioning process. For the first partition the dataset is large, so there is good statistical power to identify the variable to partition on. But to further partition the dataset on the resulting two groups, we now have fewer observations in each group, so the further you go down the tree, the lower the statistical power is to identify additional predictor variables. This is why pruning methods are required to decide when to stop the partitioning process.

CART analyses (binary recursive partitioning methods) are performed in the statistical software package R. It is 'binary' as each group of patients in a node in the tree can only be split into 2 groups. It is 'recursive' as the binary partitioning process is applied over and over again. In the first instance, a variable is selected from the set of potential predictor variables and a split point estimated which separates the outcome variable into 2 groups. The algorithm we use for recursive splitting is available in the R software package, which first examines all possible splits for all covariates and chooses the split which leads to 2 groups that are 'purer' than the current group with respect to values of the response variable. The measure of impurity used is the Gini coefficient. Once the split has been estimated the procedure is then repeated again for all observations in the first group, and recursively splits these observations further. Then the same for the second group, and so on. We decide when to stop the recursion process by using pruning methods. Firstly a large tree is grown using a trivial stopping criteria of the number of observations in each leaf, then branches are pruned from the tree that are not necessary using the cross-validation criteria. When pruning the tree a complexity parameter is added which measures the cost of adding additional nodes, and we want to identify the sub-tree of the full model that has the minimal cost. The cost-complexity measure represents a trade-off between fit and explanatory power. Once the tree has been grown, for each leaf, we calculate a simple summary statistic of the proportion of patients with the outcome of interest.

However, the performance of the optimal tree will generally over-estimate the performance of the tree on an independent dataset from a similar population, because it fits noise in the dataset which is unlikely to occur in a different set of data. This problem can be addressed by using cross-validation methods. This is done by using ensemble methods where we draw a number of bootstrap samples from the original dataset, and for each bootstrap sample build a tree. We then average the predictions across all the trees. The average performance of these models is a good estimate of the performance of the original dataset on a future independent sample.

Having conducted logistic regression and CART analyses in the development sample, the performance of the models will be assessed in the validation sample.

11. Classification criteria for AAV and PAN proposed in traditional format and in tree format.

Patient inclusion criteria:

- Adult patients aged ≥ 18 years. There is no upper age limit.
- Ability to give informed consent. In the event that a patient with vasculitis does not have capacity to give consent then an appropriate 'consultee' (as defined by the Mental Capacity Act 2005) would be consulted regarding

patient wishes. The consultee would need to confirm that the patient would want to participate in the study and sign the appropriate declaration. In the event that the patient is deceased, anonymised data (including in linked-anonymised form) about the deceased patient can be collected (i.e. not including any patient identifiers).

- New presentation or an established diagnosis of Wegener's granulomatosis, microscopic polyangiitis, Churg Strauss syndrome, giant cell arteritis, Takayasu arteritis, other primary large vessel vasculitis.

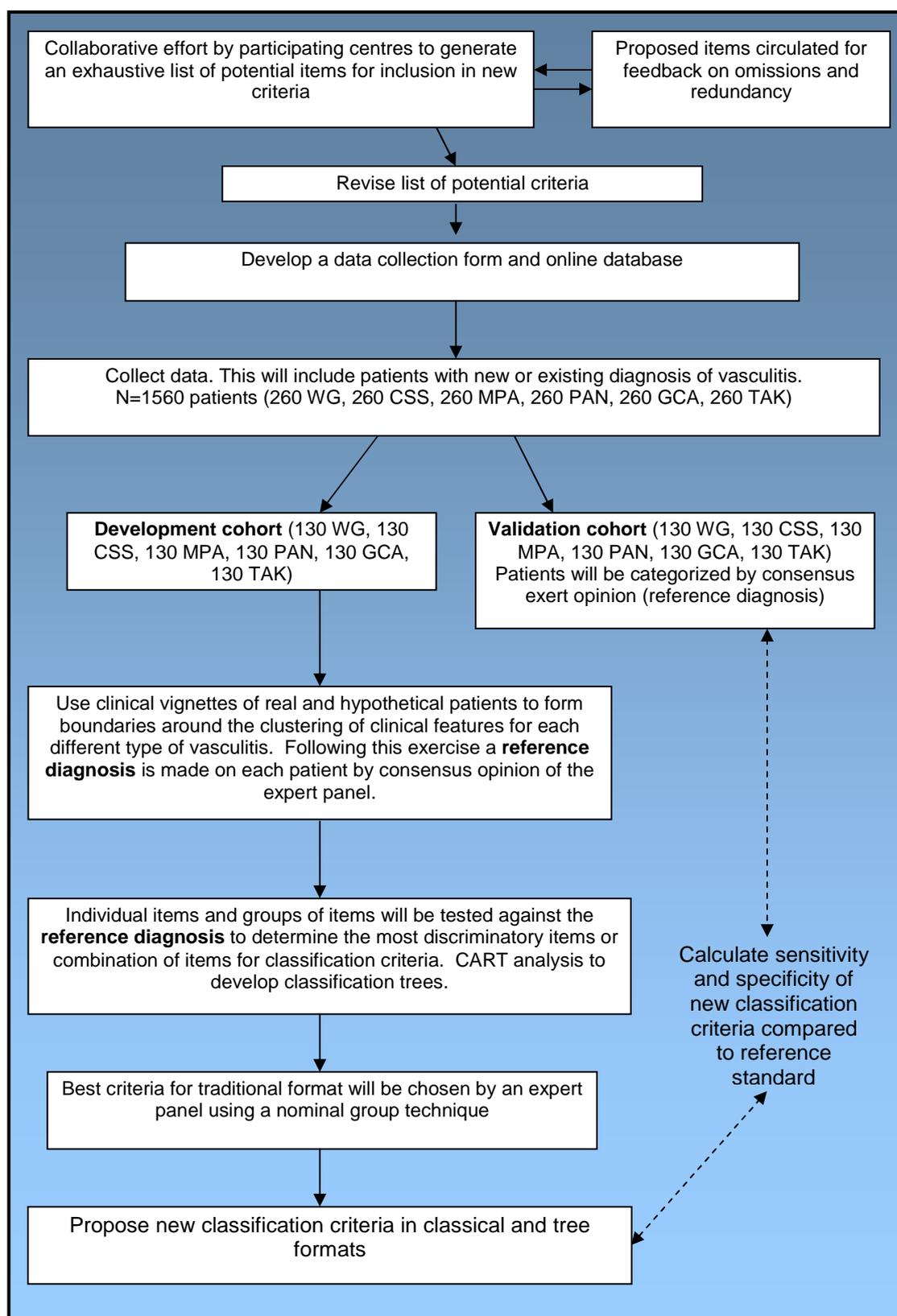
Patient exclusion criteria:

- a) Patients < 18 years of age.
- b) Inability to provide informed consent and 'consultee' does not agree for patient participation.
- c) Co-morbidities that explain the clinical symptoms and signs on which the diagnosis of vasculitis is made. E.g. infection, tumour, other inflammatory condition, etc.

Phase 1b: Validating the new classification criteria

1. The second half the patients recruited for each disease category (working diagnosis at entry of WG, MPA, CSS, PAN, GCA, TAK) will be allocated to the validation cohort.
2. Identical inclusion and exclusion criteria will apply to phase 1a.
3. The same information collected for the development cohort, will also be collected for the validation cohort and recorded on paper and on an electronic database. This would include the mandatory investigations required – which will be defined in Phase 1a.
4. All patients will be classified by consensus of the expert panel using the new classification framework developed in part 1a (after going through the clinical vignette exercise). This will form the reference diagnosis for the patient. A minimum of 100 cases of each disease category defined will be required.
5. Each patient will also be classified using the new classification criteria.
6. The results of classifying the patients using the new criteria will be compared to the reference diagnosis. (i.e. calculation of sensitivity and specificity)

Figure 2: Development and Validation of New Classification Criteria for Vasculitis



Diagnostic Criteria

We propose to develop and validate diagnostic criteria for primary systemic vasculitis. Based on current disease categories we will include WG, MPA, CSS, PAN, GCA and TAK (but this may change depending on whether new categories are created or existing categories merged as part of the classification criteria component). For the development of diagnostic criteria, we will study a minimum of 100 patients (will require approx 130 patients to allow for dropout and misdiagnosis) for each disease category. Assuming 6 disease categories, the majority of these 780 patients will have already been identified from the classification criteria component of the study and will be re used for the development and validation of diagnostic criteria. However, for the diagnostic criteria to be clinically relevant we will only include patients that are seen at the time of 1st presentation, therefore not all the 780 patients recruited for the classification criteria section of the study will be suitable, and we will need to recruit additional new patients for each of the types of vasculitis being studied.

We will use a minimum of 400 context specific controls (patients that don't have vasculitis) for AAV and PAN that will cover the spectrum of different disease presentations and severity. In addition, we will recruit a minimum of 100 context specific controls for GCA and a similar number for TAK. Different control populations are needed for AAV, GCA and TAK as they have significantly different clinical presentations. In a similar manner to cases, we will recruit 30% more patients than the minimum required to account for misdiagnosis and drop out. The same minimum number of cases and controls will be needed to validate the criteria. The first half of the patients recruited would be used to develop the criteria, and the 2nd half to validate the criteria. We will allow inclusion of patients from previously studied prospective cohorts that meet all the appropriate inclusion / exclusion criteria and have had all the appropriate clinical information and mandatory investigation (to be defined later) recorded at time of their first presentation. This is to facilitate the recruitment of sufficient patients with PAN, CSS and TAK which are rare conditions.

A summary of the methodology for developing and validating the diagnostic criteria is shown in Figure 3.

2a. Developing diagnostic criteria for AAV and PAN

Diagnostic criteria discriminate between patients with or without a specific disease in clinical settings. We will use the following clinical scenarios to choose our context specific controls:

Controls for AAV and PAN	Controls for GCA (patients must be over the age of 40)	Controls for TAK (patients must be under the age of 50)
Fever of unknown origin, raised inflammatory markers or unexplained weight loss.	Fever of unknown origin, raised inflammatory markers or unexplained weight loss	Fever of unknown origin, raised inflammatory markers or unexplained weight loss
Multi-system disease. Presentation of disease with at least 2 organs involved	New onset headache	New onset hypertension
Pulmonary-renal syndrome. Defined as haemoptysis / pulmonary haemorrhage with acute renal impairment	Sudden visual loss	Limb claudication
Acute renal failure	Jaw or tongue pain	Aortic aneurysm (>5cm)

Pulmonary symptoms: Acute respiratory distress, exacerbation of asthma or unexplained pulmonary fibrosis.		Stroke
Chronic upper airways symptoms and signs		Chronic headache
Inflammatory polyarthritis		
Acute or chronic abdominal pain		
New onset hypertension		
Peripheral blood eosinophilia		
Peripheral neuropathy (either sensory or motor)		
Referred to secondary or tertiary care with a suspicion of vasculitis.		

Most of the vasculitis cases required would have already been recruited as part of the classification criteria. However, for the diagnostic criteria to be clinically relevant we will only include patients that are seen at the time of 1st presentation. I.e. Not all the patients recruited for the classification criteria section of the study will be suitable for inclusion and therefore we will need to recruit additional new patients with the 6 types of vasculitis being studied to achieve our target number of patients.

In normal circumstances approximately 10% of patients presenting with the described scenarios will be found to eventually have a primary systemic vasculitis and the other 90% would be suitable controls. This distinction can usually be made within the first 10 days of presentation by an experienced physician. To achieve the desired spectrum of controls, we will recruit at least 40 context specific controls for each of the clinical scenarios described. We will stop recruiting controls when our target for each is met (The target number of patients will take into consideration misdiagnosis, loss to follow up / dropout). If a patient is initially labelled a 'control' and is later discovered (within the 6 month time period) of follow up to have vasculitis, then they can be used as a 'case'.

- 1 The list of potential predictor variables to be studied that were generated in developing classification criteria, data collection forms, and web based database will be identical to classification criteria.
- 2 Patient baseline evaluation and data collection:
 - a. For each clinical context outlined above patients will be evaluated at the onset of their disease. In the case of patients seen initially by non-collaborators to the study, a window of 21 days after the initial assessment is allowed for notification to a study observer.
 - b. For each patient all clinical information (as per the list developed in steps 1-3), will be recorded in paper format. This will likely include some mandatory investigations (e.g. CBC, renal function, ANCA, ESR, CRP, etc) for all patients recruited into the study.
 - c. The treating physician or nurse specialist will input the data collected onto the online database. In the case that this is unable to be done, the original paper forms will be sent to the Oxford site for data entry onto the database.
 - d. In the case of patients not seen initially by a study observer but referred within 21 days of presentation, the initial assessment by the study observer will be used as the diagnostic episode.

- e. In the case of patient from previously studied cohort being used, initial assessment must have been made by study observer within 21 days of first presentation. Also, all mandatory investigations must have been completed at the time of initial assessment.
- 3 Patient follow-up and defining a diagnosis:
 - a. The consensus final diagnosis (**reference diagnosis**) will be made at the conclusion of a 6 month follow up period. We anticipate that a definite diagnosis can be made within this time frame. This diagnosis would incorporate all available evidence and the best possible interpretation, and incorporate the reference standard developed in phase 1. Patients that are diagnosed with an alternative diagnosis to vasculitis will be the controls.
- 4 Statistical analysis:

Statistical methods for creating diagnostic criteria will be very similar to those described earlier for the classification criteria and won't be repeated again in detail. Logistic regression modelling and CART analyses will be performed to create the diagnostic criteria. The binary outcome for analysis is whether the person is a case or control (without vasculitis). We repeat the analyses for each of each type of vasculitis e.g. WG versus controls, then CSS versus controls etc.

Patient inclusion criteria:

- Adult patients aged ≥ 18 years. There is no upper age limit.
- Ability to give informed consent. In the event that a patient with vasculitis does not have capacity to give consent then an appropriate 'consultee' (as defined by the Mental Capacity Act 2005) would be consulted regarding patient wishes. The consultee would need to confirm that the patient would want to participate in the study and sign the appropriate declaration. In the event that the patient is deceased, anonymised data (including in linked-anonymised form) about the deceased patient can be collected (i.e. not including any patient identifiers).
- New presentation with a clinical suspicion of primary systemic vasculitis.

Patient exclusion criteria:

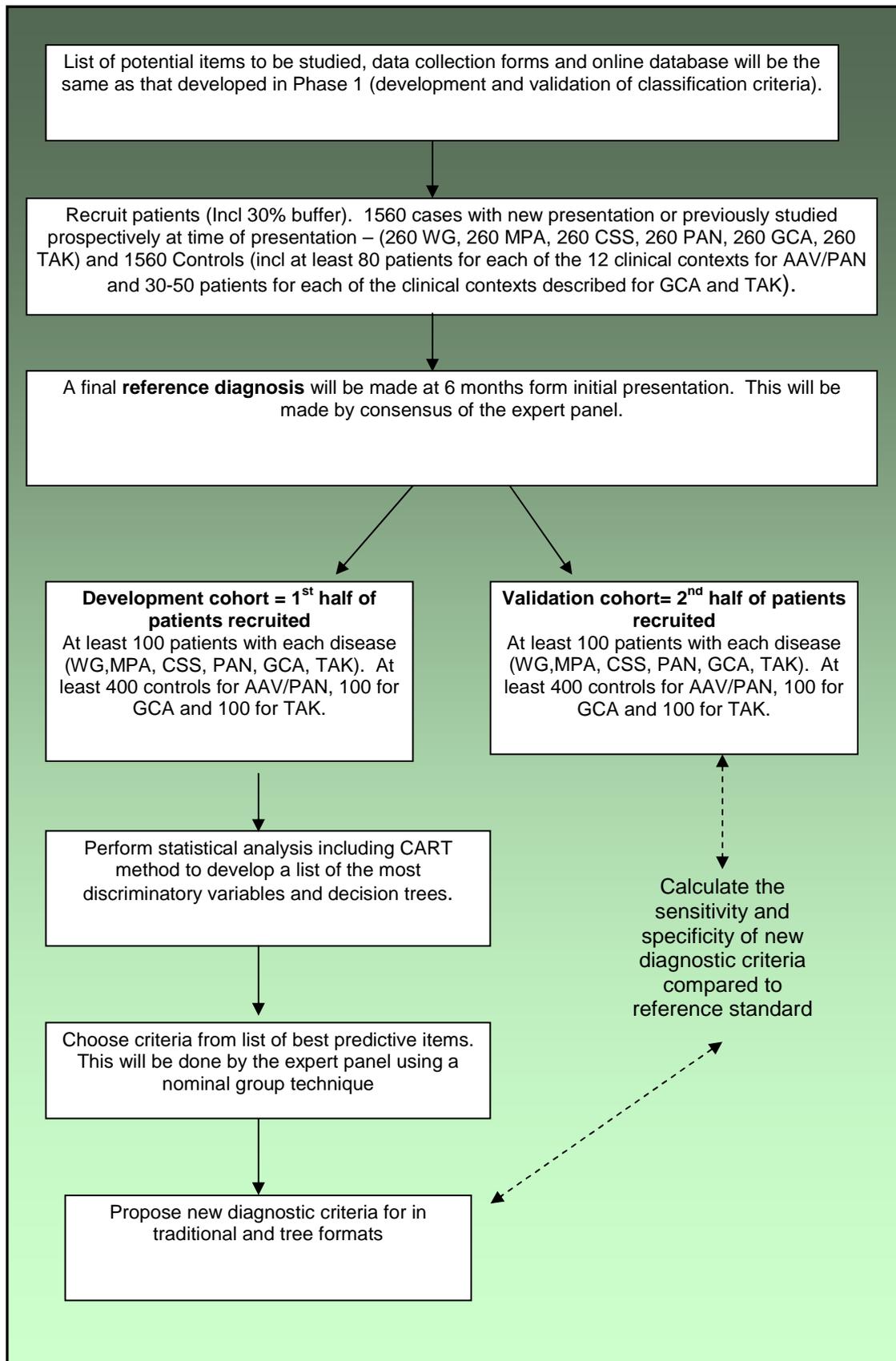
- Patients < 18 years of age
- Patient unwilling or unable to provide informed consent. If patient does not have capacity to give informed consent and 'consultee' does not think patient would want to participate.
- Known co morbidity at time of presentation that explains the clinical presentation.
- Control patient unable to provide informed consent.

Phase 2b: Validating the new diagnostic criteria

1. Identical inclusion and exclusion criteria will apply to phase 2a
2. Identical information collected for development cohort will also be collected for validation cohort and recorded on the online database (either by participating centre or by data input at Oxford site).
3. Each patient with vasculitis will have a diagnosis made based on the new diagnostic criteria utilising information collected at baseline only. The control patients will be designated as AAV/PAN control, GCA control or TAK control.

4. The reference diagnosis will be the consensus diagnosis achieved at 6 months by the expert panel taking into consideration all available information and using the new reference standard developed in phase 1.
5. The new diagnostic criteria will be compared to the reference diagnosis.

Figure 3: Development and validation of new diagnostic criteria for vasculitis



Ethical arrangements

All participating sites will need to fulfil local ethical requirements. Since this is an observational study we do not foresee any difficulties.

Verbal consent will be obtained from all clinicians responsible for the care of the potential participant in the first instance prior to a study investigator approaching their patient. After verbal consent is obtained, potential participants will then be approached by a member of the research team, and will be provided with a Participant Information Sheet and given the opportunity to discuss the research project prior to obtaining written fully informed consent.

In the instance that a patient with confirmed or clinically suspected systemic vasculitis does not have mental capacity to give informed consent a suitable 'consultee' would be identified that could provide the appropriate declaration about patient wishes. Ideally, the consultee would be someone who knows the patient well but is not acting in a professional or paid capacity ("personal consultee" under the Mental Capacity Act 2005) and are able to advise on the wishes and feelings of the patient that we are inviting to participate in this research. If this is not the case, then the research team can nominate a third party who is unconnected with the research and is willing to act as a 'nominated consultee'. It is not permissible under the Mental Capacity act for control patients definitely known not to have systemic vasculitis and who lack the capacity to give informed consent to be included in this study.

The Participant Information Sheet will welcome the potential participant to contact the research team to inform them of their decision to participate or not. A similar information sheet is available for consultees. Consent (or a declaration from a suitable consultee) will be obtained for the two structured consultations and the collection of anonymised clinical, laboratory, and radiographic data which will be recorded in electronic format, and sent to a central server in Oxford, UK.

As an optional extra to the main study, participants will also be asked to consent to the use of their data and tissue collected as part of their care for future vasculitis research through creation of a biobank which would utilize blood, DNA, urine and biopsy samples. With patient consent, additional blood (85ml) would be obtained and stored for this purpose. The creation of this biobank will conform to all the requirements in place through the Data Protection Act and Human Tissue Act including procedures for a Data Custodian who would be responsible for setting up procedures to enable access to this data. Any future research would involve a separate ethical and funding application.

Details about research tissue bank:

Name: Oxford Musculoskeletal Bio Bank Management

HTA Licence number: 1250

Ethics reference number: 09/H0606/11

Protocol version: 2 (approved 22 Feb 2010)

Serial number: PROT/NDORMS/01

Organisation: Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences

Contact person: Karolina Kliskey (karolina.kliskey@ndorms.ox.ac.uk)

Sample size requirements

We anticipate that approximately 70% of the patients recruited as cases for the classification criteria can be re used as cases for diagnostic criteria.

Classification criteria

Based on the ACR recommendation of 100 patients with disease and 100 controls, and assuming a dropout rate of 20% and misdiagnosis rate of 10% (30% in total) then we will recruit $6 \times 130 = 780$ patients for development, and 780 patients for validation. This is a total of 1560 patients. Disease controls are contained within this number, as the other diseases act as the controls.

Diagnostic criteria

Based on the ACR recommendation of a minimum of 100 patients with disease and 100 controls, and assuming a dropout rate of 20% and a misdiagnosis rate of 10% (30% in total) we will recruit 6×130 cases for development and 6×130 cases for validation. This is a total of 1560 patients. We anticipate that 70% of the cases used in the classification criteria could be re used for diagnostic criteria, therefore only an additional 30% (of the 1560 patients required) would need to be recruited. This is 468 additional patients.

Control patients for diagnostic criteria: To cover the full spectrum of disease specific presentations, we will recruit 520 controls for AAV and PAN, with at least 40 control patients presenting within each of the 12 typical clinical scenarios described. For GCA and TAK an additional 130 patients for each would be required (15-25 patients for each of the clinical contexts). An identical number of control patients will be need for validation. This is a total of 1560 control patients.

Total

Cases for classification criteria = 1560

Estimated additional cases required for diagnostic criteria = 468

Estimated total cases required = 2028

Controls for diagnostic criteria = 1560

Estimated total patients required = 3588

Checklist for the Development of Criteria Sets as recommended by the Classification and Response Criteria Subcommittee of the American College of Rheumatology Committee on Quality Measures

Recommendations	Classification criteria	Diagnostic criteria*
1. Will a comprehensive list of possible criteria be considered (content validity)?	Yes	Yes
2. Will each of the potential criteria be reliable (reproducible), precise in its measurement, easy to measure, and clinically sensible?	Yes. The potential criteria will be assessed by expert panel for these features.	Yes. The potential criteria will be assessed by expert panel for these features.
3. Are the potential criteria redundant (i.e., highly correlated)? Will this be assessed?	No - Will be assessed during statistical analysis	No - Will be assessed during statistical analysis
4. Selection of cases (patients considered to have the condition of interest): A. Will cases be chosen across the spectrum of disease severity? B. If the criteria are to be used for epidemiologic studies, will both clinical and community cases be included?	A. Yes B. Yes. The vast majority of all cases with AAV and PAN will be seen at a secondary or tertiary referral centre.	A. Yes B. Yes. The vast majority of all cases with AAV and PAN will be seen at a secondary or tertiary referral centre.
5. Selection of controls (patients considered not to have the condition of interest): A. Will the controls be chosen with a view to the intended purpose of the criteria, i.e., to distinguish individuals with disease from those without disease versus to distinguish individuals with a particular rheumatic disease from individuals with other diseases? Ideally, multiple control groups will be used.	Yes	Yes
6. Will at least 100 cases and 100 controls be chosen?	Yes	Yes
7. For each individual criteria, and for combinations of criteria, will the sensitivity and specificity for detecting and ruling out the disease of interest be calculated (construct validity, convergent and divergent validity)? Will these results, together with clinical opinion, be used to reduce the number of criteria for inclusion?	Yes	Yes
8. Are the criteria to be included those with the greatest content and construct validity? How will this be demonstrated?	Yes, expert panel (nominal group technique)	Yes, expert panel (nominal group technique)
9. Will acceptable statistical approaches be used to create the diagnostic/classification criteria from the reduced number of criteria?	Yes	Yes
10. Will the final diagnostic/classification criteria be validated in different samples of cases and controls? How will those other samples be chosen?	Yes, cases and controls randomly assigned to development or validation cohorts	Yes, cases and controls randomly assigned to development or validation cohorts
* We recognize that these guidelines do not directly pertain to diagnostic criteria but the study is useful for this proposal and will be followed.		

Project Timeline:

	*	year 1				year 2				year 3			
Recruit research staff	█												
Establish Steering Group	█												
MREC Ethics and research governance	█												
Determine potential list of items to be studied	█	█											
Develop online database	█	█											
Approve centres for participation	█	█											
Recruitment of development cohorts			█	█	█								
Recruitment of validation cohorts				█	█	█	█	█	█				
Follow up of all cohorts					█	█	█	█	█				
Recruitment and data collection monitoring			█	█	█	█	█	█	█				
Expert panel exercise using hypothetical cases to identify the most important variables to define each disease			█	█	█								
Expert panel makes reference diagnosis on individual patients						█	█	█	█				
Data analysis – developing new diagnostic and classification criteria							█	█	█				
Data analysis – validating new diagnostic and classification criteria										█			
Preparation of final report & manuscripts										█	█	█	

Key Benchmarks

Goals	Metrics for success	Expected completion date
Develop classification criteria for primary systemic vasculitis	Publish the development of classification criteria in a peer reviewed medical journal	24 months
Validate classification criteria for primary systemic vasculitis	Publish the validation of criteria in a peer reviewed medical journal	30 months
Develop diagnostic criteria for primary systemic vasculitis	Publish the development of the diagnostic criteria in a peer reviewed medical journal	24 months
Validate diagnostic criteria for primary systemic vasculitis	Publish the validation of the diagnostic criteria in a peer reviewed medical journal	30 months
Establish list of items to be studied for the classification and diagnostic criteria	Paper questionnaire developed to facilitate data collection	4 months
All sites get IRB/Ethics approval	Confirmation in writing of IRB/Ethics approval for all sites.	4 months
Develop web-based database for online data collection	Database going online	4 months
Recruit the required number of participants to achieve meaningful result to develop classification criteria	Recruit 780 suitable cases	12 months
Recruit the required number of participants to achieve meaningful result to develop diagnostic criteria	Recruit 780 suitable cases and 780 suitable controls.	12 months
Recruit the suitable number of participants to achieve meaningful result to validate classification criteria	Recruit a further 780 suitable cases.	18 months
Recruit the suitable number of participants to achieve meaningful result to validate diagnostic criteria	Recruit a further 780 suitable cases and 780 suitable controls.	18 months

Planned dissemination of results

The results will be presented at the EULAR and ACR annual scientific meetings, and published in *Annals of the Rheumatic Diseases*, and *Arthritis & Rheumatism* (The journals of EULAR and ACR respectively).

We envisage that multiple papers will be written to cover the whole scope of this project with the workload and authorship distributed amongst the ACR and EULAR contributors. Fellows will be the lead authors for some of the papers, with their respective supervisor in Europe or USA being the senior (last) author for those papers.

We will closely adhere to the guidelines developed by other ACR-EULAR collaborations regarding publication policies.

Recruiting sites

The following centres have provided written agreement to participate in the study and supplied the following estimates for the number of patients that they can recruit for AAV and PAN. The prospective recruitment of patients with PAN will be challenging, therefore we expect that we will need to use previously prospectively studied patients. These figures do not include large vessel vasculitis which has been a late addition to the proposal and we have not yet formally received responses from all sites. GCA is far more common than the rest of the vasculitides so we do not anticipate difficulty recruiting sufficient patients for this disease (at a minimum the same number as for WG should be easily possible from each participating site). Takayasu's on the other hand will be more difficult but we anticipate a large number to be recruited from Turkey where the incidence and prevalence are thought to be high.

Investigator	City	Country	WG	MPA	CSS	PAN	Control AAV
Europe							
Bajema	Leiden	Netherlands	3	5	1	0	10
Baslund	Copenhagen	Denmark	7	3	0	0	10
Basu	Aberdeen	UK	10	10	2	0	20
Blockmans	Leuven	Belgium	8	8	2	1	10
Chakravarty	Essex	UK	10	10	5	0	0
Cid	Barcelona	Spain	11	20	15	2	24
Cohen Tervaert	Maastricht	Netherlands	40	20	20	3	20
Daikeler	Basel	Switzerland	13	5	3	2	24
de Groot	Offenbach/Main	Germany	3	2	1	1	0
Flores Suarez	Mexico City	Mexico	28	16	16	10	140
Gregorini	Brescia	Italy	5	15	2	3	15
Guillevin	Paris	France					
Hauser	Zurich	Switzerland	8	8	8	4	28
Holle	Bad Bramstedt	Germany	50	10	30	2	50
Jayne	Cambridge	UK	100	50	50	10	100
Kallenberg	Groningen	Netherlands	15	10	5	5	20
Luqmani	Oxford	UK	10	5	2	0	40
Salvarani	Reggio Emilia	Italy	8	8	8	8	24
Savage	Birmingham	UK	10	10	1	0	20
Scott	Norfolk	UK	20	20	10	0	
Segelmark	Lund	Sweden	20	20	2	2	40
Sunderkotter	Munster	Germany	10	6	6	8	25
Vaglio	Parma	Italy	7	7	7	2	24
Watts	Ipswich	UK	7	3	1	0	20
North America							
Albert	Hanover, NH	USA					
Carette	Toronto	Canada	25	5	15	5	20
Chung	UCSF	USA	10	10	5	5	10
Jennette	Chapel Hill, NC	USA	11	20	15	2	24
Khalidi	Hamilton Salt Lake	Canada	13	13	7	7	39
Koenig	City, UT	USA	20	8	8	2	30
Langford	Cleveland, OH	USA	20	13	13	5	39
Maksimowicz-McKinnon	Pittsburgh, PA	USA	20	15	10	3	40
Mattheson	Rochester, MN	USA	25	15	15	15	50

Merkel	Boston, MA	USA	30	15	12	8	40
Seo	Baltimore, MD	USA	15	10	8	4	15
Spiera	New York, NY	USA	15	10	5	3	40
Walsh	Calgary	Canada	15	10	5	2	20
Weisman	Los Angeles, CA	USA					
Weyand	Stanford, CA	USA					
Other							
Suzuki/Kobayashi	Tokyo	Japan	16	16	16	16	48
Yazici/Hatemi	Istanbul	Turkey	6	2	2	4	24
Total			614	433	333	144	1103
Required			338	338	338	338	1040
% of required			182	128	92	43	106

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