# Using the International Classification of Function, Disability and Health (ICF) to compare areas of ANCA-associated vasculitis (AAV) measured in clinical trials to those important to patients with AAV and clinicians who are involved in their care

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# Abstract

## *Background*

The International Classification of Function, Disability and Health (ICF) describes health using 1424 categories from 4 components: body functions (BF), body structures (BS), activities and participation (AP) and contextual factors (environmental (EF) and personal (PF)). In this study the ICF was used to describe and compare aspects of ANCA-Associated Vasculitis (AAV) measured in clinical trials and those important to clinicians and patients.

## *Methods*

Individual interviews and focus groups were used to capture the perspective of AAV patients. Clinicians' perspective was obtained with an email-based questionnaire. Outcomes used in AAV randomized trials were extracted from results of a systematic review of literature. Identified concepts were mapped to the ICF according to previously published ICF linking rules, and the resulting lists of relevant AAV outcomes were compared descriptively.

## *Results*

Twelve individual interviews and 2 focus groups represented the patient perspective while responses from 27 clinicians yielded the clinicians' perspective. Systematic literature review identified 67 clinical trials and 28 abstracts from which measured outcomes were extracted.

All three perspectives demonstrated detailed coverage of ICF components BF and BS. In the component AP patients and clinicians identified similar ICF categories, a number of which were under-sampled by AAV trials. Contextual factors appear to be significantly more relevant to patients than clinicians and researchers.

## *Conclusion*

Patients and clinicians have different views of the relevance of various AAV outcomes, and these views differ from what is measured in clinical trials of AAV. This highlights the need for a

broad and standardized approach to developing and selecting outcomes for complex medical conditions such as AAV.

# Executive summary


## *Background*

The International Classification of Functioning, Disability and Health (ICF) is a general health status framework that classifies health using 1424 categories organized into a 4-level hierarchical structure. It covers 4 components: body functions (BF), body structures (BS), activities and participation (AP) and contextual factors (environmental (EF) and personal (PF)). In this study the ICF was used to describe aspects of ANCA-Associated Vasculitis (AAV) measured in clinical trials, those important to AAV patients and those important to clinicians and to compare them.

## *Methods*

Aspects of AAV relevant to patients were identified through interviews and focus groups involving patients from Canada, the United States and the United Kingdom. Clinicians' perspective was obtained with an email-based questionnaire asking clinicians from a wide range of geographic locations and from different clinical specialties to list items they consider relevant to patients with AAV for each of the ICF components. Outcomes used in AAV interventional randomized trials were selected from papers identified through a systematic review of literature. Identified concepts were mapped to the ICF according to previously published ICF linking rules. The ICF-based lists representing different perspectives of relevant AAV outcomes were compared descriptively.

## *Results*

Twelve individual patient interviews and 2 focus groups involving 9 patients were used to create the list of ICF categories from the patient perspective. Responses from 27 clinicians were the base of the list from clinicians' perspective. Systematic literature review identified 67 clinical trials and 28 abstracts from which outcome measures were extracted.

All three perspectives (patient, clinician, literature) demonstrated detailed coverage of ICF components BF and BS. Patients appear to focus relatively less attention on “body structures” and more on “body functions” in comparison to clinicians and clinical investigators. In the component AP, similar limitations and restrictions were identified as relevant by patients and clinicians, but these differ from those measured by instruments used in AAV trials. Clinical trials under-sampled a number of AP categories that were identified as important by both patients and clinicians, including “learning and applying knowledge”, “interpersonal interactions and relationships” and “community, social and civic life.”

Contextual factors, both environmental and personal, appear to be more relevant to patients than clinicians and researchers. Significantly fewer clinicians identified EF as significant modifiers of impact of AAV, and this difference is even larger for PF. What is measured in clinical trials is even more discordant from the patient perspective, with very few EF and PF considered in trials.

## *Conclusion*

This study demonstrates the usefulness of the ICF for standardizing heterogeneous groups of outcome measures and subsequent comparisons across the measures. Patients and clinicians have different views of the relevance of various AAV outcomes, and these views differ from what is measured in clinical trials of AAV.

These results highlight the need for a broad and systematic approach to developing and selecting outcome measures for complex medical conditions such as AAV. This need is being addressed by the Outcome Measured in Rheumatology (OMERACT) initiative that strives to standardize the process of selecting outcomes for measurement in randomized trials. The recently developed OMERACT filter 2.0 framework calls for involvement of outcome measure end users,

most important of which are patients, into the process of development of the core sets of outcome measures for clinical conditions. The framework also encourages that outcomes covering different aspects of health (pathophysiologic manifestations, life impact, economic impact and death) are to be measured in all clinical trials, and that the setting of the trial and the relevant contextual factors are to be considered and described. With gradual incorporation of these guidelines by the clinical research community the gaps between what is measured in clinical trials and what is important to the affected patients and clinicians should narrow and eventually close.

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# Abbreviations

| | |
|---|---|
| AAV | Anti-neutrophil cytoplasmic antibody-associated vasculitis |
| AB | Annelies Boonen (investigator) |
| ANCA | Anti-neutrophil cytoplasmic antibody |
| BVAS | Birmingnham Vasculitis Activity Score |
| BVAS/WG | Birmingnham Vasculitis Activity Score for Wegener's Granulomatosis (GPA) |
| CDA | Combined Damage Assessment Index |
| EGPA | Eosinophilic granulomatosis with polyangiitis |
| GPA | Granulomatosis with polyangiitis |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HRQoL | Health-related quality of life |
| ICF | International Classification of Function, Disability and Health |
| LI | Leanne Idzerda (investigator) |
| MF | Michelle Foote (investigator) |
| MPA | Microscopic polyangiitis |
| NM | Nataliya Milman (investigator) |
| OMERACT | Outcome Measures in Rheumatology |
| PAN | Polyarteritis Nodosum |
| PCORI | Patient-Centered Outcomes Research Institute |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-analyses |
| PRO | Patient-reported outcome |
| RCT | Randomized controlled trial |
| SF-36 | Short-Form questionnaire, 36 items |
| UK | United Kingdom |
| USA | United States of America |
| VDI | Vasculitis Damage Index |

# Chapter 1 Introduction

## 1.1 Background

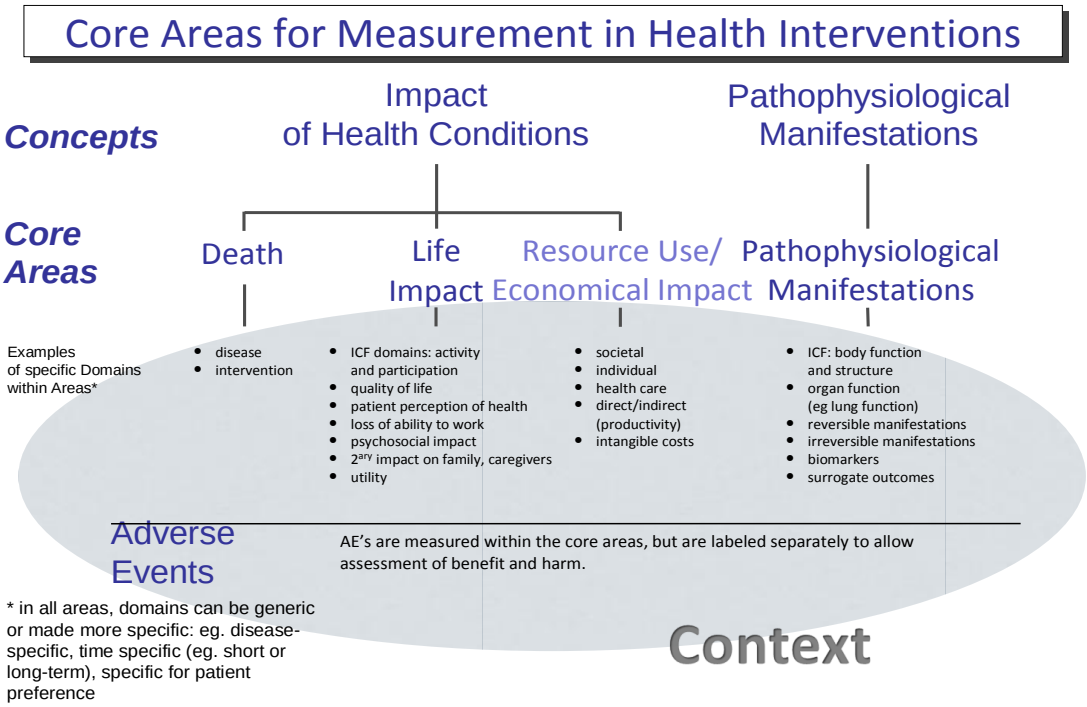
Vasculitides is a group of heterogeneous conditions characterized by inflammation of blood vessels. A large number of different vasculitides exist (1), and these vary with respect to pathophysiology, clinical manifestations, approach to treatment, and prognosis. ANCA-associated vasculitis (AAV) is among the best studied groups of vasculitides. It is characterized by the presence of ANCA (anti-neutrophil cytoplasmic antibodies), which are believed to play a pathogenic role (2). The group consists of three conditions: granulomatosis with polyangiitis (GPA, formerly Wegener' granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss Syndrome). AAV is relatively rare, with incidence ranging from 13 to 21 per million, and prevalence of about 300 per million (3). All three types of AAV are systemic conditions that can affect practically any organ system; most common organs affected are lungs and upper airways, ears, sinuses, and kidneys. Clinical presentation is variable, ranging from disease limited to ears, nose, and sinuses in some patient to life-threatening failure of kidneys, lungs, or heart in others. With the advent of effective therapy consisting of high-dose glucocorticoids combined with another immunosuppressive medication, the clinical course of AAV has changed from nearly universal early mortality to chronic conditions with high level of morbidity and substantial economic burden.

Assessment of the ability of new treatment regimens to change disease course and patients' functioning is critically important. Outcome Measures in Rheumatology (OMERACT) is an international organization that strives to develop optimal outcome measures for use in clinical trials through the application of a systematic outcome measure development and validation process (4). Recently OMERACT developed a framework, referred to as OMERACT Filter 2.0, to improve selection of areas and domains that should be covered when assessing outcomes in clinical studies (5) (see Figure 1). This

framework recommends that every outcome assessment should address each of the two broad categories of outcomes – "Pathophysiological Manifestations" and "Impact of Health Condition". The latter broad category consists of 3 areas - "Death", "Life Impact", and "Resource Use/Economic Impact;" the first 2 areas are to be measured in every clinical trial, while measurement of the third area is encouraged where appropriate. In addition, "adverse events" (toxicity or harm) are required to be addressed separately for items not already covered in "Death" and "Life Impact". The selection of specific domains in each area can depend upon the setting that should be made explicit at the start of the study. Finally, "Contextual factors" that are not the primary object of research but that may influence the interpretation of the results need to be considered. These can include personal (such as comorbidity or personal attitudes), environmental (such as geographic location or work environment), or societal (such as societal attitudes).

An OMERACT core set of outcome measures for a specific medical condition is a collection of

**Figure 1. OMERACT Filter 2.0 Framework for Development of Core Outcome Measurement Sets for Clinical Trials in Rheumatology**



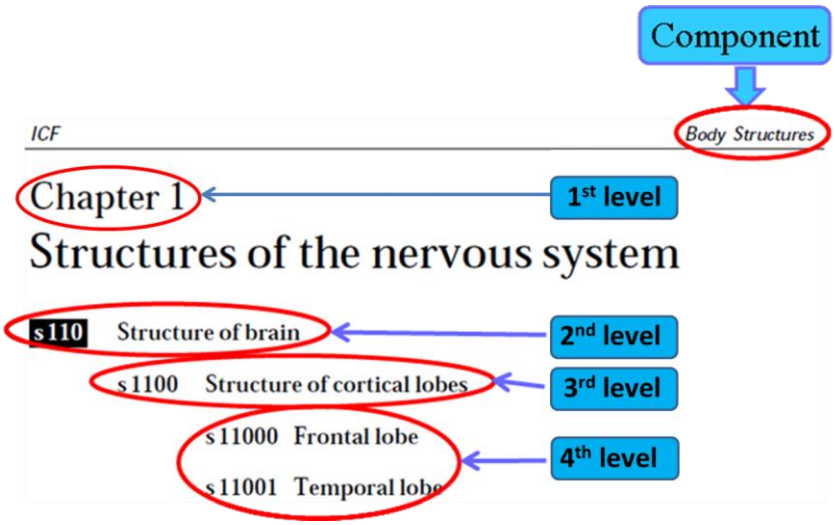
instruments that address a set of domains that cover the areas described above for a specific medical condition. The first step in creation of such a core set is identification of the domains that are relevant for the specific medical condition in question based on a review of literature and input from the outcome measure end-users which includes healthcare providers as well as patients (6). Then, instruments that measure each of the identified domains are selected (or created, in cases when no instruments that cover specific domains exist) and validated by testing their ability to satisfy properties identified by OMERACT as key features that have to be satisfied by every outcome measure - “truth”, “discrimination”, and “feasibility” (4).

This study aims to identify the domains that are relevant when determining the impact of AAV by making use of the International Classification of Functioning, Disability, and Health (ICF). The ICF is a general health status framework based on the bio-psycho-social model of health and disease, endorsed by the World Health Organization in 2001 (7). It views health as a broad concept that is described along 4 ICF “components”: (1) body functions, (2) body structures, (3) activities and participation, and (4) contextual factors (8). Health of the individual patient is viewed as being the result of the relationship between impairments of various “body functions” or “body structures”, limitations of activities, restrictions of participation and the influence of “contextual factors” which can be personal and environmental. “Contextual factors” represent the collection of individual’s personal, social and attitudinal environment that influence the relationship between the other ICF components and modify their effect on the overall health (thus they are also referred to as “contextual modifiers”); when the overall effect of the “contextual factors” is positive they are called “facilitators” of health, and when it is negative they are “barriers” to health (8).

In addition to the framework, the ICF offers a classification system to describe functioning and health using 1424 categories organized into a 4-level hierarchically nested structure covering the 4

components described above. A lower level category within a particular component represents a more detailed example (and thus a subset) of a higher level category (Figure 2). The ICF classification provides a common language for describing health and comparing health states that can be applied irrespective of the medical condition or setting in which health measurement is taking pace (8).

**Figure 2. Example of the hierarchical representation of categories in the International Classification of Functioning, Disability and Health**




*Chapters within each component represent the 1st level, while each lower-level category of a particular component represents a more detailed example (and thus a subset) of the higher level category*

The OMERACT-ICF Reference Group is an initiative to integrate the ICF into the OMERACT process (9). Amongst the various tasks of the group is development of disease-specific ICF Core Sets - selections of ICF categories that are typical and relevant to patients with individual medical conditions. These Core Sets contain the minimum number of categories that is sufficient but the maximum that are necessary to describe all aspects of health that are typical and relevant for the specific condition. The individual ICF categories can be thought of as the basic units of outcomes while the ICF core sets can serve as the external standard of "what to measure" when defining functioning of patients with the medical condition under study (9). As such, the ICF core sets can serve as the starting point for development of new outcome measure instruments (9), or of OMERACT Core Sets of outcome measures

for a particular condition. The resulting instruments (or the collection of instruments contained in the OMERACT Core Set) would address the question of "how to measure" the key outcomes of interest that constitute the ICF Core Set.

In rheumatology, the ICF Core Sets have been developed for osteoarthritis, osteoporosis, rheumatoid arthritis (10) and ankylosing spondylitis (11), but not for vasculitides. This study describes the initial stages of development of the ICF core sets for AAV, namely identifying the range of ICF categories that are currently considered in clinical trials, those considered important by health care providers, and patients. Furthermore, the importance of various aspects of AAV to 3 different end-users of the outcome measures will be compared using the ICF as the interface. The subsequent stages of development of the AAV ICF Core Sets will be completed outside of the scope of this Master's thesis and therefore will not be described in this document.

## 1.2 Objective of the study

The study described in the following chapters aims to use the ICF to identify the outcome domains that are relevant when determining the impact of AAV from three different perspectives, namely: 1) perspective of patients with AAV, 2) perspective of clinicians involved in the care of AAV patients, and 3) outcomes measured in clinical trials of AAV patients. Then, the perspectives of these 3 groups will be compared, once again using the ICF as the interface.

## 1.3 Overview of Study Design

The standardized approach to developing the ICF Core Sets is well described (10). Generally, this involves four stages; the first 3 stages consist of identifying the relevant ICF categories from the perspectives of the three main "end-users" of the core sets being developed: 1) the clinical investigators (represented by the outcomes measured in clinical trials), 2) health care providers, and 3) patients with the specific condition. The fourth stage involves identifying the most relevant ICF categories out of the 3

lists identified in the 1st three stages and putting them together to create the resulting ICF Core Set; this is usually performed using the nominal group process during a 1-2-day long consensus conference with participation of the ICF experts, clinical experts in the field of the specific condition for which the ICF Core Sets are being developed as well as patients who have the condition (10).

Stages 1 through 3 of the process of development of the ICF Core Sets for AAV are part of this study and are described in subsequent Chapters 2, 4 and 5. Chapter 3 contains the manuscript (which is related to Chapter 2) published in a peer-reviewed journal. As stated earlier, the last stage of development of the ICF Core Sets for AAV will be performed outside of the timeline of this project, and thus will not be described in this document. Instead, Chapter 6 describes the use of the ICF classification to compare the aspects of AAV that are important for determining patients' functioning and general health from the perspective of clinicians, clinical researchers, and AAV patients.

# Chapter 2 Areas of AAV measured in clinical studies

## 2.1 Objective

This sub-study was performed to identify ICF categories that are measured in randomized trials that involve patients with AAV.

## 2.2 Methods

The methods followed were in accordance with the previously described method of identifying the relevant ICF categories contained in outcome measures/instruments used in clinical trials of other musculoskeletal disorders (12). This involved 3 steps, described below.

In step 1, all relevant studies were identified through performing a comprehensive search of the literature. MEDLINE, EMBASE, and Cochrane libraries as well as clinicaltrials.gov were searched from 1991 to the time of the search (initially in December 2011, then updated in November 2013). Randomized controlled studies (RCTs) of any intervention with any comparator (placebo, standard of care, or another therapeutic intervention) on adult (age ≥ 18) patients with AAV (GPA, EGPA, or MPA as defined by the clinical trial investigators) that measured at least one outcome (any outcome) were selected. The identified systematic reviews and meta-analyses (that were identified because of the breadth of the search strategy) as well as references of the identified RCTs were searched for additional studies. The starting year (1991) for the search as well as the specific databases searched were chosen to match the procedure employed for development of ICF Core Sets for other musculoskeletal disorders (12). Two investigators (Nataliya Milman (NM) and Leanne Idzerda (LI)) independently reviewed identified studies for eligibility using selection criteria based on the criteria described above.

The original search was performed in December 2011 and an updated search was performed in November 2013, because of the length of time that passed between the original search and the analysis

and interpretation of the results. Once again, two investigators (NM and Michelle Foote (MF) independently reviewed the identified studies for eligibility. The precise search strategy for the original search can be found in Appendix A.1 and the search strategy for the updated search is in Appendix A.2. EndNote X5 program was used to manage citations.

In step 2, all outcome measures used in these studies were identified. These outcome measures included clinical, biochemical, and physiological tests, single item measures, imaging tests, biopsies, and composite outcome measure tools. In addition, the recorded baseline characteristics and the covariates were extracted in order to capture contextual factors considered in clinical trials. Again, this step was performed independently by two investigators – NM and MF; discrepancies were subsequently discussed until full agreement was reached.

In step 3 the concepts contained in the resulting list of outcomes were identified and linked to the corresponding ICF categories according to the previously established ICF linkage rules (13, 14). Briefly, this involves identifying the concepts contained in the identified outcome measures and then using the ICF linkage rules (13, 14) to "map" each concept to the most precise ICF category. When a concept cannot be linked to a specific ICF category, it is classified as either "not definable" (if it is covered by the ICF but cannot be classified to a specific category) or "not covered" (if it is not covered by the ICF). Concepts that refer to specific medical conditions were linked to the ICF category within the "body functions" or "body structures" that represents the function or structure affected by the condition. Medical conditions that imply a specific pathophysiology were additionally classified under the ICF "health condition" category.

ICF categories are organized hierarchically (see Figure 2), so that lower level categories share the attributes of the higher level categories. During the linking process, each concept contained in the identified outcome measures was linked to the lowest level category (i.e. most specific term) that

describes it, resulting in a detailed ICF-based description of the identified outcome measures. In order to make the results of mapping of the identified outcome measures more concise and easier to describe, the resulting list of ICF categories was then "summarized" at the second ICF level by replacing third- and fourth-level ICF categories with the overlying second-level category.

Although "personal factors" is a recognized subgroup of "contextual factors" in the ICF classification, the "personal factors" are currently not classified by the ICF. The general scheme for such classification proposed by Geyh et al. (15) was used as a guide when classifying "personal factors" identified as important modifiers of impact of AAV on patients. Broadly, this scheme divides the personal factors (called "Psychologic-Personal Factors" by the authors of the paper) into 3 broad "Parts" (15). Part I contains "Facts" about the individual's position in the physical, social, and temporal context, and it is further subdivided into "Sociodemographic personal characteristics", "Position in the immediate social and physical context" and "Personal history and biography". Part II represents an individual's "Experience" of the concept in question, which in this case represents living with AAV; this is further subdivided into "Feelings", "Thoughts and beliefs" and "Motives". Finally, Part III represents "Patterns" of experience and behaviour such as personality traits and habits (15).

The details of the hierarchical representation of the specific themes identified in this study were decided upon by 2 investigators (NM and AB) and the resulting proposed classification is displayed in Appendix G. In view of the fact that the resulting classification has not been accepted by the developers of the ICF, detailed representation of the identified categories will be presented without regard to their "ICF level". This will allow "re-classification" of the identified "personal factors", if necessary, at the time such classification is finalized.

The linking process was performed independently by 2 investigators knowledgeable in ICF – NM and Annelies Boonen (AB). Disagreements in linking were discussed, and in the few cases where consensus was not reached the opinion of the third individual (Alarcos Cieza) who is not involved in this study but who is an ICF expert and the lead developer of the ICF linking rules was sought.

The list of all ICF categories identified through this process made up the list of ICF categories measured in AAV clinical trials.

## 2.3 Results

### 2.3.1 Identification of relevant studies

#### *2.3.1.1 Initial search*

The initial literature search was performed on December 15 and 16, 2011. Figure 3 is the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flowchart (16) depicting selection of studies for the initial search. Five hundred and twenty three results were identified in EMBASE and MEDLINE databases combined, 118 results were identified in Cochrane library and 84 relevant studies were registered in clinicaltrials.gov, for a total of 725 results. Automatic removal of duplicates reduced the number of results to 719, and then manual removal of duplicates further reduced this to 631. Six hundred and thirty one abstracts (or titles, where abstracts could not be located) were reviewed independently by 2 investigators, NM and LI. Ninety six abstracts (or titles, where abstracts could not be located) were judged to describe potentially relevant studies.

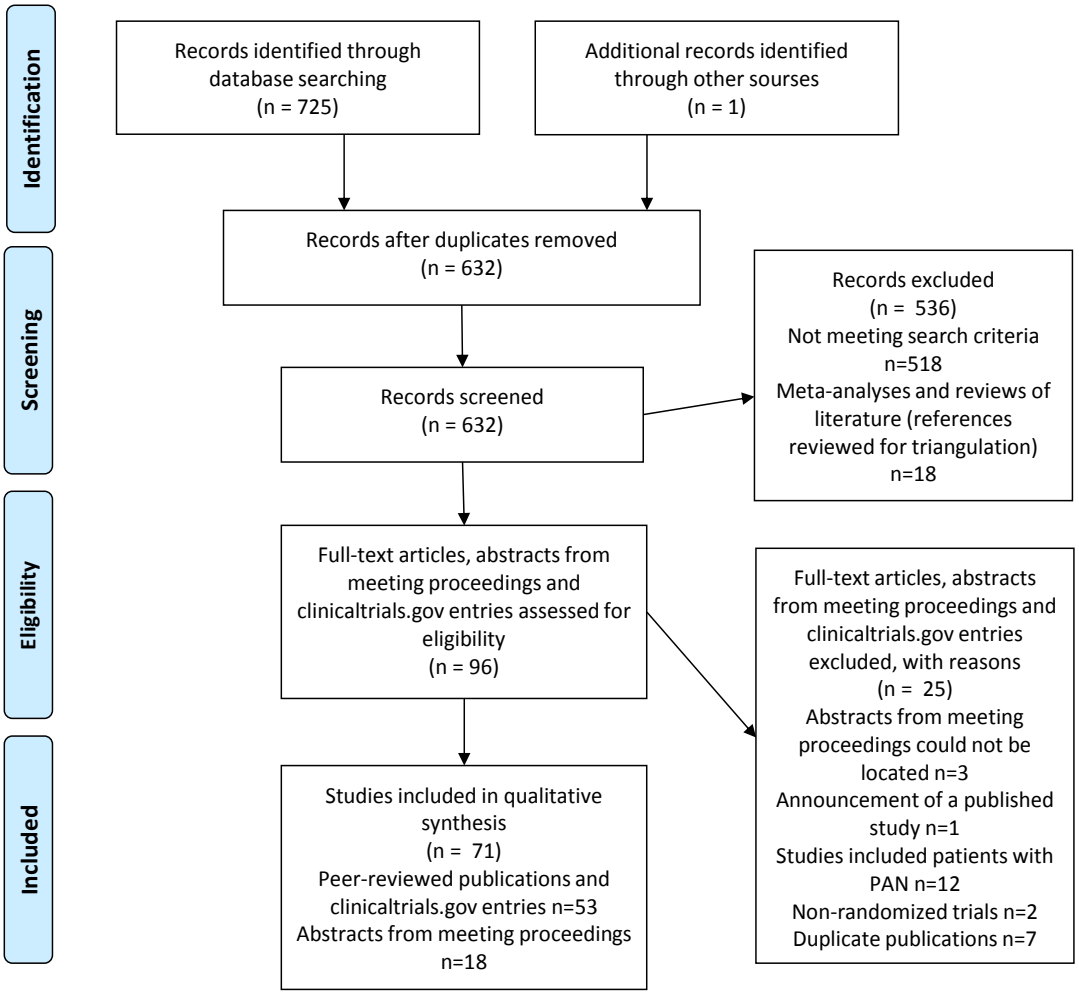
Twenty five out of the ninety six articles were excluded from the final analysis: 3 abstracts from meeting proceedings could not be located, 1 source represented a news announcement of a study that was described in a separate manuscript included in the analysis, 12 studies included patients with polyarteritis nodosum (PAN) - a type of vasculitis that is now considered distinct from AAV (1), 2 described non-randomized studies and 7 represented duplicate publications.

Reference lists of all of the included articles as well as of the systematic reviews and meta-analyses that were identified because of the breadth of the utilized search strategy were searched for additional eligible studies. One source identified in the reference list of one of the included studies was added to the list of articles for the final analysis. This additional source represented the detailed protocol for the study where it was referenced; although it by itself does not represent a RCT, we

deemed it to be of additional value for the purpose of this study – namely to identified outcomes measured in RCTs of AAV.

Overall, 53 original studies and 18 abstracts from meeting proceedings were reviewed for outcome extraction during the initial search.

**Figure 3. Selection of studies for outcome extraction during the systematic review of literature – the initial search**




### *2.3.1.2 Updated search*

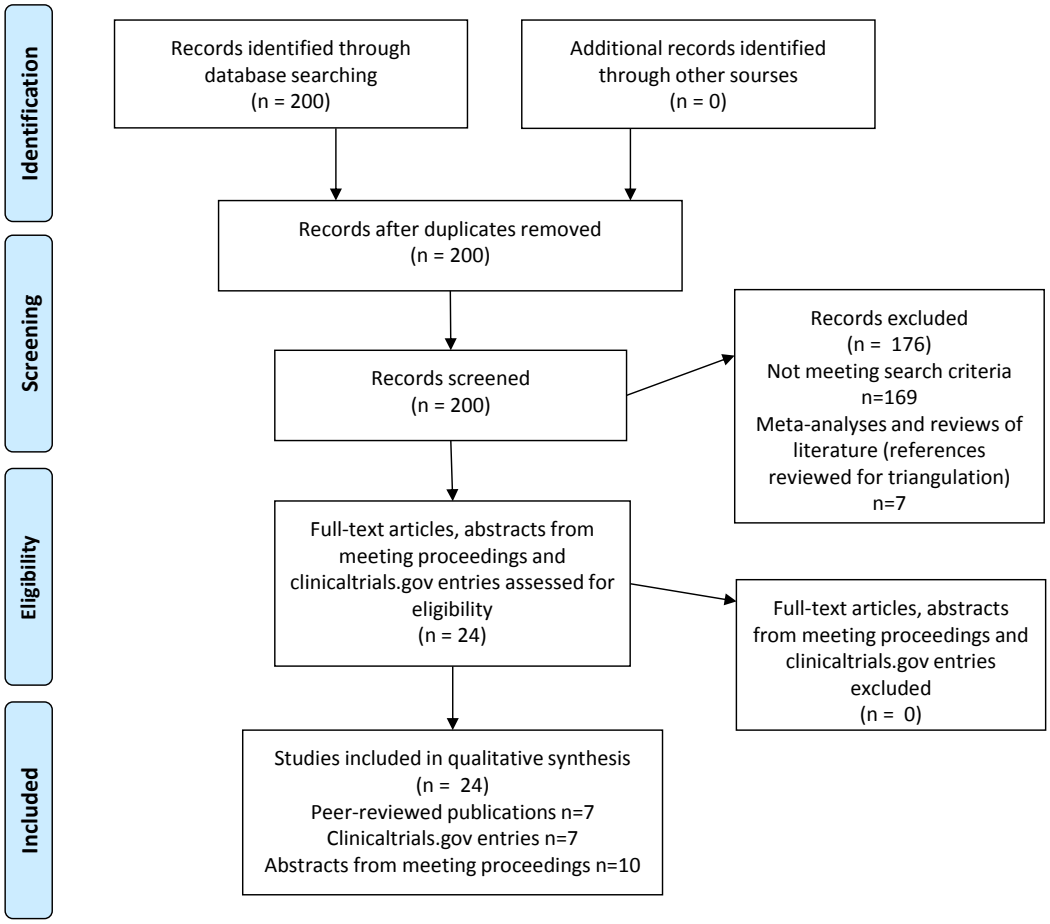
The updated literature search was performed on November 19, 2013. An additional 137 articles (published between 2011 and November 2013) were found in EMBASE, MEDLINE, and Cochrane databases combined, and an additional 63 potentially eligible studies were registered in

clinicaltrials.gov. Two investigators (NM and MF) independently reviewed the 137 abstracts and 63 clinicaltrials.gov entries. Twenty four potentially eligible studies were identified: 7 full-text manuscripts describing original studies, 10 abstracts from meeting proceedings, and 7 clinicaltrials.gov entries; these studies were analysed for outcome extraction by the same two investigators (NM and MF). In addition, 7 systematic reviews and meta-analyses (once again identified as a result of the broad search strategy employed in the study) as well as review of references of the analyzed studies were searched for additional eligible studies, and none were found. The PRISMA flowchart of the process of selection of eligible studies for the updated search is depicted in Figure 4.

### 2.3.2 Extraction of outcome measures

A large number of different types of outcomes were measured by the identified studies.

**Figure 4. Selection of studies for outcome extraction during the systematic review of literature – the updated search**



Primary outcomes in the identified studies most commonly represented one of the following:

1. Achieving a particular disease-related state, most often some form of “remission” (which can be “complete”, “partial”, “sustained”, etc.) and/or “relapse” (which can be “major”, “minor”, “severe”, etc.);
2. Achieving a particular treatment-related state, such as “treatment response”, “treatment failure,” or certain desired or undesired adjustments of medications (such as desired decreases in doses of prednisone or undesired need for intensification of immunosuppression); or
3. Some measure of survival or mortality.

The disease- and treatment- related states described above were usually defined in terms of a combination of particular scores on composite outcomes measures, biochemical tests, and specific organ manifestations of AAV.

Secondary outcomes were found to be more variable, but as a rule included some measure of adverse events – most often infections.

To facilitate analysis the extracted outcomes were grouped into seven conceptual groups: 1) disease-related states and definitions; 2) treatment-related states and definitions; 3) outcomes pertaining to specific organ manifestations including organ damage; 4) biochemical tests; 5) measures of adverse events and treatment toxicities; 6) broad concepts that measure global effects of both the disease and the treatments; and 7) composite measures of disease activity, damage, or quality of life.

Appendix B (Tables B.1-B.7) contains the list of outcomes extracted from the identified studies, divided into 7 tables reflecting the seven conceptual groups described above. The last column in each of the 7 tables provides the references of studies that measured each of the listed outcomes.

### 2.3.3 "Mapping" the identified outcomes to the ICF

Outcomes pertaining to specific organ manifestations and biochemical tests as a rule corresponded to single concepts that linked to categories in the ICF components "body functions" or "body structures". On the other hand, disease- and treatment- related states are broad concepts that could not be linked to specific categories, and according to the ICF linking rules (described in the Methods section of this chapter) most of these were labeled as "not definable" by the ICF; in the majority of cases these states were associated with definitions that employed a combination of more specific outcomes that themselves were disassembled into concepts and linked to the corresponding ICF categories individually. Similarly, each item in each of the 11 identified composite outcome measure tools was disassembled into individual concepts that were then linked to the ICF. Appendix C contains the example of linking the Birmingham Vasculitis Disease Activity (BVAS) scale – the most commonly employed composite measure of disease activity in AAV (17) (see the manuscript included in Chapter 3 for a detailed description of BVAS and other composite measure tools included in the OMERACT Core Set of outcome measures for AAV).

Tables 2-A and 2-B provide a summary of the results of mapping of all the outcome measures identified through the comprehensive literature search. Table 2-A contains categories classified by the ICF (ICF components "body functions", "body structures", "activities and participation", "environmental factors" and "personal factors", while Table 2-B contains "health conditions" and categories "not covered" or "not definable" by the ICF. Coverage of various ICF domains by each of the 7 groups of outcome measures described above is shown, followed by the summary of coverage by all outcome measures used in clinical trials on AAV patients.

Clinical trials of AAV patients measure a large number of ICF categories. Overall, outcomes identified in clinical trials of AAV patients mapped to 37 second-level categories in the ICF component

“body functions”, 28 in “body structures”, 29 in “activities and participation”, 6 in “environmental factors”; 6 “personal factors” are considered in clinical trials: age, sex, ethnic background, comorbidities, smoking status and compliance with clinical management. Six concepts linked to “health condition” group of categories (“asthma”, “cholesteatoma”, “diabetes”, “infection”, “malignancy”, and “osteoporosis”) in addition to being linked to the closest category in “body function” or “body structure” component. A number of concepts could not be linked to a specific ICF category and were considered “not covered” or “not definable” by the ICF. The “not covered” items included constructs related to “body functions” (central nervous system, cranial and peripheral nerve function, and function of paranasal sinuses) and “body structures” (sinus damage); the “not definable” constructs included “death”, concepts related to general well-being (health-related quality of life, patient and physician global assessment scores), to disease severity (limited/severe, non-/life-threatening disease, non-/organ-threatening disease), to stage of illness (relapse, remission, stable versus progressive disease), concepts related to treatment (adverse events, response to treatment), as well as concepts related to “body functions” (“infection”, “malaise”, “malignancy”, “abnormalities of physical exam”, “sepsis”, and “vital organ dysfunction”) and “body structures” (“infection”, “malignancy”, “tissue loss”, “abnormalities of physical exam”, and “damage to a vital organ”).

## Table 2-A. ICF categories covered by outcome measures in clinical trials – categories classified by the ICF and "Personal factors"

| ICF Code | | | ICF Category Description | Disease-related terms | Treatment-related terms | Specific organ manifestations | Biochemical tests | Adverse events and related outcomes | Broad unclassifiable concepts | Composite instruments | OMERACT core set# | **OVERALL for literature perspective** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Body Functions** | | | | | | | | | * | | | * |
| B1 | | | Mental functions | | | | | | | * | * | * |
| | 14 | | Orientation functions | | | | | | | * | * | * |
| | 17 | | Intellectual functions | | | | | | | * | | * |
| | 30 | | Energy and drive functions | | | | | | | * | * | * |
| | 52 | | Emotional functions | | | | | | | * | * | * |
| B2 | | | Sensory functions and pain | | | | | | | * | * | * |
| | 10 | | Seeing functions | * | | | | | | * | * | * |
| | 29 | | Seeing and related functions, other specified and unspecified | | | | | | | * | | * |
| | 30 | | Hearing functions | | | | | | | * | * | * |
| | 40 | | Sensations associated with hearing and vestibular function | | | | | | | * | | * |
| | 79 | | Additional sensory functions, other specified and unspecified | | | | | | | * | * | * |
| | 80 | | Sensation of pain | * | | | | | | * | * | * |
| | 89 | | Sensation of pain, other specified and unspecified | | | | | | | * | * | * |
| B3 | | | Voice and speech functions | | | | | | | * | * | * |
| | 10 | | Voice functions | | | | | | | * | * | * |
| B4 | | | Functions of the cardiovascular, haematological, immunological and respiratory systems | | | * | | | | * | * | * |
| | 10 | | Heart functions | * | | | | | | * | * | * |
| | 15 | | Blood vessel functions | | | * | | | | * | * | * |
| | 20 | | Blood pressure functions | | | | | | | * | * | * |
| | 30 | | Haematological system functions | | | * | * | * | | * | * | * |
| | 35 | | Immunological system functions | * | * | | * | * | | * | * | * |
| | 40 | | Respiratory functions | * | * | * | | | | * | * | * |
| | 49 | | Functions of the respiratory system, other specified and unspecified | | | | | | | * | * | * |
| | 50 | | Additional respiratory functions | * | | | | | | * | * | * |

| ICF Code | | | ICF Category Description | Disease-related terms | Treatment-related terms | Specific organ manifestations | Biochemical tests | Adverse events and related outcomes | Broad unclassifiable concepts | Composite instruments | OMERACT core set# | **OVERALL for literature perspective** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 60 | | Sensations associated with cardiovascular and respiratory functions | | | | | | | * | * | * |
| B5 | | | Functions of the digestive, metabolic and endocrine systems | | | | | | | * | * | * |
| | 25 | | Defecation functions | | | | | | | * | * | * |
| | 30 | | Weight maintenance functions | | | | | | | * | * | * |
| | 35 | | Sensations associated with the digestive system | * | | | | | | | | * |
| | 40 | | General metabolic functions | | | | | | | * | * | * |
| | 45 | | Water, mineral and electrolyte balance functions | | | | | * | | | | * |
| | 50 | | Thermoregulatory functions | * | | | | | | * | * | * |
| | 55 | | Endocrine gland function | | | | | * | | | | * |
| B6 | | | Genitourinary and reproductive functions | | | | | | | | | |
| | 10 | | Urinary excretory functions | * | | * | * | * | | * | * | * |
| | 20 | | Urination function | | | | | | | * | | * |
| | 60 | | Procreation functions | | | | | * | | | | * |
| | 79 | | Genital and reproductive functions, other specified and unspecified | | | | | | | * | * | * |
| B7 | | | Neuromusculoskeletal and movement-related functions | | | | | | | | | |
| | 29 | | Functions of the joints and bones, other specified and unspecified | | | | | | | * | * | * |
| | 30 | | Muscle power functions | | | * | | | | * | * | * |
| | 80 | | Sensations related to muscle and movement functions | | | | | | | * | * | * |
| | 98 | | Neuromusculoskeletal and movement-related functions, other specified | * | | | | | | * | * | * |
| B8 | | | Functions of the skin and related structures | | | | | | | | | |
| | 20 | | Repair functions of the skin | | | | | | | * | | * |
| **Body Structures** | | | | | | | | | * | | | * |
| S1 | | | Structures of the nervous system | | | * | | | | | | * |
| | 10 | | Structure of brain | * | | | | * | | * | * | * |
| | 20 | | Spinal cord and related structures | * | | | | | | * | * | * |
| | 98 | | Structure of the nervous system, other specified | * | | | | | | * | * | * |

| ICF Code | | | ICF Category Description | Disease-related terms | Treatment-related terms | Specific organ manifestations | Biochemical tests | Adverse events and related outcomes | Broad unclassifiable concepts | Composite instruments | OMERACT core set# | **OVERALL for literature perspective** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S2 | | | The eye, ear and related structures | | | | | | | * | * | * |
| | 10 | | Structure of eye socket | * | | | | | | * | * | * |
| | 20 | | Structure of eyeball | * | | | | | | * | * | * |
| | 30 | | Structures around eye | | | | | | | * | * | * |
| | 40 | | Structure of external ear | * | | | | | | * | * | * |
| | 50 | | Structure of middle ear | * | | | | | | * | * | * |
| | 60 | | Structure of inner ear | | | | | | | * | * | * |
| S3 | | | Structures involved in voice and speech | | | | | | | * | * | * |
| | 10 | | Structure of nose | * | * | | | | | * | * | * |
| | 20 | | Structure of mouth | | | | | | | * | * | * |
| | 30 | | Structure of pharynx | | | | | | | * | * | * |
| | 40 | | Structure of larynx | | | | | | | * | | * |
| S4 | | | Structures of the cardiovascular, immunological and respiratory systems | | | | | | | | | |
| | 10 | | Structure of cardiovascular system | * | | * | | * | | * | * | * |
| | | 0 | Heart | | | | | | | * | * | * |
| | 30 | | Structure of respiratory system | * | | | | * | | * | * | * |
| S5 | | | Structures related to the digestive, metabolic and endocrine systems | | | | | | | * | * | * |
| | 10 | | Structure of salivary glands | | | | | | | * | * | * |
| | 20 | | Structure of esophagus | | | | | | | * | * | * |
| | 40 | | Structure of intestine | * | | | | | | * | * | * |
| | 50 | | Structure of pancreas | | | | | | | * | * | * |
| | 98 | | Structures related to the digestive, metabolic and endocrine systems, other specified | | | | | | | * | * | * |
| S6 | | | Structures related to the genitourinary and reproductive systems | | | | | | | | | |
| | 10 | | Structure of urinary system | * | | | | * | | * | * | * |
| | 30 | | Structure of reproductive system | | | | | | | * | * | * |
| S7 | | | Structures related to movement | | | | | | | | | |
| | 30 | | Structure of upper extremity | * | | | | | | * | * | * |
| | 50 | | Structure of lower extremity | * | | | | | | * | * | * |
| | 60 | | Structure of trunk | | | | | | | * | * | * |

| ICF Code | | | ICF Category Description | Disease-related terms | Treatment-related terms | Specific organ manifestations | Biochemical tests | Adverse events and related outcomes | Broad unclassifiable concepts | Composite instruments | OMERACT core set# | **OVERALL for literature perspective** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 70 | | Additional musculoskeletal structures related to movement | | | | | | | * | * | * |
| S8 | | | Skin and related structures | | | | | | | | | |
| | 10 | | Structure of areas of skin | | | | | | | * | * | * |
| | 40 | | Structure of hair | | | | | | | * | * | * |
| **Activities and Participation** | | | | | | | | | | | | |
| D1 | | | Learning and applying knowledge | | | | | | | | | |
| D2 | | | General tasks and demands | | | | | | | | | |
| | 30 | | Carrying out daily routine | | | * | | | | * | * | * |
| D3 | | | Communication | | | | | | | | | |
| D4 | | | Mobility | | | | | | | * | | * |
| | 10 | | Changing basic body position | | | | | | | * | * | * |
| | 20 | | Transferring oneself | | | | | | | * | | * |
| | 29 | | Changing and maintaining body position, other specified and unspecified | | | | | | | * | | * |
| | 30 | | Lifting and carrying objects | | | | | | | * | * | * |
| | 40 | | Fine hand use | | | | | | | * | | * |
| | 45 | | Hand and arm use | | | | | | | * | * | * |
| | 50 | | Walking | | | | | | | * | * | * |
| | 55 | | Moving around | | | | | | | * | * | * |
| | 60 | | Moving around in different locations | | | | | | | * | | * |
| | 98 | | Mobility, other specified | | | | | | | * | | * |
| D5 | | | Self-care | | | | | | | * | | * |
| | 10 | | Washing oneself | | | | | | | * | * | * |
| | 20 | | Caring for body parts | | | | | | | * | | * |
| | 30 | | Toileting | | | | | | | * | | * |
| | 40 | | Dressing | | | | | | | * | * | * |
| | 50 | | Eating | | | | | | | * | | * |
| | 60 | | Drinking | | | | | | | * | | * |
| | 98 | | Self-care, other specified | | | | | | | * | | * |
| D6 | | | Domestic life | | | | | | | * | | * |
| | 20 | | Acquisition of goods and services | | | | | | | * | | * |

| ICF Code | | | | | ICF Category Description | Disease-related terms | Treatment-related terms | Specific organ manifestations | Biochemical tests | Adverse events and related outcomes | Broad unclassifiable concepts | Composite instruments | OMERACT core set# | **OVERALL for literature perspective** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 30 | | | | Preparing meals | | | | | | | * | | * |
| | 40 | | | | Doing housework | | | | | | | * | | * |
| | 49 | | | | Household tasks, other specified and unspecified | | | | | | | * | * | * |
| | 50 | | | | Caring for household objects | | | | | | | * | | * |
| | 99 | | | | Domestic life, unspecified | | | | | | | * | | * |
| D7 | | | | | Interpersonal interactions and relationships | | | | | | | | | |
| | 60 | | | | Family relationships | | | | | | | * | | * |
| D8 | | | | | Major life areas | | | | | | | | | |
| | 39 | | | | Education, other specified and unspecified | | | | | | | * | | * |
| | 50 | | | | Remunerative employment | | | | | | | * | | * |
| | 59 | | | | Work and employment, other specified and unspecified | | | | | | | * | * | * |
| D9 | | | | | Community, social and civic life | | | | | | | | | |
| | 20 | | | | Recreation and leisure | | | | | | | * | * | * |
| **Environmental Factors** | | | | | | | | | | | | | | |
| E1 | | | | | Products and technology | | | | | | | | | |
| | | 10 | | | Products or substances for personal consumption | | | | | | | | | |
| | | | 1 | | Drugs | * | * | | | * | | | | * |
| | | 15 | | | Products and technology for personal use in daily living | | | | | | | * | | * |
| | | 20 | | | Products and technology for personal indoor and outdoor mobility and transportation | | | | | | | * | | * |
| | | 98 | | | Products and technology, other specified | | | | | | | | | |
| | | | | | > Assistive products and technology | | | | | | | * | | * |
| | | | | | > Medical products and technology required as part of medical treament | | | * | | | | | | * |
| E2 | | | | | Natural environment and human-made changes to environment | | | | | | | | | |
| E3 | | | | | Support and relationships | | | | | | | * | | * |
| | | 40 | | | Personal care providers and personal assistants | | | | | | | * | | * |

| ICF Code | ICF Category Description | | | Disease-related terms | Treatment-related terms | Specific organ manifestations | Biochemical tests | Adverse events and related outcomes | Broad unclassifiable concepts | Composite instruments | OMERACT core set# | **OVERALL for literature perspective** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| E4 | | | Attitudes | | | | | | | | | |
| E5 | | | Services, systems and policies | | | | | | | | | |
| | 80 | | Health services, systems and policies | * | * | * | | * | * | | | * |
| **Personal Factors** | | | | | | | | | | | | |
| P1 | | | Facts | | | | | | | | | |
| | 10 | | Demographic characteristics | | | | | | | | | |
| | | 0 | Age | | | | | | | | | * |
| | | 2 | Gender | | | | | | | | | * |
| | | 5 | Race/ethnicity | | | | | | | | | * |
| | 20 | | Personal history and biography | | | | | | | | | |
| | | 0 | Comorbidities | | | | | | | | | * |
| P3 | | | Patterns of experience and behaviour | | | | | | | | | |
| | 10 | | Habits | | | | | | | | | |
| | | 2 | Compliance with management | | | | | | | | | * |
| | | 4 | Other habits (smoking, alcohol) | | | | | | | | | * |

[#] *"OMERACT core set" column (shaded grey) represents a subset of the preceding "composite measures" column that includes composite instruments that are included in the OMERACT core set for AAV. "*" in the cells indicate that at least one outcome measure in the corresponding group of outcome measures "maps" to the specific ICF category.*

**Table 2-B. ICF categories covered by outcome measures in clinical trials – "health conditions" and categories "not covered" and "not definable" by the ICF**

| ICF code | ICF Category Description | Disease-related terms | Treatment-related terms | Specific organ manifestations | Biochemical tests | Adverse events and related outcomes | Broad unclassifiable concepts | Composite tools | OMERACT Core Set# | Overall for clinical trials |
|---|---|---|---|---|---|---|---|---|---|---|
| **Health conditions** | | | | | | | | | | |
| | Asthma | | * | * | | | | * | * | * |
| | Cholesteatoma | | | | | | | * | | * |
| | Diabetes | | | | | | | * | * | * |
| | Infections | | | | | * | | | | * |
| | Malignancy | | | | | * | | * | * | * |
| | Osteoporosis | | | | | | | * | * | * |
| **Not covered** | | | | | | | | | | |
| Nc-bf | Central nervous system function | * | | * | | | | * | | * |
| | Brain function | | | | | | | * | * | * |
| | Cerebrospinal fluid | | | | | | | * | | * |
| | Cranial nerve palsy | * | | | | | | * | * | * |
| | Peripheral nerve function | * | | | | | | | | * |
| | Sinus function | | | | | | | * | * | * |
| Nc-bs | Cerebrospinal fluid | | | | | | | * | | * |
| | Sinuses | * | * | | | | | * | * | * |
| **Not definable** | | | | | | | | | | |
| | Adverse events | | | | | * | | | | * |
| | Complication | | | | | | | * | * | * |
| | General well-being | * | | | | | | * | * | * |
| | Global assessment, patient | | | | | | * | | | * |
| | Global assessment, physician | | | | | | * | | | * |
| | Physical health | | | | | | | | * | * |
| | HRQoL | | | | | | * | | | * |
| | Q-TWIST = quality-adjusted time without symptoms or toxicity | | | | | | * | | | * |
| | Severity of illness | | | | | | | | | |
| | Life-threatening disease | * | | | | | | | | * |
| | Limited disease | | | | | | | * | * | * |
| | Non-life-threatening disease | * | | | | | | | | * |
| | Severe disease | * | | | | | | * | * | * |

| ICF code | ICF Category Description | Disease-related terms | Treatment-related terms | Specific organ manifestations | Biochemical tests | Adverse events and related outcomes | Broad unclassifiable concepts | Composite tools | OMERACT Core Set# | Overall for clinical trials |
|---|---|---|---|---|---|---|---|---|---|---|
| | Stage of illness | | | | | | | | | |
| | Disease-free period | * | | | | | | | | * |
| | Flare / relapse | * | | | | | | * | * | * |
| | Low disease activity | * | | | | | | | | * |
| | Persistent disease / chronic disease | * | | | | | | * | * | * |
| | Progressive disease | * | | | | | | * | | * |
| | Restoration of immune tolerance | * | | | | | | | | * |
| | Stability of medical status | * | | | | | | | | * |
| | Remission | * | | | | | | | * | * |
| | Survival / death | * | | | | * | | * | * | * |
| | Treatment | * | | | | * | | | | * |
| | Feasibility | | * | | | | | | | * |
| | Safety | | * | | | * | | | | * |
| | Effect of treatment | | * | | | * | | | | * |
| | Side effects from drugs (excluding prednisone) | | * | | | * | | | | * |
| Nd - bf | Infection | | | | | * | | | | * |
| | Malaise | | | | | | | * | * | * |
| | Malignancy | | | | | * | | * | * | * |
| | Physical exam | | | | | * | | | | * |
| | Vital signs | | | | | * | | | | * |
| | Sepsis | | | | | * | | | | * |
| | Vital / critical organ | * | | | | | | | | * |
| Nd - bs | Infection | | | | | * | | | | * |
| | Malignancy | | | | | * | | * | * | * |
| | Tissue loss | | | | | | | * | * | * |
| | Physical exam | | | | | * | | | | * |
| | Vital / critical organ | * | | | | | | | | * |

*[#] "OMERACT core set" column (shaded grey) represents a subset of the preceding "composite measures" column that includes composite instruments that are included in the OMERACT core set for AAV. "*" in the cells indicate that at least one outcome measure in the corresponding group of outcome measures "maps" to the specific ICF category; hc – health condition, nc – not covered, nd – not defined, bf – body functions, bs – body structures.*

## 2.4 Descriptive analysis of results and discussion

A large number of different types of outcomes are measured in clinical trials of AAV patients. Primary outcomes most commonly consist of some combination of disease-related states (usually with study-specific definitions), treatment-related states, and a measure of survival or mortality. The disease- and treatment-related states are usually defined in terms of a combination of particular scores on composite outcomes measures, biochemical tests, and specific organ manifestations of AAV. Secondary outcomes are more variable across studies, but usually include some measure of adverse events.

The identified studies cover 106 second-level ICF categories - 37 in the ICF component "body functions", 28 in "body structures", 29 in "activities and participation", 6 in "environmental factors" and 6 in "personal factors". In addition, 6 outcomes linked to "health condition" category in addition to the closest category in "body functions" or "body structures" ICF component, and a number were "not definable" or "not covered" by the ICF.

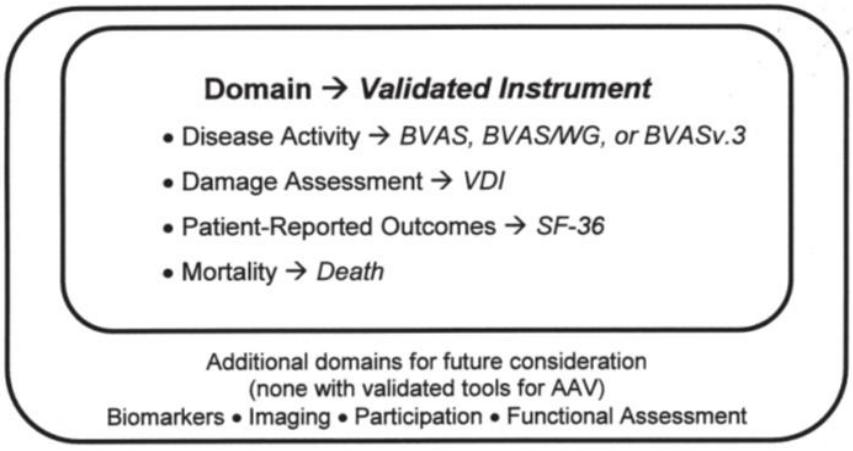
Studying the summary of the results of mapping of the outcome measures identified in clinical trials of patients with AAV (the last column in Tables 2-A and 2-B) reveals that the vast majority of identified ICF categories are represented in items contained in one or more of the 11 identified composite outcome tools (3$^{rd}$ last column in each of the tables). Outcomes that belong to the other 6 groups of outcome measures add little to the ICF coverage by the composite instruments; mainly they add broad concepts that related to various disease states, stages of disease severity, and concepts related to treatment and adverse events that linked to "not definable" or "not covered" ICF categories.

Such dominance of the overall outcome measurement in clinical trials of AAV by the composite outcome measure tools can be explained by the combination of three factors. First, a

relatively large number of composite tools is currently employed in clinical studies. Second, a large number of items that link to a large number of ICF categories from different ICF components are contained in many of these tools (the largest of these being the Combined Damage Assessment index containing 129 individual items grouped into 17 categories (18)). Third, significant heterogeneity of the existing composite tools exists with respect to their primary purpose and the scope of their use. The purpose of the instruments used in the setting of AAV includes but is not limited to 1) measuring disease activity (e.g. BVAS (17)), 2) assessing accumulated organ damage (Vasculitis Damage Index (VDI) (19)), or 3) describing patient's health-related quality of life (HRQoL) (Short Form-36 (SF-36) questionnaire) (20)). The scope of instruments used in the setting of AAV ranges from those designed for a specific subtype of AAV (the BVAS for Wegener's Granulomatosis (BVAS/WG) (21)) to generic measures that can be used in all medical conditions like the measure of HRQoL SF-36 (20).

Five out of the 11 identified composite outcome measure tools belong to the OMERACT Core Set for AAV. As discussed in the Introduction, an OMERACT Core Set for a specific medical condition represents the set of validated composite tools that are selected through a systematic process based on their ability to measure the domains determined to be relevant to the particular

**Figure 5. OMERACT Core Set of outcome measures for clinical trials in AAV**




*BVAS: Birmingham Vasculitis Activity Score; BVAS/WG: BVAS for Wegener's granulomatosis; BVASv.3: BVAS, version 3; SF-36: Medical Outcome Study Short-Form 36 survey; VDI: Vasculitis Damage Index.*

medical condition (in this case AAV) (6). The OMERACT Core Set of outcome measures for AAV is discussed in detail in the Manuscript presented in Chapter 3 of this thesis, and also is represented in Figure 5. Because of the significance of this group of outcome measures, a separate column (shaded grey) that identifies ICF categories sampled by the OMERACT Core Set for AAV was added to Tables 2-A and 2-B. Examining the last 3 columns of these tables shows that the tools of the OMERACT AAV Core Set capture the majority of the ICF categories measured in clinical trials. This observation likely stems from a combination of 2 factors: 1) inherent in the definition of the OMERACT Core Set is that it should be sufficiently broad to cover all of the relevant areas of the medical condition in question; and 2) acceptance of the AAV OMERACT Core Set by the research community as the standard of outcome measurement resulted in preferential use of the composite tools that belong to the OMERACT Core Set in clinical trials.

Exceptions to this comprehensiveness of the AAV OMERACT Core Set are the relative underrepresentation by the core set of ICF Components "Activities and Participation" and absence of coverage of contextual factors (see detailed discussion of this in the Manuscript included in Chapter 3). Although some of these areas are covered by the remaining 6 composite outcome tools, each of these tools covers only a small number of the underrepresented categories. Sampling all of these categories would necessitate using a large number of composite tools which would not be feasible for clinical trials, and even less feasible for every day clinical practice. The solution to this would be developing a vasculitis-specific outcome measure tool that will address areas that are underrepresented by the existing OMERACT AAV Core Set. The OMERACT Vasculitis Working Group is currently developing a patient-reported outcome (PRO) measure tool for patients with AAV (in collaboration with the patient perspective part of this project, as discussed in Chapter 5). When developed, this vasculitis-specific PRO tool should fill in the identified gaps in coverage of the areas that represent the impact of AAV by the existing OMERACT AAV Core Set (22).

Overall, the outcomes measured in clinical trials of patients with AAV cover a large number of ICF categories across many ICF domains. The relative representation of the specific ICF components by the collection of all of the outcomes measured in AAV clinical trials parallels that of the OMERACT Core Set for AAV, as discussed above. Namely, one can notice comprehensive coverage of ICF components "body functions" and "body structures", slightly less comprehensive coverage of "activities and participation" (with a number of broad 1$^{st}$-level categories not covered including "learning and applying knowledge" and "communication", and with a very limited coverage of "interpersonal interactions and relationships"), and minimal coverage of ICF "contextual factors" (with very few "environmental factors" and "personal factors" covered). The significance of the latter observation is discussed in detail in the manuscript that follows this discussion; the manuscript describes the use of the ICF classification as a tool for detailed analysis of outcome measure domains covered by the OMERACT AAV Core Set.

## 2.5 Strengths and limitations of the study

This study represents the first attempt at providing a detailed description of which aspects of health are measured in clinical trials of AAV. The use of the ICF classification made such description possible by providing a comprehensive "standardized language" that allows detailed characterization of different types of outcomes, resulting in one big picture that captures all outcomes measured in all clinical trials.

Although broad representation was ensured by including all randomized clinical trials (RCTs), this could be made even broader by including other types of trials, including observational trials. The main reason for limiting the sampling frame to randomized trials was that RCTs is the present focus of the work of the OMERACT initiative which this project is part of. Furthermore, a large number of large-scale RCTs are being conducted in the area of AAV, and these trials tend to employ the most comprehensive and validated outcome measures. Thus, we feel it is unlikely that important outcomes that are not measured in RCTs would be added by including other types of trials. Finally, previous efforts to develop ICF Core Sets for specific medical conditions focused exclusively on RCTs (12).

Another limitation of this study is the purely qualitative approach employed to describing the areas measured in clinical trials. Considering the different quality of included studies and the different importance of the measured outcomes, some representing primary outcomes and others merely constituting an item of a composite outcome measure, we did not feel it was appropriate to focus on frequency of occurrence of the specific outcomes. Weighing the outcomes to the quality of study or the outcome's importance would significantly complicate the analysis of this study, and would be of limited value considering that the ultimate purpose of this study is merely to inform the subsequent steps of development of ICF Core Sets for AAV.

# Chapter 3 Manuscript - Mapping of the Outcome Measures in Rheumatology (OMERACT) Core Set for ANCA-Associated Vasculitis to the International Classification of Function, Disability and Health

**Manuscript status**: Accepted, published online first

**Title**: Mapping of the Outcome Measures in Rheumatology (OMERACT) Core Set for ANCA-Associated Vasculitis to the International Classification of Function, Disability and Health

**Running head**: Using the ICF to describe OMERACT Core Set of outcome measures for AAV

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## Abstract

Objective. The International Classification of Functioning, Disability and Health (ICF) is a framework and classification of health that describes health along 4 components: “body functions”, “body structures”, “activities and participation”, and “contextual factors”. This study examined the content of instruments that constitute the Outcome Measures in Rheumatology (OMERACT) Core Set of outcome measures for ANCA-associated vasculitis (AAV) by “mapping” them to the ICF.

Methods. The content of the instruments included in the AAV Core Set were linked to the ICF by two independent investigators according to previously established ICF linkage rules.

Results. The AAV Core Set includes 3 measures of disease activity (3 versions of the Birmingham Vasculitis Activity Score), 1 damage measure (Vasculitis Damage Index), 1 patient-reported outcome (Short Form-36), and death. Linking these instruments to the ICF revealed comprehensive coverage of the ICF components “body functions” and “body structures,” limited coverage of the ICF component “activities and participation,” and complete absence of coverage of “contextual factors”.

Conclusion. ICF was found to be useful for thematic characterization of a heterogeneous group of outcome measures for AAV - a group of complex medical conditions. Linking of the instruments selected for the OMERACT AAV Core Set of outcome measures to the ICF classification revealed limitations in the representation of constructs related to life impact of AAV, represented by the ICF components “activities & participation” and “contextual factors.” Further research and methods development are needed to better incorporate important aspects of functioning and health relevant to patients into clinical trials of AAV.

## Significance and Innovations

- ICF framework was shown to be useful for analyzing a complex medical condition (ANCA-associated vasculitis) from the global bio-psycho-social perspective

- ICF-based analysis demonstrated that the instruments used to assess outcomes in clinical trials of AAV patients mainly focus on “pathophysiolgical manifestations” of AAV; they display limited ability to assess the overall “life impact” of AAV on patients

- Patient-reported outcome measure specific to AAV is needed to be able to assess the impact of AAV on patients’ quality of life

## Introduction

The International Classification of Functioning, Disability, and Health (ICF) is a general health status framework based on the bio-psycho-social model of health and disease. It was endorsed by the World Health Organization in 2001 as the international standard to describe and measure health and disability (1).

The ICF views health as a broad concept that is described along 4 ICF "components": 1) body functions, 2) body structures, 3) activities and participation, and 4) contextual factors (1). The level of functioning and health of the individual patient is viewed as being the result of the relationship between impairments of various "body functions" and "body structures", limitations in activities, restrictions in participation and the influence of "contextual factors". "Contextual factors" represent the collection of individual's personal, social and attitudinal environment that influence the relationship between the other ICF components and modify their effect on the overall health; when the overall effect of the "contextual factors" is positive they are called "facilitators" of health, and when it is negative they are "barriers" to health (1). As an example, the actions of a supporting family member to help a patient get around and preserve an acceptable level of functioning may diminish the negative effect on the patient's well-being of becoming wheelchair-bound as a result of a medical condition; "family support" in this case represents a contextual facilitator of health.

In addition to the framework, the ICF offers a classification system to describe functioning and health using 1424 categories organized into a 4-level hierarchically nested structure covering the 4 components described above. A lower level category within a particular component represents a more detailed example (and thus a subset) of a higher level category. ICF classification provides a methodology to comprehensively describe patients' general health status in a standardized approach highlighting the relationship between an individual's physical state of

health, personal or environmental factors and functioning. A number of applications of the ICF have been explored since its' endorsement in 2001, ranging from summarizing disability statistics and facilitating development of health information systems on the broad population level (2) to describing domains that are relevant when studying patients with specific medical conditions (3).

Vasculitides are complex conditions characterized by inflammation of blood vessels. ANCA-associated vasculitis (AAV) is the best studied group of vasculitides. The group consists of three conditions: granulomatosis with polyangiitis (Wegener's, GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss, EGPA). With the advent of effective therapy consisting of high-dose glucocorticoids combined with other immunosuppressive medications, the clinical course of AAV has changed from nearly universal early mortality to a chronic condition with a high level of morbidity and substantial economic burden. Consequently, outcomes for measuring the impact of AAV need to capture the breadth of the impact on physical, social and emotional aspects of health-related quality of life (HRQoL) and health resource utilization relevant to patients with AAV, in addition to measuring the physiologic consequences of the disease.

Outcome Measures in Rheumatology (OMERACT) is an international organization that strives to develop optimal outcome measures for use in clinical trials through the application of a systematic outcome measure validation process (4). The OMERACT-ICF Reference Group works to integrate the ICF into the OMERACT process (5). ICF classification provides a standardized approach to describing the existing outcome measures ("mapping"), allowing comparison of the content of different measures (5). Such content comparison could facilitate the selection of tools most appropriate for clinical settings and for conducting clinical research.

In 2010 the OMERACT community endorsed the Core Set of outcome measures for ANCA-associated vasculitis (AAV Core Set) (6). An OMERACT core set of outcome measures is a collection of validated, responsive, feasible instruments that address a set of domains of the illness under study considered crucial to assess in clinical studies (6). Selection of such instruments follows a standardized agreed-upon process (4). The AAV Core Set includes specific measures of disease activity, disease damage and patient-reported outcomes; these instruments contain a large number of items and until now no attempts have been made to understand in detail which exact aspects of functioning and health they measure. The current study addresses this question by mapping the outcome measures included in the OMERACT AAV Core Set to the ICF classification.

## Methods

### *Outcome Measures included in AAV Core Set*

The OMERACT AAV Core Set suggests using one of the versions of the Birmingham Vasculitis Activity Score (BVAS) (7-10) as a measure of disease activity, the Vasculitis Damage Index (VDI) (11) for assessment of disease-related damage, the Short Form-36 (SF-36) (12) for measurement of life impact, and death as a measure of mortality.

The 3 versions of the BVAS that are most commonly used in clinical trials are: BVASv2, BVAS/WG, and BVASv3. BVASv2 (10) is the version that emerged and became incorporated into clinical trials soon after creation of the original BVAS (7); it is frequently referred to as simply "BVAS". BVASv2 (10) was designed for use with all forms of vasculitis; it consists of 66 individual items addressing 9 organ systems. BVAS/WG is a more concise version of BVAS (34 items) specifically designed for use in patients with GPA (9). BVASv3 is another version created through item reduction (56 items) and simplification of the original BVAS (8). These 3 versions of the BVAS have been used in multicenter randomized trials of AAV and produce highly correlated summary scores (13).

The VDI consists of 64 items of damage organized by 12 organ systems commonly affected by vasculitides (11). The VDI has been used in almost all trials in AAV.

The SF-36 is a widely used generic HRQoL instrument. It contains 36 items that address 8 domains of quality of life (14) that can be further grouped into the Physical or Mental Component summary scores.

Death is the final constituent of the OMERACT AAV Core Set. When death is recorded, it is usually accompanied by the description of its cause - such as being attributable to the vasculitis, to its treatments, or unrelated to either.

### *Linking AAV Core Set Items to ICF*

Three versions of BVAS (BVASv2, BVASv3 and BVAS/WG) and the VDI were linked to the ICF according to the previously established ICF linkage rules (15, 16). Briefly, this involves first identifying constructs contained in each item of the composite instrument, followed by linkage of each construct to the most precise ICF category. When a construct cannot be linked to any ICF category, it is classified as either "not definable" (if it is covered by the ICF but cannot be classified to a specific category) or "not covered" (if it is not covered by the ICF). Constructs that refer to specific medical conditions were linked to the ICF category within the body functions or body structures that represents the function or structure affected by the condition. Medical conditions that imply a specific pathophysiology were additionally classified under the ICF "health condition" category in order to avoid losing the specific pathophysiology-related information. For example, "deafness" was linked to the ICF body function category b230 - hearing functions, while "diabetes" was linked to the ICF body function category b5401 – carbohydrate metabolism as well as to the category "hc" – health condition (diabetes). The SF-36 has been previously linked to the ICF by Cieza et al (15), and this version of linking was used for this study.

Linking was performed independently by 2 investigators (NM and AB) familiar with the ICF. Any disagreements were discussed and the linking was modified until both investigators were satisfied with the final result for each of the linked outcome measure tools. To increase efficiency of the linking process, the tools were linked sequentially, so that an agreement on the previous tool was reached by the 2 investigators before they proceeded to link the next tool.

The degree of agreement between the two investigators on linking of the composite tools was estimated by calculating the proportion of agreement in ICF second-level categories for all of the constructs contained in the composite tool, as was suggested in previous reliability studies (17).

## Results

The summary of the results of linking of the instruments contained in the OMERACT core set for AAV, grouped by the ICF component, can be found in Table 1 ("body functions"), Table 2 ("body structures"), Table 3 ("activities and participation"), and Table 4 (constructs that were linked to "health condition", "not covered", and "not defined" categories). None of the constructs contained in instruments of the AAV Core Set linked to the ICF component "contextual factors." BVASv2 contains 66 items in which 84 constructs were identified and linked to 37 second-level ICF categories (17 in "body functions" and 20 in "body structures"). BVAS/WG contains 34 items in which 47 constructs were identified and linked to 29 second-level ICF categories (9 "body functions" and 20 "body structures"). BVASv3 contains 56 items in which 71 linkable constructs were identified and linked to 40 second-level ICF categories (20 in "body functions" and 20 in "body structures"). The VDI contains 64 items in which 76 constructs were identified and linked to 35 second-level ICF categories (17 "body functions" and 18 "body structures").

Four concepts from the VDI were linked to the "health condition" category in addition to being linked to the closest category in "body function" or "body structure" component: "osteoporosis", "asthma", "diabetes", and "malignancy".

Several concepts in each of the instruments could not be linked to a specific ICF category and were considered as "not covered" (5 in BVASv2, 4 in BVAS/WG, 3 in BVASv3, and 3 in VDI) or as "not definable" (4 in BVASv2, 6 in BVAS/WG, 1 in BVASv3, and 6 in VDI). The "not covered" items included constructs related to body functions (sinus dysfunction, brain and cranial nerve dysfunction) and body structures (sinus damage); the "not definable" constructs are "death" and various disease states (limited, severe, new or worse, persistent disease, flare, and remission), "malaise", "malignancy," and "tissue loss" (Table 4).

The SF-36 (previously linked to the ICF by Cieza et al (15)) contains 11 questions that contain 36 items and 52 linkable constructs. These constructs linked to 14 second-level ICF categories, 3 in “body functions” component and 11 in the “activities and participation” component. Twelve constructs were assigned to the “not definable” category; these were “general health”, “physical health”, and levels of intensity of activity (vigorous, moderate, etc.).

Overall, the OMERACT Core Set for AAV covers 29 second-level categories within ICF component “body functions”, 27 in “body structures”, 11 in “activities and participation,” and none in “environmental factors;” 4 constructs were additionally linked to “health condition” category, 29 constructs were considered “not definable” and 16 constructs were “not covered” by the ICF classification.

The proportion of agreement between the two investigators who performed the linking (NM and AB) in ICF second-level categories for the first of the linked tools, the BVASv2, was 83%. Because BVAS/WG and BVASv3 are very similar to BVASv2 and their linking was performed after the consensus on the final linking of BVASv2 was reached by the 2 investigators, the proportion of agreement on BVAS/WG and BVASv3 was extremely high (98% and 99%, respectively). The proportion of agreement for VDI was 83%.

## Discussion

Since its endorsement in 2001(1), the ICF has steadily become incorporated into the medical field as an interface to describe and compare coverage of different health domains by existing outcome measure tools, including disease-specific (osteoarthritis (17) and ankylosing spondylitis (18)) instruments, and generic (19) tools.

The ICF classification was found to be useful for gaining insight into the exact content of the OMERACT Core Set of outcome measures for AAV. Overall, the AAV Core Set covers 29 second-level categories within ICF component "body functions", 27 second-level categories in "body structures", but only 11 second-level categories in "activities or participation" and none in "environmental factors." In addition, the AAV Core Set contains a number of concepts that linked to "health condition," "not specified," or "not definable" categories.

OMERACT recently developed a framework (OMERACT Filter 2.0 framework) and guidelines to improve selection of domains that should be considered when assessing outcomes in clinical studies (20, 21). This framework recommends that every outcome assessment should address each of the two broad categories of outcomes – "Pathophysiological Manifestations" and "Impact of Health Condition". The latter broad category consists of 3 areas - "Death", "Life Impact", and "Resource Use/Economic Impact;" the first 2 areas are to be measured in every clinical trial, while measurement of the third area is encouraged where appropriate. In addition, "adverse events" (toxicity or harm) are required to be addressed separately for items not already covered in "Death" and "Life Impact". The selection of specific domains in each area can depend upon the setting that should be made explicit at the start of the study. Identification of contextual factors that can be confounders or mediators when interpreting the outcome is encouraged. An OMERACT Core Set of outcome measure tools for a specific medical condition (such as the OMERACT Core Set for AAV discussed in this manuscript) is meant to contain at least one validated instrument to address each

of the relevant domains, as well as the minimal set of relevant contextual factors. When an instrument that sufficiently addresses an important domain is lacking, it will need to be developed. Researchers conducting clinical trials will then be able to choose amongst the instruments contained in the OMERACT Core Set for the specific medical condition in order to address all of the domains relevant to the purpose of their study.

Within the new framework, the ICF component “activities and participation” represents mainly the OMERACT area “Life Impact”, the components “body functions” and “body structures” represent “Pathophysiological Manifestations”, and the ICF “contextual factors” could serve as a starting point to define the ‘Context’ that might influence the outcomes.

Thus, the three measures of disease activity (BVASv2, BVAS/WG and BVASv3) and the measure of damage (VDI) (6) represent the area “Pathophysiological Manifestations” in the new OMERACT framework. This study confirmed that all constructs of the items from each of these instruments linked to the ICF components “body functions” and “body structures” (Tables 1 and 2). Comprehensive coverage of these components is demonstrated in this study, further validating the different versions of BVAS and the VDI as tools for measuring disease activity and disease-related damage in patients with AAV. “Life Impact,” on the other hand, is assessed in the AAV Core Set by the SF-36, a generic measure of HRQoL. The majority of its items are indeed linked to the ICF component “activities and participation.” Being a generic instrument, the SF-36 is likely limited in its ability to address the various activity limitations and restrictions of participation that are specifically relevant to patients with a complex medical condition like AAV, resulting in suboptimal coverage of “Life Impact” by the SF-36 specifically and by the AAV core set overall. In order to improve the ability to assess “Life Impact” for patients with AAV, measures that take into account patients’ views need to be developed and included into the OMERACT AAV Core Set. The OMERACT

Vasculitis Working group is currently working to develop and validate both "generic" and disease-specific patient-reported outcome tools (22).

The SF-36 can be used for economic evaluation through its derivative form, SF-6D ("short form 6 dimensions") (23). Based on extrapolation of the preference values on the responses to the different items of the SF-36 obtained from the general population, a single index measure can be estimated from any completed SF-36 questionnaire that allows for the calculation of quality-adjusted life years for use in cost-utility analysis (23). Although this application of the SF-36 has not to date been employed specifically in the setting of vasculitis, the generic nature of the instrument and its SF-6D adaptation implies that this approach should be useful for economic evaluations of treatments or disease impact of AAV.

In contrast, the OMERACT "Context" (or 'contextual factors' in the ICF language) is not addressed by the AAV Core Set to any extent. The concept of "contextual factors" has only recently entered the medical field – after the AAV Core Set was developed. Generally, the contextual modifiers are mainly relevant to various aspects of "Impact" of a medical condition – including "Life Impact", "Economic Impact" and potentially "Death"; contextual modifiers are unlikely to have a significant effect on "Pathophysiologic manifestations." Most interventional trials in AAV that make use of the instruments included in the AAV Core Set focus on specific physiologic outcomes such as renal function or the rate of complete remission; for these trials, personal and environmental contextual factors are, indeed, largely irrelevant. As acceptance of the OMERACT filter 2.0 framework (21) increases, the range of outcomes measured in clinical trials will likely expand and include more detailed and consistent assessment of "life impact;" then, contextual factors will become more relevant and their incorporation into the design and analysis of clinical trials will become necessary.

It is striking that the area “Life Impact” seems to be underrepresented compared to “Pathophysiologic manifestations” in almost all OMERACT core sets. While the core sets of outcome domains for psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis comprise between 3 (psoriatic arthritis) and 8 (ankylosing spondylitis) domains that cover “Pathophysiologic Manifestations” (24), the core sets for RA and AS contain only one domain (“physical function”) from the area “Life Impact.” The OMERACT core set for psoriatic arthritis also contains domains “participation” and HRQoL resulting in broader coverage of “Life Impact.”

The ICF offers valuable opportunities as a framework to better define ‘what to measure’ as outcomes that are relevant to patients and the society as well as to the health professionals. Disease-specific ICF Core Sets represent selections of ICF categories that are typical and relevant to patients with individual medical conditions; they are analogous to the OMERACT Core Sets of domains with the ICF categories replacing the description of domains. We scrutinized several of the existing ICF Core sets of rheumatologic conditions that have been developed to date. The ratio of the number of ICF categories from the ICF component ”body structures” to “body functions” to ”activities and participation” to “environmental factors” is 1 : 3.8 : 5.8 : 5.0 for low back pain, 1 : 2.2 : 3.2 : 2.8 for osteoarthritis, 1: 1.9 : 3.0 : 3.7 for osteoporosis, and 1 : 1.9 : 4.0 : 2.6 for rheumatoid arthritis (25) for the ICF Core Sets for the specified conditions, compared to the corresponding ratio of 2.6 : 2.5 : 1 : 0 for the non-ICF-based OMERACT AAV Core Set reported in this study. Such broader coverage of “Life Impact” domains by the ICF Core Sets relative to the existing non-ICF-based OMERACT Core Sets is likely a function of both the use of the bio-psycho-social framework of health (which is the basis of the ICF) and of the more structured approach to ICF-based Core Set development that prioritizes input of all end-users, including patients. As the similarly structured OMERACT Filter 2.0 framework gradually becomes the standard approach to development of the

new outcome measures, both newly developed and revisions to previously developed disease-specific OMERACT Core Sets should display broader coverage of "Life Impact" and the "Context."

Despite multiple advantages of using the ICF, the classification has limitations. First, although the established linking rules maximize precision of the linking process, some subjectivity to the process is inevitable. The agreement between the two investigators who did the linking in this study was between 83% and 99%. The agreement in other ICF-related studies is closer to the lower end of the agreement in this study (17), likely because the current study used a sequential approach to linking of highly similar instruments, with achievement of full agreement on previous instruments before proceeding to the subsequent ones. Disagreements occurred mainly in regards to concepts for which no perfect fit to a specific ICF category could be found. Second, despite its comprehensiveness the ICF classification is not perfectly exhaustive. Some concepts contained in the AAV Core Set instruments could not be linked to a specific ICF category and as a consequence had to be labeled as "not definable" or "not covered" (see Table 4). While some of such concepts are likely too broad to be linkable to a specific ICF category (for example "malaise" and "physical health"), others such as structure and function of paranasal sinuses, function of brain and peripheral nerves are fairly specific and as such their absence from the ICF classification likely represents a mere oversight at the time of its development. Such limitations are recognized and the ICF will likely be updated in the near future. Until such updates are available, the ICF classification will need to be supplemented with existing outcome measures and composite outcome measurement tools when studying and describing complex systemic conditions such as ANCA-associated vasculitis. Third, the ICF does not consider the concept of "time" nor the inherently time-dependent concept of "process", which is the basis of distinction between disease activity and damage. As a result, Tables 1 and 2 demonstrate significant overlap of coverage of various ICF categories between the measures of disease activity and the measure of damage. Conceptually,

disease activity measures focus on changes in body functions within specific body structures (and therefore the constructs link to both components), while the measures of damage focus on permanent disturbances of both functions and structures of the same organs. While clinically this distinction can (and should) be made, although with some difficulty (26), in the ICF it is not possible to indicate whether an impairment of a structure is temporary or permanent, resulting in such overlap.

This study demonstrates that the ICF classification is a useful framework for analyzing a complex medical condition from the global bio-psycho-social perspective. Linking the content of the OMERACT Core Set of measures for AAV revealed a detailed coverage of "body functions" and "body structures" (OMERACT "Pathophysiological Manifestations") but suggested important gaps in the coverage of the OMERACT area "Life Impact" and complete lack of coverage of "contextual factors." These results suggest the need for expanding the range of the domains that need to be addressed when assessing patients with AAV. It has been increasingly recognized that identifying the relevant domains necessitates directly engaging patients in the process of outcome measure development (27). Patients have become an indispensable part of nearly every part of the OMERACT process, among which is the work of the OMERACT Vasculitis working group to develop a vasculitis-specific patient-reported outcome measure (22).

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# Tables

## Table 3-A (Table 1 in Manuscript). Coverage by the OMERACT AAV Core Set of ICF component "Body Functions" (mapped to second-level categories)*

| ICF code | | ICF Category Description | BVAS | BVASv3 | BVAS/WG | VDI | SF-36 |
|---|---|---|---|---|---|---|---|
| B1 | | ① Mental functions | | | | 1 | |
| | 14 | ② Orientation functions | 1 | 1 | | | |
| | 17 | ② Intellectual functions | 1 | 1 | | 1 | |
| | 30 | ② Energy and drive functions | | | | | 3 |
| | 52 | ② Emotional functions | | | | | 9 |
| B2 | | ① Sensory functions and pain | 2 | | | | |
| | 10 | ② Seeing functions | | 2 | | 4 | |
| | 30 | ② Hearing functions | 3 | 2 | 2 | 1 | |
| | 79 | ② Additional sensory functions, other specified and unspecified | 1 | 1 | 1 | 1 | |
| | 80 | ② Sensation of pain | 6 | 4 | 1 | 1 | 2 |
| | 89 | ② Pain in body part, other specified | 1 | 1 | | | |
| B3 | | ① Voice and speech functions | 1 | | | | |
| | 10 | ② Voice functions | 1 | | | | |
| B4 | | ① Functions of the cardiovascular, haematological, immunological and respiratory systems | 1 | | | | |
| | 10 | ② Heart functions | 6 | 4 | | 3 | |
| | 15 | ② Blood vessel functions | | 1 | | 2 | |
| | 20 | ② Blood pressure functions | 1 | 1 | | 1 | |
| | 30 | ② Haematological system functions | | | | 1 | |
| | 35 | ② Immunological system functions | 1 | 1 | 1 | | |
| | 40 | ② Respiratory functions | 1 | 1 | 1 | 3 | |
| | 49 | ② Functions of the respiratory system, other specified and unspecified | | 1 | 1 | | |
| | 50 | ② Additional respiratory functions | 3 | 1 | | | |
| | 60 | ② Sensations related to cardiovascular & respiratory functions | 3 | 1 | | 1 | |
| B5 | | ① Functions of the digestive, metabolic and endocrine systems | 1 | | | | |
| | 25 | ② Defecation functions | 1 | 1 | | | |
| | 30 | ② Weight maintenance functions | 1 | 1 | | | |
| | 40 | ② General metabolic functions | | | | 1 | |
| | 50 | ② Thermoregulatory functions | 2 | 1 | 1 | | |
| B6 | | ① Genitourinary and reproductive functions | | | | | |
| | 10 | ② Urinary excretory functions | 6 | 6 | 3 | 3 | |
| | 79 | ② Genital & reproductive functions, specified & unspecified | | | | 1 | |
| B7 | | ① Neuromusculoskeletal and movement-related functions | | | | | |
| | 29 | ② Functions of joints and bones, other specified and unspecified | | | | 1 | |
| | 30 | ② Muscle power functions | | | | 1 | |
| | 80 | ② Sensations related to muscles and movement functions | | | | 1 | |
| | 98 | ② Neuromusculoskeletal and movement-related functions, other specified | 1 | 1 | 1 | | |

*Numbers correspond to the number of items in the instrument that mapped to the corresponding ICF category. Categories from the third and fourth levels were carried up to the corresponding second- level categories.

## Table 3-B (Table 2 in Manuscript). Coverage by the OMERACT AAV Core Set of ICF component "Body Structures" (mapped to second-level categories)*

| ICF code | | ICF Category Description | BVAS | BVASv3 | BVAS/WG | VDI | SF-36 |
|---|---|---|---|---|---|---|---|
| S1 | | ① Structures of the nervous system | | | | | |
| | 10 | ② Structure of brain | 4 | 4 | 4 | 3 | |
| | 20 | ② Spinal cord and related structures | 1 | 1 | 1 | 1 | |
| | 98 | ② Structure of the nervous system, other specified | 2 | 3 | 3 | 1 | |
| S2 | | ① The eye, ear and related structures | 2 | | | | |
| | 10 | ② Structure of eye socket | 1 | 1 | 1 | 1 | |
| | 20 | ② Structure of eyeball | 7 | 10 | 7 | 3 | |
| | 30 | ② Structures around eye | | 2 | 1 | | |
| | 40 | ② Structure of external ear | 1 | 1 | 1 | | |
| | 50 | ② Structure of middle ear | 1 | 1 | 1 | | |
| | 60 | ② Structure of inner ear | 1 | 1 | 1 | | |
| S3 | | ① Structures involved in voice and speech | 1 | | | | |
| | 10 | ② Structure of nose | 3 | 4 | 3 | 5 | |
| | 20 | ② Structure of mouth | 1 | 1 | 1 | 1 | |
| | 30 | ② Structure of pharynx | 1 | 1 | 1 | 2 | |
| S4 | | ① Structures of the cardiovascular, immunological and respiratory systems | | | | | |
| | 10 | ② Structure of cardiovascular system | 11 | 7 | 1 | 6 | |
| | 100 | ③ Heart | 4 | 2 | | 5 | |
| | 101-103 | ③ Arteries, veins, capillaries | 6 | 4 | | 1 | |
| | 30 | ② Structure of respiratory system | 8 | 7 | 6 | 3 | |
| S5 | | ① Structures related to the digestive, metabolic and endocrine systems | 1 | | | | |
| | 10 | ② Structure of salivary glands | | | 1 | | |
| | 20 | ② Structure of esophagus | | | | 1 | |
| | 40 | ② Structure of intestine | 2 | | 1 | 3 | |
| | 50 | ② Structure of pancreas | 1 | | | 1 | |
| | 98 | ② Structures related to the digestive, metabolic and endocrine systems, other specified | | 1 | | 1 | |
| S6 | | ① Structures related to the genitourinary & reproductive systems | | | | | |
| | 10 | ② Structure of urinary system | | | | 1 | |
| | 30 | ② Structure of reproductive system | 1 | 1 | | | |
| S7 | | ① Structures related to movement | | | | | |
| | 30 | ② Structure of upper extremity | 2 | 1 | 1 | | |
| | 50 | ② Structure of lower extremity | 2 | 1 | 1 | | |
| | 60 | ② Structure of trunk | | | | 1 | |
| | 70 | ② Additional musculoskeletal structures related to movement | 1 | 1 | 1 | 5 | |
| S8 | | ① Skin and related structures | | | | | |
| | 10 | ② Structure of areas of skin | 5 | 5 | 2 | 1 | |
| | 40 | ② Structure of hair | | | | 1 | |

*Numbers correspond to the number of items in the instrument that mapped to the corresponding ICF category. Categories from the third and fourth levels were carried up to the corresponding second-level categories.

**Table 3-C (Table 3 in Manuscript). Coverage by the OMERACT AAV Core Set of ICF components "Activities and Participation" (mapped to second-level categories)***

| ICF code | | ICF Category Description | BVAS | BVASv3 | BVAS/WG | VDI | SF-36 |
|---|---|---|---|---|---|---|---|
| D2 | | ① General tasks and demands | | | | | |
| | 30 | ② Carrying out daily routine | | | | | 2 |
| D4 | | ① Mobility | | | | | |
| | 10 | ② changing basic body position | | | | | 3 |
| | 30 | ② lifting and carrying objects | | | | | 2 |
| | 45 | ② hand and arm use | | | | | 2 |
| | 50 | ② walking | | | | | 3 |
| | 55 | ② moving around | | | | | 3 |
| D5 | | ① Self-care | | | | | |
| | 10 | ② Washing oneself | | | | | 1 |
| | 40 | ② dressing | | | | | 1 |
| D6 | | ① domestic life | | | | | |
| | 49 | ② household tasks, other specified and unspecified | | | | | 1 |
| D8 | | ① Major life areas | | | | | |
| | 50 | ② Remunerative employment | | | | | |
| | 59 | ② Work and employment, other specified and unspecified | | | | | 3 |
| D9 | | ① Community, social and civic life | | | | | |
| | 20 | ② Recreation and leisure | | | | | 5 |

*Numbers correspond to the number of constructs in the instrument that mapped to the corresponding ICF category. Categories from the third and fourth levels were carried up to the corresponding second-level categories.

## Table 3-D (Table 4 in Manuscript). Concepts from the AAV Core Set that could not be linked to specific ICF categories*

| ICF code | ICF category description | BVAS | BVASv3 | BVAS/WG | VDI | SF-36 | death |
|---|---|---|---|---|---|---|---|
| hc | Health condition | 0 | 0 | 0 | 4 Osteoporosis, asthma, diabetes, malignancy | | |
| nc-bf | Not covered (body functions) | 3 Sinus involvement, function of brain, cranial nerve palsy | 3 Sinus involvement, function of brain, cranial nerve palsy | 2 Sinus involvement, cranial nerve palsy | 1 Function of brain | | |
| nc - bs | Not covered (body structures) | 2 Sinus involvement (x2) | 1 Sinus involvement | 1 Sinus involvement | 2 Sinus involvement (x2) | | |
| nd | Not definable | 3 Persistent disease, new/worse disease | 1 Persistent disease | 6 Severe / limited disease, severe / limited flare, persistent disease, remission | 1 Complication | 12 General health, physical health, other | 1 |
| nd - bf | Not definable (body functions) | 1 Malaise | | | 1 Malignancy | | |
| nd - bs | Not definable (body structures) | | | | 4 Malignancy, minor / major(x2) tissue loss | | |

*Numbers correspond to the number of concepts in the instrument that mapped to the corresponding ICF category, with the concepts specified below. hc – health condition, nc – not covered, nd – not defined, bf – body functions, bs – body structures.

# Chapter 4 Areas of AAV considered important by the Clinicians

## 4.1 Objective

The objective of this sub-study was to identify ICF categories that are relevant to clinicians that are involved in the care of patients with AAV.

## 4.2 Methods

ICF categories considered relevant to AAV patients by clinicians were identified through the use of an email-based questionnaire. The questionnaire used for this study is the first of the 3 planned rounds of a Delphi exercise that was performed in order to obtain the "clinician perspective" list of ICF categories that will contribute to the eventual development of the ICF Core Sets for AAV. The aim of the steps 2 and 3 of the Delphi exercise is to narrow the initial list of ICF categories down to a smaller list of ICF categories that are considered most important by clinician. This list will then be considered for inclusion in the final list of ICF Core Sets for AAV. Because the aim of this sub-study is to capture the breadth of areas of AAV considered from different perspectives, the results of the initial open-ended questionnaire are used in this sub-study.

This study was approved by the Ottawa Hospital Research Ethics Board (protocol ID: 20120829-01H).

### 4.2.1 Identification of study participants

Clinicians from around the world, including physicians from relevant specialties (rheumatologists, nephrologists, respirologists, internists, immunologists and ear, nose and throat (ENT) surgeons) as well as allied health professionals with special interest in vasculitis were identified through consultation with the major vasculitis societies, including the Canadian Vasculitis Network (CanVasc), the Vasculitis Clinical Research Consortium (VCRC), and the European Vasculitis Study Group (EUVAS). In cases where the contact information of the potential participants was not

publicly available on the society website, the custodians of the corresponding society were contacted and asked to forward the invitation to the potential participants.

Identified clinicians were contacted via email with the invitation to participate in the study (see a copy of the invitation letter in Appendix D). To increase the number of potential participants, all clinicians who were contacted via email were asked to forward the email invitation to any other clinical experts that they believed would be appropriate for this study.

Clinicians who agreed to participate were asked to read the "Participant Information and Implied Consent" document which provided details about the study and outlined the procedure (see Appendix E for a copy of this document). Their response with the completed questionnaire constituted their consent to participate (this represents "implied" consent). The copy of the questionnaire sent to potential participants can be found in Appendix F.

### 4.2.2 Identification of ICF categories considered important to AAV patients by participating clinicians

The questionnaire administered to study participants was an open-ended questionnaire that provided a brief explanation of the meaning of each of the 4 ICF components ("body functions", "body structures", "activity and participation", and "contextual [personal and environmental] factors"), and then asked the participants to list up to 30 items they considered typical and/or relevant to patients with AAV for each ICF component (see Appendix F).

All items identified by each clinician who responded to the survey were then "linked" to the ICF according to the previously established ICF linkage rules (13, 14) and then summarized on the 2nd ICF level by replacing third- and fourth-level ICF categories with the overlying second-level category (see "Methods" section of Chapter 2 for a more detailed description of the linking process). The prevalence of identification (expressed as %) was calculated for each of the ICF categories; this represented the percentage of participating clinicians who identified at least one

item that linked to the corresponding ICF category. In addition, the 1st level summary prevalence of identification (expressed as %) was calculated in order to allow high-level comparison of relative prevalence of identification of various broad ICF categories by the clinical experts. As discussed in Chapter 2, in view of the fact that the classification of personal factors is at this point preliminary, detailed representation of the identified categories will be presented without regard to their "ICF level" in order to allow "re-classification" of the identified "personal factors", if necessary, at the time such classification is finalized. Additionally, the high-level summary prevalence of identification (expressed as %) will be calculated for the main categories in each of the broad "Parts" of personal factors in order to allow high-level comparison, as described above for the other ICF components.

## 4.3 Results

### 4.3.1 Study participants

Invitation to participate in the study was sent to 82 clinical experts from all continents: 28 from North America (5 from Canada, 3 from Mexico, 20 from USA), 12 from Central and South America (2 from Argentina, 1 from Brazil, 4 from Chile, 1 from Columbia, 1 from Ecuador, 1 from Guatemala and 2 from Peru), 19 from Europe (2 from Denmark, 1 from France, 1 from Germany, 1 from Italy, 1 from Netherlands, 2 from Spain, 2 from Sweden, and 9 from the United Kingdom), 16 from Asia (2 from China, 6 from Japan and 8 from Turkey), 6 from Australia

**Table 4-A. Demographic characteristics of clinicians**

| Characteristic | Number out of 27 respondents | Number out of 82 clinicians contacted |
|---|---|---|
| Geographic location | | |
| North America | 8 | 28 |
| Canada | 3 | 5 |
| Mexico | | 3 |
| USA | 5 | 20 |
| Central and South America | 3 | 12 |
| Argentina | | 2 |
| Brazil | 1 | 1 |
| Chile | 2 | 4 |
| Columbia | | 1 |
| Ecuador | | 1 |
| Guatemala | | 1 |
| Peru | | 2 |
| Europe | 10 | 19 |
| Denmark | 1 | 2 |
| France | | 1 |
| Germany | | 1 |
| Italy | | 1 |
| Netherlands | | 1 |
| Spain | 2 | 2 |
| Sweden | 1 | 2 |
| UK | 6 | 9 |
| Asia | 4 | 16 |
| China | | 2 |
| Japan | 1 | 6 |
| Turkey | 3 | 8 |
| Australia | 1 | 6 |
| New Zealand | 1 | 1 |
| Clinical designation | | |
| Rheumatologist | 14 | 35 |
| Nephrologist | 3 | 22 |
| Respirologist | 1 | 8 |
| ENT surgeon | 5 | 11 |
| Immunologist | 1 | 1 |
| Internist | 2 | 2 |
| Allied health professional | 1 | 3 |
| Years in practice | | |
| >0 - 5 | 3 | Not available |
| >5 - 10 | 3 | Not available |
| >10 - 15 | 5 | Not available |
| >15 - 20 | 7 | Not available |
| >20 - 30 | 5 | Not available |
| >30 | 4 | Not available |
| Cases of AAV seen per week | | |
| 0-2 | 9 | Not available |
| >2 - 5 | 9 | Not available |
| >5 - 10 | 3 | Not available |
| >10-20 | 5 | Not available |
| >20 | 1 | Not available |
| Cases of AAV seen in lifetime | | |
| 25-50 | 4 | Not available |
| >50 - 100 | 7 | Not available |
| >100 - 200 | 6 | Not available |
| >200 - 500 | 7 | Not available |
| >500 | 3 | Not available |
| Academic / non-academic | 25 / 2 | Not available |

and 1 from New Zealand. These clinicians belonged to a number of different clinical specialties, including 35 rheumatologists, 22 nephrologists, 8 respirologists, 11 ear, nose and throat surgeons, 2 internists, 1 immunologist and 3 allied health professionals.

The original invitation to participate was sent out on May 30, 2013. A reminder was sent out to those participants who did not reply to the original invitation on July 2, 2013 (12 responses were received by that time). A final reminder was sent out to the remaining potential participants on August 15, 2013 (26 responses were received by that time) with the warning that the study will close on August 31, 2013. One additional clinician responded by the study closing date, yielding a total of 27 participants. This produced the overall response rate of 33%. Table 4-A depicts demographic characteristics of the 82 clinicians who were invited to participate as well as 27 clinicians who participated.

### 4.3.2 ICF categories considered important for determining impact of AAV by participating clinicians

Clinicians involved in care of patients with AAV identified a large number of ICF categories as relevant to patients with AAV (see Tables 4-B, 4-C and 4-D). Overall, 51 2$^{nd}$-level categories were identified in the ICF component "body functions", 33 in "body structures", 46 in "activities and participation", and 32 in "environmental factors" (Table 4-B). Thirty seven categories were identified as important "personal factor" modifiers of the impact of AAV (Table 4-C).

Seven items linked to "health condition" group of categories ("asthma", "avascular necrosis", "depression", "diabetes", "malignancy", "obstructive sleep apnea", and "osteoporosis") in addition to being linked to the closest category in "body function" or "body structure" component. A number of concepts could not be linked to a specific ICF category and were considered as "not covered" or as "not definable" by the ICF. The "not covered" items included "diagnosis", "clinical research", "activities related to medical care", "environmental factors"

(environmental safety, information about disease and treatments, work environment, and living arrangement), items related to “body functions” (functions of the brain, spinal cord, cranial and peripheral nerves, functions of nose, paranasal sinuses, mucosa, and liver), and items related to “body structures” (sinus damage and retroperitoneal fibrosis). The identified “not definable” items included concepts related to stage of illness (“relapse”), the broad concept “physical health”, adverse events (including side effects of medications), “activities and participation” items (using technology, independence in activities), items related to “body functions” (bleeding, cyanosis, malignancy, tongue function), and items related to “body structures” (cyanosis, ENT disease, esthetical appearance, facial deformities, malignancy, mucosal disease, tissue loss, and cartilage damage). Table 4-D summarizes items that represented “health conditions” as well as the “not covered” and “not definable” items.

**Table 4-B. ICF categories identified as important in determining impact of AAV by clinicians – categories classified by the ICF**

| ICF code | | | ICF Category Description | Percent of participants[#] |
|---|---|---|---|---|
| **Body Functions** | | | | |
| B1 | | | Mental functions | ***85*** |
| | 14 | | Orientation functions | 7 |
| | 17 | | Intellectual functions | 22 |
| | 26 | | Temperament and personality functions | 48 |
| | 30 | | Energy and drive functions | 44 |
| | 34 | | Sleep functions | 37 |
| | 44 | | Memory functions | 11 |
| | 52 | | Emotional functions | 30 |
| | 64 | | Higher-level cognitive functions | 4 |
| | 67 | | Mental functions of language | 4 |
| | 80 | | Experience of self and time functions | 4 |
| B2 | | | Sensory functions and pain | ***96*** |
| | 10 | | Seeing functions | 81 |
| | 15 | | Functions of structures adjoining the eye | 11 |
| | 29 | | Seeing and related functions, other specified and unspecified | 7 |
| | 30 | | Hearing functions | 89 |
| | 35 | | Vestibular functions | 11 |
| | 50 | | Taste function | 11 |
| | 55 | | Smell function | 37 |
| | 65 | | Touch function | 15 |
| | 79 | | Additional sensory functions, other specified and unspecified | 26 |
| | 80 | | Sensation of pain | 63 |
| | 89 | | Sensation of pain, other specified and unspecified | 19 |
| B3 | | | Voice and speech functions | ***26*** |
| | 10 | | Voice functions | 22 |
| | 20 | | Articulation functions | 4 |
| | 40 | | Alternative vocalization functions | 7 |
| B4 | | | Functions of the cardiovascular, haematological, immunological and respiratory systems | ***100*** |
| | 10 | | Heart functions | 41 |
| | 15 | | Blood vessel functions | 7 |

| ICF code | | | ICF Category Description | Percent of participants[#] |
|---|---|---|---|---|
| | 20 | | Blood pressure functions | 44 |
| | 30 | | Haematological system functions | 41 |
| | 35 | | Immunological system functions | 15 |
| | 40 | | Respiratory functions | 93 |
| | 50 | | Additional respiratory functions (cough, hemoptysis) | 30 |
| | 55 | | Exercise tolerance functions | 19 |
| | 60 | | Sensations associated with cardiovascular and respiratory functions | 48 |
| B5 | | | Functions of the digestive, metabolic and endocrine systems | ***59*** |
| | | | > Functions of the digestive system | 26 |
| | 10 | | Ingestion function | 7 |
| | 15 | | Digestive functions | 7 |
| | 25 | | Defecation functions | 19 |
| | 30 | | Weight maintenance functions | 26 |
| | 40 | | General metabolic functions | 19 |
| | 45 | | Water, mineral and electrolyte balance functions | 11 |
| | 50 | | Thermoregulatory functions | 19 |
| | 55 | | Endocrine gland function | 22 |
| B6 | | | Genitourinary and reproductive functions | ***96*** |
| | 10 | | Urinary excretory functions | 96 |
| | 20 | | Urination function | 4 |
| | 40 | | Sexual function | 19 |
| | 60 | | Procreation functions | 33 |
| B7 | | | Neuromusculoskeletal and movement-related functions | ***67*** |
| | 10 | | Mobility of joint functions | 26 |
| | 29 | | Functions of the joints and bones, other specified and unspecified | 26 |
| | 30 | | Muscle power functions | 59 |
| | 98 | | Neuromusculoskeletal and movement-related functions, other specified | 11 |
| B8 | | | Functions of the skin and related structures | ***15*** |
| | 10 | | Protective functions of the skin | 4 |
| | 20 | | Repair functions of the skin | 4 |
| **Body Structures** | | | | |
| S1 | | | Structures of the nervous system | ***93*** |
| | 10 | | Structure of brain | 56 |

| ICF code | | | ICF Category Description | Percent of participants[#] |
|---|---|---|---|---|
| | 20 | | Spinal cord and related structures | 7 |
| | 30 | | Structure of meninges | 7 |
| | 40 | | Structure of sympathetic nervous system | 4 |
| | 50 | | Structure of parasypathetic nervous system | 4 |
| | 98 | | Structure of the nervous system, other specified | 81 |
| S2 | | | The eye, ear and related structures | ***96*** |
| | | | > Ear and related structures | 52 |
| | | | > Eye and related structures | 70 |
| | 10 | | Structure of eye socket | 44 |
| | 20 | | Structure of eyeball | 26 |
| | 30 | | Structures around eye | 22 |
| | 40 | | Structure of external ear | 26 |
| | 50 | | Structure of middle ear | 37 |
| S3 | | | Structures involved in voice and speech | ***100*** |
| | 10 | | Structure of nose | 100 |
| | 20 | | Structure of mouth | 30 |
| | 30 | | Structure of pharynx | 48 |
| | 40 | | Structure of larynx | 4 |
| S4 | | | Structures of the cardiovascular, immunological and respiratory systems | ***85*** |
| | 10 | | Structure of cardiovascular system | 48 |
| | 20 | | Structure of immune system | 7 |
| | 30 | | Structure of respiratory system | 85 |
| S5 | | | Structures related to the digestive, metabolic and endocrine systems | ***44*** |
| | | | > Structures related to the digestive system | 44 |
| | 10 | | Structure of salivary glands | 7 |
| | 40 | | Structure of intestine | 37 |
| | 50 | | Structure of pancreas | 4 |
| | 60 | | Structure of liver | 4 |
| | 70 | | Structure of gall bladder and ducts | 4 |
| S6 | | | Structures related to the genitourinary and reproductive systems | ***85*** |
| | 10 | | Structure of urinary system | 85 |
| | | 0 | Kidneys | 81 |
| | 30 | | Structure of reproductive system | 11 |

| ICF code | | | ICF Category Description | Percent of participants[#] |
|---|---|---|---|---|
| S7 | | | Structures related to movement | ***81*** |
| | 10 | | Structure of head and neck region | 7 |
| | 30 | | Structure of upper extremity | 52 |
| | 50 | | Structure of lower extremity | 56 |
| | 60 | | Structure of trunk | 41 |
| | 70 | | Additional musculoskeletal structures related to movement | 63 |
| | | 0 | Bones | 30 |
| | | 1 | Joints | 37 |
| | | 2 | Muscles | 26 |
| S8 | | | Skin and related structures | ***70*** |
| | 10 | | Structure of areas of skin | 70 |
| | 30 | | Structure of nails | 4 |
| | 40 | | Structure of hair | 11 |
| **Activities and Participation** | | | | |
| D1 | | | Learning and applying knowledge | ***26*** |
| | 10 | | Watching | 4 |
| | 15 | | Listening | 11 |
| | 66 | | Reading | 15 |
| | 70 | | Writing | 11 |
| D2 | | | General tasks and demands | ***52*** |
| | 10 | | Undertaking a single task | 4 |
| | 30 | | Carrying out daily routine | 44 |
| | 40 | | Handling stress and other psychological demands | 4 |
| D3 | | | Communication | ***11*** |
| | 30 | | Speaking | 7 |
| | 50 | | Conversation | 4 |
| | 60 | | Using communication devices and techniques | 7 |
| D4 | | | Mobility | ***59*** |
| | 10 | | Changing basic body position | 7 |
| | 15 | | Maintaining a body position | 4 |
| | 20 | | Transferring oneself | 7 |
| | 30 | | Lifting and carrying objects | 15 |
| | 40 | | Fine hand use | 11 |

| ICF code | | | ICF Category Description | Percent of participants[#] |
|---|---|---|---|---|
| | 45 | | Hand and arm use | 11 |
| | 50 | | Walking | 37 |
| | 55 | | Moving around | 19 |
| | 60 | | Moving around in different locations | 4 |
| | 70 | | Using transportation | 11 |
| | 75 | | Driving | 26 |
| D5 | | | Self-care | ***56*** |
| | 10 | | Washing oneself | 22 |
| | 30 | | Toileting | 11 |
| | 40 | | Dressing | 19 |
| | 50 | | Eating | 19 |
| | 60 | | Drinking | 11 |
| | 70 | | Looking after one's health | 41 |
| D6 | | | Domestic life | ***52*** |
| | 20 | | Acquisition of goods and services | 26 |
| | 30 | | Preparing meals | 19 |
| | 40 | | Doing housework | 30 |
| | 50 | | Caring for household objects | 26 |
| | 60 | | Assisting others | 30 |
| D7 | | | Interpersonal interactions and relationships | ***52*** |
| | 20 | | Complex interpersonal interactions | 4 |
| | 40 | | Formal relationships | 7 |
| | 50 | | Informal social relationships | 7 |
| | 60 | | Family relationships | 37 |
| | 70 | | Intimate relationships | 37 |
| D8 | | | Major life areas | ***78*** |
| | 30 | | Higher education | 4 |
| | 45 | | Acquiring, keeping and terminating a job | 11 |
| | 50 | | Remunerative employment | 74 |
| | 55 | | Non-remunerative employment | 4 |
| | 59 | | Work and employment, other specified and unspecified | 4 |
| | 70 | | Economic self-sufficiency | 4 |
| D9 | | | Community, social and civic life | ***85*** |

| ICF code | | | ICF Category Description | Percent of participants[#] |
|---|---|---|---|---|
| | 10 | | Community life | 15 |
| | 20 | | Recreation and leisure | 85 |
| | 30 | | Religion and spirituality | 11 |
| **Environmental Factors** | | | | |
| E1 | | | Products and technology | ***63*** |
| | 20 | | Products and technology for personal indoor and outdoor mobility and transportation | 11 |
| | 25 | | Products and technology for communication | 11 |
| | 35 | | Products and technology for employment | 7 |
| | 55 | | Design, construction and building products and technology of buildings for private use | 11 |
| | 65 | | Assets | 37 |
| | 98 | | Products and technology, other specified | 41 |
| | | | > Assistive products and technology | 33 |
| | | | > Medical products and technology required as part of medical treatment | 15 |
| E2 | | | Natural environment and human-made changes to environment | ***30*** |
| | 10 | | Physical geography | 19 |
| | 25 | | Climate | 4 |
| | 60 | | Air quality | 4 |
| | 98 | | Natural environment and human-made changes to environment, other specified | 7 |
| E3 | | | Support and relationships | ***93*** |
| | 10 | | Immediate family | 63 |
| | 20 | | Friends | 19 |
| | 25 | | Acquaintances, peers, colleagues, neighbours and community members | 7 |
| | 40 | | Personal care providers and personal assistants | 7 |
| | 50 | | Domesticated animals | 7 |
| | 55 | | Health professionals | 19 |
| | 98 | | Support and relationships, other specified | 19 |
| E4 | | | Attitudes | ***30*** |
| | 10 | | Individual attitudes of immediate family members | 15 |
| | 20 | | Individual attitudes of friends | 4 |
| | 25 | | Individual attitudes of acquaintances, peers, colleagues, neighbours and community members | 15 |
| | 30 | | Individual attitudes of people in positions of authority | 4 |

| ICF code | | | ICF Category Description | Percent of participants[#] |
|---|---|---|---|---|
| | 50 | | Individual attitudes of health professionals | 11 |
| | 60 | | Societal attitudes | 7 |
| E5 | | | Services, systems and policies | ***96*** |
| | 20 | | Open space planning services, systems and policies | 4 |
| | 30 | | Utilities services, systems and policies | 4 |
| | 35 | | Communication services, systems and policies | 4 |
| | 40 | | Transportation services, systems and policies | 4 |
| | 60 | | Media services, systems and policies | 4 |
| | 70 | | Social security services, systems and policies | 22 |
| | 80 | | Health services, systems and policies | 74 |
| | | 0 | Health services | 19 |
| | | 1 | Health systems | 67 |
| | | | > Access to care (financial including health insurance) | 59 |
| | | | > Access to care (excluding financial) | 33 |
| | | | > Access to care during travel | 7 |
| | | 3 | Health policies | 11 |
| | 90 | | Labour and employment services, systems and policies | 48 |
| | 98 | | Services, systems and policies, other specified | 4 |

*[#]Numbers represent % of respondents who identified at least one item in the corresponding category or its lower level subcategories; numbers in regular black font represent the % for the specific category, underlined numbers in bold and italics represent 1st level summary % (see text for description of how summary % was calculated)*

**Table 4-C. ICF categories identified as important in determining impact of AAV by clinicians – "personal factors"**

| ICF code | | | | ICF Category Description | Percent of participants[#] |
|---|---|---|---|---|---|
| P1 | | | | **Facts** | ***52*** |
| | 10 | | | Demographic characteristics | ***30*** |
| | | 0 | | Age | 11 |
| | | 1 | | Education level | 15 |
| | | 2 | | Gender/sex role | 7 |
| | | 3 | | Health literacy | 15 |
| | | 4 | | Occupation | 19 |
| | | 5 | | Race/ethnicity | 11 |
| | 20 | | | Personal history and biography | ***22*** |
| | | 0 | | Comorbidities | 22 |
| | 30 | | | Position in the immediate social and physical context | ***37*** |
| | | 0 | | Family | |
| | | | 0 | Marital status | 4 |
| | | | 1 | Family planning | 7 |
| | | 1 | | Economic | |
| | | | 0 | Socioeconomic status | 4 |
| | | | 1 | Income | 37 |
| | | | 2 | Financial independence | 4 |
| P2 | | | | **Experience** | ***41*** |
| | 20 | | | Thoughts and beliefs | ***41*** |
| | | 0 | | Attitude towards medical care | 4 |
| | | | 0 | Attitude to access to medical care | 4 |
| | | | 2 | Attitude to complementary medicine | 4 |
| | | | 3 | Interest in own health | 11 |
| | | | 5 | Attitude towards medications and other treatments | 11 |
| | | | 7 | Attitude towards physicians and other health care providers | 7 |
| | | 1 | | Psychological reaction to disease | |
| | | | 0 | Concern about appearance | 15 |
| | | | 5 | Effects of rare & "unknown" nature of disease | 4 |
| | | | 6 | Psychological effects of being physically unwell | 4 |
| | | 2 | | Disease becoming a constant threat | |

| ICF code | | | | ICF Category Description | Percent of participants[#] |
|---|---|---|---|---|---|
| | | | 0 | Worrying about body cues | 4 |
| | | | 6 | Effect of unpredictable / uncertain nature of disease | 4 |
| | 30 | | | Motives | ***11*** |
| | | 0 | | Need to reassess life goals due to limited abilities | |
| | | | 3 | Work / career ambitions | 7 |
| P3 | | | | **Patterns of experience and behavior** | ***78*** |
| | 10 | | | Habits | ***41*** |
| | | 0 | | Dietary habits | 11 |
| | | 1 | | Fitness | 4 |
| | | 2 | | Compliance with management | 30 |
| | | 3 | | Health behaviors | 11 |
| | | 4 | | Other habits (smoking, EtOH) | 26 |
| | 20 | | | Personality | ***52*** |
| | | 0 | | Effect of personality of impact of disease | 52 |
| | | | 0 | Positive attitude | 15 |
| | 30 | | | Adaptation to chronic illness | ***22*** |
| | | 0 | | Go on with life | 4 |
| | | 1 | | Attributing negative events to disease | 4 |
| | | 3 | | Search for explanation - why me? | 4 |
| | | 5 | | Strategies to facilitate adaptation | 11 |

[#]Numbers represent % of respondents who identified at least one item in the corresponding category or its lower level subcategories; numbers in regular black font represent the % for the specific category, underlined numbers in bold and italics represent summary % at the level of Parts and its major divisions (see text for description of how summary % is calculated)

**Table 4-D. ICF categories identified as important in determining impact of AAV by clinicians – health conditions, not covered and not definable factors**

| ICF code | ICF Category Description | Percent of participants[#] |
|---|---|---|
| **Health Conditions** | | |
| | Asthma | 19 |
| | Avascular necrosis | 15 |
| | Depression | 11 |
| | Diabetes | 11 |
| | Malignancy | 11 |
| | Obstructive sleep apnea | 7 |
| | Osteoporosis | 26 |
| **Not covered** | | |
| | Diagnosis (process) | 4 |
| | Clinical research | 4 |
| Nc-bf | Central nervous system function | 15 |
| | Brain function | 4 |
| | Cranial nerve palsy | 19 |
| | Spinal cord dysfunction | 4 |
| | Hepatic function | 4 |
| | Nasal functions | 15 |
| | Peripheral nerve function | 52 |
| | Sinus function | 4 |
| Nc-bs | Retroperitoneal space | 4 |
| | Sinuses | 52 |
| Nc-ap | Activities related to medical care | 19 |
| nc - env | Environmental safety | 7 |
| | Information about disease & drugs | 11 |
| | Work environment | 52 |
| | Living arrangement | 15 |
| **Not definable** | | |
| | General well-being | |
| | Physical health | 4 |
| | Stage of illness | 4 |
| | Flare / relapse | 4 |

| ICF code | ICF Category Description | Percent of participants[#] |
|---|---|---|
| | Treatment | |
| | Side effects from drugs (excluding prednisone) | 30 |
| | Side effects of prednisone | 26 |
| Nd - bf | Bleeding | 4 |
| | Cyanosis | 4 |
| | Malignancy | 11 |
| | Tongue function | 4 |
| Nd - bs | Cyanosis | 4 |
| | Esthetical appearance | 26 |
| | Face | 4 |
| | Malignancy | 11 |
| | Mucosa | 15 |
| | Tissue loss | 7 |
| | Cartilage | 4 |
| Nd - ap | Ability to do physical activity | |
| | Using / operating technology | 19 |
| | Other miscellaneous activities | 4 |
| | Independence in activities | 11 |

[#]Numbers represent % of respondents who identified at least one item in the corresponding category; *hc – health condition, nc – not covered, nd – not defined, bf – body functions, bs – body structures, ap – activities and participation, env – environmental factors.*

## 4.4 Descriptive analysis of results and discussion

Clinicians identified a wide range of ICF categories from each of the ICF components as relevant to determining the impact of AAV on patients. Generally the prevalence of identification of various "body functions" and "body structures" was relatively high while the majority of categories in ICF components "activities and participation" and "contextual factors" were identified relatively infrequently (see prevalence values for high level categories (in underlined bolded and italicised font) in Tables 4-B and 4-C.

Four out of 8 1st level "body function" categories (called ICF "chapters") and 5 out of 8 "body structures" chapters were identified by >80% respondents, and 3 chapters in each of these components were identified by >90% respondents. In contrast, only one of the nine chapters in ICF component "activity and participation" (namely "Community, social and civic life") was identified by 85% of respondents with majority being identified by <60%.

Contextual factors appear to be even less important to clinicians with the exception of the "environmental" chapters "Support and relationships" and "Services, systems and policies" each of which was mentioned by >90% of respondents; majority of remaining groups of contextual factors were mentioned by <40% of respondents. "Personal factors" were identified as relevant to determining the impact of AAV even less frequently, with the majority of individual categories identified by <20% of respondents. "Personal factors" that were identified more frequently were "comorbidities" (identified by 22%), income (37%), "compliance with management" (30%), "other habits" (26%) and "effect of personality on impact of disease" (52%). Even summarizing the individual personal factors on the highest level within each of the three individual "Parts" (see underlined bolded and italicised numbers in Table 4-C) reveals that majority of broad groups of personal factors were identified by <40% of respondents (the 2 exceptions are "Habits" identified by 41% and "Personality" identified by 52%).

Physicians have traditionally focused on managing diseases rather than considering patients and their health in the broad sense (23). Introduction and acceptance of the bio-psycho-social model of health and its' derivatives such as the ICF framework and the OMERACT Filter 2.0 framework (described in the Introduction and in the included Manuscript) resulted in gradual expansion of the role of clinical care to address the impact of the disease in the context of patient's surrounding environment and life circumstances (5). A large number of randomized controlled studies evaluate interventions to promote clinicians to employ a "patient-centred approach" to clinical care (23). As these interventions are applied in practice, increasing number of health professionals will be aware of the importance of factors other than the physiologic effects of disease in determining patient's function and general health.

## 4.5 Strengths and limitations of the study

The use of an email-based questionnaire allowed for considerable geographic breadth of the study population: clinical experts from 12 countries across all continents were included. Such geographic scope allowed for inclusion of specialists practicing in the setting of different types of medical systems and different economies, enhancing the external validity of the study. Furthermore, clinicians from a variety of different subspecialties that are routinely involved in the care of AAV were included, minimizing the bias that could result from the tendency of clinicians to identify aspects of AAV that are related to the area of their expertise.

Despite such variability, selection bias likely represents the main thread to validity in this study. Three sampling frames were used to recruit participants for this study: 1) the Vasculitis Clinical Research Consortium (VCRC), 2) the Canadian Vasculitis Network (CanVasc) and 3) the European Vasculitis Study Group (EUVAS). Although geographically broad, these sampling frames mainly focus on North American and European investigators, with a much smaller proportion of clinicians from other parts of the world. The geographic scope was enhanced by asking the potential participants to forward the invitation to the study to their colleagues in under-represented countries and in under-represented clinical specialties (which were specified). Additional selection bias was introduced by restricting the participants to those who read and write English, since the study description and the questionnaire were written in English. We did not feel that it was feasible to translate the questionnaire into different languages for the purpose of increasing geographic scope. Furthermore, the ICF classification is only available in English at this time.

Another consequence of the sampling frame representing large vasculitis societies is that the vast majority (25/27) of participants practice medicine in academic centres; majority of these clinicians are involved in clinical research in addition to their clinical practice. Such study sample will

likely bias the clinicians' perspective towards aspects of AAV that are relevant to the more severe cases of AAV that tend to be seen in tertiary academic centres, and influenced by the clinicians' involvement in research. At the same time, preferential selection of academic clinicians is necessary in order to ensure that clinical experts with sufficient experience in caring for patients with vasculitits are included in this study. AAV is a rare condition, and the vast majority of clinicians who do not specialize in this area will not have sufficient exposure to these cases to provide expert opinion. As a rule, specialty referral centres focus on clinical research in addition to clinical care, and thus the clinical experts tend to be researchers at the same time. Thus, while such selection bias limits the generalizability of these results to the tertiary care setting, such limitation is acceptable in view of AAV representing a rare condition the bulk of which is managed in academic centres that participate in clinical research.

Although the email-based approach used to gather clinician perspective allowed us to capture clinicians from a wide range of geographic locations, the approach has its limitations. Lack of the opportunity of face-to-face discussion or clarification of the details of the study could result in inaccurate or incomplete responses, if the participants did not completely understand the instructions or had limited amount of time to complete the questionnaire. Indeed, some returned questionnaires were rather brief with only few items provided for some of the ICF categories. Incomplete or incompletely accurate responses by the participants represent potential information bias that could in turn result in a threat to the study's internal validity.

Perhaps the main limitation of email-based approach to this study is the overall low response rate of 33%. Studies consistently show that although email-based surveys make survey administration logistically easier and allow for faster responses (24), they result in lower response rates compared to surveys conducted in-person or sent out by mail (24, 25). Reassuringly, the

response rate observed in this study is consistent with the reported rates for email-based questionnaires of 30-40% (24-26). These numbers were also supported by a meta-analysis (26) of 68 web-based surveys that showed the overall mean response rate of 39.6% for all surveys and 34.6% for the 56 surveys with complete data. Interestingly, the same meta-analysis (26) found a number of predictors of enhanced response rates, the most significant of which were the number of contacts of the candidate participants, using personalized contacts and pre-contacting the candidates preparing them for the study. Although the candidates were not pre-contacted in this study, a total of 3 reminders were sent to the non-respondents, with the last reminder addressing the candidates by name (thus being personalized). Notably, for several countries none of the several contacted clinicians responded to the survey; specifically 1 non-responding clinician was contacted in each of Columbia, Ecuador, Guatemala, France, Germany, Italy and Netherlands, 2 in Argentina, Peru and China and 3 in Mexico. Because of the small number of clinicians who were contacted in each of these non-responding countries (1 to 3) and because of the large number of countries that were contacted, the conclusion that the underrepresentation of the above named countries represents a systematic bias cannot be made. Once again, it is important to note that despite the low response rate to the clinician online survey, the resulting sample contains representatives from all continents and from each of the contacted clinical subspecialty (rheumatology, nephrology, pulmonology, ear nose and throat surgery, immunology, internal medicine and allied health specialties).

# Chapter 5 Areas of AAV important to patients

## 5.1 Objective

The objective of this sub-study was to identify ICF categories that are relevant to patients with AAV through the use of qualitative research approach.

## 5.2 Background

### 5.2.1 Qualitative approach

A number of qualitative approaches exist to allow selection of the appropriate research strategy for a qualitative study depending on its goal. This qualitative study borrows its' main characteristics from the phenomenological approach (27) because of its primary aim to explore personal experiences of patients living with AAV; however, 2 notable adaptations to the traditional phenomenological research design were employed. First, this study did not focus as much on the cognitive "essence" of participants' experience typical for phenomenological studies but more on the "facts" of what constitutes the effects of the disease and what are the significant modifiers of such effects. Secondly and related to the first adaptation, a structured ICF classification system was used to describe the results in this study in contrast to the usual exploratory way of identification of themes based on the collected information in the typical phenomenological qualitative studies (27). As these modifications add structure to the process of data collection and data analysis, we expect the results of this study to also be more structured and perhaps somewhat less subjective that those that would come from the more traditional qualitative studies.

### 5.2.2 Methods of qualitative data collection

Two broad types of qualitative data collection strategies exist – observations and interviews (27); a number of specific approaches exist for each. This study makes use of the two most commonly employed types of interviewing strategies, namely individual interviews and focus groups.

Individual semi-structured interviews are informal discussions between an interviewer and a patient that are frequently used in health care research (28). These interviews are guided by a variable number of leading questions posed by the interviewer (called "prompts") that set the direction for the discussion, but they allow the participant to divert the discussion and elaborate on various topics he or she considers relevant (28). The relatively flexible design of semi-structured interviews allows identification of areas that are of importance to the participants, and the private one-on-one setting allows in-depth probing of themes that could be difficult for patients to discuss in presence of other participants.

Focus groups are group discussions that usually involve one facilitator and a variable number of participants (most commonly 4-6) (28). Similar to semi-structured interviews, focus groups are frequently guided by a series of questions that are posed by the facilitator; the participants are then encouraged to have a free discussion on each of the posed topics amongst themselves. Focus groups tend to produce a less in-depth but broader type of information compared to individual interviews.

### 5.2.3 Qualitative sampling strategy

The effect of a medical condition on patients is dependent on a number of characteristics such as the nature of the specific medical condition, its severity and duration, patient's demographic characteristics and social support network (29). In order to capture the range of effects of the medical condition, the study population should be representative of the studied population with respect to these important characteristics. In quantitative studies this can be achieved through randomization, stratification, or adjusting on the important modifiers (called confounders). These methods are not applicable to qualitative studies. Furthermore, achieving breadth of the sample size is not always desirable in typical qualitative studies that often aim to obtain an in-depth view of the experience of a relatively small group of individuals (27). As

discussed above, this study represents a modification to qualitative approach – it employs qualitative interviews but aims to gather factual information that ideally should be representative of all patients with AAV (to the extent possible in a relatively small study). Consequently, a sampling strategy that would achieve sufficient breadth of the study population that is to be studied qualitatively was desired. To achieve this goal one could aim to maximize variation on characteristics that are most likely to affect the outcome (30). The most important potential modifiers of the effect of AAV based on previous studies and the clinical experience of investigators of this study are the specific type of AAV (i.e. GPA, EGPA, and MPA) (31), duration of disease (that was grouped into <2 years or >= 2 years) as well as patient's age, sex, and country of residence (32).

In order to actively select the most productive sample to answer the research question (30), purposive sampling strategy was used to select study participants (27). To facilitate purposive recruitment a purposive sampling grid that reflected the most important modifiers of the impact of AAV (discussed above) was designed (the sampling grid can be seen in Appendix J). Using the sampling grid, patients with characteristics that would ensure homogeneous distribution of subjects between the different cells of the purposive sampling grid were preferentially sought and recruited.

### 5.2.4 Assessing saturation

US Department of Health and Human Services Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH) have developed standards for research in the area of patient-reported outcomes (PRO) (33); these include recommendations for methods of conducting qualitative research. The guidelines stress the importance of "saturation" – point when additional research no longer provides useful information (30). Qualitative research in the field of

outcome measures is expected to 1) be designed to achieve saturation, and 2) assess and document saturation when reporting the study (30).

A paper by Guest et al (34) describes a thorough systematic approach to documenting saturation. The authors suggest developing a structured codebook that represents a systematic way of assigning thematic codes to statements extracted from patient interviews. As new themes arise with sequential interviews, the codebook is updated. Thorough documentation of the process of codebook development will allow determination of saturation – the point when no new codes are added and the definitions of the existing codes are not modified with subsequent interviews. The saturation table is a visual way of representing the process of codebook development that allows assessment of saturation. The most commonly used version of the saturation table lists the codebook themes in the rows and individual interviews in the columns, and indicates the first appearance of each theme in the individual cells (30). In this kind of saturation table, the point of saturation is judged to occur when no new themes are identified and the definitions of the existing codes are not modified with subsequent interviews.

In this study we will employ the general approach to assessing and documenting saturation described by Guest (34), with one important modification – we are using the ICF classification instead of the more traditional thematic codebook. We feel this modification is appropriate because of the structured nature of the ICF and the relatively stringent and well-defined rules for mapping of the thematic concepts to the categories in the ICF classification (13, 14). We will use the saturation table to document saturation, with the 2$^{nd}$-level ICF categories listed in the rows and individual interviews listed in the columns.

### 5.2.5 Estimating sample size

The concept of "saturation" described above is closely related to sample size – the sample size of a qualitative study in the field of outcome measure development needs to be sufficiently large to achieve the point of saturation (30). This would imply that the sample size can only be determined at the end of the study; in practice, it is important to be able to estimate the sample size at the planning stage of the study in order to estimate time and resources required for the study.

A number of investigators have attempted to develop strategies for predicting sample size in qualitative research, and for individual interviews this varies between 1 and 200 depending on the objective of the study, the qualitative approach used and the heterogeneity of study subjects (30). The paper by Guest et al used a systematic approach to study the subject of sample size in qualitative research (34). They conducted sequential interviews (eventually reaching a sample size of 60) and used various techniques for assessing saturation after each group of 5 sequential interviews. The authors concluded that regardless of the specific technique used for assessing saturation, data saturation had mostly occurred by the $12^{th}$ interview and recommended that the sample size of 12 be used for individual interviews that aim "to understand common perceptions and experiences among a group of relatively homogeneous individuals" (30). As this appears to be a practical approach that matches the needs of this study, we chose to perform 12 interviews.

Naturally the sampling strategy (described in section 5.2.3) has consequences for the sample size that is needed to achieve saturation (30). Using "purposive sampling" with aim of ensuring variability in the spectrum of certain characteristics (described above) implies that the study sample will display some level of heterogeneity. Thus, it is likely that 12 interviews, while sufficient for most "relatively homogeneous" populations, will not be enough to achieve saturation in our population of patients with AAV. Being aware of this issue, we chose to start with 12

interviews and after analyzing the results to perform additional interviews as necessary to achieve saturation.

## 5.3 Methods

### 5.3.1 Overview

Patients' perspective of relevant areas of AAV was obtained through a combination of a series of individual semi-structured interviews performed at the Ottawa Hospital in Ottawa, Canada and at the Nuffield Health Sciences Centre in Oxford, United Kingdom (UK), as well as 2 patient focus groups performed at Boston University School of Public Health in Boston, Massachusetts, United States of America (USA).

This study was conducted in collaboration with the international project titled "Patient-Reported Outcome (PRO) development for ANCA Associated Vasculitis Study Collaboration" (will be referred to as AAV PRO project for the purpose of simplicity). The final aim of the collaborating project was to develop a vasculitis-specific measure of PRO (22). The initial stage of that project involved a series of individual qualitative interviews that had the same purpose as the "patient perspective" part of this project, namely to determine the impact of AAV on patients' overall health and HRQoL. To broaden the scope of the captured patient perspective for the AAV PRO project, the patient perspective part of the project described in this thesis (conducted in Ottawa, Canada) became one of the 3 participating sites in the AAV PRO project (the other 2 sites being the Nuffield Health Sciences Centre in Oxford, United Kingdom (UK) and the University of Pennsylvania, United States of America (USA)). Common interview prompts were used for the individual interviews performed at each of the three sites (the interview script can be found in Appendix H), and the anonymous transcripts were shared securely by the participating centres. Selected interviews performed as part of the AAV PRO project at Oxford, UK were used for this study (see below for details).

In addition, 2 pilot focus groups were performed during the planning stage of the AAV PRO project at the Boston University School of Public Health in Boston, USA. These were performed

before the collaboration between this project and the AAV PRO project was established, and as a result the focus groups had a different set of prompts from those used in this study (Appendix I contains the scrip for the focus groups). Furthermore, as the patients participating in these focus groups did not consent to allow sharing of the focus group transcripts with the investigators of this project, the summary of the focus groups (created by the investigators of this "pilot" AAV PRO project) as opposed to the original transcripts was used for this project. The general purpose of the focus groups was similar to that of this study, namely to assess the impact of AAV on patients. Thus despite the use of different focus group prompts the information gathered at the focus group discussions was directly relevant to this study and was included in order to broaden the patient perspective of the impact of AAV on function and overall health.

This study (including its collaboration with the AAV PRO project) received the approval of the Ottawa Hospital's Research Ethics Board (protocol # 20120604-01H).

### 5.3.2 Recruitment of participants and data collection

#### *5.3.2.1 Recruitment and data collection for individual interviews performed in Ottawa, Canada*

A convenience sample of patients attending rheumatology clinics at the Ottawa Hospital's Arthritis Centre was used for recruitment of patients for individual interviews. Rheumatologists practicing at the arthritis centre were approached with an invitation to recruit their patients to the study (see a copy of the letter to physicians in Appendix K).

Patients were eligible for enrolment into the study (as well as into the collaborating AAV PRO study) if they satisfied all 3 of the following criteria:

1) Were ≥ 18 years old;

2) Had the diagnosis of one of the AAV, namely Granulomatosis with Polyangiitis (GPA), Microscopic Polyangiitis (MPA), or eosinophilic GPA (EGPA), satisfying either the 1990 American

College of Rheumatology (ACR) classification criteria (35, 36), the 1994 Chapel Hill Consensus Conference (CHCC) definitions for vasculitides including MPA (37), or the 2012 revised International CHCC Nomenclature definitions for vasculitides (1); and

3) Had sufficient knowledge of English language to be able to participate in an interview conducted in English.

Potentially eligible patients were identified by their treating rheumatologists during their medical visits and invited to participate in the study. Interested patients received the "Participant Information and Consent Form" (see Appendix L for a copy of this form). Patients who agreed to participate notified Dr. Nataliya Milman (NM) of their intentions. NM then contacted the patients and took them through the formal consent process that included explaining the details of the study and answering any questions, and individual interviews were scheduled with the interested patients. All individual interviews at the Ottawa Hospital (Ottawa, Canada) were performed by NM. As subsequent interviews were taking place, the purposing sampling grid was filled out and further recruitment was directed towards the specific groups of patients who were not represented by the accumulated patient sample.

In-depth semi-structured interviews lasting between 30 and 60 minutes were conducted with the study participants in the conference room of the Ottawa Hospital's Arthritis Centre. The aim of the interviews was to assess the impact of AAV on patient's function and general health addressing the various ICF components: impairment of body functions and body structures, limitations in activities, restrictions in participation, and relevance of contextual factors including environmental and personal factors. The interviews started in an open-ended fashion, asking the participants to describe the course of their AAV and ways in which AAV affected their lives. Patients were prompted to elaborate on relevant topics and to provide clarification where necessary.

Interview prompts (the script for which can be found in Appendix H) were then used to cover the specific questions of importance that were not covered by the preceding discussion. Interviews were recorded with a tape-recorder with patients' permission.

#### *5.3.2.2 Recruitment and data collection at other sites*

Recruitment of participants and data collection for individual semi-structured interviews performed as part of the collaborating AAV PRO project in Oxford, UK and in Philadelphia, USA was similar to that described above for Ottawa, Canada. Briefly, this involved recruiting patients who satisfied eligibility criteria (same as described for Ottawa site) from the convenience sample of the outpatient rheumatology clinics at each of the participating sites. Each of the 2 sites obtained their local ethics approval for their study and for the collaboration with the study described in this thesis. The procedure for recruitment at the 2 sites was also similar to that described for Ottawa, but each site had their own version of the "Participant Information and Consent" form approved by their local ethics board. As discussed above, the same interview prompts were used to facilitate the semi-structured interviews at the 2 sites of the collaborating AAV PRO project resulting in collection of the same type of information. Interviews performed at Oxford and Philadelphia were recorded with permission of the participants, as described for Ottawa.

In addition to conducting the individual semi-structured interviews the experience obtained from 2 focus groups performed during the "piloting" stage of the collaborating AAV PRO project was incorporated into this study in order to maximize the breadth of coverage of the patient perspective. Similar to the recruitment strategy at the 3 sites performing individual interviews, the participants for the focus groups represented a convenience sample of patients who attended the outpatient rheumatology clinics at the Boston University School of Public Health and satisfied the inclusion criteria (which were the same as those described for Ottawa). As discussed above, these focus groups used different prompts to facilitate their discussions (the script for the focus groups

can be found in Appendix I), and the summary of the focus groups (created by an investigators of the "piloting" AAV PRO project) as opposed to the original transcripts was used for this project because the focus group participants did not consent to sharing the transcripts of the focus groups.

### 5.3.3 Data analysis

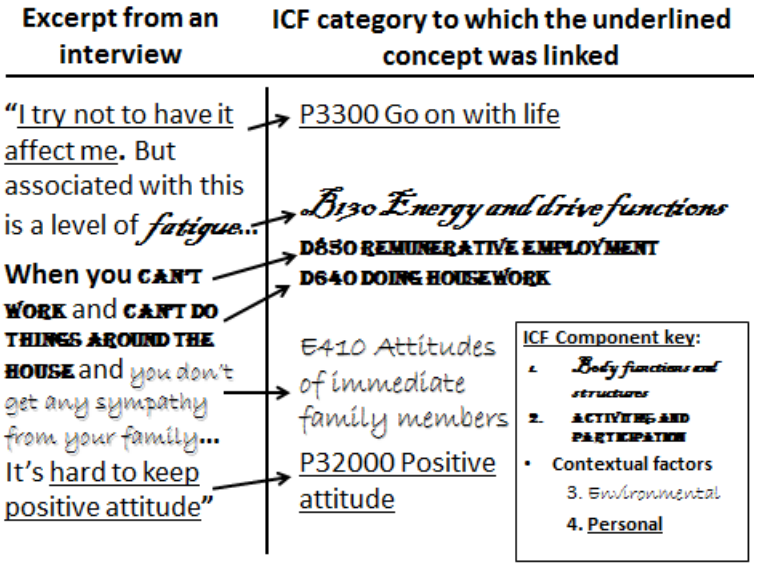
Tape-recordings of the first 3 interviews performed in Ottawa were transcribed by NM, and then professional transcription services (with subsequent proofreading by NM) were used to transcribe subsequent interviews done in Ottawa as well as all interviews performed as part of the collaborating AAV PRO project (the site investigators for each of the other sites performed the proofreading for their corresponding transcripts). The verbal transcripts were then reviewed in detail, and all meaningful statements were identified. For the purpose of this analysis, a meaningful statement was defined as the smallest excerpts of text that has independent meaning relevant to the purpose of this study. Then, basic concepts each pertaining to one impairment of a body function or structure, limitation in activities or restrictions in participation, or a relevant contextual factor (environmental or personal) were identified and "linked" to the most precise ICF category according to the previously established ICF linking rules (13, 14) (see the "Methods" section of Chapter 2 for a more detailed description of the linking process).

Because the summary of the pilot focus groups was used, it was not possible to separate results obtained from each individual focus group. Thus, the summary of the focus groups was analyzed as a whole using the same approach as described above for individual interviews. Consequently, the results obtained from analysing the 2 focus groups are presented as a single "observation" similar to how results obtained from each individual interview are presented.

The identified ICF categories from components "body functions", "body structures", "activities and participation", and "environmental factors" were summarized on the 2$^{nd}$ ICF level by

replacing third- and fourth-level ICF categories with the overlying second-level category, while "personal factors," "health conditions" as well as "not covered" and "not definable" categories were presented in detail as identified. Also similar to what was done for the clinicians' perspective (Chapter 4), prevalence of identification (expressed as % out of total number of individual interviews) was calculated for each of the identified categories. Figure 6 provides an example of analysis of a short segment of a study interview.

**Figure 6. Example of ICF-based analysis of a short extract from a patient interview**




### 5.3.4 Comparing identified categories by country of origin or by specific diagnosis

To look for differences by country of origin, we compared (descriptively) categories identified by patients interviewed in Ottawa, Canada to those identified in Oxford, UK and in Boston, USA. Specifically we looked for categories that were either identified by the majority (at least 70%) of individually interviewed patients from one particular country but by none of the patients (individually interviewed or participating in a focus group) from any other country, or for categories identified during the focus groups conducted in USA but not identified by any of the patients interviewed in Canada or the UK (no individual interviews conducted in USA were included in this study).

Similarly, we performed descriptive analysis to look for differences by the specific diagnosis (GPA, EGPA and MPA). As for the comparison by country of origin, we looked for categories that were identified by the majority (at least 70%) of individually interviewed patients with the specific diagnosis but by none of the individually interviewed patients with any of the other 2 diagnoses. Because the focus groups contained a mixture of patients with 2 of the 3 types of AAV (GPA and EGPA) and because we were not able to separate the data available to us by the specific diagnosis, focus groups were excluded from the analysis by the specific diagnosis.

## 5.4 Results

### 5.4.1 Patient demographics

Twelve individual interviews (10 done in Ottawa, Canada and 2 done as part of the collaborating AAV PRO project in Oxford, UK) and 2 focus groups including a total of 9 patients were included in this study. Table 5-A summarizes the demographic characteristics of the participants of the individual interviews and the focus groups.

**Table 5-A. Demographic characteristics of patients participating in individual interviews and focus groups**

| Demographic characteristic | | Individual interviews (out of 12) | Focus groups (out of 9) |
|---|---|---|---|
| Female / Male | | 7 / 5 | 4 / 5 |
| Age at time of diagnosis | | | |
| | 18 - <40 | 2 | 3 |
| | 40 - <60 | 4 | 6 |
| | 60 + | 6 | 0 |
| Age at time of interview | | | |
| | 18 - <40 | 1 | 1 |
| | 40 - <60 | 2 | 7 |
| | 60+ | 9 | 1 |
| Geographic location | | | |
| | Canada | 10 | |
| | UK | 2 | |
| | USA | | 9 |
| Working at the time of diagnosis | | 8 | N/A |
| Working at the time of interview | | 4 | N/A |

*Numbers in the cells contain number of patients; UK United Kingdom; USA United States of America, N/A information not available*

Table 5-B depicts the resulting purposive sampling grid for patients who participated in the 12 individual interviews and the 2 focus groups.

After having conducted 10 interviews on patients recruited at the Ottawa Hospital we had a significant under-representation of patients with MPA, which is the rarest of the 3 AAVs. In order to speed up the process of patient recruitment and also to diversify the geographic origin of the study patient population we used transcripts from 2 individual interviews that were performed as part of the collaborating AAV PRO project at the Nuffield Health Sciences Centre in Oxford, UK (1 with recent and 1 with distant diagnosis of MPA). Notably, these 2 interviews represented the only 2 patients with MPA in the study sample of the Oxford group of investigators of the AAV PRO project, highlighting the rare nature of this diagnosis.

**Table 5-B. Purposive sampling grid for individual patient interviews**

| | **GPA**<br>Age/Gender(ID) | **MPA**<br>Age/Gender(ID) | **EGPA**<br>Age/Gender(ID) |
|---|---|---|---|
| Disease duration <2 years | 61/F/(I9_Ot)<br>51/M(Fo1)<br>43/M(Fo2) | 70/F(I12_Ox) | 47/M/(I3_Ot) |
| Disease duration >2 years | 64/M(I1_Ot)<br>64/M(I4_Ot)<br>63/M(I6_Ot)<br>32/F(I7_Ot)<br>57/F(I8_Ot)<br>65/M(Fo3)<br>54/F(Fo7)<br>65/F(Fo8) | 73/F(I10_Ot)<br>83/M(I11_Ox) | 68/F(I2_Ot)<br>63/F(I5_Ot)<br>45/M(Fo4)<br>50/F(Fo5)<br>42/M(Fo6)<br>30/F(Fo9) |

*GPA: granulomatosis with polyangiitis; MPA: microscropic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; age = age at time of interview; gender: F = female, M = male; ID = unique study identifier; identifiers starting with "Fo" indicate focus group participants (all from Boston, USA); identifiers starting with "I" indicate participants of individual interviews - prefix "Ot" for patients interviewed in Ottawa, Canada and "Ox" for patients interviewed in Oxford, United Kingdom; underlined entries indicate patients with active disease at the time of interview.*

### 5.4.2 Areas of AAV identified as important by patients with AAV

A large number of ICF categories covering each of the ICF components were identified as important by the study participants. All ICF categories identified by patients as relevant in determining the impact of AAV are listed in the Tables 5-C, 5-D and 5-E. Table 5-C depicts the classified ICF components ("body functions", "body structures", "activities and participation", and "environmental factors"); Table 5-D depicts "personal factors" and Table 5-E contains "health conditions", "not covered" and "not definable" categories. The first 12 columns of each table represent the sequential 12 individual interviews (first 10 performed in Ottawa, Canada and the last 2 in Oxford, UK), column 13 contains combined results from the 2 focus groups performed in Boston, USA; the last column of each of the three tables displays the prevalence of identification (expressed as % of total number of individual interviews) for each of the identified ICF categories.

Overall, 42 second level categories in the ICF component “body functions”, 18 “body structures”, 40 “activities and participation”, and 34 “environmental factors” were identified by patients as relevant for determining the impact of AAV. Sixty two categories were identified as important “personal factor” modifiers of the impact of AAV by the participating patients.

Eight items linked to “health condition” group of categories (“asthma”, “avascular necrosis”, “depression”, “diabetes”, “infections”, “malignancy”, “osteoarthritis ”, and “Raynaud’s syndrome”) in addition to being linked to the closest category in “body function” or “body structure” component. A number of concepts could not be linked to a specific ICF category and were considered as “not covered” or as “not definable” by the ICF. The “not covered” items included the process of “diagnosis” and “clinical research”, “activities related to medical care”, “environmental factors” (information about disease and treatments, living arrangement, stress, and work environment), “body functions” (functions of the gallbladder, nose, sinuses, and mucus production) and “ body structures” (sinus damage); the “not definable” items included concepts related to stage of illness (relapse, remission, and stable disease), broad concepts related to general well-being (“mental / psychological health”, “physical health”, and “health-related quality of life”), concepts related to treatment (effects of treatments and side effects), “activities and participation” items (ability to do physical activity, independence in activities, planning for future, and using/operating technology), and “infections” (which represent both “body functions” and “body structures”).

**Table 5-C. ICF categories identified in patient focus groups and individual interviews - classified ICF components**

| ICF Code | | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Body Functions** | | | | | | | | | | | | | | | | |
| B1 | | Mental functions | | | | | | | | | | | | | | |
| | 10 | Consciousness functions | | | | | | | | √ | | √ | | √ | | 33 |
| | 26 | Temperament and personality functions | | | √ | | | √ | √ | √ | √ | | √ | √ | √ | 58 |
| | 30 | Energy and drive functions | √ | | | | √ | √ | √ | √ | √ | √ | √ | √ | √ | 75 |
| | 34 | Sleep functions | √ | | √ | √ | √ | | √ | √ | | | √ | √ | √ | 67 |
| | 47 | Psychomotor functions | | √ | | | | | | | | | √ | | √ | 8 |
| | 52 | Emotional functions | | | √ | | | | √ | √ | √ | √ | √ | | √ | 50 |
| | 80 | Experience of self and time functions | | √ | | | √ | | √ | √ | √ | | √ | | √ | 42 |
| B2 | | Sensory functions and pain | | | | | | | | | | | | | | |
| | 10 | Seeing functions | | | | | | | | √ | √ | | | | | 16 |
| | 15 | Functions of structures adjoining the eye | | | | | | | √ | | | | | | | 8 |
| | 20 | Sensations associated with the eye and adjoining structures | | | | √ | | | | | | | √ | | √ | 8 |
| | 30 | Hearing functions | √ | | | √ | √ | | √ | √ | √ | | √ | | √ | 50 |
| | 40 | Sensations associated with hearing and vestibular function | | | | | | | √ | | √ | | √ | | √ | 16 |
| | 50 | Taste function | | | | | | | | √ | | | | | | 8 |
| | 55 | Smell function | | | | | | | √ | √ | | | | | | 16 |
| | 79 | Additional sensory functions, other specified and unspecified | | | | | | | | | | | √ | √ | √ | 16 |
| | 80 | Sensation of pain | √ | √ | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | 92 |
| B3 | | Voice and speech functions | | | | | | | | | | | | | | |
| | 10 | Voice functions | | √ | | | | | | √ | | | √ | | √ | 16 |

| ICF Code | | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B4 | | Functions of the cardiovascular, haematological, immunological and respiratory systems | | | | | | | | | | | | | | |
| | 10 | Heart functions | | | √ | | | | | | | | | | | 8 |
| | 15 | Blood vessel functions | | | | | | | | | | | | √ | | 8 |
| | 20 | Blood pressure functions | | | | √ | | | | | | | | | | 16 |
| | 30 | Haematological system functions | | | | | | | | | | √ | | | | 16 |
| | 35 | Immunological system functions | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | 92 |
| | 40 | Respiratory functions | √ | √ | √ | √ | | √ | √ | √ | √ | √ | √ | | √ | 82 |
| | 49 | Functions of the respiratory system, other specified and unspecified | | √ | | √ | | | √ | | | | | | | 25 |
| | 50 | Additional respiratory functions | √ | √ | √ | √ | | | | √ | √ | | √ | √ | √ | 58 |
| | 55 | Exercise tolerance functions | √ | | √ | √ | √ | | | √ | √ | √ | √ | | √ | 58 |
| | 60 | Sensations associated with cardiovascular and respiratory functions | | √ | √ | √ | | √ | √ | √ | √ | √ | √ | | √ | 67 |
| | 69 | Additional functions and sensations of the cardiovascular and respiratory systems, other specified and unspecified | | | | | | | | | | | √ | | √ | 0 |
| B5 | | Functions of the digestive, metabolic and endocrine systems | | | | | | | | | | | | | | |
| | 10 | Ingestion function | | | | | | | √ | | | | | | | 16 |
| | 15 | Digestive functions | | | | | | | √ | | | | | | | 16 |
| | 30 | Weight maintenance functions | | | | √ | √ | √ | √ | √ | √ | | √ | √ | √ | 67 |
| | 35 | Sensations associated with the digestive system | | | | | √ | | | | √ | | | | | 16 |
| | 40 | General metabolic functions | | | | | | | | | | | √ | | √ | 8 |

| ICF Code | | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 45 | Water, mineral and electrolyte balance functions | | √ | | √ | | | | | √ | √ | √ | | √ | 42 |
| | 50 | Thermoregulatory functions | | | | | | √ | | | | √ | | | | 16 |
| | 55 | Endocrine gland function | | | | | | | √ | | | | | | | 8 |
| B6 | | Genitourinary and reproductive functions | | | | | | | | | | | | | | |
| | 10 | Urinary excretory functions | | √ | | √ | | | √ | √ | √ | √ | √ | √ | √ | 67 |
| | 60 | Procreation functions | | | | | | | √ | | | | | | | 8 |
| B7 | | Neuromusculoskeletal and movement-related functions | | | | | | | | | | | | | | |
| | 10 | Mobility of joint functions | √ | √ | | | √ | √ | | | √ | | | | | 42 |
| B8 | | Functions of the skin and related structures | | | | | | | | | | | | | | |
| | 10 | Protective functions of the skin | | √ | | √ | | | | | | | | | | 16 |
| | 20 | Repair functions of the skin | | √ | | √ | | | | | | | | | | 16 |
| | 40 | Sensation related to the skin | | | | | | | | | | | | √ | | 8 |
| **Body Structures** | | | | | | | | | | | | | | | | |
| S1 | | Structures of the nervous system | | | | | | | | | | | | | | |
| | 30 | Structure of meninges | | | | | | | | | | | √ | | √ | 0 |
| S2 | | The eye, ear and related structures | | | | | | | | | | | | | | |
| | 20 | Structure of eyeball | | | | √ | | √ | | √ | √ | | | | | 33 |
| | 30 | Structures around eye | | | | | | | √ | | | | | | | 8 |
| | 40 | Structure of external ear | | | | | | | 1 | | | | | | | 8 |
| | 50 | Structure of middle ear | √ | | | √ | √ | | | | | | √ | | √ | 25 |
| S3 | | Structures involved in voice and speech | | | | | | | | | | | | | | |
| | 10 | Structure of nose | | √ | | √ | √ | √ | √ | √ | | √ | √ | √ | √ | 67 |
| | 20 | Structure of mouth | | | | | | √ | | | | | | | | 8 |

| ICF Code | | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S4 | | Structures of the cardiovascular, immunological and respiratory systems | | | | | | | | | | | | | | |
| | 10 | Structure of cardiovascular system | √ | | | | | | | | | √ | | √ | | 25 |
| | 30 | Structure of respiratory system | √ | √ | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | 83 |
| S5 | | Structures related to the digestive, metabolic and endocrine systems | | | | | | | | | | | | | | |
| | 50 | Structure of pancreas | | | | | | | | | | | | √ | | 8 |
| | 60 | Structure of liver | | | | | | | | | | | | √ | | 8 |
| | 70 | Structure of gall bladder and ducts | | | | | | | | √ | | | | | | 8 |
| S6 | | Structures related to the genitourinary and reproductive systems | | | | | | | | | | | | | | |
| | 10 | Structure of urinary system | | | | | | √ | √ | √ | | √ | √ | √ | √ | 42 |
| S7 | | Structures related to movement | | | | | | | | | | | | | | |
| | 50 | Structure of lower extremity | | | | | | | | | | | √ | | √ | 8 |
| | 60 | Structure of trunk | | | √ | | | | | | | | | | | 8 |
| | 70 | Additional musculoskeletal structures related to movement | √ | √ | | | √ | √ | √ | | √ | | | | | 50 |
| S8 | | Skin and related structures | | | | | | | | | | | | | | |
| | 10 | Structure of areas of skin | | √ | | √ | | √ | | | | | √ | √ | √ | 33 |
| | 40 | Structure of hair | | | | | | | | √ | √ | | √ | | √ | 16 |
| **Activities and Participation** | | | | | | | | | | | | | | | | |
| D1 | | Learning and applying knowledge | | | | | | | | | | | | | | |
| | 10 | Watching | | | | | | | | √ | | | √ | | √ | 8 |
| | 66 | Reading | | | | | | | | √ | √ | | √ | | √ | 16 |
| D2 | | General tasks and demands | | | | | | | | | | | | | | |

| ICF Code | | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 10 | Undertaking a single task | √ | | | | | | | | | | | | | 8 |
| | 40 | Handling stress and other psychological demands | | | | | | | | √ | √ | √ | | √ | | 33 |
| D3 | | Communication | | | | | | | | | | | | | | |
| | 30 | Speaking | | | | | | √ | | | | | | √ | | 16 |
| | 60 | Using communication devices and techniques | | | | | √ | √ | | | | | | √ | | 25 |
| D4 | | Mobility | | | | | | | | | | | | | | |
| | 10 | Changing basic body position | √ | √ | | | √ | | | | √ | | | | | 42 |
| | 15 | Maintaining a body position | | | | | | | | | √ | | | | | 16 |
| | 20 | Transferring oneself | | | | | √ | | | | √ | | | | | 16 |
| | 30 | Lifting and carrying objects | | | | | | | √ | √ | | | | | | 16 |
| | 40 | Fine hand use | | | | | | | | | √ | | | √ | | 16 |
| | 45 | Hand and arm use | | | | | √ | | √ | | | | | | | 16 |
| | 50 | Walking | √ | | √ | √ | | | √ | | √ | | √ | | √ | 50 |
| | 55 | Moving around | √ | | | √ | | | √ | √ | √ | | | | | 50 |
| | 60 | Moving around in different locations | | √ | | | √ | | | √ | | | | | | 33 |
| | 65 | Moving around using equipment | | | | | | | | | | | √ | | √ | 8 |
| | 70 | Using transportation | | | | | | | | | | √ | | | | 16 |
| | 75 | Driving | | | | | | √ | | √ | | √ | | | | 25 |
| D5 | | Self-care | | | | | | | | | | | | | | |
| | 10 | Washing oneself | | | | | √ | | | | √ | | | | | 25 |
| | 20 | Caring for body parts | | | | | | | | | √ | | | | | 8 |
| | 40 | Dressing | | | | | √ | | | | √ | | | | | 16 |
| | 70 | Looking after one's health | | √ | | √ | √ | √ | √ | √ | | √ | √ | √ | √ | 67 |
| D6 | | Domestic life | | | | | | | | | | | | | | |

| ICF Code | | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 20 | Acquisition of goods and services | | | | | | | | √ | | | √ | | | 16 |
| | 30 | Preparing meals | | | | | | | √ | | √ | | | | | 16 |
| | 40 | Doing housework | | | | | | | √ | | √ | | √ | √ | √ | 33 |
| | 50 | Caring for household objects | | | √ | √ | | | | | √ | √ | | √ | | 42 |
| | 60 | Assisting others | | | √ | | | | | √ | | | √ | | √ | 16 |
| D7 | | Interpersonal interactions and relationships | | | | | | | | | | | | | | |
| | 30 | Relating with strangers | | | | | √ | | | | | | √ | | √ | 8 |
| | 40 | Formal relationships | | | | | | | | | √ | | √ | | √ | 8 |
| | 50 | Informal social relationships | | | | | √ | | | √ | | | √ | | √ | 16 |
| | 60 | Family relationships | | | √ | | √ | | √ | √ | | √ | √ | | √ | 42 |
| | 70 | Intimate relationships | | | | √ | | | | | | | √ | | √ | 8 |
| D8 | | Major life areas | | | | | | | | | | | | | | |
| | 30 | Higher education | | | | | | | √ | √ | | | | | | 16 |
| | 45 | Acquiring, keeping and terminating a job | √ | | √ | | | | | √ | √ | | √ | | √ | 42 |
| | 50 | Remunerative employment | √ | √ | √ | | √ | √ | √ | √ | √ | | √ | | √ | 67 |
| | 55 | Non-remunerative employment | | | | | | | √ | √ | √ | | | | | 25 |
| | 70 | Economic self-sufficiency | | | | | | | √ | √ | | | | | | 16 |
| D9 | | Community, social and civic life | | | | | | | | | | | | | | |
| | 10 | Community life | | √ | | | | | √ | √ | | | √ | | √ | 25 |
| | 20 | Recreation and leisure | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | 100 |
| | 30 | Religion and spirituality | | | | | | | | | | √ | √ | | | 16 |
| **Environmental Factors** | | | | | | | | | | | | | | | | |
| E1 | | Products and technology | | | | | | | | | | | | | | |
| | 10 | Products or substances for personal consumption | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | 100 |

| ICF Code | | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | > drugs | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | 100 |
| | 15 | Products and technology for personal use in daily living | | √ | | √ | √ | | | | | | | | | 33 |
| | 20 | Products and technology for personal indoor and outdoor mobility and transportation | | | | | | | | | | | √ | | √ | 8 |
| | 25 | Products and technology for communication | | | | √ | | | | √ | | | | | | 25 |
| | 30 | Products and technology for education | √ | √ | √ | | √ | √ | √ | √ | | √ | √ | | √ | 75 |
| | 35 | Products and technology for employment | | √ | | | | | | | | | | | √ | 8 |
| | 50 | Design, construction and building products and technology of buildings for public use | | | | | | | √ | √ | | | | | | 16 |
| | 55 | Design, construction and building products and technology of buildings for private use | | | √ | | | | | √ | | √ | | | | 25 |
| | 65 | Assets | | | √ | | | | √ | √ | | √ | √ | | √ | 42 |
| | 98 | Products and technology, other specified | √ | | √ | √ | √ | √ | √ | √ | | √ | √ | √ | √ | 83 |
| E2 | | Natural environment and human-made changes to environment | | | | | | | | | | | | | | |
| | 10 | Physical geography | | | √ | | | √ | √ | √ | | | | √ | | 50 |
| | 25 | Climate | | √ | | | √ | √ | | | | | | √ | | 42 |
| | 60 | Air quality | | √ | | | √ | | | | | | | | | 16 |
| | 98 | Natural environment and human-made changes to environment, other specified | | √ | √ | | √ | | | √ | | √ | | | | 42 |
| E3 | | Support and relationships | | | | | | | | | | | | | | |
| | 10 | Immediate family | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | 92 |

| ICF Code | | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 20 | Friends | | √ | | | | | | √ | √ | | √ | √ | √ | 42 |
| | 25 | Acquaintances, peers, colleagues, neighbours and community members | | | | | | | | | | | √ | | √ | 8 |
| | 40 | Personal care providers and personal assistants | | | √ | | | | | | | √ | | √ | | 25 |
| | 45 | Strangers | | | | | | | | | | | √ | | √ | |
| | 55 | Health professionals | | √ | | √ | √ | √ | √ | √ | √ | √ | √ | | √ | 75 |
| | 98 | Support and relationships, other specified | | | | | √ | | √ | √ | √ | √ | | √ | | 58 |
| E4 | | Attitudes | | | | | | | | | | | | | | |
| | 10 | Individual attitudes of immediate family members | √ | | √ | √ | √ | √ | √ | √ | | | √ | | √ | 58 |
| | 20 | Individual attitudes of friends | | | | | | | | | | | √ | | √ | 8 |
| | 25 | Individual attitudes of acquaintances, peers, colleagues, neighbours and community members | | √ | √ | √ | | | | | | | √ | | √ | 33 |
| | 45 | Individual attitudes of strangers | | √ | | | √ | √ | | | | | √ | | √ | 33 |
| | 50 | Individual attitudes of health professionals | √ | | | √ | √ | √ | √ | √ | | √ | √ | √ | √ | 75 |
| E5 | | Services, systems and policies | | | | | | | | | | | | | | |
| | 25 | Housing services, systems and policies | | | | | | | | | | | | | | 8 |
| | 30 | Utilities services, systems and policies | | | | | | | | | | | | √ | | 8 |
| | 35 | Communication services, systems and policies | | | | | | | | √ | | | | | | 8 |
| | 40 | Transportation services, systems and policies | | | √ | | | | | | | | | | | 16 |
| | 60 | Media services, systems and policies | | | | | | | | √ | | | | | | 8 |

| ICF Code | | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 70 | Social security services, systems and policies | | | | | | √ | | √ | √ | | | | | 25 |
| | 80 | Health services, systems and policies | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | 100 |
| | 90 | Labour and employment services, systems and policies | | √ | | | | | | √ | √ | | | | | 25 |

*"√" in the cells indicates that at least one item identified by a patient in the specific individual interview or the focus groups "mapped" to the specific ICF category. Numbers represent % of individually interviewed patients who identified at least one item in the corresponding category. Columns with solid single line borders represent individually interviewed patients from Ottawa, Canada; columns with double borders represent individually interviewed patients from Oxford, UK; column with dashed borders represent the 2 focus groups (combined) performed in Boston, USA. Columns shaded white represent individually interviewed patients with GPA; dark-shaded columns represent individually interviewed patients with EGPA; light shaded columns represent individually interviewed patients with MPA*

**Table 5-D. ICF categories identified in patient focus groups and individual interviews - "personal factors"**

| Proposed classification | | | | Category description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **P1** | | | | **Facts** | | | | | | | | | | | | | | |
| | 10 | | | Demographic characteristics (I defined them as "factors that are not modifiable") | | | | | | | | | | | | | | |
| | | 0 | | Age | | | | | | | | √ | √ | √ | √ | | | 33 |
| | | 3 | | Health literacy | | | | | | | | √ | | √ | √ | √ | | 33 |
| | | 4 | | Occupation | | | | | | | √ | √ | | | | | | 16 |
| | 20 | | | Personal history and biography | | | | | | | | | | | | | | |
| | | 0 | | Comorbidities | | | | | | | | | √ | √ | √ | √ | √ | 33 |
| | | 2 | | Personal and family circumstances | | | | | √ | | | √ | √ | √ | | √ | | 42 |
| | 30 | | | Position in the immediate social and physical context | | | | | | | √ | √ | | | | | | 16 |
| | | 0 | | Family | | | | | | | √ | √ | | | | | | 16 |
| | | 1 | | Economic | | | | | | | √ | √ | | | | | | 16 |
| | | | 1 | Income | | | | | | | √ | √ | | | | | | 16 |
| | | | 2 | Financial independence | | | | | | | | √ | | | √ | | | 16 |
| **P2** | | | | **Experience** | | | | | | | | | | | | | | |
| | 10 | | | Feelings | | | | | | | | | | | | | | |
| | | 0 | | Emotions / moods | | | | | √ | | √ | √ | | | | √ | √ | 33 |
| | 20 | | | Thoughts and beliefs | | | | | | | | | | | | | | |
| | | 0 | | Attitude towards medical care | | | | | | √ | | | √ | √ | | | | 100 |
| | | | 0 | Attitude to | | | | | √ | √ | | √ | | √ | | | | 33 |

| Proposed classification | | | | Category description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | access to medical care | | | | | | | | | | | | | | |
| | | | 1 | Attitude to the process of diagnosis | √ | | √ | √ | √ | | | √ | √ | √ | | √ | | 67 |
| | | | 2 | Attitude to complementary medicine | | | | | | | | √ | | | | | | 8 |
| | | | 3 | Interest in own health | | √ | | √ | | √ | √ | √ | √ | √ | √ | √ | √ | 75 |
| | | | 4 | Personal views of the medical aspect of disease | √ | | | | √ | √ | √ | √ | √ | √ | √ | √ | | 75 |
| | | | 5 | Attitude towards medications and other treatments | √ | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | 92 |
| | | | 6 | Satisfaction with monitoring | | | | √ | | √ | | √ | | | √ | √ | | 42 |
| | | | 7 | Attitude towards physicians and other health care providers | √ | √ | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | 92 |
| | | | 8 | Trust or distrust of medical care | √ | √ | √ | | | | | √ | √ | √ | | √ | √ | 58 |
| | | 1 | | Psychological reaction to disease | √ | | | | | | | √ | | | | | | 8 |
| | | | 0 | Concern about appearance | | √ | | √ | √ | √ | √ | √ | √ | √ | | √ | √ | 75 |
| | | | 1 | Increased appreciation of what life gives | | | | √ | | √ | √ | √ | | | | √ | √ | 42 |
| | | | 2 | Effect of not knowing what's going on before diagnosis | | | | | √ | | | | √ | | √ | √ | | 33 |
| | | | 3 | Relief versus fear after diagnosis | | | | | | | √ | | √ | | √ | | | 25 |
| | | | 4 | Effect of AAV on others | | | √ | | | √ | | | | | | √ | √ | 25 |
| | | | 5 | Effects of rare & "unknown" nature of disease | | | | √ | | | √ | √ | √ | | √ | √ | √ | 50 |

| Proposed classification | | | | Category description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 6 | Psychological effects of being physically unwell | | | √ | | | | | √ | √ | √ | √ | | √ | 42 |
| | | | 7 | Sense that life is over / AAV dominates | | | | | | | | √ | | | | | √ | 8 |
| | | | 8 | Positive effects (other than appreciation) | | | | √ | | | √ | √ | | √ | | | √ | 33 |
| | | 2 | | Disease becoming a constant threat | | | | | | | | | | √ | | | √ | 100 |
| | | | 0 | Worrying about body cues | | | | | | | √ | √ | √ | | | √ | √ | 33 |
| | | | 1 | Worry about future flares | | | √ | | | | | √ | √ | | | | √ | 25 |
| | | | 3 | Effects of incurable nature of disease | | | | | | √ | √ | | √ | | √ | | √ | 33 |
| | | | 4 | Worry about prognosis / death | | √ | √ | √ | | √ | √ | √ | √ | √ | √ | √ | | 83 |
| | | | 5 | Worry about side effects of drugs | | | | √ | | √ | | √ | √ | | | | √ | 75 |
| | | | 6 | Worry about weak immune system | | √ | √ | √ | √ | | | √ | | √ | | | √ | 50 |
| | | | 7 | Effect of unpredictalbe / uncertain nature of disease | √ | | √ | √ | | √ | √ | √ | √ | | √ | √ | √ | 75 |
| | 30 | | | Motives | | | | | | | | | | | | | | |
| | | 0 | | Need to reassess life goals due to limited abilities | | | | | | | | | | | | | | |
| | | | 0 | Change of physical ability | | √ | √ | | | | | √ | | | | | √ | 25 |
| | | | 1 | Change of overall potential | √ | | √ | | | | | √ | | | | | √ | 25 |
| | | | 2 | Ability to travel | | | √ | √ | | | | √ | | √ | | | | 33 |

| Proposed classification | | | | Category description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 3 | Work / career ambitions | | | √ | | | | | √ | | | | | √ | 16 |
| **P3** | | | | **Patterns of experience and behavior** | | | | | | | | | | | | | | |
| | 10 | | | Habits | | | | | | | | | | | | | √ | |
| | | 0 | | Dietary habits | | √ | | | | | | | | √ | | √ | √ | 25 |
| | | 1 | | Fitness | | √ | | | | √ | √ | | | | | √ | √ | 33 |
| | | 2 | | Compliance with management | | | | | | √ | | | | √ | √ | | | 25 |
| | | 3 | | Health behaviors | | √ | | | √ | | √ | √ | | √ | | √ | | 50 |
| | | 4 | | Other habits (smoking, EtOH) | | | | | | | | | √ | | √ | | | 16 |
| | 20 | | | Personality | | | | | | | | | | | | | √ | |
| | | 0 | | Effect of personality of impact of disease | | | | | | | √ | √ | √ | √ | √ | √ | √ | 83 |
| | | | 0 | Positive attitude | √ | | | √ | √ | √ | √ | | | √ | √ | √ | √ | 0 |
| | | 1 | | Disease changing personality / life | √ | | √ | | | | √ | √ | | | √ | √ | √ | 50 |
| | 30 | | | Adaptation to chronic illness | | | √ | | | | √ | √ | | √ | | | √ | 33 |
| | | 0 | | Go on with life | √ | √ | | | | √ | √ | √ | √ | √ | √ | | | 67 |
| | | 1 | | Attributing negative events to disease | | | | | | | √ | √ | | | | | √ | 16 |
| | | 2 | | Denial | √ | | | | | | √ | | | | | | | 16 |
| | | 3 | | Search for explanation - why me? | | √ | √ | | √ | √ | | √ | √ | | √ | | | 58 |
| | | 4 | | Comparing self to others | | | | √ | √ | √ | | | √ | √ | √ | √ | √ | 58 |
| | | 5 | | Strategies to facilitate adaptation | | | | | | | | √ | | √ | √ | √ | | 33 |

| Proposed classification | | | | Category description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 6 | | Seeking sympathy | √ | | | | | | | √ | | | | | √ | 16 |
| | | 7 | | Sense of uniqueness of their case | | | √ | | | | | √ | | | √ | | √ | 25 |

*"√" in the cells indicates that at least one item identified by a patient in the specific individual interview or the focus groups "mapped" to the specific ICF category. Numbers represent % of individually interviewed patients who identified at least one item in the corresponding category. Columns with solid single line borders represent individually interviewed patients from Ottawa, Canada; columns with double borders represent individually interviewed patients from Oxford, UK; column with dashed borders represent the 2 focus groups (combined) performed in Boston, USA. Columns shaded white represent individually interviewed patients with GPA; dark-shaded columns represent individually interviewed patients with EGPA; light shaded columns represent individually interviewed patients with MPA.*

**Table 5-E. ICF categories identified in patient focus groups and individual interviews - "health conditions" and categories that are "not covered" or "not definable" by the ICF**

| ICF Code | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Health conditions | | | | | | | | | | | | | | | |
| | Asthma | | √ | √ | | | | | | | | | | √ | 16 |
| | Avascular necrosis | | | | | | | | | | | | | √ | |
| | Depression | | | | | | | √ | | | √ | | | √ | 16 |
| | Diabetes | | | | | | | | | | | √ | | √ | 8 |
| | Infections | | √ | | √ | √ | | | √ | | √ | | | | 42 |
| | Malignancy | | | | | | | | | | | √ | √ | √ | 16 |
| | Osteoarthritis | | | | | | | | | | √ | | | | 8 |
| | Raynaud's | | | | | | | | | | | | √ | | 8 |
| Not covered | | | | | | | | | | | | | | | |
| | Diagnosis (process) | √ | | √ | | √ | | √ | √ | √ | √ | √ | √ | | 75 |
| | Clinical research | | | | | | | | √ | | √ | √ | | | 25 |
| nc-bf | Gallbladder dysfunction | | | | | | | | √ | | | | | | 8 |
| | Mucus production | | √ | | | | | | | | √ | | | | 16 |
| | Nasal functions | | | | | √ | | √ | | | | | | √ | 16 |
| | Sinus dysfunction | | √ | | √ | √ | | √ | √ | | √ | | | √ | 50 |
| nc-bs | sinuses | | √ | | √ | √ | | √ | √ | √ | √ | | | √ | 58 |
| nc-ap | Activities related to medical care | | | | | | | | | √ | √ | √ | | √ | 25 |
| nc-env | Information about disease & drugs | √ | | √ | | √ | | √ | √ | √ | √ | √ | | | 67 |
| | Work environment | | √ | | | | √ | | | √ | | | | √ | 25 |
| | Living arrangement | | √ | | | | | | √ | | √ | √ | √ | | 42 |
| | Stress | | √ | | | | √ | | √ | √ | √ | | √ | | 50 |
| Not definable | | | | | | | | | | | | | | | |
| | General well-being | | | √ | | √ | √ | √ | √ | √ | √ | √ | √ | √ | 75 |
| | Mental/psychological health | | | | | | | √ | | | | | | √ | 8 |

| ICF Code | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups | % prevalence in interviews |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Physical health (also nd-bs) | | | | √ | | | | √ | | | | √ | | 25 |
| | HRQOL | | | | | | | | | | | | | √ | |
| | Stage of illness | | | | | | | | | | | | | √ | 58 |
| | Flare / relapse | | | √ | | √ | √ | √ | √ | | √ | | | √ | 50 |
| | Stable disease | | | √ | | | | | √ | | | | | | 16 |
| | Remission | | | | | √ | √ | | √ | √ | | | | √ | 33 |
| | Survival / death | | | | √ | | | | | | √ | √ | | √ | 25 |
| | Treatment | | | | | | | | | | | | | √ | 92 |
| | Effect of treatment | | | √ | | √ | √ | √ | √ | √ | √ | √ | √ | √ | 75 |
| | Side effects from drugs | | | | √ | √ | √ | √ | √ | √ | √ | | √ | √ | 67 |
| | >> Side effects of prednisone | | √ | √ | √ | √ | √ | √ | √ | √ | √ | | | √ | 75 |
| nd-bf | Infection | | √ | | | √ | | | | | √ | | | | 25 |
| nd-bs | Infection | | √ | | | √ | | | | | √ | | | | 25 |
| nd-ap | Ability to do physical activity (exercise or ADL) | | | | | | | √ | √ | | √ | | | √ | 25 |
| | Using / operating technology | | | | | √ | √ | | | | | | | √ | 16 |
| | Independence in activities | | | | | | | | √ | | | | | | 8 |
| | Planning for future | | | | √ | | | √ | | | | √ | √ | √ | 33 |

*"√" in the cells indicates that at least one item identified by a patient in the specific individual interview or the focus groups "mapped" to the specific ICF category. Numbers represent % of individually interviewed patients who identified at least one item in the corresponding category. Columns with solid single line borders represent individually interviewed patients from Ottawa, Canada; columns with double borders represent individually interviewed patients from Oxford, UK; column with dashed borders represent the 2 focus groups (combined) performed in Boston, USA. Columns shaded white represent individually interviewed patients with GPA; dark-shaded columns represent individually interviewed patients with EGPA; light shaded columns represent individually interviewed patients with MPA; hc – health condition, nc – not covered, nd – not defined, bf – body functions, bs – body structures, ap – activities and participation, env – environmental factors.*

### 5.4.3 Patient perspective by AAV diagnosis or country of residence

We examined Tables 5-C, 5-D and 5-E for evidence of a trend of significant differences in relevance of various ICF categories to the impact of AAV on patients from different countries (USA, Canada, and UK) and on patients with each of the three specific AAV (GPA, MPA, and EGPA). For convenience of comparison, Tables 5-C, 5-D and 5-E are coded according to patients' country of origin and the specific type of AAV (see legend in the tables for the coding key).

All categories identified by at least 70% of individually interviewed patients at either Canada or the UK were also identified by at least one individually interviewed patient at the other site or by participants of the focus groups. Two categories were exclusively identified by the participants of the focus group (from USA) – the health condition "avascular necrosis of the hip" which is a severe complication of the prolonged use of high dose corticosteroids (the main treatment of AAV) and the non-definable by the ICF term "HRQoL".

Comparing identified ICF categories by the specific diagnosis revealed several differences. Two ICF categories were identified exclusively by patients with EGPA: environmental factor "E260 Air quality" and health condition "asthma"; one category "S220 Structure of the eyeball" was uniquely identified by the patients with GPA; and one category "b279; additional sensory functions, other specified and unspecified" was identified exclusively by patients with MPA.

### 5.4.4 Assessing data saturation

"Data saturation" tables that show how ICF categories were identified over the course of the sequential 12 interviews followed by the 2 focus groups (the results of which were combined and presented in 1 column) are displayed in Appendix M (Tables M.1-M.3). The last row of each of the three tables displays the number of new categories (2$^{nd}$ level categories for the classified ICF components and all categories for "personal factors", "health conditions", "not covered" and "not definable" concepts) identified at each of the individual interviews and at the focus groups.

Although the majority of new ICF categories were identified in the first half of the interviews, some new ICF categories continued to be added by subsequent interviews, including the last interview (which added 2 categories in the ICF component “body functions”, 2 in “body structures”, 1 “environmental factor” and 1 health condition) and the 2 focus groups. The information obtained from the summary of the focus groups added 1 new health condition (avascular necrosis of the hip) and 1 non-definable by the ICF term HRQoL.

## 5.5 Descriptive analysis of results and discussion

In summary, participating patients identified 42 second level categories in the ICF component "body functions", 18 "body structures" and 40 "activities and participation;" 34 "environmental factors " and 62 "personal factors" were identified as important modifiers of the impact of AAV (see Tables 5-C and 5-D). In addition, a number of items identified by patients were linked to "health condition", "not definable" and "not covered" groups of categories (see Table 5-E).

When the identified categories were compared between patients from different countries (Canada, USA and UK), the only difference that was found were 2 categories that were exclusively identified by the participants of the focus group from USA – the health condition "avascular necrosis of the hip" and the non-definable by the ICF term "HRQoL". The differences in the identified ICF categories between patients with different types of AAV (GPA, EGPA and MPA) were more notable. Specifically, patients with GPA uniquely identified category "S220 Structure of the eyeball;" patients with EGPA uniquely identified health condition "asthma" and the environmental factor "E260 Air quality;" and patients with MPA uniquely identified category "b279; additional sensory functions, other specified and unspecified."

### 5.5.1 Discussion of patient perspective by country of residence

Although the presence of geographic diversity (2 continents, 3 countries) is a strength of this study, comparison of relevance of the specific ICF categories between the 3 countries was not the primary objective of the study, and consequently the study design limits the meaningfulness of such comparison.

The main feature of the study design that limits our ability to compare participating countries is that the USA is represented by patients who participated in 2 focus groups that were performed outside of the scope of this study. As was discussed in the "Methods" section of this

chapter, the data from these focus groups was included in order to broaden the scope of sampling of the patient perspective, which is the main purpose of this study. However, inclusion of the focus groups introduces 4 factors that represent important confounders for comparing patients from USA to those from Canada and the UK. These factors are: 1) the fact that the focus groups represent a different technique of data collection that may introduce differences independent of the country of origin; 2) different prompts were used for the focus groups which likely influenced the type of collected information; 3) the focus groups were performed several years prior to the individual interviews performed in Ottawa and Oxford which could introduce time-related differences that are independent of country of origin; and 4) the summary of the focus group data as opposed to the original transcripts were used for this analysis which likely resulted in data that is less representative of the patient perspective compared to the original transcripts of individual interviews performed in Canada and the UK. It is likely that the term "HRQoL" arose in the focus group data and not during any of the individual interviews precisely as a result of one of the differences of the focus group technique discussed above. "HRQoL" represents a term that would only be used by those familiar with the language employed in health-related research. This term was likely introduced either by the investigator who was conducting the focus groups or by the investigator who wrote the focus group summary. If this presumption is true, this term does not truly represent the perspective of AAV patients.

Another significant limitation is the small size of the study and the resulting even smaller size of the country-specific subgroups. Only 2 interviews of patients from Oxford, UK were included in the analysis. Furthermore, as discussed above using the summary of the 2 focus group performed in Boston, USA likely resulted in a less detailed data and the resulting smaller effective sample size compared to if the original transcripts of the 2 focus groups involving a total of 9 patients were used. It is likely that the first appearance of the health condition category "avascular necrosis of the

hip" in the last column of Table 5-E that represents the focus groups performed in Boston, USA is merely a result of the small size of the study. Avascular necrosis of the hip is a serious side effect of prolonged use of high dose corticosteroids – the standard of initial therapy for AAV all around the world. The prevalence of avascular necrosis of the hip amongst patients with ANCA vasculitis is relatively low, estimated at 0.4% in the first year of disease (38) and at 0.7% at long term follow up (mean of 7.1 years) (39). Thus, it is not surprising that this condition did not come up in the first 12 individual interviews. Increasing the sample size to broaden patients' perspective was precisely the purpose of adding the focus group data despite the limitations of the focus group data discussed above. In view of absence of a plausible reason to suspect country-specific differences in incidence of avascular necrosis of the hip, we will conclude that the exclusive appearance of this category during the USA-based focus groups is merely a statistical occurrence and not a signal of a true country-specific difference.

In conclusion, it is unlikely that the identified country-specific differences (namely the 2 categories uniquely identified at the focus groups performed in USA) represent true differences that are attributable to different geographic origin. At the same time, it is possible that increasing the size of this study and the country-specific subgroups could uncover important country-specific differences. This is a limitation of this study which we believe is acceptable in view of the fact that country-specific comparison does not constitute the primary purpose of this study.

### 5.5.2 Discussion of patient perspective by specific type of AAV

Similar to the situation with geographic diversity, while the use of purposive sampling to ensure patient variability on the most important demographic and clinical characteristics strengthens the study by ensuring that a spectrum of potential effects of AAV is captured, the small size of the study and the even smaller size of certain patient subgroups limits the strength of

conclusions that can be drawn about variability in prevalence of the specific ICF categories between diagnosis-specific subgroups of patients.

Keeping in mind this limitation, several categories uniquely identified by patients with each of the 3 specific diagnoses are worth discussing. The two ICF categories identified exclusively by patients with EGPA, namely the environmental factor "E260 Air quality" and the health condition "asthma," likely do represent a true unique characteristic of this condition. Severe asthma is the main clinical manifestation (and a major diagnostic criterion (36)) of EGPA (and not GPA or MPA)), and asthma is often triggered by various allergens thus making "air quality" an important determinant of extent of control of the disease. Similarly, the body structure category "S220 Structure of the eyeball" that was uniquely identified by the patients with GPA is consistent with the significantly more frequent involvement of the eyes with GPA compared to EGPA and MPA. In contrast, the significance of the category "B279; additional sensory functions, other specified and unspecified" being uniquely identified by patients with MPA is uncertain. To clarify this, we reviewed the original transcripts of the two MPA patients who identified this category. In the case of the first patient the concept that mapped to the category B279 is "sensation of thirst", which represents a sign of renal failure this patient developed as a result of her vasculitis. Notably, although renal failure (and as a result the associated symptom of thirst) is relatively more common in MPA compared to GPA and EGPA, this difference is not dramatic and thus the fact that "thirst" was identified exclusively by patients with MPA is likely a result of the small sample size of this study, similar to the discussion that pertained to avascular necrosis of the hip in section 5.5.1. In case of the second patient the concept that linked to the category B279 is "numbness of fingers during attacks of Raynaud's phenomenon", the latter representing a syndrome of blood vessel reactivity that represents a condition that this patient had before the diagnosis of vasculitis. This condition came up in the interview because it worsened at the time of diagnosis of vasculitis, but

the relevance of such worsening to the vasculitis itself is not clear. Thus in both cases, identification of the category B279 exclusively by the 2 patients with MPA is not likely to represent the true difference attributable to the specific diagnosis. These 2 symptoms were observed in two patients with MPA and none of the patients with the other types of AAV most likely by chance alone, in view of the small size of the study. Increasing the number of subjects in this study likely would result in disappearance of category B279 as a unique feature of MPA.

Notably, although the 2 concepts "sensation of thirst" and "numbness of fingers" discussed above link to the same ICF category "B279; additional sensory functions, other specified and unspecified", they represent different symptoms that clinically have little relation to each other. This points to an additional limitation of the ICF classification (see Chapter 3 for discussion of other limitations of ICF), namely that more than one specific concept can link to the same ICF category. It is important to keep such lack of specificity of the ICF categories in mind when interpreting the results of ICF-based comparisons in various contexts as was done in this study. The limitations of the ICF will be further discussed in Chapter 7.

### 5.5.3 Discussion of data saturation

As discussed in section 5.4.4, although the number of categories identified at the last several interviews is relatively small, even the last interview and the data obtained from the focus groups added some (although few) new categories to the list of ICF categories patients consider relevant in determining their function and overall health (see appendix M). Based on the definition of saturation discussed in section 5.2.4 of this chapter full saturation was not reached in this study.

We examined the specific categories added by the last interview to determine whether they are conceptually significant, which would indicate that their identification at the last interview represents lack of "conceptual saturation." The latter concept is introduced in a detailed review of

saturation by Kerr et al (30) precisely in the context of determining the significance of the specific newly identified themes for determining overall saturation. The "conceptual" significance of the specific categories was assessed through determining their relevance to the primary purpose of this study, namely determining the impact of AAV on patients' function and general health. This required reviewing the specific categories within the context in which they were mentioned by the patients in the original interview transcripts, as was done in sections 5.5.1 and 5.5.2 when determining the significance of the unique categories identified by patients from different countries and with different types of AAV.

In the last interview, 2 "body functions", 2 "body structures", 1 environmental factor and 1 health condition were identified. The newly identified health condition as well as one of the 2 new categories in the ICF component "body functions" ("b415 blood vessel functions") refer to worsening of pre-existing "Raynaud's phenomenon" experienced by the last interviewed patient, and the new "environmental factor", "e530 "Utility services, systems and policies" refers to the same patient having to increase heating in her house due to the Raynaud's phenomenon. As was already discussed in section 5.5.2, the Raynaud's phenomenon represents a comorbidity that is unlikely to be related to AAV. The second new category in the ICF component "body functions" identified in the last interview was "b840 Sensations related to the skin." It refers to itchy rash that was part of the allergic reaction to an antibiotic given to the patient for a presumed infection – again, a condition that is not directly related to AAV. Two "body structure" categories that were newly identified in the last interview were "S550 Structure of pancreas" and "S560 Structure of liver." These categories refer to involvement of these organs with AAV. They represent extremely rare manifestations of the vasculitis that will not be relevant to the vast majority of AAV patients.

It is important to note that despite the fact that the 2 focus groups were performed more than 1 year before the first individual interview in Ottawa was conducted, we chose to place them in the last column of the saturation table to highlight the primary importance of the individual interviews. The focus groups were included to enhance diversity of the patient perspective, but the data obtained from the focus groups is likely of smaller value for the purpose of this study compared to individual interviews due to the factors discussed in section 5.5.1. Also as discussed in section 5.5.1, the term "HRQoL" added by the focus group likely does not truly represent the perspective of AAV patients, and the health condition avascular necrosis of the hip represents a relatively rare complication of AAV treatment that will not be relevant to the majority of AAV patients.

The above discussion suggests that the categories added by the latter part of the interviewing process represent either 1) specific comorbidities or circumstances of the particular patients that are unrelated to AAV or 2) concepts related to relatively uncommon manifestations of AAV. Because the purpose of this study is to identify items that are typical impairments of body functions or structures, limitations of activities and participation an personal and environmental modifiers of impact of AAV, items that appear in the last several interviews are not conceptually significant and therefore do not constitute a conceptually significant compromise to saturation.

## 5.6 Strengths and limitations of the study

The main strengths of this study is the open-ended exploratory approach to obtaining patients' perspective. The use of qualitative research designs such as individual interviews and focus groups is increasingly employed to obtain patient perspective in clinical research (30, 40). As discussed earlier in this chapter, qualitative approach is the appropriate strategy when people's living experience of a concept is under study. The purpose of this study was precisely that - to obtain patients' perspective on the effect of living with AAV, and to include all aspects of patients' experience. Both focus groups performed in Boston, USA, and the individual interviews performed in Canada and the UK started broadly and allowed patients to bring up any themes they considered relevant. The discussion did not incorporate the existing knowledge about AAV (such as existing questionnaires) or the investigator's beliefs of what constitutes the significant effects of AAV on patients, reducing the potential for influencing patients' views.

While the qualitative nature of the "patient perspective" part of this study is mainly a strength, its logistically difficult and time-consuming nature resulted in a relatively small sample size. Twelve individual interviews were conducted as it was felt to be the minimal appropriate number of interviews (see section 5.2.5) to achieve saturation. Complete saturation was not achieved after 12 interviews, as discussed above. It would be appropriate to perform additional interviews, particularly considering that we anticipated at the study planning stage that 12 interviews may not be enough in our study population that is not ideally homogenous. However, analyzing the saturation table revealed that "conceptual" saturation was largely achieved, suggesting that the items that would be added by additional interviews are unlikely to be conceptually significant

Another consequence of the small sample size of 12 individual interviews as well as the relatively short duration of the study and the rare nature of certain target groups of patients

(particularly MPA and EGPA patients with duration of disease of <2 years), is that the individual subgroups ended up being very small, some containing only a single patient (see the purposive sampling grid in Table 5-B). As a result, we were not able to perform meaningful comparison of the identified ICF categories between the groups of importance - between the 3 types of AAV, between short (<2 years) and longer duration of disease, and between patients from different geographic regions. Comparison between geographic locations was further complicated by the fact that a different strategy of data collection (namely focus groups as opposed to individual interviews) was employed with patients from the USA compared to patients from Canada and the UK. Descriptive analysis of the items identified by different participant subgroups revealed no signals of significant differences beyond those that are expected (see discussion in sections 5.5.1 and 5.5.2). More importantly, the purpose of ensuring variability of subjects was to capture the scope of the effect of AAV as opposed to enabling comparison between different subgroups. Achievement of "conceptual" saturation suggests that this purpose was achieved.

The inevitable subjectivity inherent in qualitative research results in potential for certain sources of information bias. The process of interviewing is dependent on the interviewer, with the degree of such dependence been a function of the interviewer's experience and skill. Although the aim was to keep the interviews open-ended, pre-specified prompts were used to ensure coverage of all relevant topics, and such prompts could sway the participant's train of thought a certain direction that would not have come up without prompting. In Ottawa, NM interviewed her own patients; it is possible that the patients felt uncomfortable to talk about certain topics in front of their physician, resulting in biased information. Finally, the analysis of the interview transcripts is to some degree a subject of the researcher's interpretation, and such interpretation may not be completely reflective of the patients' views. The subjectivity of analysis was minimized in this study by the use of the standardized ICF classification, as discussed above.

As for the clinicians' perspective described in Chapter 4, the main thread to validity in this study is likely selection bias. English-speaking patients from 3 countries, namely Canada, USA and the UK, were included in this analysis. It is likely that patients' perspective is significantly influenced by access to various services and therapies, by other specifics of the medical system and by cultural standards. Because it was not feasible to perform interviews and focus groups in other geographic locations and in different languages for this study, the resultant limitations to geographic generalizability of this study was unavoidable.

Although we tried to ensure variability on the most important potential effect modifiers (age, sex, duration and severity of disease and the specific diagnosis), the participants represent convenience samples of patients in the three participating rheumatology practices. This implies that a variety of the sample specific characteristics, like the specific practices of the participating clinics and of the treating physicians, could bias the results. Perhaps the most notable of such characteristics is that similar to the sample for the clinicians' perspective, all of the included patients were recruited from academic practices at tertiary care vasculitis referral centres. As discussed in chapter 4, the preferential inclusion of patients attending vasculitis referral centres likely means that the participants of this study tend to have more severe disease as well as better access to various services and new therapies compared to patients treated in remote community rheumatology practices, suggesting that this represents a threat to the external validity of the study. Expanding the sampling frame of this study to other countries and community practices would be useful, but is well beyond the relatively small scope of this study.

# Chapter 6 Comparison of areas of AAV measured in clinical trials to those important to patients with AAV and clinicians who are involved in their care.

## 6.1 Objective

The objective of this sub-study was to compare areas of AAV measured in clinical trials to those important to AAV patients and clinicians involved in their care.

## 6.2 Methods

The lists of ICF categories identified in the 3 sub-studies described above (literature review, clinicians' perspective and patients' perspective) were combined together into one table. Areas covered by the three perspectives were compared descriptively.

Quantitative comparison of differences in representation of individual ICF categories was not performed in view of 2 important biases such comparison could introduce. First, the large size of the ICF and the large number of individual categories would invariably result in high potential for finding differences by chance alone (referred to as multiple comparison bias). Secondly, different methods were used to study different perspectives. The results of the analysis of the systematic review of literature are purely qualitative (each category is labeled with a binary indicator as either "sampled" or "not sampled" in the trials) making quantitative analysis not possible. At the same time, while percent prevalence values were calculated for both patient perspective and clinicians' perspective, their direct comparison would not be meaningful because different methods of data collection were used for these 2 perspectives (semi-structured interviews for patients versus online questionnaire for clinicians).

Similar to what was described in Chapter 4, for each of the classified ICF components (body functions, body structures, activities and participation and environmental factors) the prevalence of identification (expressed as % of participants) is displayed for each of the 2$^{nd}$ level ICF categories of the patients' perspective and the clinicians' perspective; the 1$^{st}$ level summary prevalence (also

expressed as %) is additionally displayed for the 1st level categories to allow high-level comparison. For “personal factors” that are currently not classified by the ICF (see Chapter 2 for more detailed discussion of “personal factors”), prevalence values for the specific categories were displayed; high-level summary prevalence values were calculated for the main categories in each of the broad “Parts” of personal factors.

## 6.3 Results

Tables 6-A, 6-B and 6-C contain the summary of results, displaying all ICF categories measured in AAV-related clinical trials, those identified as important by patients with AAV, and those identified by clinicians who care for these patients. Table 6-A contains classified categories from ICF components "body functions", "body structures", "activities and participation", and "environmental factors"; Table 6-B contains "personal factors" and Table 6-C contains "health conditions" and concepts that are "not covered" or "not definable" by the ICF.

A large number of ICF categories were identified as relevant when determining the impact of AAV from the three perspectives. Overall, 61 2nd level categories were identified in the component "body functions" by all 3 perspectives combined - 42 were identified by patients, 51 by clinicians, and 37 were measured in clinical trials. Of these, 24 were identified in each of the 3 perspectives, 9 were identified by clinicians and measured in clinical trials but not identified by patients, 3 were identified by patients and measured in clinical trials but not identified by clinicians and 11 were identified by patients and clinicians but not measured in clinical trials; 5 2nd-level categories were uniquely identified by patients, 7 by clinicians and 2 were measured in clinical trials but not identified by patients or clinicians.

Thirty five 2nd-level categories in the ICF component "body structures" were identified by 3 perspectives combined - 18 were identified by patients, 33 by clinicians, and 27 measured in clinical trials. Of these, 15 were identified by each of the 3 perspectives, 10 by clinicians and clinical trials but not patients and 3 by patients and clinicians but not clinical trials; 5 2nd-level categories in the component "body structures" were uniquely identified by clinicians and 2 were measured in clinical trials but not identified by patients or clinicians.

Fifty five 2nd level categories in the ICF component "activities and participation" were identified by the 3 perspectives combined - 40 were identified by patients, 46 by clinicians and 29 were measured in clinical trials. Of these, 17 were identified by each of the 3 perspectives, 5 by clinicians and clinical trials but not patients, 1 by patients and clinical trials but not clinicians and 21 by patients and clinicians but not clinical trials; 2 2nd-level categories were uniquely identified by patients, 3 by clinicians and 6 were measured in clinical trials but not identified by patients or clinicians.

Thirty nine 2nd-level "environmental factors" were identified as important modifiers of the impact of AAV - 34 were identified by patients, 32 by clinicians and 6 were measured in clinical trials. Of these, 4 were identified by each of the 3 perspectives, 1 by patients and clinical trials but not clinicians and 24 by patients and clinicians but not clinical trials; 6 2nd-level categories were uniquely identified by patients and 4 by clinicians.

Finally, 68 "personal factor" modifiers of the impact of AAV were identified (62 by patients, 37 by clinicians and 6 considered in clinical trials). Of these, 4 personal factors were identified by all 3 perspectives, 28 were uniquely identified by patients, 4 by clinicians, 30 were identified by patients and clinicians but not measured in clinical trials and 2 were identified by clinicians and measured in clinical trials but were not identified by patients.

Twelve items linked to "health condition" ICF category in addition to being linked to the appropriate "body function" or "body structure" category. In addition, a number of items were labelled as "not covered" and "non-definable" by the ICF. These items are displayed in Table 6-C and are discussed in more detail in the "Results" section for each of the three individual perspectives.

**Table 6-A. Comparison of ICF categories measured in AAV clinical trials to those identified as important by patients with AAV and clinicians involved in care of AAV patients – classified ICF components**

| ICF code | ICF Category Description | Patients' Perspective | | Clinicians' perspective | Clinical trials | |
|---|---|---|---|---|---|---|
| | | Overall for patient perspective | Prevalence in interviews[#] | Prevalence in clinician Delphi[#] | OMERACT Core Set | Overall for literature perspective |
| **Body Functions** | | | | | | |
| B1 | Mental functions | * | ***100*** | ***85*** | * | * |
| 10 | Consciousness functions | * | 33 | | | |
| 14 | Orientation functions | | | 7 | * | * |
| 17 | Intellectual functions | | | 22 | | * |
| 26 | Temperament and personality functions | * | 58 | 48 | | |
| 30 | Energy and drive functions | * | 75 | 44 | * | * |
| 34 | Sleep functions | * | 67 | 37 | | |
| 44 | Memory functions | | | 11 | | |
| 47 | Psychomotor functions | * | 8 | | | |
| 52 | Emotional functions | * | 50 | 30 | * | * |
| 64 | Higher-level cognitive functions | | | 4 | | |
| 67 | Mental functions of language | | | 4 | | |
| 80 | Experience of self and time functions | * | 42 | 4 | | |
| B2 | Sensory functions and pain | | ***92*** | ***96*** | * | * |
| 10 | Seeing functions | * | 16 | 81 | * | * |
| 15 | Functions of structures adjoining the eye | * | 8 | 11 | | |
| 20 | Sensations associated with the eye and adjoining structures | * | 8 | | | |
| 29 | Seeing and related functions, other specified and unspecified | | | 7 | | * |
| 30 | Hearing functions | * | 50 | 89 | * | * |
| 35 | Vestibular functions | | | 11 | | |
| 40 | Sensations associated with hearing and vestibular function | * | 16 | | | * |
| 50 | Taste function | * | 8 | 11 | | |

| ICF code | ICF Category Description | Patients' Perspective | | Clinicians' perspective | Clinical trials | |
|---|---|---|---|---|---|---|
| 55 | Smell function | * | 16 | 37 | | |
| 65 | Touch function | | | 15 | | |
| 79 | Additional sensory functions, other specified and unspecified | * | 16 | 26 | * | * |
| 80 | Sensation of pain | * | 92 | 63 | * | * |
| 89 | Sensation of pain, other specified and unspecified | | | 19 | * | * |
| B3 | Voice and speech functions | * | ***16*** | ***26*** | * | * |
| 10 | Voice functions | * | 16 | 22 | * | * |
| 20 | Articulation functions | | | 4 | | |
| 40 | Alternative vocalization functions | | | 7 | | |
| B4 | Functions of the cardiovascular, haematological, immunological and respiratory systems | * | ***100*** | ***100*** | * | * |
| 10 | Heart functions | * | 8 | 41 | * | * |
| 15 | Blood vessel functions | * | 8 | 7 | * | * |
| 20 | Blood pressure functions | * | 16 | 44 | * | * |
| 30 | Haematological system functions | * | 16 | 41 | * | * |
| 35 | Immunological system functions | * | 92 | 15 | * | * |
| 40 | Respiratory functions | * | 82 | 93 | * | * |
| 49 | Functions of the respiratory system, other specified and unspecified | * | 27 | | * | * |
| 50 | Additional respiratory functions (cough, hemoptysis) | * | 50 | 30 | * | * |
| 55 | Exercise tolerance functions | * | 58 | 19 | | |
| 60 | Sensations associated with cardiovascular and respiratory functions | * | 67 | 48 | * | * |
| 69 | Additional functions and sensations of the cardiovascular and respiratory systems, other specified and unspecified | * | | | | |
| B5 | Functions of the digestive, metabolic and endocrine systems | | ***83*** | ***59*** | | |
| 10 | Ingestion function | * | 16 | 7 | | |
| 15 | Digestive functions | * | 16 | 7 | | |
| 25 | Defecation functions | | | 19 | * | * |
| 30 | Weight maintenance functions | * | 67 | 26 | * | * |
| 35 | Sensations associated with the digestive system | * | 16 | | | * |
| 40 | General metabolic functions | * | 8 | 19 | * | * |

| ICF code | ICF Category Description | Patients' Perspective | | Clinicians' perspective | Clinical trials | |
|---|---|---|---|---|---|---|
| 45 | Water, mineral and electrolyte balance functions | * | 42 | 11 | | * |
| 50 | Thermoregulatory functions | * | 16 | 19 | * | * |
| 55 | Endocrine gland function | * | 8 | 22 | | * |
| B6 | Genitourinary and reproductive functions | | ***67*** | ***96*** | | |
| 10 | Urinary excretory functions | * | 67 | 96 | * | * |
| 20 | Urination function | | | 4 | | * |
| 40 | Sexual function | | | 19 | | |
| 60 | Procreation functions | * | 8 | 33 | | * |
| 79 | Genital and reproductive functions, other specified and unspecified | | | | * | * |
| B7 | Neuromusculoskeletal and movement-related functions | * | ***50*** | ***67*** | | |
| 10 | Mobility of joint functions | * | 42 | 26 | | |
| 29 | Functions of the joints and bones, other specified and unspecified | | | 26 | * | * |
| 30 | Muscle power functions | | | 59 | * | * |
| 80 | Sensations related to muscle and movement functions | | | | * | * |
| 98 | Neuromusculoskeletal and movement-related functions, other specified | | | 11 | * | * |
| B8 | Functions of the skin and related structures | | ***25*** | ***15*** | | |
| 10 | Protective functions of the skin | * | 16 | 4 | | |
| 20 | Repair functions of the skin | * | 16 | 4 | | * |
| 40 | Sensation related to the skin | * | 8 | | | |
| **Body Structures** | | | | | | |
| S1 | Structures of the nervous system | | ***0*** | ***93*** | | * |
| 10 | Structure of brain | | | 56 | * | * |
| 20 | Spinal cord and related structures | | | 7 | * | * |
| 30 | Structure of meninges | * | | 7 | | |
| 40 | Structure of sypathetic nervous system | | | 4 | | |
| 50 | Structure of parasypathetic nervous system | | | 4 | | |
| 98 | Structure of the nervous system, other specified | | | 81 | * | * |
| S2 | The eye, ear and related structures | | ***58*** | ***96*** | * | * |
| | > Ear and related structures | * | 42 | 52 | * | * |
| | > Eye and related structures | * | 42 | 70 | * | * |

| ICF code | | | ICF Category Description | Patients' Perspective | | Clinicians' perspective | Clinical trials | |
|---|---|---|---|---|---|---|---|---|
| | 10 | | Structure of eye socket | | | 44 | * | * |
| | 20 | | Structure of eyeball | * | 25 | 26 | * | * |
| | 30 | | Structures around eye | * | 8 | 22 | * | * |
| | 40 | | Structure of external ear | * | 8 | 26 | * | * |
| | 50 | | Structure of middle ear | * | 25 | 37 | * | * |
| S3 | | | Structures involved in voice and speech | * | ***67*** | ***100*** | * | * |
| | 10 | | Structure of nose | * | 67 | 100 | * | * |
| | 20 | | Structure of mouth | * | 16 | 30 | * | * |
| | 30 | | Structure of pharynx | | | 48 | * | * |
| | 40 | | Structure of larynx | | | 4 | | * |
| S4 | | | Structures of the cardiovascular, immunological and respiratory systems | | ***83*** | ***85*** | | |
| | 10 | | Structure of cardiovascular system | * | 25 | 48 | * | * |
| | 20 | | Structure of immune system | | | 7 | | |
| | 30 | | Structure of respiratory system | * | 83 | 85 | * | * |
| S5 | | | Structures related to the digestive, metabolic and endocrine systems | | ***16*** | ***44*** | * | * |
| | 10 | | Structure of salivary glands | | | 7 | * | * |
| | 20 | | Structure of esophagus | | | | * | * |
| | 40 | | Structure of intestine | | | 37 | * | * |
| | 50 | | Structure of pancreas | * | 8 | 4 | * | * |
| | 60 | | Structure of liver | * | 8 | 4 | | |
| | 70 | | Structure of gall bladder and ducts | * | 8 | 4 | | |
| | 98 | | Structures related to the digestive, metabolic and endocrine systems, other specified | | | | * | * |
| S6 | | | Structures related to the genitourinary and reproductive systems | | ***42*** | ***85*** | | |
| | 10 | | Structure of urinary system | * | 42 | 85 | * | * |
| | | 0 | Kidneys | * | | 81 | | * |
| | | 1 | Bladder | * | | | | * |
| | 30 | | Structure of reproductive system | | | 11 | * | * |
| S7 | | | Structures related to movement | | ***58*** | ***81*** | | |
| | 10 | | Structure of head and neck region | | | 7 | | |
| | 30 | | Structure of upper extremity | | | 52 | * | * |
| | 50 | | Structure of lower extremity | * | | 56 | * | * |

| ICF code | | | ICF Category Description | Patients' Perspective | | Clinicians' perspective | Clinical trials | |
|---|---|---|---|---|---|---|---|---|
| | 60 | | Structure of trunk | * | 8 | 41 | * | * |
| | 70 | | Additional musculoskeletal structures related to movement | * | 50 | 63 | * | * |
| | | 0 | Bones | * | | 30 | | |
| | | 1 | Joints | * | | 37 | | |
| | | 2 | Muscles | | | 26 | | |
| S8 | | | Skin and related structures | | ***50*** | ***70*** | | |
| | 10 | | Structure of areas of skin | * | 33 | 70 | * | * |
| | 30 | | Structure of nails | | | 4 | | |
| | 40 | | Structure of hair | * | 16 | 11 | * | * |
| **Activities and Participation** | | | | | | | | |
| D1 | | | Learning and applying knowledge | | ***16*** | ***26*** | | |
| | 10 | | Watching | * | 8 | 4 | | |
| | 15 | | Listening | | | 11 | | |
| | 66 | | Reading | * | 16 | 15 | | |
| | 70 | | Writing | | | 11 | | |
| D2 | | | General tasks and demands | | ***42*** | ***52*** | | |
| | 10 | | Undertaking a single task | * | | 4 | | |
| | 30 | | Carrying out daily routine | | | 44 | * | * |
| | 40 | | Handling stress and other psychological demands | * | 33 | 4 | | |
| D3 | | | Communication | | ***16*** | ***11*** | | |
| | 30 | | Speaking | * | 16 | 7 | | |
| | 50 | | Conversation | | | 4 | | |
| | 60 | | Using communication devices and techniques | * | 25 | 7 | | |
| D4 | | | Mobility | * | ***100*** | ***59*** | | * |
| | 10 | | Changing basic body position | * | 42 | 7 | * | * |
| | 15 | | Maintaining a body position | * | 16 | 4 | | |
| | 20 | | Transferring oneself | * | 16 | 7 | | * |
| | 29 | | Changing and maintaining body position, other specified and unspecified | | | | | * |
| | 30 | | Lifting and carrying objects | * | 16 | 15 | * | * |
| | 40 | | Fine hand use | * | 16 | 11 | | * |
| | 45 | | Hand and arm use | * | 16 | 11 | * | * |

| ICF code | | | ICF Category Description | Patients' Perspective | | Clinicians' perspective | Clinical trials | |
|---|---|---|---|---|---|---|---|---|
| | 50 | | Walking | * | 50 | 37 | * | * |
| | 55 | | Moving around | * | 50 | 19 | * | * |
| | 60 | | Moving around in different locations | * | 25 | 4 | | * |
| | 65 | | Moving around using equipment | * | 8 | | | |
| | 70 | | Using transportation | * | 16 | 11 | | |
| | 75 | | Driving | * | 25 | 26 | | |
| | 98 | | Mobility, other specified | | | | | * |
| D5 | | | Self-care | * | ***92*** | ***56*** | | * |
| | 10 | | Washing oneself | * | 25 | 22 | * | * |
| | 20 | | Caring for body parts | * | 8 | | | * |
| | 30 | | Toileting | | | 11 | | * |
| | 40 | | Dressing | * | 16 | 19 | * | * |
| | 50 | | Eating | | | 19 | | * |
| | 60 | | Drinking | | | 11 | | * |
| | 70 | | Looking after one's health | * | 67 | 41 | | |
| | 98 | | Self-care, other specified | | | | | * |
| D6 | | | Domestic life | | ***67*** | ***52*** | | * |
| | 20 | | Acquisition of goods and services | * | 16 | 26 | | * |
| | 30 | | Preparing meals | * | 16 | 19 | | * |
| | 40 | | Doing housework | * | 33 | 30 | | * |
| | 49 | | Household tasks, other specified and unspecified | | | | * | * |
| | 50 | | Caring for household objects | * | 42 | 26 | | * |
| | 60 | | Assisting others | * | 16 | 30 | | |
| | 99 | | Domestic life, unspecified | | | | | * |
| D7 | | | Interpersonal interactions and relationships | * | ***58*** | ***52*** | | |
| | 20 | | Complex interpersonal interactions | | | 4 | | |
| | 30 | | Relating with strangers | * | 8 | | | |
| | 40 | | Formal relationships | * | 8 | 7 | | |
| | 50 | | Informal social relationships | * | 16 | 7 | | |
| | 60 | | Family relationships | * | 42 | 37 | | * |
| | 70 | | Intimate relationships | * | 8 | 37 | | |
| D8 | | | Major life areas | | ***67*** | ***78*** | | |
| | 30 | | Higher education | * | 16 | 4 | | |

| ICF code | | | ICF Category Description | Patients' Perspective | | Clinicians' perspective | Clinical trials | |
|---|---|---|---|---|---|---|---|---|
| | 39 | | Education, other specified and unspecified | | | | | * |
| | 45 | | Acquiring, keeping and terminating a job | * | 33 | 11 | | |
| | 50 | | Remunerative employment | * | 67 | 74 | | * |
| | 55 | | Non-remunerative employment | * | 25 | 4 | | |
| | 59 | | Work and employment, other specified and unspecified | | | 4 | * | * |
| | 70 | | Economic self-sufficiency | * | 16 | 4 | | |
| D9 | | | Community, social and civic life | | ***100*** | ***85*** | | |
| | 10 | | Community life | * | 25 | 15 | | |
| | 20 | | Recreation and leisure | * | 100 | 85 | * | * |
| | 30 | | Religion and spirituality | * | 16 | 11 | | |
| **Environmental Factors** | | | | | | | | |
| E1 | | | Products and technology | | ***100*** | ***63*** | | |
| | 10 | | Products or substances for personal consumption | * | 100 | | | |
| | | 1 | Drugs | * | 100 | | | * |
| | 15 | | Products and technology for personal use in daily living | * | 25 | | | * |
| | 20 | | Products and technology for personal indoor and outdoor mobility and transportation | * | 8 | 11 | | * |
| | 25 | | Products and technology for communication | * | 25 | 11 | | |
| | 30 | | Products and technology for education | * | 75 | | | |
| | 35 | | Products and technology for employment | * | | 7 | | |
| | 50 | | Design, construction and building products and technology of buildings for public use | * | 16 | | | |
| | 55 | | Design, construction and building products and technology of buildings for private use | * | 25 | 11 | | |
| | 65 | | Assets | * | 42 | 37 | | |
| | 98 | | Products and technology, other specified | * | 82 | 41 | | * |
| | | | > Assistive products and technology | * | | 33 | | * |
| | | | > Medical products and technology required as part of medical treatment | * | | 15 | | * |
| E2 | | | Natural environment and human-made changes to environment | | ***92*** | ***30*** | | |
| | 10 | | Physical geography | * | 50 | 19 | | |
| | 25 | | Climate | * | 42 | 4 | | |
| | 60 | | Air quality | * | 8 | 4 | | |

| ICF code | | | ICF Category Description | Patients' Perspective | | Clinicians' perspective | Clinical trials | |
|---|---|---|---|---|---|---|---|---|
| | 98 | | Natural environment and human-made changes to environment, other specified | * | 42 | 7 | | |
| E3 | | | Support and relationships | * | ***92*** | ***93*** | | |
| | 10 | | Immediate family | * | 92 | 63 | | |
| | 20 | | Friends | * | 42 | 19 | | |
| | 25 | | Acquaintances, peers, colleagues, neighbours and community members | * | 9 | 7 | | |
| | 40 | | Personal care providers and personal assistants | * | 25 | 7 | | * |
| | 45 | | Strangers | * | | | | |
| | 50 | | Domesticated animals | | | 7 | | |
| | 55 | | Health professionals | * | 75 | 19 | | |
| | 98 | | Support and relationships, other specified | * | 58 | 19 | | |
| E4 | | | Attitudes | * | ***92*** | ***30*** | | |
| | 10 | | Individual attitudes of immediate family members | * | 58 | 15 | | |
| | 20 | | Individual attitudes of friends | * | 8 | 4 | | |
| | 25 | | Individual attitudes of acquaintances, peers, colleagues, neighbours and community members | * | 33 | 15 | | |
| | 30 | | Individual attitudes of people in positions of authority | | | 4 | | |
| | 45 | | Individual attitudes of strangers | * | 33 | | | |
| | 50 | | Individual attitudes of health professionals | * | 75 | 11 | | |
| | 60 | | Societal attitudes | | | 7 | | |
| E5 | | | Services, systems and policies | | ***100*** | ***96*** | | |
| | 20 | | Open space planning services, systems and policies | | | 4 | | |
| | 25 | | Housing services, systems and policies | * | 8 | | | |
| | 30 | | Utilities services, systems and policies | * | 8 | 4 | | |
| | 35 | | Communication services, systems and policies | * | 8 | 4 | | |
| | 40 | | Transportation services, systems and policies | * | 16 | 4 | | |
| | 60 | | Media services, systems and policies | * | 8 | 4 | | |
| | 70 | | Social security services, systems and policies | * | 25 | 22 | | |
| | 80 | | Health services, systems and policies | * | 100 | 74 | | |
| | | 0 | Health services | * | 100 | 19 | | * |
| | | 1 | Health systems | * | 75 | 67 | | |
| | | 2 | Health policies | | | 11 | | |

| ICF code | | | ICF Category Description | Patients' Perspective | | Clinicians' perspective | Clinical trials | |
|---|---|---|---|---|---|---|---|---|
| | 90 | | Labour and employment services, systems and policies | * | 27 | 48 | | |
| | 98 | | Services, systems and policies, other specified | | | 4 | | |

*"*" in the cells indicate that at least one item that "mapped" to the specific ICF category was identified by at least one of participating patients (1st column) or in at least one of the identified clinical trials (last 2 columns). #Numbers represent % of participants (out of 12 individual interviews for patient perspective and out of 27 respondents for clinicians' perspective) who identified at least one item in the corresponding category or its lower level subcategories; numbers in regular font represent the % for the specific 2nd level category, underlined and italicised bold numbers represent the % for the 1st level summary.*

**Table 6-B. Comparison of ICF categories measured in AAV clinical trials to those identified as important by patients with AAV and clinicians involved in care of AAV patients – "personal factors"**

| Proposed ICF code | ICF Category Description | Patients' Perspective | | Clinicians' Perspective | Clinical trials | |
|---|---|---|---|---|---|---|
| | | Overall for patient perspective | Prevalence in interviews[#] | Prevalence in clinician Delphi[#] | OMERACT Core Set | Overall for literature perspective |
| P1 | **Facts** | | ***58*** | ***52*** | | |
| 10 | Demographic characteristics | | ***50*** | ***30*** | | |
| 0 | Age | * | 36 | 11 | | * |
| 1 | Education level | | | 15 | | |
| 2 | Gender/sex role | | | 7 | | * |
| 3 | Health literacy | * | 33 | 15 | | |
| 4 | Occupation | * | 18 | 19 | | |
| 5 | Race/ethnicity | | | 11 | | * |
| 20 | Personal history and biography | | ***50*** | ***22*** | | |
| 0 | Comorbidities | * | 33 | 22 | | * |
| 2 | Personal and family circumstances | * | 42 | | | |
| 30 | Position in the immediate social and physical context | * | ***25*** | ***37*** | | |
| 0 | Family | | | | | |
| 0 | Marital status | | | 4 | | |
| 1 | Family planning | | | 7 | | |
| 1 | Economic | | | | | |
| 0 | Socioeconomic status | | | 4 | | |
| 1 | Income | * | 16 | 37 | | |
| 2 | Financial independence | * | 16 | 4 | | |
| P2 | **Experience** | | ***100*** | ***41*** | | |
| 10 | Feelings | | ***33*** | ***0*** | | |
| 0 | Emotions / moods | * | 33 | | | |
| 20 | Thoughts and beliefs | | ***100*** | ***41*** | | |
| 0 | Attitude towards medical care | * | 100 | 4 | | |

| Proposed ICF code | | | | ICF Category Description | Patients' Perspective | | Clinicians' Perspective | Clinical trials | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 0 | Attitude to access to medical care | * | 33 | 4 | | |
| | | | 1 | Attitude to the process of diagnosis | * | 67 | | | |
| | | | 2 | Attitude to complementary medicine | * | 8 | 4 | | |
| | | | 3 | Interest in own health | * | 75 | 11 | | |
| | | | 4 | Personal views of the medical aspect of disease | * | 75 | | | |
| | | | 5 | Attitude towards medications and other treatments | * | 92 | 11 | | |
| | | | 6 | Satisfaction with monitoring | * | 42 | | | |
| | | | 7 | Attitude towards physicians and other health care providers | * | 92 | 7 | | |
| | | | 8 | Trust or distrust of medical care | * | 58 | | | |
| | | 1 | | Psychological reaction to disease | * | 100 | | | |
| | | | 0 | Concern about appearance | * | 75 | 15 | | |
| | | | 1 | Increased appreciation of what life gives | * | 42 | | | |
| | | | 2 | Effect of not knowing what's going on before diagnosis | * | 33 | | | |
| | | | 3 | Relief versus fear after diagnosis | * | 25 | | | |
| | | | 4 | Effect of AAV on others | * | 25 | | | |
| | | | 5 | Effects of rare & "unknown" nature of disease | * | 50 | 4 | | |
| | | | 6 | Psychological effects of being physically unwell | * | 42 | 4 | | |
| | | | 7 | Sense that life is over / AAV dominates | * | 8 | | | |
| | | | 8 | Positive effects (other than appreciation) | * | 33 | | | |
| | | 2 | | Disease becoming a constant threat | * | | | | |
| | | | 0 | Worrying about body cues | * | 33 | 4 | | |
| | | | 1 | Worry about future flares | * | 25 | | | |
| | | | 3 | Effects of incurable nature of disease | * | 33 | | | |
| | | | 4 | Worry about prognosis / death | * | 92 | | | |
| | | | 5 | Worry about side effects of drugs | * | 75 | | | |
| | | | | Worry about weak immune system | * | | | | |
| | | | 6 | Effect of unpredictable / uncertain nature of disease | * | 50 | 4 | | |
| | | | 7 | Effect of unpredictable / uncertain nature of disease | * | 75 | | | |
| | 30 | | | Motives | * | ***50*** | ***11*** | | |

| Proposed ICF code | | | | ICF Category Description | Patients' Perspective | | Clinicians' Perspective | Clinical trials | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0 | | Need to reassess life goals due to limited abilities | | | | | |
| | | | 0 | Change of physical ability | * | 25 | | | |
| | | | 1 | Change of overall potential | * | 25 | | | |
| | | | 2 | Ability to travel | * | 33 | | | |
| | | | 3 | Work / career ambitions | * | 16 | 7 | | |
| P3 | | | | **Patterns of experience and behavior** | | ***100*** | ***78*** | | |
| | 10 | | | Habits | * | ***75*** | ***41*** | | |
| | | 0 | | Dietary habits | * | 25 | 11 | | |
| | | 1 | | Fitness | * | 33 | 4 | | |
| | | 2 | | Compliance with management | * | 25 | 30 | | * |
| | | 3 | | Health behaviors | * | 50 | 11 | | |
| | | 4 | | Other habits (smoking, EtOH) | * | 16 | 26 | | * |
| | 20 | | | Personality | * | ***92*** | ***52*** | | |
| | | 0 | | Effect of personality of impact of disease | * | 83 | 52 | | |
| | | | 0 | Positive attitude | * | | 15 | | |
| | | 1 | | Disease changing personality / life | * | 50 | | | |
| | 30 | | | Adaptation to chronic illness | * | ***100*** | ***22*** | | |
| | | 0 | | Go on with life | * | 67 | 4 | | |
| | | 1 | | Attributing negative events to disease | * | 16 | 4 | | |
| | | 2 | | Denial | * | 16 | | | |
| | | 3 | | Search for explanation - why me? | * | 58 | 4 | | |
| | | 4 | | Comparing self to others | * | 58 | | | |
| | | 5 | | Strategies to facilitate adaptation | * | 25 | 11 | | |
| | | 6 | | Seeking sympathy | * | 16 | | | |
| | | 7 | | Sense of uniqueness of their case | * | 25 | | | |

*"*" in the cells indicate that at least one item that "mapped" to the specific ICF category was identified by at least one of participating patients or in at least one of the identified clinical trials.*
*[#]Numbers represent % of participants (out of 12 individual interviews for patient perspective and out of 27 respondents for clinicians' perspective) who identified at least one item in the corresponding category; numbers in regular font represent the % for the specific category (not summarized), underlined and italicised bold numbers represent the summary at the level of Parts and their major divisions.*

**Table 6-C. Comparison of ICF categories measured in AAV clinical trials to those identified as important by patients with AAV and clinicians involved in care of AAV patients – "health conditions" and concepts "not covered" and "not definable" by the ICF**

| ICF code | ICF Category Description | Patients' Perspective | | Clinicians' Perspective | Clinical trials | |
|---|---|---|---|---|---|---|
| | | Overall for patient perspective | Prevalence in interviews[#] | Prevalence in clinician Delphi[#] | OMERACT Core Set | Overall for literature perspective |
| **Health Conditions** | | | | | | |
| | Asthma | * | 16 | 19 | * | * |
| | Avascular necrosis | * | | 15 | | |
| | Cholesteatoma | | | | | * |
| | Depression | * | 16 | 11 | | |
| | Diabetes | * | 8 | 11 | * | * |
| | Fibromyalgia | | | | | |
| | Infections | * | 42 | | | * |
| | Malignancy | * | 16 | 11 | * | * |
| | Obstructive sleep apnea | | | 7 | | |
| | Osteoarthritis | * | 8 | | | |
| | Osteoporosis | | | 26 | * | * |
| | Raynaud's syndrome | * | 8 | | | |
| **Not covered** | | | | | | |
| | Diagnosis (process) | * | 75 | 4 | | |
| | Clinical research | * | 25 | 4 | | |
| Nc-bf | Central nervous system function | | | 15 | | * |
| | Brain function | | | 4 | * | * |
| | Cerebrospinal fluid | | | | | * |
| | Cranial nerve palsy | | | 19 | * | * |
| | Spinal cord dysfunction | | | 4 | | |
| | Gallbladder dysfunction | * | 8 | | | |
| | Hepatic function | | | 4 | | |
| | Mucus production | * | 16 | | | |

| ICF code | ICF Category Description | Patients' Perspective | | Clinicians' Perspective | Clinical trials | |
|---|---|---|---|---|---|---|
| | Nasal functions | * | 16 | 15 | | |
| | Peripheral nerve function | | | 52 | | * |
| | Sinus function | * | 50 | 4 | * | * |
| Nc-bs | Cerebrospinal fluid | | | | | * |
| | Retroperitoneal space | | | 4 | | |
| | Sinuses | * | 58 | 52 | | * |
| Nc-ap | Activities related to medical care | * | 27 | 19 | | |
| nc-env | Environmental safety | | | 7 | | |
| | Information about disease & drugs | * | 67 | 11 | | |
| | Work environment | * | 25 | 52 | | |
| | Living arrangement | * | 42 | 15 | | |
| | Stress | * | 50 | | | |
| **Not definable** | | | | | | |
| | Adverse events | | | | | * |
| | Complication | | | | * | * |
| | General well-being | * | 75 | | * | * |
| | Global assessment, patient | | | | | * |
| | Global assessment, physician | | | | | * |
| | Mental/psychological health | * | 8 | | | |
| | Physical health | * | 25 | 4 | | |
| | HRQoL | * | | | | * |
| | Q-TWIST = quality-adjusted time without symptoms or toxicity | | | | | * |
| | Severity of illness | | | | | |
| | Life-threatening disease | | | | | * |
| | Limited disease | | | | * | * |
| | Non-life-threatening disease | | | | | * |
| | Severe disease | | | | * | * |
| | Stage of illness | | | 4 | | |
| | Disease-free period | | | | | * |
| | Flare / relapse | * | 50 | 4 | * | * |
| | Low disease activity | | | | | * |
| | Persistent disease / chronic disease | | | | * | * |

| ICF code | ICF Category Description | Patients' Perspective | | Clinicians' Perspective | Clinical trials | |
|---|---|---|---|---|---|---|
| | Progressive disease | | | | | * |
| | Restoration of immune tolerance | | | | | * |
| | Stability of medical status | * | 16 | | | * |
| | Remission | * | 33 | | | * |
| | Survival / death | * | 25 | | * | * |
| | Treatment | | | | | * |
| | Feasibility | | | | | * |
| | Safety | | | | | * |
| | Effect of treatment | * | 67 | | | * |
| | Side effects from drugs (excluding prednisone) | * | 83 | 30 | | * |
| | Side effects of prednisone | * | 75 | 26 | | |
| Nd - bf | Bleeding | | | 4 | | |
| | Cyanosis | | | 4 | | |
| | Infection | * | 25 | | | * |
| | Malaise | | | | * | * |
| | Malignancy | | | 11 | * | * |
| | Physical exam | | | | | * |
| | Vital signs | | | | | * |
| | Sepsis | | | | | * |
| | Tongue function | | | 4 | | |
| | Vital / critical organ | | | | | * |
| Nd - bs | Cyanosis | | | 4 | | |
| | Esthetical appearance | | | 26 | | |
| | Face | | | 4 | | |
| | Infection | * | 25 | | | * |
| | Malignancy | | | 11 | | * |
| | Mucosa | | | 15 | | |
| | Tissue loss | | | 7 | | * |
| | Cartilage | | | 4 | | |
| | Physical exam | | | | | * |
| | Vital / critical organ | | | | | * |
| Nd - ap | Ability to do physical activity | * | 25 | | | |
| | Using / operating technology | * | 8 | 19 | | |

| ICF code | ICF Category Description | Patients' Perspective | | Clinicians' Perspective | Clinical trials | |
|---|---|---|---|---|---|---|
| | Other miscellaneous activities | | | 4 | | |
| | Independence in activities | * | 8 | 11 | | |
| | Planning for future | * | 33 | | | |

*"*" in the cells indicate that at least one item that "mapped" to the specific ICF category was identified by at least one of participating patients or in at least one of the identified clinical trials.*
*#Numbers represent % of participants (out of 12 individual interviews for patient perspective and out of 27 respondents for clinicians' perspective) who identified at least one item in the corresponding category; hc – health condition, nc – not covered, nd – not defined, bf – body functions, bs – body structures, ap – activities and participation, env – environmental factors.*

## 6.4 Discussion of comparison of areas of AAV measured in clinical trials to those important to patients with AAV and clinicians who are involved in their care

Patients' and clinicians' views of relevance of various AAV outcomes are somewhat different, and these views differ from what is measured in clinical trials of AAV.

### 6.4.1 Comparison for ICF components "body functions" and "body structures"

Examining Table 6-A reveals that all 3 perspectives (patients', clinicians' and that of clinical trials) demonstrate detailed coverage of ICF components "body functions" and "body structures." Patients appear to focus relatively less attention on "body structures" and more on "body functions" in comparison to clinicians and clinical trials. The ratio for the number of identified categories in "body functions" to "body structures" for patients is 2.3 compared to 1.5 for clinicians and 1.4 for outcomes measured in clinical trials. No categories in the ICF component "body structures" were uniquely identified by patients. In contrast, many of the "body structures" that were not identified by patients were identified with high prevalence by clinicians – "structure of brain" identified by 56% of responding clinicians (mainly in reference to strokes), damage to peripheral nerves identified by 81% of clinicians, structure of eye socket by 44%, structure of pharynx by 48%, and upper extremity disruptions such as ischemic digits and gangrene by 52%; all of these categories are also measured in clinical trials. Such discrepancy between views of clinicians and researchers on the one hand and patients on the other can be explained by the fact that these are relatively rare but very severe manifestations of AAV that many patients do not themselves experience and consequently do not identify. For some of these categories, patients may be unaware of the presence of a specific structural impairment while recognizing its functional consequence. As an example, damage to peripheral nerves may be experienced by a patient as "inability to move foot"; this will link to the ICF body function category "mobility of joint function" and not to the body structure category "peripheral nerve".

Clinicians and researchers have the knowledge about the whole spectrum of clinical manifestations of AAV, and they tend to identify the most severe (even if very rare) manifestations being aware that the clinical and functional consequences of these manifestations, when they occur, are very significant. This observation is similar to findings by Herlyn et al (41) who studied patient perspective on the most important aspects of vasculitis by using a disease-specific questionnaire developed for the purpose of their study. The authors found that the most common items identified by patients as most bothersome were fatigue, pain, and musculoskeletal symptoms – items that are common but that most clinicians consider as relatively "mild." At the same time, patients in that study did not prioritize the more severe but less frequent cardiopulmonary and central nervous systems manifestations that were ranked as "most important" by clinical experts in a different study by Seo et al (18), or "hard outcomes" like dialysis- and oxygen- dependency that are often the focus of clinical trials.

### 6.4.2 Comparison for ICF component "activities and participation"

Similar limitations of "activities and participation" were identified as relevant by patients and clinicians, but these differ from those measured in AAV clinical trials. While some areas of "activities and participation" are sampled in clinical trials to a significant detail (namely "Mobility" and "Self-care"), others are either not covered at all (namely "Learning and applying knowledge" and "Communication") or covered to a very limited extent (such as "Interpersonal interactions and relationships" and "Community, social and civic life", where only a single 2$^{nd}$-level category is sampled in all of the identified clinical trials ("Family relationships" and "Recreation and leisure", respectively)).

Patients experience the limitations in activities and restrictions of ability to participate in various life situations as a result of their AAV or its treatments, and they share their experiences with their health care providers making them aware of the importance of these limitations.

However, the vast majority of clinical trials performed to date focus on measuring the effects of interventions (most commonly pharmacologic agents) on the physiologic activity or progression of disease. Assessing effects of interventions on patients' activities and participation in life situations is emerging as an important part of clinical studies only in the last few years, with incorporation of patient values and preferences into the new Grading of Recommendations Assessment, Development and Evaluation (GRADE) system of rating evidence and strength of recommendations (42), with the establishment by the US congress of the Patient-Centered Outcomes Research Institute (PCORI) that encourages research that studies what "people in the population of interest notice and care about" (43), and with establishment of patient input as an critical constituent of the OMERACT process (4).

### 6.4.3 Comparison for ICF "Contextual factors"

Contextual factors, both environmental and personal, appear to be more relevant to patients than clinicians and clinical trials. Significantly fewer clinicians identified various "environmental factors" as significant modifiers of impact of AAV compared to patients. Studying Table 6-A reveals that the prevalence of nearly every "environmental factor" is higher for patient interviews compared to clinicians' perspective, with many prevalence values being substantially different. Notably, the few "environmental factors" identified exclusively by clinicians tend to represent the public policy-level factors including "Health policies", "Open space planning services, systems and policies" (which refers to planning of city streets that would be accommodating to people with disabilities), and "Societal attitudes," highlighting the increasingly recognized role of clinicians as health advocates.

This difference in importance of "environmental factors" is even bigger between the patient perspective and what is measured in clinical trials; only 6 2$^{nd}$-level "environmental factor" categories were addressed in identified AAV clinical trials. Broad categories not measured in clinical

trials include “Natural environment and human-made changes to environment” which includes physical geography and climate and “Attitudes” of various groups of significant others, of health professionals and of society. At least one category from each of these broad groups was mentioned by 75% and 92% of patients, respectively, which highlights the significant gap between what is important to patients and what is measured in clinical trials. “Help from other individuals” in performing various tasks and activities that mapped to the ICF category “e340 Personal care providers and personal assistants” was the only item that belonged to the broad area “Support and relationships” that was measured in clinical trials; in contrast, 92% of the patients identified at least one category from “Support and relationships” as important in determining the impact of AAV. While “Personal care providers and personal assistants” was only identified by 25% of patients, other categories that are not measured in clinical trials including “Immediate family”, “Friends”, “Health professionals” and “others in a similar situation” (the latter mapped to ICF category “e398 Support and relationships, other specified”) appeared to be more important to patients (they were identified by 92%, 42%, 75%, and 58% of patients, respectively). Similarly, various “health services” such as medical procedures and requirement for hospitalization are the only “Services, systems and policies” addressed by clinical trials. While these services were also important to both patients and clinicians, a number of other categories from the broad area “Services, systems and policies” that are not measured in clinical trials were identified by both patients and clinicians; most notable examples of these are “Social security services, systems and policies” that include social support and various types of insurance (identified by 25% of patients and 22% of clinicians) and “Labour and employment services, systems and policies” that includes capacity of the work places to accommodate patients’ changed abilities, unemployment insurance and worker’s compensation (identified by 27% of patients and 48% of physicians).

Examining table 6-B reveals that the discordance between the patient perspective on the one side and clinicians' and researchers' perspectives on the other is even greater for the ICF component "personal factors". Similar to what was observed for "environmental factors", studying the prevalence of identification of different items by patients versus clinicians shows that relatively fewer clinicians identify "personal factors" as significant modifiers of effect of AAV for nearly every "personal factor" category. Furthermore, clinicians tend to focus on personal "Facts" (1st Part of "personal factors") as well as the characteristics of experience and behaviour that are directly relevant to medical care such as health-related habits, compliance with medical care, and strategies of coping with the medical illness. "Income", "compliance with management" and "health habits" are the only 3 "personal factors" that were identified by greater proportion of clinicians compared to patients. In contrast, patients tend to stress personal "Experience" and "Patterns of experience and behaviour" (2nd and 3rd broad "Parts" of "personal factors") as can be seen from the large number of categories belonging to these 2 broad parts identified by patients; in contrast, only few of these categories were identified by clinicians, and even for those few the prevalence of identification was very low.

Once again, the discrepancy in regards to personal factors is even greater between patient perspective and what is measured in clinical trials, with the latter considering only 6 specific "personal factors": age, sex, ethnic background, comorbidities, smoking and compliance with medical treatment. These personal factors are recorded as baseline characteristics or covariates that can act as confounders or effect modifiers in the studied relationship between the intervention and the outcomes of interest.

The concept of "contextual factors" that could act as modifiers of the effect of a medical condition on patient's function and general health has entered the medical field very recently. "Context" is part of the recently developed OMERACT Filter 2.0 framework for developing core sets

of outcome measures for clinical trials. The framework defines “contextual factors” as “those that are not the primary object of research but that may influence the results or the interpretation of the results” (44). As discussed earlier, many interventional trials performed to date (and thus included into this analysis) focused on specific physiologic outcomes such as renal function or a score on a composite measure of disease activity or damage; for these trials, personal and environmental contextual factors were, indeed, largely irrelevant because they would not have an effect on the outcomes of interest even if they were measured. The recent guidelines on outcome measurement in clinical trials call towards incorporating into every clinical trial a range of outcomes from different core areas of outcome measurement, including outcomes assessing “life impact” (44) that are likely very susceptible to the effects of various contextual factors. Some contextual factors, particularly those that are not “modifiable” such as patients’ age, socioeconomic status, the state of economy of their place of residence and the quality of patient’s social support system will merely constitute potential effect modifiers or confounders that will need to be adjusted for when assessing the relationship between the studied intervention and the outcome of interest. Other factors could be potentially modifiable, and as such could become targets for subsequent interventions (for example psychological counselling for developing of healthy coping strategies) or policy changes (for example enhancing financial support for essential health services). With gradual acceptance of the OMERACT filter 2.0 framework (or its subsequent modifications) as the standard for the process of outcome measure development, contextual factors will gradually become incorporated into the design and analysis of clinical trials. The degree of importance of these contextual factors will depend on the primary purpose of the trials (the “setting” in the OMERACT framework), ranging from recognition of their irrelevance in phase I and II trials of pharmacologic effects of new therapeutic agents to potentially crucial role along with the studied interventions for

trials on effects of non-pharmacologic interventions such as self-management strategies or support groups.

## 6.5 Strengths and limitations of the study

This study captured three different views of AAV - that of patients, clinicians, and the clinical trials. It yielded a comprehensive picture of relevant areas when determining the impact of AAV on patients' function and overall health. The use of the ICF allowed direct comparison of the three perspectives of AAV despite the fact that they were studied using different approaches – patient perspective was captured using individual semi-structured interviews and focus groups, clinicians' view was captured via an email-based questionnaire, and a comprehensive literature review was used to identify aspects of AAV measured in clinical trials. The descriptive comparison of the different perspectives of the same medical condition performed in this study introduces yet another application of the ICF, alongside its current uses to compare the content of different outcome measures and the impact of different medical conditions (9).

The study has considerable geographic breadth, particularly for clinicians' perspective. The use of an email-based questionnaire allowed us to include clinical experts from 12 countries across all continents; in addition, experts from 7 medical specialties that are routinely involved in clinical care of patients with AAV provided their opinion, adding to the diversity of the study population. The scope is smaller for patients due to the logistic difficulties of conducting patient interviews in different countries; still, 3 countries from 2 continents were included (USA and Canada as well as the UK) which provides substantial geographic breadth. Similarly, all interventional studies regardless of country of origin or primary purpose were included into extraction of the outcome measures used in clinical trials. Notably, although we did not limit our search to a particular language, the majority of the identified studies (and all of those that were deemed eligible for outcome extraction) were published in English. This is likely because AAV is a rare condition and primarily international approach to studying AAV is employed; consequently, many of the identified

studies and most of the larger ones involve many centres across several countries that are ultimately published in international journals in English language.

The study has a number of limitations. Although we feel that the use of the ICF is a significant strength, the ICF classification and its use as a framework for comparison of the scope of identified areas of importance has limitations. Some of these limitations were already covered in the "Discussion" section of the Manuscript included in Chapter 3 of this thesis. Briefly, the limitations discussed in Chapter 3 included presence of some degree of subjectivity to the process of linking of constructs to the ICF, imperfect coverage by the ICF of the various aspects that can be relevant when studying complex multisystem conditions like AAV and lack of consideration by the ICF of concepts of time and process. An additional limitation of the ICF classification specific to the aim of this study, namely to compare the perspectives of patients, clinicians and clinical investigators is that its large size and a very large number of individual categories would invariably introduce the multiple comparison bias if we were to attempt to compare the perspectives quantitatively. Such comparison would further be complicated by the fact that different approaches were used to study the different perspectives. Consequently, we took a descriptive approach to the comparison and looked for patterns in related groups of ICF categories. Such broader approach to comparing the perspectives is also likely conceptually easier to interpret and is clinically more meaningful than comparing individual categories. Finally, as was briefly discussed in Chapter 5 despite the comprehensiveness of the ICF and the apparent specificity of its categories, many of these specific categories capture a range of impairments of body functions or body structures, limitations of activities, restrictions of participation or contextual factors. As a result, a number of related (as defined by the ICF) but at times clinically distinct concepts may be represented by a single ICF category. When making use of the ICF as tool for comparison in various contexts, it is important to avoid comparing different concepts mistakenly assuming they are one concept

because they link to one ICF category. This can be done by cross-referencing the results of such comparisons against the original clinical context, as was done when comparing ICF categories identified by patients with different specific types of AAV in Chapter 5.

Although the qualitative approach is useful to identify areas of AAV relevant to various stakeholders, this should ideally be supplemented with quantitative data to provide information on prevalence of the various impairments and limitations identified by patients, and frequency of identification of these areas by clinicians. Furthermore, prioritization of the degree of impairments and limitations and the extent of their impact on patients' functioning and health would provide invaluable data that cannot be obtained using exclusively qualitative approach. Such prioritization of both the patients' and the clinicians' perspectives is planned to be the next step in this endeavor of using the ICF to study AAV. This will be carried out outside of the timeframe of this Master's thesis.

# Chapter 7 Concluding discussion

## 7.1 Summary of study findings

ICF proved to be useful as a framework for detailed description of areas important for determining the impact of AAV on patients' function and general health from the point of view of 1) patients with AAV, 2) clinicians who treat AAV patients and 3) clinical trials; it also facilitated standardized comparison of identified areas of AAV from the three perspectives.

The ICF classification is consistent with the bio-psycho-social model of disease, and as such highlights the relationship between physical effects of the medical condition (represented by the ICF components "body functions" and "body structures"), patient's functioning and participation in life activities (represented by ICF component "activities and participation"), and contextual factors that could be either facilitators or barriers to patient's ability to adjust (both physically and psychologically) to their diagnosis (represented by ICF "personal" and "environment factors").

Patients, clinicians, and clinical investigators identify a variety of factors from each of these areas as relevant for determining the overall effect of AAV, but the relative importance of these areas and of the individual items within the ICF components differ.

Comparing the views of patients and clinicians reveals that various impairments of "body structures" appear to be more important to clinicians than patients. Furthermore, patients more frequently identified both environmental and personal factors as being significant modifiers of the impact of AAV. Clinicians tend to focus on hard "factual" factors such as demographics, comorbidities, availability of health services and social support while the range of factors identified by patients is much broader and dominated by the more intangible factors like attitudes of those around them and their own reactions and thoughts.

Outcomes measured in clinical trials of patients with AAV are not entirely representative of the areas identified as important by patients and clinicians. Clinical trials do not measure the whole spectrum of limitations in activities and restrictions of participation identified by patients and clinicians, they consider only a small number of environmental and personal factors – the latter likely because contextual factors became recognized as relevant for interpreting the measured outcomes very recently. The areas that are under-sampled by clinical trials are those that tend to be more important to patients compared to clinicians. This is likely a consequence of the fact that both the clinical trials and the composite tools used in these trials are designed by the clinical investigators, the majority of whom are also clinicians who are involved in the care of patients with AAV.

Up until recently, patients were not part of the process of development of outcome measures even for instruments that aim to capture "patient reported outcomes" (PRO); as an example, SF-36 - a validated measure of HRQoL that is included in the OMERACT AAV Core Set (see the Manuscript in Chapter 3 of this thesis for further discussion of the OMERACT AAV Core Set) – is designed to be filled out by the patients (which makes it a PRO measure), but was developed exclusively by clinicians. In recent years the discordance of views of the impact of vasculitis between patients on one side and clinicians and clinical investigators on the other is becoming increasingly recognized (32), and with that comes the recognition of importance of including patient perspective in the development of vasculitis-specific outcome measures (41). PCORI was recently established to advance patient-centered research that studies aspects of health relevant to patients (43). The OMERACT initiative has revolutionized the role of patients in the process of outcome measure development, with patient representatives actively participating in nearly every part of the OMERACT process (41).

Furthermore, the OMERACT process encourages participation of all end-users of the outcome measures in the process of their development. In addition to patients, the end-users of the health-related outcome measures could include clinicians and clinical investigators (the 3 perspectives considered in this study) but also health economists and policy makers as well as the manufacturers of pharmacologic agents (44, 45). The extent and the timing of participation of the various end-users is variable and needs to be tailored to the specific purpose of the outcome measure, the stage of its development, and the extent of relevance to the specific end-user (44).

The OMERACT initiative has broadened the scope of outcome measurement in clinical trials and standardised the process of its development. The recently developed OMERACT Filter 2.0 framework (depicted in Figure 1) recommends that outcome assessment in clinical trials address (a) the "Impact of the health condition" (which includes "Life Impact", "Economic Impact / Resource use", and "Death"), mainly represented by the ICF component "activities and participation", "environmental factors" (although the latter mainly correspond to the "contextual factors") and the "not covered" concept "death" respectively and (b) the "Pathophysiological Manifestations", represented by the ICF components "body functions" and "body structures"; the framework then recommends that (c) the "contextual factors" be considered when interpreting the outcomes outlined above (5). With eventual incorporation of this framework as the standard of outcome measurement and with increased inclusion of patients and other end-users into the process of outcome measure development the gaps observed in this study between areas measured in clinical trials and those identified as important by patients and physicians as the main outcome measure end-users should narrow and eventually close.

## 7.2 Significance of the study and implications for the future

This study identified and compared factors that are considered important for determining the impact of AAV on patients' health by 3 main end users of clinical outcome measures: 1) the patients, 2) the clinicians, and 3) the clinical researchers. The identified areas were analyzed in the context of the recently developed OMERACT filter 2.0 framework for developing the cores sets of outcome measures for clinical conditions (44). Important discrepancies were identified between patient perspective on the one side and views of clinicians and clinical investigators on the other. The goal of medical research and medical care in general is to make patients "better"; consequently, those aspects that are of importance to patients should be an invariable part of outcome measurement in clinical practice and in clinical research. The results of this study thus call for the need for 1) a more systematic approach to outcome measure development that takes into account views of all outcome measure end users the most important of which are patients and 2) development of new outcome measures that are responsive to the spectrum of the needs of patients with AAV – a group of complex multisystem chronic conditions. Both of these needs are being addressed by the work of the OMERACT initiative – the first goal through continuous evolution of recommended standards for developing outcome measures (46) and the second through the work of the OMERACT Vasculitis Working group towards developing a disease-specific patient-reported outcome instrument for AAV (22).

This study represents the initial stages of development of the ICF Core Sets for AAV. The ultimate aim of the ICF Core Sets is to identify the set of basic outcomes (represented by the individual ICF categories) that would represent the standard of "what" needs to be measured in clinical trials (and potentially in clinical practice) of AAV patients. Then, developing appropriate outcome measure tools (as just discussed above) that would enable measuring identified items would address the question of "how to measure" these areas of importance. All three perspectives

discussed and compared in this study will be captured within the ultimately resulting ICF Core Sets for AAV, enhancing our ability to capture the broader scope of impact of AAV, and ultimately improving clinicians' and clinical researchers' responsiveness to the needs of patients with AAV.

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# Appendices

## Appendix A. Search strategy for the comprehensive literature search of outcome measures in ANCA-associated vasculitis

### Appendix A.1. Initial search performed on Dec 15, 2011

#### *1. Databases: Embase and Medline*

Classic+Embase <1947 to 2011 December 14>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to Present>

---

ANCA associated vasculitis/ (1410)
Wegener granulomatosis/ (14699)
Churg Strauss syndrome/ (4413)
wegener$.tw. (12738)
Churg strauss.tw. (3653)
microscopic polyangiitis/ (1021)
microscopic polyangiitis.tw. (1873)
microscopic polyarteritis.tw. (526)
(Granulomatosis adj4 polyangiitis).tw. (759)
(ANCA$ adj5 vasculitis).tw. (2916)
(antineutrophil cytoplasm$ antibod$ adj5 vasculitis).tw. (860)
(anti neutrophil cytoplasm$ antibod$ adj5 vasculitis).tw. (462)
(allergic adj (granulomatosis or angiitis)).tw. (458)
or/1-13 (23870)
random$.tw. (1279638)
factorial$.tw. (33311)
crossover$.tw. (80648)
cross over.tw. (34967)
placebo$.tw. (312093)
(doubl$ adj blind$).tw. (233794)
(singl$ adj blind$).tw. (21305)
assign$.tw. (369417)
allocat$.tw. (121464)
volunteer$.tw. (289682)
crossover procedure/ (31672)
double blind procedure/ (106723)
randomized controlled trial/ (619554)
single blind procedure/ (14569)
or/15-28 (2157115)
14 and 29 (686)
30 use emczd (421)
exp anti-neutrophil cytoplasmic antibody-associated vasculitis/ (8155)
Antibodies, Antineutrophil Cytoplasmic/ and vasculitis/ (2985)
wegener$.tw. (12738)

Churg strauss.tw. (3653)
microscopic polyangiitis.tw. (1873)
microscopic polyarteritis.tw. (526)
(Granulomatosis adj4 polyangiitis).tw. (759)
(ANCA$ adj5 vasculitis).tw. (2916)
(antineutrophil cytoplasm$ antibod$ adj5 vasculitis).tw. (860)
(anti neutrophil cytoplasm$ antibod$ adj5 vasculitis).tw. (462)
(allergic adj (granulomatosis or angiitis)).tw. (458)
or/32-42 (21651)
randomized controlled trial.pt. (323095)
controlled clinical trial.pt. (84091)
randomi?ed.ab. (629679)
placebo.ab. (299789)
clinical trials as topic/ (168439)
randomly.ab. (381681)
trial.ti. (230557)
or/44-50 (1460278)
43 and 51 (504)
52 use prmz (270)
31 or 53 (691)
remove duplicates from 54 (523)

### *2. Cochrane database*

#1 MeSH descriptor Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis explode all trees
#2 MeSH descriptor Antibodies, Antineutrophil Cytoplasmic explode all trees
#3 MeSH descriptor Vasculitis, this term only
#4 (#2 AND #3)
#5 (wegener*):ti,ab,kw or (Churg strauss*):ti,ab,kw or (microscopic polyangiitis):ti,ab,kw or (microscopic polyarteritis):ti,ab,kw
#6 (Granulomatosis AND polyangiitis):ti,ab,kw or (ANCA* AND vasculitis):ti,ab,kw or (antineutrophil cytoplasm* antibod* AND vasculitis):ti,ab,kw or (anti neutrophil cytoplasm* antibod* ANd vasculitis):ti,ab,kw
#7 (allergic granulomatosis):ti,ab,kw or (allergic angiitis):ti,ab,kw
#8 (#1 OR #4 OR #5 OR #6 OR #7)
Limited to Cochrane Central 118

### *3. ClinicalTrials.gov*

anca OR wegeners OR Churg Strauss OR Anti-neutrophil cytoplasmic antibodies OR microscopic polyangiitis OR microscopic polyarteritis

# Appendix A.2. Updated search performed on November 17, 2013

## *1. Medline Database*

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

---

exp Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/ (7888)
Antibodies, Antineutrophil Cytoplasmic/ and vasculitis/ (1603)
wegener$.tw. (6100)
Churg strauss.tw. (1902)
microscopic polyangiitis.tw. (1032)
microscopic polyarteritis.tw. (250)
(Granulomatosis adj4 polyangiitis).tw. (645)
(ANCA$ adj5 vasculitis).tw. (1704)
(antineutrophil cytoplasm$ antibod$ adj5 vasculitis).tw. (562)
(anti neutrophil cytoplasm$ antibod$ adj5 vasculitis).tw. (316)
(allergic adj (granulomatosis or angiitis)).tw. (180)
or/1-11 (11596)
randomized controlled trial.pt. (390286)
controlled clinical trial.pt. (89931)
randomi?ed.ab. (372221)
placebo.ab. (163988)
clinical trials as topic/ (175429)
randomly.ab. (216609)
trial.ti. (132060)
or/13-19 (959774)
12 and 20 (355)
limit 21 to yr="2012 - 2013" (53)
201112$.ed. (80702)
21 and 23 (2)
22 or 24 (55)

## *2. Embase Database*

Database: Embase Classic+Embase <1947 to 2013 November 18>

---

ANCA associated vasculitis/ (1959)
Wegener granulomatosis/ (10286)
Churg Strauss syndrome/ (3556)
wegener$.tw. (8097)
Churg strauss.tw. (2503)
microscopic polyangiitis/ (1285)
microscopic polyangiitis.tw. (1298)
microscopic polyarteritis.tw. (274)
(Granulomatosis adj4 polyangiitis).tw. (805)
(ANCA$ adj5 vasculitis).tw. (2299)
(antineutrophil cytoplasm$ antibod$ adj5 vasculitis).tw. (596)
(anti neutrophil cytoplasm$ antibod$ adj5 vasculitis).tw. (353)
(allergic adj (granulomatosis or angiitis)).tw. (289)
or/1-13 (16821)
random$.tw. (881759)
factorial$.tw. (22974)
crossover$.tw. (50029)

cross over.tw. (22698)
placebo$.tw. (207225)
(doubl$ adj blind$).tw. (151859)
(singl$ adj blind$).tw. (14461)
assign$.tw. (241983)
allocat$.tw. (83183)
volunteer$.tw. (186355)
crossover procedure/ (39301)
double blind procedure/ (123367)
randomized controlled trial/ (362661)
single blind procedure/ (18546)
or/15-28 (1444582)
14 and 29 (573)
limit 30 to yr="2012 - 2013" (108)
201112$.dd. (91240)
30 and 32 (7)
31 or 33 (115)

### *3. Cochrane database*

EBM Reviews - Cochrane Central Register of Controlled Trials <October 2013>
---
exp Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/ (54)
Antibodies, Antineutrophil Cytoplasmic/ and vasculitis/ (20)
wegener$.tw. (61)
Churg strauss.tw. (22)
microscopic polyangiitis.tw. (17)
microscopic polyarteritis.tw. (2)
(Granulomatosis adj4 polyangiitis).tw. (14)
(ANCA$ adj5 vasculitis).tw. (53)
(antineutrophil cytoplasm$ antibod$ adj5 vasculitis).tw. (16)
(anti neutrophil cytoplasm$ antibod$ adj5 vasculitis).tw. (10)
(allergic adj (granulomatosis or angiitis)).tw. (1)
or/1-11 (135)
randomized controlled trial.pt. (325102)
controlled clinical trial.pt. (82480)
randomi?ed.ab. (199702)
placebo.ab. (109107)
clinical trials as topic/ (33010)
randomly.ab. (87904)
trial.ti. (105608)
or/13-19 (489660)
12 and 20 (109)
limit 21 to yr="2011 - 2013" (20)

### *4. ClinicalTrials.gov*

wegener OR wegeners OR wegener's OR Churg strauss OR polyangiitis OR polyarteritis OR ANCA OR Anti-neutrophil cytoplasmic antibodies or Antineutrophil cytoplasmic antibodies | updated from 12/15/2011 to 11/19/2013

## Appendix B. List of outcomes extracted from identified studies with sources

Table B.1. Disease-related states and definitions and vitality

| Disease-related grouping | Disease-related term | Definition of disease-related term or grouping (where available) | Source |
|---|---|---|---|
| Disease activity / extent | | | |
| | Chronic disease activity | | NCT00482066 |
| | Limited disease | Satisfaction of all of the following conditions:<br>Serum creatinine <=1.4mg/dL and absence of rise in serum creatinine more than 25% above baseline<br>absence of rbc casts in urine<br>Pulmonary involvement "circumscribed, with room air pO2>70mmHg or room air O2 sat by pulse oximetry > 92%<br>No involvement of any other critical organs that without immediate institution of maximal therapy threatens function of organ and/or patient's life | WGET Research Group; Control Clin Trials 2002; 23(4):450-68. |
| | Low disease activity | Persistence of <=2 minor BVAS items | NCT01446211 |
| | Progressive disease | Persistence of hematuria and proteinuria, with absence of improvement in GFR, or continuation of a major non-renal item on BVAS, at 6 weeks | Jones; N Engl J Med. 2010:363(3):211 |
| | Severe disease | Patient who does not satisfy definition of limited disease | WGET Research Group; Control Clin Trials 2002; 23(4):450-68. |
| Disease-free period | | Period between remission and first relapse or study end | de Groot; Kidney Blood Press Res 2005; 28:153.<br>De Groot; Kidney Blood Press Res 2003;26:249-302 abstract #90<br>de Groot; Ann Intern Med 2009; 150(10):670<br>Hiemstra JAMA 2010; 304(21):2381 |
| Relapse/flare | | No definition | NCT00040248<br>NCT00307645<br>Hiemstra; JAMA 2010;304(21):2381<br>Jayne; Q J Med 2000; 93(7):433<br>Cohen; Arthritis Rheum. 2007;57(4):686<br>NCT00307671<br>NCT01405807<br>Han; Am J Nephrol 2011;33:185 |

| Disease-related grouping | Disease-related term | Definition of disease-related term or grouping (where available) | Source |
|---|---|---|---|
| | | | Menthon; Clin Exp Rheumatol 2011; 29(Suppl.64):S63<br>Faurschou; Arthritis Rheum. 2012; 64(10):3472 |
| | | BVAS score 1+ | Pagnoux; N Engl J Med. 2008;359:2790<br>NCT00349674<br>Jones; N Engl J Med. 2010; 363(3):211 |
| | | One of:<br>Active glomerulonephritis (definition of "relapse), as defined by one of:<br>>=30% decrease in renal function + microscopic hematuria with red-cell cases<br>or:<br>Evidence of acute necrotizing lesions on renal biopsy<br>Pulmonary infiltrates with or without cavitation with rising serum C=Reactive protein in absence of infection or cancer<br>Sinusitis, otitis, ulceration of nasal mucosa, or a proliferative nasal mass, in combination with necrotizing granulomatous inflammation on biopsy<br>Progressive mononeuritis multiplex, cranial=nerve palsy, cerebral vasculitis, necrotizing scleritis, orbital pseudotumor, progressive tracheal stenosis with ctive disease on biopsy, peripheral gangrene, or necrotizing vasculitis of medium-sized or small muscular arteries. | Stegeman; N Engl J Med. 1996; 335(1):16. |
| | | Reoccurrence of symptoms attributable to active WG after complete or partial remission of at least 3 months | Metzler; Rheumatology 2007;46:1087 |
| | | New major systemic manifestations of WG, or worsening of initial symptoms | Guillevin; Arthritis Rheum. 40(12):2187 |
| | | Recurrence or new development of at least 1 manifestation of vasculitis (Wegener's granulomatosis) | Ribi; Arthritis Rheum. 2008; 58(2):586<br>Cohen; Arthritis Rheum. 2007; 57(4):686-93.<br>de Groot; Arthritis Rheum. 1996; 39(12):2052 |
| | | Recurrence or first appearance of disease activity sufficient to warrant an increase in dosage | Haubitz; Arthritis Rheum. 1998; 41(10):1835 |
| | Major relapse | | NCT00748644 |
| | | Life- or organ-threatening disease activity requiring increase PRD and a switch to CYC | Metzler; Rheumatology 2007; 46:1087 |
| | | BVAS > 10 at end of maintenance treatment | NCT 748644 |

| Disease-related grouping | Disease-related term | Definition of disease-related term or grouping (where available) | Source |
|---|---|---|---|
| | | Development of major organ involvement (eg – alveolar hemorrhage, abdominal pain, neuropathy) | Ribi; Arthritis Rheum. 2008; 58(2):586 |
| | | Major organ involvement / threat | Ribi; Arthritis Rheum. 2008; 58(2):588<br>Hiemstra; JAMA 2010; 304(21):2381<br>de Groot; Arthritis Rheum. 2005; 52(8):2461 |
| | | At least 1 major BVAS item | NCT01446211<br>de Groot; Ann Intern Med. 2009;150(10):670<br>Jayne; N Engl J Med. 2003; 349(1):36 |
| | | Required re-introduction of an immunosuppressant | Cohen; Arthritis Rheum. 2007; 57(4):686 |
| | | One of (attributable to active vasculitis):<br>30% increase of serum creatinine or 25% decrease of GFR within 3 months or focal necrotizing GN on histology<br>Clinical, radiologic or bronchoscopic evidence of pulmonary hemorrhage<br>Vision threat related to retinal vasculitis<br>New multifocal neurologic lesions or mononeuritis multiplex<br>GI hemorrhage or perforation<br>Proteinuria > 1g/day, cardiomyopathy and/or CNS involvement | Samson; Journal of Autoimmunity 2013; 43:60 |
| | Minor relapse | | NCT00748644 |
| | | Non-life-threatening flare, treated by transient increase of CS and/or MTX/leflunomide | Metzler; Rheumatology 2007; 46:1087<br>Hiemstra; JAMA 2010; 304(21):<br>de Groot; Arthritis Rheum. 2005;52(8):2461 |
| | | BVAS <=10 | NCT 748644 |
| | | occurrence or reappearance of CSS features without evidence of major organ involvement (eg – fever, arthralgias, and/or eosinophilia) | Ribi; Arthritis Rheum 2008; 58(2):586 |
| | | at least 3 minor BVAS, with no major BVAS | NCT01446211<br>Jayne; N Engl J Med. 2003; 349(1):36<br>de Groot; Ann Intern Med. 2009; 150(10):670 |
| | | Transient GC dose intensification sufficed | Cohen; Arthritis Rheum. 2007; 57(4):686 |
| | Time to relapse | | de Groot; Kidney Blood Press Res 2005; 28:153.<br>NCT01697267<br>NCT01663623 |
| | Relapse rate | | Rihova; Prague Med |

| Disease-related grouping | Disease-related term | Definition of disease-related term or grouping (where available) | Source |
|---|---|---|---|
| | at various time points | | Rep. 2004;105(1):64.<br>NCT00414128.<br>NCT00647166.<br>NCT00482066.<br>Harper; Ann Rheum Dis 2012;71:955<br>NCT01933724 |
| Remission | | No definition | Kidney blood press Res 2003;26:249 (abstract #27)<br>NCT01697267 |
| | | No clinic signs of vasculitis, improved or stable renal function, no active urine sediments and BVAS1=0, BVAS2<1 | Hu; Nephrol Dial Transplant 2008 23:1307 |
| | | BVAS indicating the absence of signs of new or worse disease activity, with persistent disease activity for no more than one item | Jayne; N Engl J Med. 2003; 349(1):36<br>de Groot; Ann Intern Med. 2009; 150(10):670<br>de Groot; Arthritis Rheum. 2005; 52(8):2461 |
| | | Stabilization or attenuation of clinical symptoms and normalization of lab abnormalities with continuous treatment | Guillevin; Arthritis Rheum. 1995; 38(11):1638<br>Guillevin; Arthritis Rheum. 1992; 35(2):208<br>Guillevin; J Rheumatol. 1991; 18(4):567 |
| | | BVAS=0 | Hiemstra; JAMA 2010 304(21):2381<br>Pagnoux; N Engl J Med 2008;359:2790<br>NCT00349674. |
| | | BVAS/WG=0 | WGET Research Group; Control Clin Trials 2002; 23(4):450 |
| | | BVAS=0 for 2 months | Jones; N Engl J Med 2010; 363:211 |
| | | BVAS 0 under stable prednisone < 7.5 | Han; Am J Nephrol 2011;33:185 |
| | | BVAS/WG of 0 with prednisone off at 6 months | Stone; N Engl J Med 2010; 363:221 |
| | | BVAS=0 for 2 months on a stable prednisone <=10 | NCT1446211 |
| | Complete remission | BVAS=0 | Menthon, Clin Exp Rheumatol 2011; 29(S64):S63 |
| | | BVAS 0 for at least 1 mo | NCT01405807 |
| | | Improvement of general condition, no new manifestations of WG, and return of ESR to normal | Guillevin; Arthritis Rheum 40(12):2187 |
| | | Absence of clinical and biologic manifestations of active vasculitis for a t least 3 months | Ribi; Arthritis Rheum. 2008; 58(2):586 |

| Disease-related grouping | Disease-related term | Definition of disease-related term or grouping (where available) | Source |
|---|---|---|---|
| | | | Cohen; Arthritis Rheum. 2007 May 15; 57(4):686 |
| | | General condition improved, no new manifestations of WG, ESR returned to normal | Guillevin; Arthritis Rheum. 1997; 40(12):2187 |
| | | No pathologic findings in clinical, radiologic, and seroimmunologic paramaters | de Groot; Arthritis Rheum. 1996; 39(12):2052 |
| | | Absence of symptoms or signs attributable to active vasculitis, with BVAS 0-1 | Haubitz; Arthritis Rheum. 1998; 41(10):1835 |
| | Partial remission | Partial regression of clinical manifestations and BVAS decrease of >50%) | Menthon; Clin Exp Rheumatol 2011; 29(S64):S63 |
| | Sustained remission | No definition | Jones; J Am Soc Nephrol 2008; 19<br>Guillevin; Arthritis Rheum. 1997; 40(12):2187<br>Menthon; Clin Exp Rheumatol 2011; 29(Suppl.64):S63<br>Walsh; Trials 2013;14:73 |
| | | Absence of disease activity (BVAS 0) for at least 6 months | Jones, N Engl J Med. 2010: 363(3):211 |
| | | Maintenance of a BVAS/WG score of 0 over 3 consecutive trial visits | WGET Research Group; Control Clin Trials 2002; 23(4):450 |
| | | Remission at 3mos sustained for 6mos | NCT00482066 |
| | | Remission at 6mos sustained for 12mos | NCT00482066 |
| | | No relapse during 24 mos after remission | NCT00647166 |
| | time to remission | | de Groot; Kidney Blood Press Res 2005; 28:153 |
| Restoration of immune tolerance | | Complete remission off immunosuppressive and steroids, reconstitution of peripheral blood B cell count (CD19+ >=80% of baseline), absence of ANCA, normal response to neoantigens | Specks; Open Arthritis Journal, 2011; 4:1 |
| Vitality | | | |
| | Death | | Pagnoux; N Engl J Med 2008; 359:2790<br>Rihova; Prague Med Rep. 2004; 105(1):64<br>Salant; Nat Clin Pract Nephrol. 2008; 4(1):14<br>Jones; N Engl J Med. 2010; 363(3):211<br>Ribi; Arthritis Rheum. 2008; 58(2):586<br>Jayne; J Am Soc Nephrol 2007; 18: 2180 |

| Disease-related grouping | Disease-related term | Definition of disease-related term or grouping (where available) | Source |
|---|---|---|---|
| | | | Cohen; Arthritis Rheum. 2007; 57(4):686<br>Haubitz; Arthritis Rheum. 1998 41(10):1835<br>Hu; Nephrol Dial Transplant 2008; 23:1307<br>Hiemstra; JAMA 2010; 304(21):238<br>de Groot; Ann Intern Med. 2009; 150(10):670<br>de Groot; Arthritis Rheum. 2005; 52(8):2461<br>NCT00647166<br>NCT00748644<br>de Groot; Arthritis Rheum. 1996; 39(12):2052<br>Guillevin; J Rheumatol. 1991; 18(4):567<br>Jayne; N Engl J Med. 2003; 349(1):36<br>Han; Am J Nephrol 2011; 33:185<br>Menthon; Clin Exp Rheumatol 2011; 29(Suppl.64):S63<br>Walsh; Trials 2013;14:73<br>Walsh; Kidney International 2013; 84:397 |
| | | All-cause mortality | NCT00987389 |
| | | Time to death / mortality | Ribi; Arthritis Rheum. 2008; 58(2):586<br>WGET Research Group; Control Clin Trials 2002; 23(4):450 |
| | Survival | overall | Ribi; Arthritis Rheum. 2008; 58(2):586<br>Jayne; J Am Soc Nephrol 2007; 18: 2180<br>Haubitz; Arthritis Rheum. 1998; 41(10):1835<br>NCT00307671<br>NCT01408836<br>de Groot; Ann Intern Med. 2009; 150(10):670<br>Harper; Ann Rheum Dis 2012;71:955<br>Samson; Journal of |

| Disease-related grouping | Disease-related term | Definition of disease-related term or grouping (where available) | Source |
|---|---|---|---|
| | | | Autoimmunity 2013; 43:60 |
| | | Cumulative | de Groot; Kidney Blood Press Res 2005; 28:153 Faurschou; Arthritis Rheum. 2012; 64(10):3472 |
| | | Disease-free survival | Ribi; Arthritis Rheum. 2008; 58(2):586 NCT00103792 Samson; Journal of Autoimmunity 2013; 43:60 |
| | | Event-free survival (survival without relapse or discontinuation of study drug due to adverse event) | Pagnoux, N Eng J Med. 2008: 359(26):2790 |
| | | Relapse-free survival | Sanders; Kidney Blood Press Res 2005; 28:153 Faurschou; Arthritis Rheum. 2012; 64(10):3472 |

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Table B.2. Treatment-related terms and definitions

| Measure category | Treatment-related measure | Treatment-related measure - definition | Source |
|---|---|---|---|
| Change of medications | | | |
| | Ability to switch from CYC to MTX at 3-6 months after randomization | | WGET Research Group; Control Clin Trials 2002; 23(4):450 |
| | Need for addition or change of IS | | Samson; Journal of Autoimmunity 2013; 43 |
| | Need to go to CYC (from abatacept) | | NCT00482066 |
| | Need for second-line drugs for initial therapeutic failure or relapse | | Ribi; Arthritis Rheum. 2008; 58(2):587<br>Guillevin; Arthritis Rheum. 1992; 35(2):208 |
| | Need for CS dose increase | | NCT01933724<br>NCT01940094 |
| | | Dose escalation more than 2x previous and >30mg/day | Samson; Journal of Autoimmunity 2013; 43:60 |
| | Need for therapeutic adjustment | Manifestations not severe enough to be considered treatment failure or flare: Eosinophil count increases, isolated asthma, sinusitis or rhinitis exacerbations, requirement of CS=dose increase of less than twice and < 30mg | Samson; Journal of Autoimmunity 2013; 43:60 |
| Corticosteroid measures | | | |
| | Ability to taper steroids | | NCT01598857 |
| | Corticosteroid dose at different time points | | NCT00482066<br>Han; Am J Nephrol 2011; 33:185<br>Jones; N Engl J Med. 2010; 15;363(3):211<br>Guillevin; Arthritis Rheum. 1997; 40(12):2187.<br>Guillevin; Arthritis Rheum. 1992; 35(2):208<br>Menthon; Clin Exp Rheumatol 2011; 29(Suppl.64):S63 |
| | Coming off of steroids | | Cohen; Arthritis Rheum. 2007; 57(4):686<br>de Groot; Arthritis Rheum. 1996; 39(12):2052 |
| | CS dependence at end of study | | Ribi; Arthritis Rheum. 2008; 58(2):586<br>NCT00647166 |
| | CS dose of 0 at 6 months | | Stone; N Engl J Med 2010; 363:221 |
| | Completing CS treatment regimen | | WGET Research Group; Control Clin Trials 2002; 23(4):450 |
| | Cumulative dose of CS | | Rihova; Prague Med Rep. 2004; 105(1):64<br>NCT00307645<br>Hiemstra; JAMA |

| Measure category | Treatment-related measure | Treatment-related measure - definition | Source |
|---|---|---|---|
| | | | 2010;304(21):2381<br>NCT01446211<br>de Groot; Ann Intern Med. 2009; 150(10):670<br>de Groot; Arthritis Rheum. 2005; 52(8):2461<br>NCT00748644<br>NCT00307671<br>NCT01405807<br>NCT01363388<br>ISRCTN28528813<br>Specks; Open Arthritis Journal, 2011; 4:1<br>NCT01697267<br>NCT01731561 |
| | Duration of CS treatment | | NCT00748644<br>NCT01363388<br>Guillevin; J Rheumatol. 1991; 18(4):567<br>Harper; Ann Rheum Dis 2012;71:955<br>Faurschou; Arthritis Rheum 2012; 64(10):3472<br>NCT01731561 |
| | Rate of reduction of CS dose | | Metzler; Rheumatology 2007; 46;1087<br>ISRCTN76658104<br>de Groot; Arthritis Rheum. 1996; 39(12):2052 |
| Other immunosuppressive measures | | | |
| | Cumulative dose of AZA | | NCT00307671<br>NCT00307645 |
| | Cumulative dose of CYC | | Rihova; Prague Med Rep. 2004; 105(1):64<br>Haubitz; Arthritis Rheum. 1998; 41(10):1835<br>Hiemstra; JAMA 2010; 304(21):2381<br>de Groot; Ann Intern Med. 2009; 150(10):670<br>ISRCTN28528813<br>Guillevin; Arthritis Rheum. 1997; 40(12):2187 |
| | cumulative dose of MTX | | WGET Research Group; Control Clin Trials 2002; 23(4):450 |
| | Cumulative dose of MMF | | NCT00307645 |
| | Duration of CYC treatment | | Faurschou; Arthritis Rheum 2012; 64(10):3472 |
| | Duration of immunosuppression (other than steroids) | | Harper; Ann Rheum Dis 2012; 71:955;<br>Faurschou; Arthritis Rheum 2012; 64(10):3472 |
| | Reaching target dose of study | | Hiemstra; JAMA |

| Measure category | Treatment-related measure | Treatment-related measure - definition | Source |
|---|---|---|---|
| | drug | | 2010;304(21):2381 |
| | Reduction in immunosuppressive drug doses | | Jayne; Q J Med 2000; 93(7):433<br>ISRCTN76658104 |
| Intolerance of treatment resulting in withdrawal from study | | | Specks; Open Arthritis Journal, 2011; 4:1 |
| Response to treatment | | | |
| | Response rate | Response = BVAS<=2 within 24 weeks of trial entry, maintained till end of trial (week 52) | NCT01446211 |
| | | Maintenance of pre-existing partial or complete remission for at least 6 mo | de Groot; Arthritis Rheum. 1996; 39(12):2052 |
| | | More than 50% reduction in BVAS | Jayne; Q J Med 2000; 93(7):433<br>ISRCTN76658104.<br>ISRCTN28528813. |
| | | Complete or partial remision | NCT01405807 |
| | Response duration | BVAS≤2 until relapse | NCT01446211 |
| | Time to response | Response = BVAS ≤ 2 | NCT01446211 |
| Safety of therapy (long-term = 4 years) | | | NCT01586858 |
| Safety / Tolerability of therapy; feasibility of therapy | | | Bekker; Nephrology Dial Transplant 2012; 27(S2):ii419 |
| Failure of treatment | | | |
| | Treatment failure | Failure to achieve treatment response, or relapse | NCT01405807<br>Guillevin; J Rheumatol. 1991; 18(4):567<br>Guillevin; Arthritis Rheum. 1997; 40(12):2187<br>Guillevin; Arthritis Rheum. 1992; 35(2):208 |
| | | Absence of remission, or new clinical manifestations | Menthon; Clin Exp Rheumatol 2011; 29(Suppl.64):S63 |
| | | Absence of remission, new manifestations of vasculitis, or death while receiving treatment | Ribi; Arthritis Rheum. 2008; 58(2):586<br>Cohen; Arthritis Rheum. 2007; 57(4):686 |
| | Primary treatment failure | Remission not achieved | Jayne; N Engl J Med. 2003; 349(1):36<br>Cohen; Arthritis Rheum. 2007; 57(4):686<br>NCT00647166 |
| | Time to treatment failure | | NCT01598857 |

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Table B.3. Outcomes pertaining to specific organ manifestations

| Organ involved | Outcome | Outcome specification / definition | Source |
|---|---|---|---|
| Brain | Cardiovascular morbidity | | Harper; Ann Rheum Dis 2012;71:955 |
| Heart | Cerebrovascular morbidity | | Harper; Ann Rheum Dis 2012;71:955 |
| Muscle | Manual muscle testing | | Taniguchi; J Allergy Clin Immunol 127(2) |
| Peripheral blood vessels | Venous Distensibility Index (not new but moved from composite measures to specific organs) | | ISRCTN28528813 |
| Pulmonary | | | |
| | Asthma exacerbation | | Cohen; Arthritis Rheum 2007; 57(4) :686 |
| Renal | | | |
| | Creatinine | | Pagnoux; N Engl J Med 2008;359:2790<br>Jayne; J Am Soc Nephrol 2007; 18: 2180<br>Haubitz; Arthritis Rheum. 1998; 41(10):1835<br>Hu; Nephrol Dial Transplant 2008; 23: 1307<br>de Groot; Arthritis Rheum. 2005; 52(8):2461<br>NCT01408836<br>Guillevin; Arthritis Rheum. 1997; 40(12):2187<br>Jayne; N Engl J Med. 2003; 349(1):36<br>Han; Am J Nephrol 2011; 33:185<br>Harper; Ann Rheum Dis 2012; 71:955 |
| | Dialysis | Dialysis dependence, new | Jones; J Am Soc Nephrol 2008; 19<br>Jones; N Engl J Med 2010; 363:211 |
| | | Dialysis, maintenance | Han; Am J Nephrol 2011;33:185. |
| | | Dialysis, recovery | Jones; J Am Soc Nephrol 2008; 19<br>Haubitz, Clin Exp Innunology 1995; 101(s1):43<br>Jones; N Engl J Med 2010; 363:211<br>Jayne; J Am Soc Nephrol 2007; 18: 2180<br>Haubitz; Arthritis Rheum. 1998; 41(10):1835 |
| | End-stage renal disease development | | Salant; Nat Clin Pract Nephrol. 2008; 4(1):14<br>Jayne; J Am Soc Nephrol 2007; 18: 2180<br>Haubitz; Arthritis Rheum. 1998; 41(10):1835<br>de Groot; Ann Intern Med. 2009; 150(10):670<br>NCT01408836<br>Guillevin; Arthritis Rheum. 1997; 40(12):2187<br>Menthon; Clin Exp Rheumatol 2011; 29(S64):S63<br>Harper; Ann Rheum Dis 2012;71:955<br>Faurschou; Arthritis Rheum 2012; 64(10):3472<br>Walsh; Kidney International 2013; 84:397<br>Jones; N Engl J Med. 2010; 363:211 |
| | | Definition: Hemodialysis, | Walsh; Trials 2013;14:73 |

| Organ involved | Outcome | Outcome specification / definition | Source |
|---|---|---|---|
| | | peritoneal dialysis, CRRT, or renal transplantation | |
| | Estimated GFR | | Han; Am J Nephrol 2011; 33:185.<br>Jayne; J Am Soc Nephrol 1999; 10:p105A; A0540<br>Jones; N Engl J Med. 2010; 363(3):211<br>NCT01446211<br>Jayne; N Engl J Med. 2003; 349(1):36<br>Hiemstra; JAMA 2010; 304(21):2381<br>de Groot; Ann Intern Med. 2009; 150(10):670 |
| | | GFR, median | Jones; J Am Soc Nephrol 2008; 19<br>Jones; APMIS Authors Journal Compilation 2009; A24<br>Jones; N Engl J Med. 2010; 363(3):211 |
| | | GFR, change in | Jones; N Engl J Med. 2010; 363(3):211 |
| | Proteinuria | | Hiemstra; JAMA 2010; 304(21):2381<br>Han; Am J Nephrol 2011; 33:185<br>Menthon; Clin Exp Rheumatol 2011; 29(S64):S63<br>Szpirt; Nephrol Dial Transplant 2011; 26:206 |
| | | 24-hour protein | Han; Am J Nephrol 2011; 33:185<br>Jayne; J Am Soc Nephrol 1999; 10:p105A; A0540 |
| | Renal function | | NCT00301652<br>Jayne; J Am Soc Nephrol 2007; 18: 2180<br>Haubitz; Arthritis Rheum. 1998; 41(10):1835<br>Hu; Nephrol Dial Transplant 2008; 23:1307<br>de Groot; Ann Intern Med. 2009; 150(10):670<br>Guillevin; Arthritis Rheum. 1997; 40(12):2187<br>Han; Am J Nephrol 2011; 33:185<br>Harper; Ann Rheum Dis 2012; 71:955 |
| | Renal insufficiency | | Guillevin; Arthritis Rheum. 1997; 40(12):2187 |
| | Renal recovery | Dialysis independence and serum creatinine < 500 at 3 months | Salant; Nat Clin Pract Nephrol. 2008; 4(1):14<br>NCT01408836<br>Chen; Nephrology Dialysis Tranplant 2012; 27(S2):ii61 |
| | Renal survival | | NCT01408836<br>Harper; Ann Rheum Dis 2012;71:955<br>NCT01586858 |
| Venous thromboembolism (not new but moved it to specific organ manifestations from adverse events) | | | Stone; N Engl J Med 2010; 363:221<br>Harper; Ann Rheum Dis 2012; 71:955 |

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Table B.4. Biochemical tests

| Test / measure | Specification | Source |
|---|---|---|
| Anti-neutrophil cytoplasmic antibody (ANCA) | Not specified | NCT00748644<br>Chen; Nephrology Dialysis Transplant 2012; 27(S2):ii61<br>NCT01586858 |
| | Perinuclear (P-) and cytoplasmic (C-) ANCA, at various time points | Pagnoux; N Engl J Med 2008; 359:2790<br>Jones; N Engl J Med. 2010; 363(3):211 |
| | cANCA/proteinase-3 (pr3) titre | Metzler; Rheumatology 2007; 46;1087<br>de Groot; Arthritis Rheum. 1996; 39(12):2052 |
| | pANCA/myeloperoxidase (mpo) titre | Han; Am J Nephrol 2011;33:185 |
| | Titers over time | NCT00103792<br>NCT00307645<br>Jayne; Q J Med 2000; 93(7):433<br>Haubitz; Arthritis Rheum. 1998; 41(10):1835<br>Hu; Nephrol Dial Transplant 2008; 23:1307<br>Menthon; Clin Exp Rheumatol 2011; 29(S64):S63 |
| | Seroconversion (positive to negative) | Jones; J Am Soc Nephrol 2008; 19 |
| | Time to ANCA negativity | NCT00482066 |
| B-cell level | | Jones, N Engl J Med 2010; 363(3):211 |
| | CD19+ B-lyphocyte count, peripheral blood | Stone; N Engl J Med 2010; 363:221<br>NCT01731561 |
| Complement level | | NCT01275287 |
| Creatinine – see “specific organ manifestations” -> “renal function” | | |
| C-reactive protein (CRP) | | Metzler; Rheumatology 2007; 46:1087<br>NCT00307645<br>Jayne; N Engl J Med. 2003; 349(1):36<br>Jayne; Q J Med 2000; 93(7):433<br>de Groot; Ann Intern Med. 2009; 150(10):670<br>de Groot; Arthritis Rheum. 2005; 52(8):2461<br>ISRCTN76658104<br>Specks; Open Arthritis Journal 2011; 4:1 |
| Eosinophil count | | Cohen Arthritis Rheum. 2007; 57(4):686<br>Samson; Journal of Autoimmunity 2013; 43:60 |

| Test / measure | Specification | Source |
|---|---|---|
| Erythrocyte sedimentation rate (ESR) | | Metzler; Rheumatology 2007; 46;1087<br>Jayne; N Engl J Med. 2003; 349(1):36<br>de Groot; Arthritis Rheum. 2005; 52(8):2461<br>ISRCTN76658104<br>Guillevin; Arthritis Rheum. 1997; 40(12):2187<br>Guillevin; Arthritis Rheum. 1995; 38(11):1638<br>Specks; Open Arthritis Journal 2011; 4:1 |
| Human anti-chimeric antibody | | Jones, N Engl J Med 2010; 363(3):211 |
| White blood cell count | Leukocyte, lymphocyte, and neutrophil count | de Groot; Arthritis Rheum. 2005; 52(8):2461<br>Haubitz, Clin Exp Innunology 1995; 101(s1):43 |
| Platelet count | | Haubitz; Arthritis Rheum. 1998; 41(10):1835<br>Stone; N Engl J Med 2010; 363:221 |
| Soluble interleukin-2 receptor (sIL-2R) serum levels | | de Groot; Arthritis Rheum. 1996; 39(12):2052 |
| Total Immunoglobulin G (IgG) level | | Jane Q J Med 2000; 93:433 |

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Table B.5. Outcomes related to adverse events

| Outcome | Definition | Sources |
|---|---|---|
| Adverse event (AE) rate | | Pagnoux; N Engl J Med 2008 ;359:2790<br>Rihova; Prague Med Rep. 2004;105(1):64<br>Salant; Nat Clin Pract Nephrol. 2008; 4(1):14<br>Jones; N Engl J Med. 2010; 363(3):211<br>Metzler; Rheumatology 2007; 46;1087<br>NCT00103792<br>Hiemstra; JAMA 2010; 304(21):2381<br>NCT01446211<br>Jayne; N Engl J Med. 2003; 349(1):36<br>Jayne; Q J Med 2000; 93(7):433<br>Cohen; Arthritis Rheum. 2007; 57(4):686<br>Hu; Nephrol Dial Transplant 2008; 23:1307<br>de Groot; Ann Intern Med. 2009; 150(10):670<br>de Groot; Arthritis Rheum. 2005; 52(8):2461<br>NCT00307593<br>NCT00647166<br>NCT00748644<br>NCT00307671<br>NCT01363388<br>de Groot; Arthritis Rheum. 1996; 39(12):2052<br>Guillevin; Arthritis Rheum. 1992; 35(2):208<br>Han; Am J Nephrol 2011; 33:185<br>Menthon; Clin Exp Rheumatol 2011;29(S64):S63 |
| | AE requiring discontinuation of the study drug or causing death | Pagnoux; N Engl J Med 2008; 359:2790 |
| AE, drug-related | | NCT00040248 |
| AE, serious | | NCT01446211<br>Guillevin; Arthritis Rheum. 1995; 38(11):1638<br>Guillevin; Arthritis Rheum. 1992; 35(2):208<br>Guillevin; J Rheumatol. 1991;18(4):567<br>Walsh; Trials 2013;14:73 |
| | AE requiring hospitalization and/or life threatening | Rihova; Prague Med Rep. 2004; 105(1):64<br>Jones; N Engl J Med. 2010; 363(3):211 |
| AE, non-severe | | NCT01405807 |
| AE, severe | | Metzler; Rheumatology 2007; 46:1087<br>Jayne; N Engl J Med. 2010; 349(1):36<br>Jayne; J Am Soc Nephrol 2007; 18: 2180<br>Hiemstra; JAMA 2010; 304(21):2381<br>de Groot; Arthritis Rheum. 2005; 52(8):2461 |

| Outcome | Definition | Sources |
|---|---|---|
| | | NCT01405807<br>NCT01408836<br>Guillevin; Arthritis Rheum. 1997; 40(12):2187<br>NCT01697267 |
| | Grade 3-4 as per WHO toxicity criteria | Cohen; Arthritis Rheum. 2007; 57(4):686 |
| | Grades 3-5 as per NCI | Jones; N Engl J Med. 2010; 363(3):211 |
| | Fatal or life-threatening as per WHO | Menthon; Clin Exp Rheumatol 2011; 29(S64):S63 |
| Bone fracture | | Faurschou; Arthritis Rheum 2012; 64(10):3472 |
| Cystitis, drug-induced | | Stone; N Engl J Med 2010; 363:221 |
| Death – see vitality | | |
| Deep vein thrombosis / pulmonary embolus | | WGET Research Group; Control Clin Trials 2002; 23(4):450 |
| Gonadal toxicity (measured by FSH level) | | Haubitz; Arthritis Rheum. 1998; 41(10):1835 |
| Hospitalizations | | WGET Research Group; Control Clin Trials 2002; 23(4):450<br>Stone; N Engl J Med 2010; 363:221 |
| Human anti-chimeric antibody testing | | Jones; N Engl J Med 2010; 363:211 |
| IgG level, total – see biochemical tests | | Jane; Q J Med 2000; 93:433 |
| infections | | Pagnoux; N Engl J Med 2008; 359:2790<br>Rihova; Prague Med Rep. 2004; 105(1):64<br>Salant; Nat Clin Pract Nephrol. 2008; 4(1):14<br>Jones; N Engl J Med. 2010; 363(3):211<br>Metzler; Rheumatology 2007; 46;1087<br>NCT01446211<br>Haubitz; Arthritis Rheum. 1998 41(10):1835<br>Hiemstra; JAMA 2010;304(21):2381<br>de Groot; Ann Intern Med. 2009; 150(10):670<br>de Groot; Arthritis Rheum. 2005; 52(8):2461<br>de Groot; Arthritis Rheum. 1996; 39(12):2052<br>Guillevin; Arthritis Rheum. 1997; 40(12):2187<br>Guillevin; Arthritis Rheum. 1995; 38(11):1638<br>Guillevin; Arthritis Rheum. 1992; 35(2):208<br>Guillevin; J Rheumatol. 1991; 18(4):567<br>Menthon; Clin Exp Rheumatol 2011; 29(S64):S63-71<br>Walsh; Trials 2013;14:73<br>Faurschou; Arthritis Rheum 2012; 64(10):3472<br>NCT01697267 |

| Outcome | Definition | Sources |
|---|---|---|
| Infusion reactions | | Stone; N Engl J Med 2010; 363:221 |
| Leukopenia | | Haubitz, Clin Exp Innunology 1995; 101(s1):43 |
| Life-threatening adverse events | | Jayne; J Am Soc Nephrol 1999; 10:p105A; A0540. |
| Neutropenia | | Haubitz, Clin Exp Innunology 1995; 101(s1):43 |
| Malignancy | | Pagnoux; N Engl J Med 2008; 359:2790<br>Jones; N Engl J Med. 2010; 15;363(3):211<br>Ribi; Arthritis Rheum. 2008; 58(2):586<br>Metzler; Rheumatology 2007; 46;1087<br>Hiemstra; JAMA 2010; 304(21):2381<br>Guillevin; Arthritis Rheum. 1997; 40(12):2187<br>Guillevin; Arthritis Rheum. 1995; 38(11):1638<br>Guillevin; Arthritis Rheum. 1992; 35(2):208<br>Guillevin; J Rheumatol. 1991; 18(4):567<br>Menthon; Clin Exp Rheumatol 2011; 29(S64):S63<br>Harper; Ann Rheum Dis 2012; 71:955<br>Faurschou; Arthritis Rheum 2012; 64(10):3472<br>NCT01586858 |
| Safety | | NCT00414128<br>Smith; Nephrology Dial Transplant 2013; 28(S1):i180 |
| Sepsis | | Harper; Ann Rheum Dis 2012; 71:955 |
| | Adverse events, physical exam abnormalities, vital signs, clinical lab tests (including blood chemistry, hematology, and urinalysis) | NCT01363388 |
| Stroke | | Stone; N Engl J Med 2010; 363:221 |
| Thrombocytopenia | | Haubitz; Arthritis Rheum. 1998 41(10):1835<br>Stone; N Engl J Med 2010; 363:221 |
| Treatment withdrawal due to drug intolerance | | Hiemstra; JAMA 2010; 304(21):2381 |

NCT######## refers to the trial number on the ClinicalTrials.gov website; ISRCTN######## refers to the trial number on the Controlled-trials.com website.

Table B.6. Broad concepts that measure global effects of disease and/or treatments

| Outcome | Sources |
|---|---|
| Cumulative organ damage | NCT00103792<br>Rihova; Prague Med Rep. 2004; 105(1):64 |
| Health related quality of life (HRQoL) | NCT00482066<br>Walsh; Trials 2013;14:73 |
| Need for health care facilities | NCT00647166 |
| Patient global assessment | ISRCTN76658104<br>WGET Research Group; Control Clin Trials 2002; 23(4):450-68<br>ClinicalTrials.gov# NCT01940094; |
| Physician's global assessment | ISRCTN76658104<br>WGET Research Group; Control Clin Trials 2002; 23(4):450<br>Stone; N Engl J Med 2010; 363:221 |
| Q-TWiST (quality-adjusted time without symptoms or toxicity) | Pagnoux; Arthritis Rheum 2012; 64(10S):S708 |

NCT######## refers to the trial number on the ClinicalTrials.gov website; ISRCTN######## refers to the trial number on the Controlled-trials.com website.

Table B.7. Composite tools / instruments

| Composite tool | Source |
|---|---|
| Activity of daily living (ADL) scale | NCT00647166 |
| Birmingham Vasculitis Activity Score (BVAS), versions 1-3 | Pagnoux; N Engl J Med 2008; 359:2790<br>Ribi; Arthritis Rheum. 2008 Feb;58(2):586<br>Metzler; Rheumatology 2007; 46;1087<br>Jayne; N Engl J Med. 2003; 349(1):36<br>Jayne; J Am Soc Nephrol 2007; 18:2180<br>Jayne; Q J Med 2000; 93(7):433<br>Cohen; Arthritis Rheum. 2007; 57(4):686<br>Haubitz; Arthritis Rheum. 1998; 41(10):1835<br>Hu; Nephrol Dial Transplant 2008; 23:1307<br>de Groot; Ann Intern Med. 2009; 150(10):670<br>de Groot; Arthritis Rheum. 2005; 52(8):2461<br>NCT00647166<br>Han; Am J Nephrol 2011; 33:185<br>Menthon; Clin Exp Rheumatol 2011; 29(S64):S63<br>Samson; Journal of Autoimmunity 2013; 43:60<br>NCT01663623<br>NCT01586858 |
| BVAS for Wegener's granulomatosis (BVAS-WG) | WGET Research Group; Control Clin Trials 2002; 23(4):450<br>Stone; N Engl J Med 2010; 363:221<br>NCT01697267<br>NCT01598857 |
| Combined damage assessment (CDA) | NCT01405807<br>NCT01697267 |
| Disease Extent Index = extended ELK-classification | de Groot; Arthritis Rheum. 39(12):2052<br>Metzler Kidney Blood Press Res 2005, 28:196<br>Metzler Rheumatology 2007; 46:1087<br>de Groot; Arthritis Rheum. 2005, 52(8):2461 |
| Extent of disease index by Reinhold-Keller (based on extended ELK classification) | Haubitz, Arthritis Rheum. 1998; 41(10):1835 |
| EQ-5D questionnaire | NCT01446211<br>NCT00987389<br>ISRCTN07757494<br>Walsh; Trials 2013;14:73 |
| Five Factor Score | Cohen; Arthritis Rheum. 2007; 57(4):686 |
| Health Assessment Questionnaire (HAQ) | NCT00647166<br>NCT00307671<br>NCT00349674 |
| Short Form Survey (36 questions) SF-36 | Pagnoux; N Engl J Med 2008; 359:2790<br>Metzler; Rheumatology 2007; 46:1087<br>Jayne; N Engl J Med. 2003; 349(1):36<br>Jayne; J Am Soc Nephrol 2007; 18:2180<br>de Groot; Arthritis Rheum. 2005; 52(8):2461<br>NCT00647166<br>NCT00307671<br>NCT01405807<br>NCT01446211<br>Stone; N Engl J Med 2010; 363:221<br>Jones; N Engl J Med. 2010; 363(3):211<br>Walsh; Trials 2013;14:<br>NCT01697267 |

| Composite tool | Source |
|---|---|
| | NCT01940094 |
| Vasculitis Damage Index (VDI) | Jones; N Engl J Med. 2010; 363(3):211.<br>NCT01446211<br>NCT00307645<br>Hiemstra; JAMA 2010; 304(21):2381<br>Jayne; N Engl J Med. 2003; 349(1):36<br>Jayne; J Am Soc Nephrol 2007; 18: 2180<br>de Groot; Ann Intern Med. 2009; 150(10):670<br>de Groot; Arthritis Rheum. 2005; 52(8):2461<br>NCT00647166<br>NCT00307671<br>Samson; Journal of Autoimmunity 2013; 43:60<br>Stone; N Engl J Med 2010; 363:221<br>NCT01586858 |

NCT######## refers to the trial number on the ClinicalTrials.gov website; ISRCTN######## refers to the trial number on the Controlled-trials.com website.

## Abbreviations for Appendix B

| | |
|---|---|
| AE | adverse events |
| ANCA | antineutrophil cytoplasmic antibody |
| AZA | azathioprine |
| BVAS | Birthmingham Vasculitis Activity Score |
| CRP | C-reactive protein |
| CYC | cyclophosphamide |
| ESR | erythrocyte sedimentation rate |
| GFR | glomerular filtration rate |
| MMF | mycophenolate moefetil |
| MTX | methotrexate |
| NCI | National Cancer Institute |
| VDI | Vasculitis Damage Index |
| WHO | World Health Organization |

## Appendix C. Birmingham Vasculitis Activity Score (BVAS) linked to ICF

| BVAS item | ICF category | Additional information |
|---|---|---|
| Persistent | Nc – persistent disease | |
| New/worse | Nc – new/worse disease | |
| *1. General* | | |
| a. malaise | nc-bf not covered (body functions) | malaise |
| b. myalgia | b28018 pain in body part, other specified | myalgia |
| c. arthralgia / arthritis | b28016 pain in joints | |
| | S7701 joints<br>→ (b4358 immunological system functions, other specified)* | inflammation |
| d. headache | b28010 pain in the head and neck | headache |
| e. fever (<38.5) | b5500 body temperature | < 38.5°C |
| f. fever (≥38.5) | b5500 body temperature | ≥38.5°C |
| g. weight loss (≥2kg) | b530 weight maintenance functions | weight loss ≥ 2kg |
| *2. Cutaneous* | | |
| a. infarct | s810 structure of areas of skin<br>→ (s4101, s4103 structure of arteries and capillaries)* | infarct |
| b. purpura | s810 structure of areas of skin<br>→ (s4103 structure of capillaries)* | purpura |
| c. other skin vasculitis | s810 structure of areas of skin<br>s4101-s4103 structure of arteries, veins, and capillaries<br>→ (b4358 immunological system functions, other specified)* | inflammation |
| d. ulcer | s810 structure of areas of skin | ulcer |
| e. gangrene | s730, s750 structure of upper and lower extremity<br>→ (s4101 structure of arteries)* | gangrene |
| f. multiple digit gangrene | s73028, s75028 structure of hand, ankle and foot, other specified<br>→ (s4101 structure of arteries)* | multiple digits |
| *3. Mucous Membranes/Eyes* | | |
| a. mouth ulcers | s320 structure of mouth | ulcer |
| b. genital ulcers | s6303, s6305 structure of penis, vagina and external genitalia<br>s8103 structure of areas of the skin of pelvic region | ulcers |
| c. significant proptosis | s210, s220 structure of eye socket and eyeball | proptosis |
| d. red eye conjunctivitis | s2200 conjunctiva, sclera, choroid<br>→ (b4358 immunological system functions, other specified)* | inflammation |
| e. red eye epi/scleritis | s2200(x2)# conjunctiva, sclera, choroid | inflammation |

| BVAS item | ICF category | Additional information |
|---|---|---|
| | → (b4358 immunological system functions, other specified)* | |
| f. blurred vision | b21023 visual picture quality | seeing blurry |
| g. sudden visual loss | b210 seeing functions | visual loss |
| *h. ophthalmic opinion* | | |
| i. no active vasculitis | B2 seeing and related functions<br>S2 eye and related structures<br>s4101-s4103 structure of arteries, veins, and capillaries<br>→ (b4358 immunological system functions, other specified)* | inflammation |
| j. uveitis | s2200 conjunctiva, sclera, choroid<br>→ (b4358 immunological system functions, other specified)* | inflammation |
| k. retinal exudates | s2203 structure of retina<br>→ (s4103 structure of capillaries)* | exudates |
| l. retinal hemorrhage | s2203 structure of retina<br>→ (s4101-s4103 structure of arteries, veins, and capillaries)* | hemorrhage |
| *4. Ear, Nose, Throat (ENT)* | | |
| a. nasal obstruction | s3102 structure of nasal fossae | |
| b. bloody nasal discharge | s310 structure of nose<br>→ (s4101-s4103 structure of arteries, veins, and capillaries)* | bloody nasal discharge |
| c. nasal crusting | s310 structure of nose | nasal crusting |
| d. sinus involvement | nc-bs,bf not covered (body structures, body functions) | sinus involvement |
| e. hearing loss | b230 hearing functions | hearing loss |
| f. hoarseness/stridor | b3101 quality of voice | hoarseness |
| | b460 sensations associated with cardiovascular and respiratory functions | stridor |
| *g. ENT opinion* | | |
| h. no active vasculitis | B2 hearing and vestibular functions, taste and smell functions<br>B3 Voice and speech functions<br>S2 ear and related structures<br>S3 structures involved in voice and speech<br>Nc-bf, bs function and structure of paranasal sinuses<br>s4101-s4103 structure of arteries, veins, and capillaries<br>→ (b4358 immunological system functions, other specified)* | inflammation |
| i. granulomatous sinusitis | nc-bs not covered (body strucutres)<br>→ (b4358 immunological system functions, other specified)* | structure of sinuses<br>granulomatous inflammation |

| BVAS item | ICF category | Additional information |
|---|---|---|
| j. conductive hearing loss | b230 hearing functions<br>s240-s250 structure of external and middle ear | Conductive hearing loss |
| k. sensorineural hearing loss | b230 hearing functions<br>s260, s1106, s11001 structure of the inner ear, cranial nerves, or temporal lobe | sensorineural hearing loss |
| l. significant subglottic inflammation | S3308 Structure of pharynx, other specified<br>b4358 immunological system functions, other specified | Subglottic inflammation |
| *5. Chest* | | |
| a. persistent cough | b450 additional respiratory functions | cough |
| b. dyspnea or wheeze | b460(x2)# sensations associated with cardiovascular and respiratory functions | dyspnea, wheeze |
| c. haemoptysis / haemorrhage | b450 additional respiratory functions<br>→ (s4101-s4103 structure of arteries, veins, and capillaries)* | hemoptysis |
| | s4301 structure of lungs<br>→ (s4101-s4103 structure of arteries, veins, and capillaries)* | Hemorrhage |
| *d. chest radiology performed* | | |
| e. no active vasculitis | s430 structure of respiratory system<br>s4101-s4103 structure of arteries, veins, and capillaries<br>→ (b4358 immunological system functions, other specified)* | inflammation |
| f. nodules or cavities | s4301(x2)# lungs | nodules, cavities |
| g. pleural effusion / pleurisy | s4308(x2)# structure of respiratory system, other specified | pleura |
| h. infiltrate | s4301 lungs | infiltrate |
| i. massive hemoptysis or alveolar hemorrhage | b450 additional respiratory functions<br>→ (s4101-s4103 structure of arteries, veins, and capillaries)* | massive hemoptysis |
| | s4301 structure of lungs<br>→ (s4101-s4103 structure of arteries, veins, and capillaries)* | massive alveolar hemorrhage |
| j. respiratory failure | b440 respiration functions | |
| *6. Cardiovascular* | | |
| a. aortic incompetence | b410 heart functions | aortic insufficiency |
| | s41008 structure of heart, other specified | aortic valve |
| b. pericardial pain/rub | b28011 pain in chest | pericardial |
| | b4108 heart functions, other | pericardial rub |

| BVAS item | ICF category | Additional information |
|---|---|---|
| | specified | |
| c. ischaemic cardiac pain | b28011 pain in chest<br>b4103 blood supply to the heart | |
| d. congestive cardiac failure | b410 heart functions | congestive cardiac failure |
| *e. cardiology opinion/tests* | | |
| f. no active vasculitis | B4 Cardiovascular system functions<br>s410 structure of cardiovascular system<br>s4101-s4103 structure of arteries, veins, and capillaries<br>→ (b4358 immunological system functions, other specified)* | inflammation |
| g. pericarditis | s4108 structure of cardiovascular system, other specified<br>→ (b4358 immunological system functions, other specified)* | pericardium<br><br>inflammation |
| h. myocardial infarct / angina | s4100 structure of heart<br>→ (b4103 blood supply to the heart)* | myocardial infarct |
| | b28011 – pain in chest<br>b4103 blood supply to the heart | angina |
| i. cardiomyopathy | b410 heart functions<br>s4100 heart | cardiomyopathy |
| *7. Abdominal* | | |
| a. severe abdominal pain | b28012 pain in stomach or abdomen | |
| b. bloody diarrhoea | b5251 fecal consistency<br>→ (s4101-s4103 structure of arteries, veins, and capillaries)* | bloody diarrhea |
| *c. surgical opinion / tests* | | |
| d. no active vasculitis | B5 Functions related to the digestive system<br>S5 Structures related to the digestive system<br>s4101-s4103 structure of arteries, veins, and capillaries<br>→ (b4358 immunological system functions, other specified)* | inflammation |
| e. gut perforation/infarct | s540 structure of intestine | perforation |
| | s540 structure of intestine<br>→ (s4101, s4104 structure of arteries and capillaries)* | infarct |
| f. acute pancreatitis | S550 structure of pancreas<br>→ (b4358 immunological system functions, other specified)* | Inflammation |
| *8. Renal* | | |
| hypertension (diastolic > | b4200 increased blood pressure | diastolic > 95mmHg |

| BVAS item | ICF category | Additional information |
|---|---|---|
| 95mmHg) | | |
| b. proteinuria >1+ / >0.2g/24h | b610 urinary excretory functions | proteinuria >1+ / >0.2g/24h |
| c. hematuria >1+ / >10rbc/ml | b610 urinary excretory functions | hematuria >1+ / >10rbc/ml |
| d. creatinine 125-249µmol/l | b6100 filtration of urine | creatinine 125-249µmol/l |
| e. creatinine 250-499µmol/l | b6100 filtration of urine | creatinine 250-499µmol/l |
| f. creatinine >500µmol/l | b6100 filtration of urine | creatinine >500µmol/l |
| g. rise in creatinine >30% or fall in creatinine clearance >25% | b6100 filtration of urine | rise in creatinine >30% or fall in creatinine clearance >25% |
| *9. Nervous system* | | |
| a. organic confusion/dementia | b114 – orientation functions | confusion |
| | b117 – intellectual functions | dementia |
| b. seizures (not hypertensive) | nc-bf not covered (body functions) | function of brain |
| c. stroke | s110 structure of brain<br>→ (s4101-s4103 structure of arteries, veins, and capillaries)* | |
| d. cord lesion | s1200 structure of spinal cord | |
| e. sensory peripheral | b279 additional sensory functions, other specified and unspecified<br>s198 – structure of the nervous system, other specified | peripheral neuropathy (sensory)<br>sensory peripheral nerves |
| f. cranial nerve palsy | nc-bf not covered (body functions)<br>s1106 - structure of cranial nerves | cranial nerve palsy |
| g. motor mononeuritis multiplex | b798 Neuromusculoskeletal and movement-related functions, other specified<br>s198 – structure of the nervous system, other specified | palsy of multiple motor nerves |
| *10. Other* | | |

ICF categories specified after the right arrow → represent the cause of the impairment represented by the ICF category in the previous row; # (x2) following ICF category code indicates that 2 distinct constructs contained in the same questionnaire item map to the same ICF category code

## Appendix D. Letter inviting clinicians to participate in the study

### Invitation to participate in a study: ICF Core Sets for ANCA-Associated Vasculitis– Expert Perspective

**Principal Investigator: Dr. Nataliya Milman, U of Ottawa**

**Dear Colleague**,

You are being asked to participate in a study "ICF Core Sets for ANCA-Associated Vasculitis (Expert Perspective)".

The general aim of this study is to apply the ICF (International Classification of Functioning, Disability, and Health) to the field of ANCA-Associated Vasculitis.

ICF is a classification system that describes functioning and health by considering the contribution of 4 interacting "components" – body functions, body structures, activities and participation, and contextual factors (which includes personal and environmental factors). Since its introduction in 2001 by the World Health Organization, this classification system has been used to describe the impact on patients' overall function of a number of medical conditions.

The specific aim of this study is to develop the ICF Core Sets for ANCA-Associated Vasculitis. ICF Core Sets are selections of the ICF categories that are relevant to a specific disease. These ICF Core Sets can then be used as a reference of what needs to be measured when describing the impact of ANCA-Associated Vasculitis on patients' function and general health.

We are recruiting medical experts with an interest in vasculitis from a number of relevant specialties to participate in the "Expert Perspective" part of this study. It aims to determine which aspects of ANCA-Associated Vasculitis are particularly relevant to the medical experts caring for patients with these conditions. This will be done through a 3-round Delphi exercise administered via email. We anticipate that each of the rounds will take at most 15 minutes to complete.

We would appreciate your involvement. If you agree to participate, please read through the "Study Information and Implied Consent" form attached to this email, and fill out "Delphi round I" exercise also attached. Note that your reply with a completed Delphi exercise will constitute implied consent.

In addition, regardless of whether or not you choose to participate, if you know other clinicians with an expertise in vasculitis (including physicians in any relevant specialties or allied health professionals) your willingness to pass this email on to them would be greatly appreciated.

Thank you for helping us with this research.

Sincerely,

Dr. Nataliya Milman

Clinical fellow (vasculitis), University of Ottawa

## Appendix E. Participant information sheet and implied consent form for clinicians

# Information Sheet and Implied Consent Form

***ICF Core Sets for ANCA-Associated Vasculitis – Clinical Expert Perspective***

**Principal Investigator:** **Dr. Nataliya Milman**

**Sponsor:** **The Arthritis Society / Canadian Rheumatology Association / UCB Pharma**

### Introduction

You are being asked to participate in this research project because of your expertise in working with patients with ANCA-Associated Vasculitis (AAV).

This form contains detailed information about the study. Please, note that "implied consent" will be used for this study, meaning that your return of the filled-out questionnaire (round 1 of 3 Delphi questionnaire) constitutes your informed consent to participate.

### Background, Purpose and Design of the Study

ICF is a classification system that describes functioning and health by considering the contribution of 4 interacting "components" – body functions, body structures, activities and participation, and contextual factors (which includes personal and environmental factors). Since its introduction in 2001 by the World Health Organization, this classification system has been used to study the impact on patients' overall function of a number of medical conditions. This study will explore the application of the ICF to AAV.

More specifically, this study aims to develop ICF Core Sets for AAV. ICF Core Sets are selections of the ICF categories that are relevant to a specific disease. These ICF Core Sets can then be used as a reference of what needs to be measured when describing the impact of AAV on patients' function and general health.

The overall study will consist of several parts which will look at the impact of ANCA-Associated Vasculitis from different perspectives, including from the perspective of the available literature, from the opinion of clinical experts, and from the perspective of patients. You are being asked to participate in the "Clinical Expert" part of the study. The primary goal of this part of the study is to find out which aspects of ANCA-Associated Vasculitis are particularly relevant to clinicians caring for patients with AAV. This information will then be used to create a list (the "Core Set") of most important aspects of AAV.

## Study Procedures

The “Clinical Expert” part of this study will consist of a 3-round Delphi exercise. In the first round, which is included with this email, you are asked to list aspects of patient’s health that you consider most important for determining the impact of AAV. You will need to consider patient’s health along the 4 ICF “components” – body functions, body structures, activities and participation, and contextual factors (personal and environmental). In rounds 2 and 3, you will be asked to select which of the items identified by all of the participating clinical experts you consider important. Items identified as important by at least 80% of the participating experts will be translated into ICF language (according to existing rules) and added to the list for potential inclusion into the final ICF Core Set.

Please note that the Delphi exercise will be carried out in English, and therefore sufficient knowledge of written English language is necessary for participation in the study.

## Study Duration

We plan to allow approximately 1 month for each round of the Delphi questionnaire. Thus, your participation in the study will span up to 3 months.

## Possible Side Effects and/or Risks

We do not anticipate any risks associated with this study.

We anticipate that each round of Delphi questionnaire will take you at most 15 minutes to complete, which adds up to 45 minutes of your time for the whole study.

## Benefits of the Study

You will not receive any direct benefit from your participation in this study. The main benefit is helping us with this research project, which, we hope, will advance our understanding of the impact of AAV on overall health of the patients, and of the role that ICF can play in facilitating such understanding.

## Withdrawal from the Study

You have the right to withdraw from the study at any time. If you decide to withdraw, we would appreciate if you could notify us of your intentions by contacting Dr. Nataliya Milman. Please note that because the results of each previous round of the Delphi exercise are incorporated into the subsequent phases, it may not be possible to remove your input from the study if you choose to withdraw after completing at least 1 phase of the Delphi.

## Study Costs/ Compensation

You will not be paid to participate in this research study.

## Confidentiality

All personal information will be kept confidential, unless release is required by law. Representatives of the Ottawa Hospital Research Ethics Board, as well as the Ottawa Hospital Research Institute, may review study-related information under the supervision of Dr. Nataliya Milman and/or her staff for audit purposes.

You will not be identifiable in any publications or presentations resulting from this study, unless you explicitly give permission for such identification.
As a participant of the study you will be assigned a unique study ID. The file that links your study ID to your personal information (name and email address) will be stored separately from all other study-related material in a password-protected file accessible only to Dr. Milman on the secure hospital server. All information which leaves the hospital will be coded with an independent study number.

Upon receipt of your completed Delphi exercise (via email), the document will be coded with the unique study ID and all identifying information will be removed; then, the document will be printed and added to your study file (only identified by study ID), and the email will be permanently deleted. Your study file will be securely stored in a locked cabinet in a locked research office at the Ottawa Hospital Arthritis Centre.

All study files will be kept securely for a period of 10 years after the study has been completed. All paper records will be stored in a locked file and/or office. All electronic records will be stored on a hospital server, again only accessible by Dr. Nataliya Milman and her staff. At the end of the retention period, all paper records will be disposed of in confidential waste or shredded, and all electronic records will be deleted.

## Voluntary Participation

Your participation in this study is voluntary.

## New Information About the Study

You will be told of any new findings during the study that may affect your willingness to continue to participate in this study.

## Questions about the Study

If you have any questions about this study, please contact Dr. Nataliya Milman.

The Ottawa Hospital Research Ethics Board (OHREB) has reviewed this protocol. The OHREB considers the ethical aspects of all research studies involving human participants at The Ottawa Hospital. If you have any questions about your rights as a research participant, you may contact the Chairperson of the Ottawa Hospital Research Ethics Board at 613-798-5555, extension 14902.

## Consent

As was stated earlier, your return of the completed Delphi round 1 questionnaire will constitute your implied consent to the above conditions and your willingness to participate in the study.

## Appendix F. Questionnaire used for identification of areas of AAV considered important by the Clinicians

# ICF Core Sets for ANCA-Associated Vasculitis – Clinical Expert Perspective

**Brief information about yourself** (please put "*" besides answers that apply)

Primary work setting:

academic___ community___ other _____

What is your clinical designation?

Physician___ --> rheumatologist___ nephrologist___ respirologist___
ENT___ other _____

Allied health professional___ --> RN___ PT___ OT___
other _____

What country do you work in? _____

How long have you been working in your clinical specialty (years)? _____

How many cases (approximately) of ANCA-vasculitis do you see each week? _____

How many cases of ANCA-vasculitis have you seen in your career? _____

Do you agree to be acknowledged in the planned publication(s) that will arise from this Delphi exercise? _____

Please proceed to the next page.

Please recall that ICF classification describes health along 4 interacting "components" – 1) body functions, 2) body structures, 3) activities and participation, and 4) environmental factors. In this questionnaire, we want to determine **which aspects of each of these components you think play an important role in determining your patient's overall health and function**.

**Body Functions** component covers physiological processes of the human body. We are asking you to **list up to 30 body functions that you believe to be frequently affected in patients with AAV, and that therefore need to be considered when assessing health and function of these patients**. Please, do not include description of structural damage in this section, as it will be covered in the next session (Body Structure).

Eg: decreased renal function from previous kidney involvement. "Decreased renal function" would be an item under "Body Functions" component, while a "structural kidney damage" would go into the next section (Body Structure)

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**Body Structures** component captures physical disruptions of the body. Please, **list up to 30 body structures that you believe to be frequently affected by AAV, and therefore need to be considered when assessing health and function of AAV patients**

Eg: saddle nose deformity, loss of digit, compression fracture of spine

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Please, proceed to the next page

**Activities and Participation** captures individual's abilities to carry out tasks and their engagement in various life situations. In this section, please **list up to 30 types of activities and participation which you think are the most relevant to the assessment of function in patients with AAV**

Eg: performing activities of daily living, engaging in sports and social outings

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Please, proceed to the next page

**Contextual factors** include personal and environmental factors that could influence health either in a positive or in a negative way. Please, list **up to 30 personal or environmental factors that you think are most relevant for patients with AAV**

Eg: personal attitudes, relationships, medical devices, health policy

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End of questionnaire. Thank you for your time!

## Appendix G. Proposed classification of "personal factors" identified as relevant to patients with AAV

| Proposed ICF code | | | | ICF Category Description |
|---|---|---|---|---|
| P1 | | | | Facts |
| | 10 | | | Demographic characteristics |
| | | 0 | | Age |
| | | 1 | | Education level |
| | | 2 | | Gender/sex role |
| | | 3 | | Health literacy |
| | | 4 | | Occupation |
| | | 5 | | Race/ethnicity |
| | 20 | | | Personal history and biography |
| | | 0 | | Comorbidities |
| | | 2 | | Personal and family circumstances |
| | 30 | | | Position in the immediate social and physical context |
| | | 0 | | Family |
| | | | 0 | Marital status |
| | | | 1 | Family planning |
| | | 1 | | Economic |
| | | | 0 | Socioeconomic status |
| | | | 1 | Income |
| | | | 2 | Financial independence |
| P2 | | | | Experience |
| | 10 | | | Feelings |
| | | 0 | | Emotions / moods |
| | 20 | | | Thoughts and beliefs |
| | | 0 | | Attitude towards medical care |
| | | | 0 | Attitude to access to medical care |
| | | | 1 | Attitude to the process of diagnosis |
| | | | 2 | Attitude to complementary medicine |
| | | | 3 | Interest in own health |
| | | | 4 | Personal views of the medical aspect of disease |
| | | | 5 | Attitude towards medications and other treatments |
| | | | 6 | Satisfaction with monitoring |
| | | | 7 | Attitude towards physicians and other health care providers |
| | | | 8 | Trust or distrust of medical care |
| | | 1 | | Psychological reaction to disease |
| | | | 0 | Concern about appearance |
| | | | 1 | Increased appreciation of what life gives |
| | | | 2 | Effect of not knowing what's going on before diagnosis |

| Proposed ICF code | | | | ICF Category Description |
|---|---|---|---|---|
| | | | 3 | Relief versus fear after diagnosis |
| | | | 4 | Effect of AAV on others |
| | | | 5 | Effects of rare & "unknown" nature of disease |
| | | | 6 | Psychological effects of being physically unwell |
| | | | 7 | Sense that life is over / AAV dominates |
| | | | 8 | Positive effects (other than appreciation) |
| | | 2 | | Disease becoming a constant threat |
| | | | 0 | Worrying about body cues |
| | | | 1 | Worry about future flares |
| | | | 2 | Effects of incurable nature of disease |
| | | | 3 | Worry about prognosis / death |
| | | | 4 | Worry about side effects of drugs |
| | | | 5 | Worry about weak immune system |
| | | | 6 | Effect of unpredictable / uncertain nature of disease |
| | | | 7 | Effect of unpredictable / uncertain nature of disease |
| | 30 | | | Motives |
| | | 0 | | Need to reassess life goals due to limited abilities |
| | | | 0 | Change of physical ability |
| | | | 1 | Change of overall potential |
| | | | 2 | Ability to travel |
| | | | 3 | Work / career ambitions |
| P3 | | | | Patterns of experience and behavior |
| | 10 | | | Habits |
| | | 0 | | Dietary habits |
| | | 1 | | Fitness |
| | | 2 | | Compliance with management |
| | | 3 | | Health behaviors |
| | | 4 | | Other habits (smoking, alcohol) |
| | 20 | | | Personality |
| | | 0 | | Effect of personality of impact of disease |
| | | | 0 | Positive attitude |
| | | 1 | | Disease changing personality / life |
| | 30 | | | Adaptation to chronic illness |
| | | 0 | | Go on with life |
| | | 1 | | Attributing negative events to disease |
| | | 2 | | Denial |
| | | 3 | | Search for explanation - why me? |
| | | 4 | | Comparing self to others |
| | | 5 | | Strategies to facilitate adaptation |
| | | 6 | | Seeking sympathy |
| | | 7 | | Sense of uniqueness of their case |

## Appendix H. Script of prompts for Semi-Structured Interviews at Ottawa, Canada

Script for Interviews and / or Focus Groups

Remind participant(s) that the session will be recorded for the purposes of analysis, and that all disclosed information will be kept confidential
For the interviewees who are known to the interviewer as patients, state the following: "You and I have seen each other recently/regularly as part of your medical care, but for the purpose of this interview I would ask you to talk to me as if this is the first time we'd met and don't assume that I will know anything about your situation"

Tell me the story of your condition up to now
*(If not volunteered by patient:)*
*When and how it started*
*How it was diagnosed*
*How it was treated*

Is your condition active right now or in remission?

How does having this condition and/or its treatments affect you right now?
Any other ways your condition (and/or its treatments) affects you? (ask several times)
*(Prompts for if not volunteered by patient:)*
*Discuss most bothersome symptoms (physical and mental)*
*Discuss how disease affects your abilities to do things you want to do and participate in activities / life situations you want to participate in*
*Examples – hobbies, work, social gatherings*
*Discuss any factors external to yourself and your condition that play a role in how your disease affects your life*
*Examples – relationships, society, medical system*

What is different in the way your condition affects you when it's in a flare (or when it's in remission, if patient is in a flare now)?
*Same prompts as for effect of disease "right now"*

Inserted below is the script for the AAV PRO study that is conducted in collaboration with the present study. At this point the interviewer should check to ensure that all questions below have been addressed during the previous discussion. Any questions that have not been addressed should be asked at this point.

<u>BEGINNING</u>

Describe the physical symptoms of vasculitis you first noticed

When did the physical symptoms start?

Describe the psychological symptoms of vasculitis you first noticed

When did the psychological symptoms start?

Describe how your symptoms changed as time went on

If not already covered - how did these symptoms affect your day to day life?

DIAGNOSIS

Tell me about the time when you first got your diagnosis

Describe how getting the diagnosis of vasculitis affected you

TREATMENTS

Describe how the treatment for vasculitis affected you
Good/bad affects
Timing of effects
Effects other than physical
Effect on day to day life

If you have had other treatments for vasculitis, please describe in the same way (repeat until all treatments described)
Good/bad affects
Timing of effects
Effects other than physical
Effect on day to day life

Any annoying side effects?

REMISSION
We know that patients can continue to have symptoms even when the vasculitis is described as “in remission” or “stable” or “successfully treated” by their doctors…

Describe how you feel when your vasculitis is stable (ie not flaring)
Good/bad aspects
Timing of changes or fluctuations
Effects other than physical
Effect on day to day life

DISEASE FLARES

Patients will sometimes have a return of their original symptoms or new symptoms will start, this can be described as “having a flare”.

How would you describe “having a flare”?

Describe what you notice physically when your symptoms start to flare

Describe what you notice psychologically when your symptoms start to flare

Over what period of time does the flare develop?

What words would you use to describe how bad a flare is?

How could you grade how severe a flare/ symptoms are?

How does having a flare affect your day to day life?

Tell me about any clues you get that the vasculitis is about to, or is starting to, flare up

Tell me about what do you do when you think a flare is starting?
What helps
What makes it worse

What thoughts do you have about future flares?

<u>FOCUS ON IMPACT ON LIFE:</u>

We want to know how having vasculitis has affected your life, both the good and bad. Let’s start with ….

How have your everyday activities – the things that you normally do - changed since the vasculitis started? (involving family, work and leisure)

How has the way you plan your day or week changed? (eg family, work and leisure)

How about the way you make big or long-term plans (eg holidays, family, moving house, changing relationships, or job etc)- has this changed?

Can you think of anything that has either helped you or made things worse since you have had vasculitis? For example relationships, support groups, medical help, technology?

<u>ANY POSITIVES:</u>

Tell me about any positive effects of having vasculitis

AND FINALLY

Is there anything else we should know about your experience of having vasculitis that we haven't already talked about?

We are creating a questionnaire to capture the effects of vasculitis from the patient perspective, what would you want to make sure was included in such a questionnaire?

Is there anything else you'd like to add?

Of everything we discussed what would you say is the most important or biggest effect of your condition on your life?

## Appendix I. Script of prompts for Focus Groups performed in Boston, USA

### VASCULITIS FOCUS GROUP TOPICS: VCRC-OMERACT PROVE PROJECT

It will be important for patients to understand that when we say "vasculitis" that we mean their disease. They may only think of it as Wegener's granulomatosis or microscopic polyangiitis, or Churg-Strauss syndrome (these three are all types of vasculitis and comprise the "ANCA-associated vasculitis" group).

1. How does vasculitis affect your life?

2. How do you feel when your disease (vasculitis) is active?

3. Does having vasculitis affect you in ways other than physically?

4. If fatigue is mentioned:
    a. What terms best describe the fatigue that is associated with vasculitis?
    b. How is the fatigue associated with your disease different from fatigue you have experience from other causes?

5. What are the worst things about having vasculitis?

6. What specific symptoms related to your vasculitis or your treatment bother you?
    a. Could probe for specific problems such as ear, nose, or throat issues
    b. Could ask for quantification

7. How have the medicines you have received for treatment of vasculitis affected you?

8. Does your vasculitis affect you in ways that your physician never or rarely asks about?
    a. *What important aspects of your vasculitis do you think your physician is unaware of?*
    b. *What aspects of your disease do you think are important, but that your physician may not understand or ask about?*
    c. *Are there specific symptoms that you feel are suggestive of active vasculitis that your physician never addresses?*

9. How does having vasculitis impact your life?
    a. Physical
    b. Mental
    c. Emotional
    d. Social
    e. Quality

10. How has having vasculitis changed your life?

## Appendix J. Purposive sampling grid for individual patient interviews

| | **GPA**<br>Age/Gender(ID) | **MPA**<br>Age/Gender(ID) | **CSS**<br>Age/Gender(ID) |
|---|---|---|---|
| Disease duration <2 years | | | |
| Disease Duration >2 years | | | |

Legend: GPA: granulomatosis with polyangiitis; MPA: microscropic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; age = age at time of interview; ID = unique study identifier.

## Appendix K. Letter to physicians at Ottawa Hospital inviting them to refer patients for enrolment into the study

# ATTENTION: All Rheumatologists at the Ottawa Hospital's Arthritis Centre

## Invitation to enroll your patients into a study: ICF Core Sets for ANCA-Associated Vasculitis – Patient Perspective

**Principal Investigator: Dr. Nataliya Milman**

**Dear Colleague**,

You are invited to contribute your patients for this study.

The general aim of this study is to apply the ICF (International Classification of Functioning, Disability, and Health) to the field of ANCA-Associated Vasculitis (AAV).

The ICF is a classification system to describe functioning and health from a broad bio-psycho-social perspective. Since its introduction in 2001 by the World Health Organization, this classification system has been used to study the impact on patients' overall function relater to a number of medical conditions. This study will aim to apply the ICF to AAV.

We are currently recruiting patients to participate in one part of this study ("Patient Perspective") which aims to determine which aspects of AAV are particularly relevant to the patients with these conditions. We are looking for up to 36 patients who will participate in a 1 to 2-hour long discussion of their experience with their disease, either in the form of a personal interview or in the form of a focus group involving 4-6 patients.

The eligibility criteria for participation are:

age 18 and over, and
diagnosis of one of the ANCA-Associated Vasculitides, namely Granulomatosis with Polyangiitis (Wegener's), Microscopic Polyangiitis, or Churg-Strauss Syndrome
Sufficient knowledge of English language to be able to participate in an interview conducted in English

If you are seeing in your clinic a patient who meets the above criteria and is potentially interested in participating, please contact Dr. Nataliya Milman immediately.

Dr. Milman will speak to your patient (immediately) about the study and will take care of the enrollment of patients who agree to participate.

If you are unable to contact Dr. Milman at the time of your encounter with the patient, please provide your patient with the study Information and Consent form (to be found in the

rheumatology clinic in a folder labeled “ICF in Vasculitis Study”), and ask the patient to contact Dr. Milman at their convenience (Dr. Milman’s contact information can be found on the study Information and Consent form).

Thank you in advance for your help with this study!

Sincerely,

Dr. Nataliya Milman

## Appendix L. Participant information and consent form for participating patients

# Information Sheet and Consent Form for Interview

### *ICF Core Sets for ANCA-Associated Vasculitis – Patient Perspective*

**Principal Investigator: Dr. Nataliya Milman**

**(Please contact Dr. N. Milman to set up your interview if you agree to participate in this study)**

**Sponsor: The Arthritis Society / Canadian Rheumatology Association / UCB Pharma**

**Introduction**

You are being asked to participate in this research project because you have been diagnosed with one of the conditions known as "ANCA-Associated Vasculitis" (AAV).

Please read this Information Sheet and Consent Form carefully and ask as many questions as you like before deciding whether to participate in this research study. You can discuss this decision with your family, friends and your health-care team.

**Background, Purpose and Design of the Study**

The International Classification of Functioning, Disability, and Health (ICF) is a classification system used to describe functioning and health from a broad perspective that takes into account individual's personal attitudes and environmental influences. Since its introduction in 2001 by the World Health Organization, this classification system has been used to study the impact on patients' overall function related to a number of medical conditions. This study will aim to apply the ICF to AAV – the condition which you have been diagnosed with.

The overall study will consist of several parts which will look at the impact of AAV from different perspectives, including from the perspective of the available literature, from the opinion of clinical experts, and from the perspective of patients. Your role would be to participate in the "Patient perspective" part of the study. The primary goal of this part of the study is to find out which aspects of AAV are particularly relevant to patients that suffer from these conditions. This information will then be used to create a list (called the "Core Set") of the most important aspects of AAV that will need to be assessed at all clinical visits, and/or in all clinical trials of patients with AAV.

The "Patient Perspective" part of this study will start with a combination of patient interviews and focus groups. You are asked to participate in an individual interview. We will be interviewing between 16 and 36 patients. The purpose of the interviews is to discuss the effect that AAV has on the life of the patient living with the condition.

Analysis of the interviews will result in a list of aspects of AAV that are particularly relevant to the participating patients. This list will be incorporated with other parts of this study in order to produce a final list ("the Core Set") of different aspects of disease that are most important in AAV.

**Study Procedures**

If you consent to participate in this study, we will arrange a time (most likely in the evening) for the interview to take place, most likely in a conference room at the Ottawa Hospital Arthritis Centre.

The interview will last between 1 and 1.5 hours. Each interview will involve 1 patient and 1 or 2 interviewers. The interviewers will introduce the topics to be discussed, and lead the interview as appropriate. The discussion will be audio recorded and then analyzed according to the standard procedure used to get the necessary information out of the interview recordings. During the interview, if you are asked to discuss topics that you do not feel comfortable talking about, you may choose not to answer and the interviewer will move to the next question.

Please note that this study is performed in collaboration with another international study designed to develop a patient-reported outcome measurement tool specific to AAV (named Patient reported outcome development for ANCA associated Vasculitis Study Collaboration). That study will perform interviews with AAV patients with the same purpose of describing the impact of AAV on patients' quality of life. Therefore, these two studies will have the same interview questions and will share the interview recordings, interview transcripts, or the results of the analysis. As a result, the information collected during your interview may be shared (in a confidential fashion) with the investigators of the other study.

Please note that because the interviews will be conducted in English, sufficient knowledge of spoken English language is necessary for participation in the interview.

**Study Duration**

We anticipate that the entire study will last approximately 1 year, with an estimated completion in June of 2013. Since your role in the study will be to participate in an interview, your participation in the study will be completed after your interview.

**Possible Side Effects and/or Risks**

Because of the observational nature of this study, we do not anticipate any side effects or risks associated with this study.

**Benefits of the Study**

You may not receive any direct benefit from your participation in this study. Your participation may allow the researchers to better characterize those aspects of AAV that are particularly relevant to patients with the disease. Incorporation of this information into everyday practice and research will result in medical care that is better suited to the needs of the patients, resulting in the potential benefit to patients in the future.

**Withdrawal from the Study**

You have the right to withdraw from the study at any time without any impact to your current and future care at the Ottawa Hospital. If you decide to withdraw, you should notify one of the study members as soon as possible.

Please, note that after analysis the information obtained during your interview is pooled together with information obtained from interviews with other patients, and it will no longer be possible to separate your contribution from that of others. Therefore, if you withdraw from the study after your interview has been analyzed, the information contributed by you during your interview will still be used for the purposes of the study.

You have the right to check your study records and request changes if the information is not correct. However, to ensure the scientific integrity of the study, some of your records related to the study may not be available for your review until after the study has been completed.

**Study Costs**

You will not be paid to participate in this research study. However, you will be reimbursed for parking during your interview.

**Confidentiality**

All personal health information will be kept confidential, unless release is required by law. Representatives of the Ottawa Hospital Research Ethics Board, as well as the Ottawa Hospital Research Institute, may review your original study records under the supervision of Dr. Nataliya Milman's staff for audit purposes.

You will not be identifiable in any publications or presentations resulting from this study. No identifying information will leave the Ottawa Hospital. All information which leaves the hospital will be coded with an independent study number and will not contain any identifying information. This also applies to sharing of the results of your interview with the investigators of the collaborative study (see study procedures section above).

The link between your name and the independent study number will only be accessible by Dr. Nataliya Milman and/or her staff. The link and study files will be stored separately and securely. Both files will be kept for a period of 10 years after the study has been completed. The audio recordings will be deleted immediately after being transcribed. All paper records will be stored in a locked file and/or office. All electronic records will be stored on a hospital server, again only accessible by Dr. Nataliya Milman and her staff. At the end of the retention period, all paper records will be disposed of in confidential waste or shredded, and all electronic records will be deleted.

**Voluntary Participation**

Your participation in this study is voluntary. If you choose not to participate, your decision will not affect the care you receive at this Institution at this time, or in the future. You will not have any penalty or loss of benefits to which you are otherwise entitled.

**Questions about the Study**

**If you have any questions about this study, or to confirm your willingness to participate, please contact Dr. Nataliya Milman.**

The Ottawa Hospital Research Ethics Board (OHREB) has reviewed this protocol. The OHREB considers the ethical aspects of all research studies involving human participants at The Ottawa Hospital. If you have any questions about your rights as a research participant, you may contact the Chairperson of the Ottawa Hospital Research Ethics Board at 613-798-5555, extension 14902.

## Consent Form

**(Please also notify Dr. Milman of your intention to participate – see contact information above)**

***ICF Core Sets for ANCA-Associated Vasculitis – Patient Perspective***

**Consent to Participate in Research**

I understand that I am being asked to participate in a research study about ANCA-Associated Vasculitis. This study has been explained to me by _____.

I have read this 4-page Information Sheet and Consent Form (or have had this document read to me). All my questions have been answered to my satisfaction. If I decide at a later stage in the study that I would like to withdraw my consent, I may do so at any time.

I voluntarily agree to participate in this study.

A copy of the signed Information Sheet and/or Consent Form will be provided to me.

**Signatures**

_____

Participant's Name (Please Print)

_____ _____

Participant's Signature Date

**Investigator Statement (or Person Explaining the Consent)**

I have carefully explained to the research participant the nature of the above research study. To the best of my knowledge, the research participant signing this consent form understands the nature, demands, risks and benefits involved in participating in this study. I acknowledge my responsibility for the care and well being of the above research participant, to respect the rights and wishes of the research participant, and to conduct the study according to applicable Good Clinical Practice guidelines and regulations.

_____

Name of Investigator/Delegate (Please Print)

_____ _____

Signature of Investigator/Delegate Date

## Appendix M. Patient interview saturation tables

Table M.1. Patient interview saturation table for classified ICF components

| ICF Code | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Body Functions** | | | | | | | | | | | | | | |
| B1 | Mental functions | | | | | | | | | | | | | |
| 10 | Consciousness functions | | | | | | | | √ | | | | | |
| 26 | Temperament and personality functions | | | √ | | | | | | | | | | |
| 30 | Energy and drive functions | √ | | | | | | | | | | | | |
| 34 | Sleep functions | √ | | | | | | | | | | | | |
| 47 | Psychomotor functions | | √ | | | | | | | | | | | |
| 52 | Emotional functions | | | √ | | | | | | | | | | |
| 80 | Experience of self and time functions | | √ | | | | | | | | | | | |
| B2 | Sensory functions and pain | | | | | | | | | | | | | |
| 10 | Seeing functions | | | | | | | | √ | | | | | |
| 15 | Functions of structures adjoining the eye | | | | | | | √ | | | | | | |
| 20 | Sensations associated with the eye and adjoining structures | | | | √ | | | | | | | | | |
| 30 | Hearing functions | √ | | | | | | | | | | | | |
| 40 | Sensations associated with hearing and vestibular function | | | | | | | √ | | | | | | |
| 50 | Taste function | | | | | | | | √ | | | | | |
| 55 | Smell function | | | | | | | √ | | | | | | |
| 79 | Additional sensory functions, other specified and unspecified | | | | | | | | | | | √ | | |
| 80 | Sensation of pain | √ | | | | | | | | | | | | |
| B3 | Voice and speech functions | | | | | | | | | | | | | |
| 10 | Voice functions | | √ | | | | | | | | | | | |
| B4 | Functions of the cardiovascular, | | | | | | | | | | | | | |

| ICF Code | | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | haematological, immunological and respiratory systems | | | | | | | | | | | | | |
| | 10 | Heart functions | | | √ | | | | | | | | | | |
| | 15 | Blood vessel functions | | | | | | | | | | | | √ | |
| | 20 | Blood pressure functions | | | | √ | | | | | | | | | |
| | 30 | Haematological system functions | | | | | | | | | | √ | | | |
| | 35 | Immunological system functions | √ | | | | | | | | | | | | |
| | 40 | Respiratory functions | √ | | | | | | | | | | | | |
| | 49 | Functions of the respiratory system, other specified and unspecified | | √ | | | | | | | | | | | |
| | 50 | Additional respiratory functions | √ | | | | | | | | | | | | |
| | 55 | Exercise tolerance functions | √ | | | | | | | | | | | | |
| | 60 | Sensations associated with cardiovascular and respiratory functions | | √ | | | | | | | | | | | |
| | 69 | Additional functions and sensations of the cardiovascular and respiratory systems, other specified and unspecified | | | | | | | | | | | √ | | |
| B5 | | Functions of the digestive, metabolic and endocrine systems | | | | | | | | | | | | | |
| | 10 | Ingestion function | | | | | | | √ | | | | | | |
| | 15 | Digestive functions | | | | | | | √ | | | | | | |
| | 30 | Weight maintenance functions | | | | √ | | | | | | | | | |
| | 35 | Sensations associated with the digestive system | | | | | √ | | | | | | | | |
| | 40 | General metabolic functions | | | | | | | | | | | √ | | |
| | 45 | Water, mineral and electrolyte balance functions | | √ | | | | | | | | | | | |
| | 50 | Thermoregulatory functions | | | | | | √ | | | | | | | |
| | 55 | Endocrine gland function | | | | | | | √ | | | | | | |
| B6 | | Genitourinary and reproductive functions | | | | | | | | | | | | | |

| ICF Code | | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 10 | Urinary excretory functions | | √ | | | | | | | | | | | |
| | 60 | Procreation functions | | | | | | | √ | | | | | | |
| B7 | | Neuromusculoskeletal and movement-related functions | | | | | | | | | | | | | |
| | 10 | Mobility of joint functions | √ | | | | | | | | | | | | |
| B8 | | Functions of the skin and related structures | | | | | | | | | | | | | |
| | 10 | Protective functions of the skin | | √ | | | | | | | | | | | |
| | 20 | Repair functions of the skin | | √ | | | | | | | | | | | |
| | 40 | Sensation related to the skin | | | | | | | | | | | | √ | |
| **Body Structures** | | | | | | | | | | | | | | | |
| S1 | | Structures of the nervous system | | | | | | | | | | | | | |
| | 30 | Structure of meninges | | | | | | | | | | | √ | | |
| S2 | | The eye, ear and related structures | | | | | | | | | | | | | |
| | 20 | Structure of eyeball | | | | √ | | | | | | | | | |
| | 30 | Structures around eye | | | | | | | √ | | | | | | |
| | 40 | Structure of external ear | | | | | | | √ | | | | | | |
| | 50 | Structure of middle ear | √ | | | | | | | | | | | | |
| S3 | | Structures involved in voice and speech | | | | | | | | | | | | | |
| | 10 | Structure of nose | | √ | | | | | | | | | | | |
| | 20 | Structure of mouth | | | | | | √ | | | | | | | |
| S4 | | Structures of the cardiovascular, immunological and respiratory systems | | | | | | | | | | | | | |
| | 10 | Structure of cardiovascular system | √ | | | | | | | | | | | | |
| | 30 | Structure of respiratory system | √ | | | | | | | | | | | | |
| S5 | | Structures related to the digestive, metabolic and endocrine systems | | | | | | | | | | | | | |
| | 50 | Structure of pancreas | | | | | | | | | | | | √ | |
| | 60 | Structure of liver | | | | | | | | | | | | √ | |

| ICF Code | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 70 | Structure of gall bladder and ducts | | | | | | | | √ | | | | | |
| S6 | Structures related to the genitourinary and reproductive systems | | | | | | | | | | | | | |
| 10 | Structure of urinary system | | | | | | √ | | | | | | | |
| S7 | Structures related to movement | | | | | | | | | | | | | |
| 50 | Structure of lower extremity | | | | | | | | | | | √ | | |
| 60 | Structure of trunk | | | √ | | | | | | | | | | |
| 70 | Additional musculoskeletal structures related to movement | √ | | | | | | | | | | | | |
| S8 | Skin and related structures | | | | | | | | | | | | | |
| 10 | Structure of areas of skin | | √ | | | | | | | | | | | |
| 40 | Structure of hair | | | | | | | | √ | | | | | |
| **Activities and Participation** | | | | | | | | | | | | | | |
| D1 | Learning and applying knowledge | | | | | | | | | | | | | |
| 10 | Watching | | | | | | | | √ | | | | | |
| 66 | Reading | | | | | | | | √ | | | | | |
| D2 | General tasks and demands | | | | | | | | | | | | | |
| 10 | Undertaking a single task | √ | | | | | | | | | | | | |
| 40 | Handling stress and other psychological demands | | | | | | | | √ | | | | | |
| D3 | Communication | | | | | | | | | | | | | |
| 30 | Speaking | | | | | | √ | | | | | | | |
| 60 | Using communication devices and techniques | | | | | √ | | | | | | | | |
| D4 | Mobility | | | | | | | | | | | | | |
| 10 | Changing basic body position | √ | | | | | | | | | | | | |
| 15 | Maintaining a body position | | | | | | | | | √ | | | | |
| 20 | Transferring oneself | | | | | √ | | | | | | | | |

| ICF Code | | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 30 | Lifting and carrying objects | | | | | | | √ | | | | | | |
| | 40 | Fine hand use | | | | | | | | | √ | | | | |
| | 45 | Hand and arm use | | | | | √ | | | | | | | | |
| | 50 | Walking | √ | | | | | | | | | | | | |
| | 55 | Moving around | √ | | | | | | | | | | | | |
| | 60 | Moving around in different locations | | √ | | | | | | | | | | | |
| | 65 | Moving around using equipment | | | | | | | | | | | √ | | |
| | 70 | Using transportation | | | | | | | | | | √ | | | |
| | 75 | Driving | | | | | | √ | | | | | | | |
| D5 | | Self-care | | | | | | | | | | | | | |
| | 10 | Washing oneself | | | | | √ | | | | | | | | |
| | 20 | Caring for body parts | | | | | | | | | √ | | | | |
| | 40 | Dressing | | | | | √ | | | | | | | | |
| | 70 | Looking after one's health | | √ | | | | | | | | | | | |
| D6 | | Domestic life | | | | | | | | | | | | | |
| | 20 | Acquisition of goods and services | | | | | | | | √ | | | | | |
| | 30 | Preparing meals | | | | | | | √ | | | | | | |
| | 40 | Doing housework | | | | | | | √ | | | | | | |
| | 50 | Caring for household objects | | | √ | | | | | | | | | | |
| | 60 | Assisting others | | | √ | | | | | | | | | | |
| D7 | | Interpersonal interactions and relationships | | | | | | | | | | | | | |
| | 30 | Relating with strangers | | | | | √ | | | | | | | | |
| | 40 | Formal relationships | | | | | | | | | √ | | | | |
| | 50 | Informal social relationships | | | | | √ | | | | | | | | |
| | 60 | Family relationships | | | √ | | | | | | | | | | |
| | 70 | Intimate relationships | | | | √ | | | | | | | | | |

| ICF Code | | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D8 | | Major life areas | | | | | | | | | | | | | |
| | 30 | Higher education | | | | | | | √ | | | | | | |
| | 45 | Acquiring, keeping and terminating a job | √ | | | | | | | | | | | | |
| | 50 | Remunerative employment | √ | | | | | | | | | | | | |
| | 55 | Non-remunerative employment | | | | | | | √ | | | | | | |
| | 70 | Economic self-sufficiency | | | | | | | √ | | | | | | |
| D9 | | Community, social and civic life | | | | | | | | | | | | | |
| | 10 | Community life | | √ | | | | | | | | | | | |
| | 20 | Recreation and leisure | √ | | | | | | | | | | | | |
| | 30 | Religion and spirituality | | | | | | | | | | √ | | | |
| **Environmental Factors** | | | | | | | | | | | | | | | |
| E1 | | Products and technology | | | | | | | | | | | | | |
| | 10 | Products or substances for personal consumption | √ | | | | | | | | | | | | |
| | | > drugs | √ | | | | | | | | | | | | |
| | 15 | Products and technology for personal use in daily living | | √ | | | | | | | | | | | |
| | 20 | Products and technology for personal indoor and outdoor mobility and transportation | | | | | | | | | | | √ | | |
| | 25 | Products and technology for communication | | | | √ | | | | | | | | | |
| | 30 | Products and technology for education | √ | | | | | | | | | | | | |
| | 35 | Products and technology for employment | | √ | | | | | | | | | | | |
| | 50 | Design, construction and building products and technology of buildings for public use | | | | | | | √ | | | | | | |
| | 55 | Design, construction and building products and technology of buildings for private use | | | √ | | | | | | | | | | |

| ICF Code | | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 65 | Assets | | | √ | | | | | | | | | | |
| | 98 | Products and technology, other specified | √ | | | | | | | | | | | | |
| E2 | | Natural environment and human-made changes to environment | | | | | | | | | | | | | |
| | 10 | Physical geography | | | √ | | | | | | | | | | |
| | 25 | Climate | | √ | | | | | | | | | | | |
| | 60 | Air quality | | √ | | | | | | | | | | | |
| | 98 | Natural environment and human-made changes to environment, other specified | | √ | | | | | | | | | | | |
| E3 | | Support and relationships | | | | | | | | | | | | | |
| | 10 | Immediate family | | √ | | | | | | | | | | | |
| | 20 | Friends | | √ | | | | | | | | | | | |
| | 25 | Acquaintances, peers, colleagues, neighbours and community members | | | | | | | | | | | √ | | |
| | 40 | Personal care providers and personal assistants | | | √ | | | | | | | | | | |
| | 45 | Strangers | | | | | | | | | | | √ | | |
| | 55 | Health professionals | | √ | | | | | | | | | | | |
| | 98 | Support and relationships, other specified | | | | | √ | | | | | | | | |
| E4 | | Attitudes | | | | | | | | | | | | | |
| | 10 | Individual attitudes of immediate family members | √ | | | | | | | | | | | | |
| | 20 | Individual attitudes of friends | | | | | | | | | | | √ | | |
| | 25 | Individual attitudes of acquaintances, peers, colleagues, neighbours and community members | | √ | | | | | | | | | | | |
| | 45 | Individual attitudes of strangers | | √ | | | | | | | | | | | |
| | 50 | Individual attitudes of health professionals | √ | | | | | | | | | | | | |

| ICF Code | | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| E5 | | Services, systems and policies | | | | | | | | | | | | | |
| | 25 | Housing services, systems and policies | | | | | | | | | | | √ | | |
| | 30 | Utilities services, systems and policies | | | | | | | | | | | | √ | |
| | 35 | Communication services, systems and policies | | | | | | | | √ | | | | | |
| | 40 | Transportation services, systems and policies | | | √ | | | | | | | | | | |
| | 60 | Media services, systems and policies | | | | | | | | √ | | | | | |
| | 70 | Social security services, systems and policies | | | | | | √ | | | | | | | |
| | 80 | Health services, systems and policies | √ | | | | | | | | | | | | |
| | 90 | Labour and employment services, systems and policies | | √ | | | | | | | | | | | |
| Number of new categories identified | | | 27 | 25 | 12 | 6 | 9 | 6 | 16 | 11 | 4 | 3 | 11 | 5 | 0 |

*"√" in the individual cells represents the first occurrence of the specific category in a focus group or an individual interview. Columns with solid single line borders represent individually interviewed patients from Ottawa, Canada; columns with double borders represent individually interviewed patients from Oxford, UK; column with dashed borders represent the 2 focus groups (combined) performed in Boston, USA. Columns shaded white represent individually interviewed patients with GPA; dark-shaded columns represent individually interviewed patients with EGPA; light shaded columns represent individually interviewed patients with MPA.*

Table M.2. Patient interview saturation table for ICF component "Personal factors"

| Proposed classification | | | | Category description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **P1** | | | | **Facts** | | | | | | | | | | | | | |
| | 10 | | | Demographic characteristics (I defined them as "factors that are not modifiable") | | | | | | | | | | | | | |
| | | 0 | | Age | | | | | | | | √ | | | | | |
| | | 3 | | Health literacy | | | | | | | | √ | | | | | |
| | | 4 | | Occupation | | | | | | | √ | | | | | | |
| | 20 | | | Personal history and biography | | | | | | | | | | | | | |
| | | 0 | | Comorbidities | | | | | | | | | √ | | | | |
| | | 2 | | Personal and family circumstances | | | | | √ | | | | | | | | |
| | 30 | | | Position in the immediate social and physical context | | | | | | | √ | | | | | | |
| | | 0 | | Family | | | | | | | √ | | | | | | |
| | | 1 | | Economic | | | | | | | √ | | | | | | |
| | | | 1 | Income | | | | | | | √ | | | | | | |
| | | | 2 | Financial independence | | | | | | | | √ | | | | | |
| **P2** | | | | **Experience** | | | | | | | | | | | | | |
| | 10 | | | Feelings | | | | | | | | | | | | | |
| | | 0 | | Emotions / moods | | | | | √ | | | | | | | | |
| | 20 | | | Thoughts and beliefs | | | | | | | | | | | | | |
| | | 0 | | Attitude towards medical care | | | | | | √ | | | | | | | |
| | | | 0 | Attitude to access to medical care | | | | | √ | | | | | | | | |
| | | | 1 | Attitude to the process of diagnosis | √ | | | | | | | | | | | | |
| | | | 2 | Attitude to complementary medicine | | | | | | | | √ | | | | | |

| Proposed classification | | | | Category description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 3 | Interest in own health | | √ | | | | | | | | | | | |
| | | | 4 | Personal views of the medical aspect of disease | √ | | | | | | | | | | | | |
| | | | 5 | Attitude towards medications and other treatments | √ | | | | | | | | | | | | |
| | | | 6 | Satisfaction with monitoring | | | | √ | | | | | | | | | |
| | | | 7 | Attitude towards physicians and other health care providers | √ | | | | | | | | | | | | |
| | | | 8 | Trust or distrust of medical care | √ | | | | | | | | | | | | |
| | | 1 | | Psychological reaction to disease | √ | | | | | | | | | | | | |
| | | | 0 | Concern about appearance | | √ | | | | | | | | | | | |
| | | | 1 | Increased appreciation of what life gives | | | | √ | | | | | | | | | |
| | | | 2 | Effect of not knowing what's going on before diagnosis | | | | | √ | | | | | | | | |
| | | | 3 | Relief versus fear after diagnosis | | | | | | | √ | | | | | | |
| | | | 4 | Effect of AAV on others | | | √ | | | | | | | | | | |
| | | | 5 | Effects of rare & "unknown" nature of disease | | | | √ | | | | | | | | | |
| | | | 6 | Psychological effects of being physically unwell | | | √ | | | | | | | | | | |
| | | | 7 | Sense that life is over / AAV dominates | | | | | | | | √ | | | | | |

| Proposed classification | | | | Category description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 8 | Positive effects (other than appreciation) | | | | √ | | | | | | | | | |
| | | 2 | | Disease becoming a constant threat | | | | | | | | | | √ | | | |
| | | | 0 | Worrying about body cues | | | | | | | √ | | | | | | |
| | | | 1 | Worry about future flares | | | √ | | | | | | | | | | |
| | | | 3 | Effects of incurable nature of disease | | | | | | √ | | | | | | | |
| | | | 4 | Worry about prognosis / death | | √ | | | | | | | | | | | |
| | | | 5 | Worry about side effects of drugs | | | | √ | | | | | | | | | |
| | | | 6 | Worry about weak immune system | | √ | | | | | | | | | | | |
| | | | 7 | Effect of unpredictalbe / uncertain nature of disease | √ | | | | | | | | | | | | |
| | 30 | | | Motives | | | | | | | | | | | | | |
| | | 0 | | Need to reassess life goals due to limited abilities | | | | | | | | | | | | | |
| | | | 0 | Change of physical ability | | √ | | | | | | | | | | | |
| | | | 1 | Change of overall potential | √ | | | | | | | | | | | | |
| | | | 2 | Ability to travel | | | √ | | | | | | | | | | |
| | | | 3 | Work / career ambitions | | | √ | | | | | | | | | | |
| **P3** | | | | **Patterns of experience and behavior** | | | | | | | | | | | | | |
| | 10 | | | Habits | | | | | | | | | | | | | |
| | | 0 | | Dietary habits | | √ | | | | | | | | | | | |

| Proposed classification | | | | Category description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | | Fitness | | √ | | | | | | | | | | | |
| | | 2 | | Compliance with management | | | | | | √ | | | | | | | |
| | | 3 | | Health behaviors | | √ | | | | | | | | | | | |
| | | 4 | | Other habits (smoking, EtOH) | | | | | | | | | √ | | | | |
| | 20 | | | Personality | | | | | | | | | | | | | |
| | | 0 | | Effect of personality of impact of disease | | | | | | | √ | | | | | | |
| | | | 0 | Positive attitude | √ | | | | | | | | | | | | |
| | | 1 | | Disease changing personality / life | √ | | | | | | | | | | | | |
| | 30 | | | Adaptation to chronic illness | | | √ | | | | | | | | | | |
| | | 0 | | Go on with life | √ | | | | | | | | | | | | |
| | | 1 | | Attributing negative events to disease | | | | | | | √ | | | | | | |
| | | 2 | | Denial | √ | | | | | | | | | | | | |
| | | 3 | | Search for explanation - why me? | | √ | | | | | | | | | | | |
| | | 4 | | Comparing self to others | | | | √ | | | | | | | | | |
| | | 5 | | Strategies to facilitate adaptation | | | | | | | | √ | | | | | |
| | | 6 | | Seeking sympathy | √ | | | | | | | | | | | | |
| | | 7 | | Sense of uniqueness of their case | | | √ | | | | | | | | | | |
| New categories identified | | | | | 13 | 9 | 7 | 6 | 4 | 3 | 9 | 6 | 2 | 1 | 0 | 0 | 0 |

*"√" in the individual cells represents the first occurrence of the specific category in a focus group or an individual interview. Columns with solid single line borders represent individually interviewed patients from Ottawa, Canada; columns with double borders represent individually interviewed patients from Oxford, UK; column with dashed borders represent the 2 focus groups (combined) performed in Boston, USA. Columns shaded white represent individually interviewed patients with GPA; dark-shaded columns represent individually interviewed patients with EGPA; light shaded columns represent individually interviewed patients with MPA.*

Table M.3. Patient interview saturation table for "health conditions" and categories that are "not covered" or "not definable" by the ICF

| ICF | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Health conditions** | | | | | | | | | | | | | | |
| | Asthma | | √ | | | | | | | | | | | |
| | Avascular necrosis | | | | | | | | | | | | | √ |
| | Depression | | | | | | | √ | | | | | | |
| | Diabetes | | | | | | | | | | | √ | | |
| | Infections | | √ | | | | | | | | | | | |
| | Malignancy | | | | | | | | | | | √ | | |
| | Osteoarthritis | | | | | | | | | | √ | | | |
| | Raynaud's | | | | | | | | | | | | √ | |
| **Not covered** | | | | | | | | | | | | | | |
| | Diagnosis (process) | √ | | | | | | | | | | | | |
| | Clinical research | | | | | | | | √ | | | | | |
| nc-bf | Gallbladder dysfunction | | | | | | | | √ | | | | | |
| | Mucus production | | √ | | | | | | | | | | | |
| | Nasal functions | | | | | √ | | | | | | | | |
| | Sinus dysfunction | | √ | | | | | | | | | | | |
| nc-bs | sinuses | | √ | | | | | | | | | | | |
| nc-ap | Activities related to medical care | | | | | | | | | √ | | | | |
| nc-env | Information about disease & drugs | √ | | | | | | | | | | | | |
| | Work environment | | √ | | | | | | | | | | | |
| | Living arrangement | | √ | | | | | | | | | | | |
| | Stress | | √ | | | | | | | | | | | |
| **Not definable** | | | | | | | | | | | | | | |
| | General well-being | | | √ | | | | | | | | | | |
| | Mental/psychological health | | | | | | | √ | | | | | | |
| | Physical health | | | | √ | | | | | | | | | |

| ICF | ICF Category Description | Patient_01_Ot | Patient_02_Ot | Patient_03_Ot | Patient_04_Ot | Patient_05_Ot | Patient_06_Ot | Patient_07_Ot | Patient_08_Ot | Patient_09_Ot | Patient_10_Ot | Patient_11_Ox | Patient_12_Ox | Focus groups |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (also nd-bs) | | | | | | | | | | | | | |
| | HRQOL | | | | | | | | | | | | | √ |
| | Stage of illness | | | | | | | | | | | | | |
| | Flare / relapse | | | √ | | | | | | | | | | |
| | Stable disease | | | √ | | | | | | | | | | |
| | Remission | | | | | √ | | | | | | | | |
| | Survival / death | | | | √ | | | | | | | | | |
| | Treatment | | | | | | | | | | | | | |
| | Effect of treatment | | | √ | | | | | | | | | | |
| | Side effects from drugs | | | | √ | | | | | | | | | |
| | >> Side effects of prednisone | | √ | | | | | | | | | | | |
| nd-bf | Infection | | √ | | | | | | | | | | | |
| nd-bs | Infection | | √ | | | | | | | | | | | |
| nd-ap | Ability to do physical activity (exercise or ADL) | | | | | | | √ | | | | | | |
| | Using / operating technology | | | | | √ | | | | | | | | |
| | Independence in activities | | | | | | | | √ | | | | | |
| | Planning for future | | | | √ | | | | | | | | | |
| New categories identified | | 2 | 11 | 4 | 4 | 2 | 0 | 3 | 3 | 1 | 1 | 2 | 1 | 2 |

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