**Project Title:** External validation and Finalization of Provisional American College of Rheumatology Classification Criteria for Sjögren's Syndrome

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**Background, Challenge or Opportunity:** Sjögren’s syndrome (SS) is a multisystem autoimmune disease characterized by salivary and lacrimal glands hypofunction. Because of its multi-organ involvement and autoimmune etiology, it is overseen by rheumatologists in collaboration with ophthalmologists and oral medicine specialists. While there have been 11 classification or diagnostic criteria published for SS since 1965, until recently none had been endorsed by the American College of Rheumatology (ACR) or European League Against Rheumatism (EULAR). During the past decade, the most commonly used classification criteria have been the American European Consensus Group (AECG) criteria. In April 2012, new classification criteria developed within the UCSF-led Sjögren’s International Collaborative Clinical Alliance (SICCA) registry, an NIH-funded contract, were provisionally approved by ACR. While the criteria set has been quantitatively validated using patient data, definitive endorsement by ACR will require a validation in an external data set.

Although the AECG criteria have not been endorsed by ACR or EULAR, they have proven useful in a range of studies and are widely used in practice. The challenge is now to get universal acceptance of the ACR criteria by the SS scientific community. Recent validation analyses revealed a high level of concordance between the ACR and AECG criteria. However, the degree of correspondence was decreased when more flexibility was allowed within the AECG definition. Although both criteria sets involve similar component tests, the AECG criteria allow substitutions for alternatives, and also allow the use of symptoms of dry eyes and mouth in classifying patients. The provisional ACR criteria are based solely on objective tests.

**Purpose/Objectives:**

1) To create an ACR-EULAR international working group of SS investigators/experts
2) To perform an external validation of the Provisional ACR classification criteria for SS developed by our group at UCSF in collaboration with the ACR-EULAR working group
3) To finalize and obtain definitive approval by ACR and EULAR of a unique set of classification criteria for SS

**Methods/Approach:** An ACR-EULAR collaborative group of SS scientists and clinician-experts will be created to obtain buy-in from this group for the need for a unique set of criteria that will be endorsed by ACR and EULAR, and universally accepted in the scientific community. The external validation will be performed in a European cohort of patients (cohort identified), and a systematic comparison between ACR and AECG criteria in this cohort will be performed, to better understand the similarities and differences between the 2 criteria sets. Input from the ACR-EULAR working group for the development of an analysis plan will be sought, and a data-driven consensus methodology will be used to develop the final set of criteria.

**Outcomes and Evaluation:** The final outcome is the development of a final set of classification criteria for SS approved by ACR and EULAR and endorsed by the SS scientific community. Intermediary outcomes include 1) successfully convening an ACR-EULAR working group; 2) performing the external validation; 3) arriving to a consensus within the working group on the analysis plan comparing AECG and ACR criteria. To-date outcomes 1) and 2) have been achieved.
Sjögren’s syndrome
Recent validation analyses revealed a high level of consistency between the provisional ACR and AECG criteria, and their application was shown to be similar to the AECG criteria in terms of sensitivity and specificity under a number of pre-specified scenarios defined with respect to key criteria components for the ocular, oral and multisystem autoimmune manifestations of the disease. The definition of “gold standard” classification for these analyses will be varied to allow substitutions for alternatives, and allow use of symptoms with or without objective tests.

The provisional ACR classification criteria for SS require at least 2 out of the following 3 items for disease classification: 1. Ocular symptoms (at least one) 2. Oral symptoms (at least one) 3. Dry mouth >3 months

Methods/Approach

A working group of SS experts will be invited to review the definition and criteria set, to ensure that the two criteria sets blend smoothly. There will be to perform external validation of the new provisional ACR criteria, and to conduct a detailed comparison of the provisional ACR and AECG criteria sets to determine which set is the “gold standard” classification for these analyses will be varied to allow substitutions for alternatives, and allow use of symptoms with or without objective tests.

The provisional ACR classification criteria were developed using a consensus-based data-driven process in a large cohort of 1362 participants recruited from 6 countries in 4 continents. The target population was individuals from the general population who had been suspected on symptoms of dry eyes and/or oral symptoms.

The AECG criteria require at least 4 of the following 6 items, with items I or IV at a single mandatory requirement, or any 3 of the 4 objective criteria (‘primary syncts’), in addition to the subjective symptom set: I. Ocular symptoms (at least one) II. Oral symptoms (at least one) III. Dry mouth >3 months IV. Recurrent or persistent swollen salivary glands V. Need liquids to swallow dry foods VI. Ocular Signs (at least one)

A report detailing the results of the validation and cohort comparison will be circulated to the expert panel members 1 month prior to the meeting for review. A presentation of the provisional ACR and AECG criteria will be summarized as short clinical vignettes to be considered by the expert panel for their expert opinion and endorsement. A consensus methodology voting process, although the 12-15% participation rate of the potential members from Europe, Australia, Asia, North and South America. All but 1 accepted to participate

1) Identified members of ACR-EULAR Working Group with help from Xavier Mariette, former EULAR president, and collaborator of SICCA co-PI who did her sabbatical in his lab
2) Invited members to join Working Group as SICCA PI and lead epidemiologist, I took the lead on this process. Identified 32 potential members from all around the world, Asia, North and South America. All but 1 accepted to participate

3) Submitted grant proposal to ACR-EULAR Collaborative International Clinical Trials Fund to fund travel for ACR-EULAR Group at the stage of the NGT consensus methodology meeting

4) Convened an exploratory meeting of a sub-set of the ACR-EULAR Group mainly rheumatologists attending the ACR annual meeting in DC in Nov 2012. The SS Foundation or SFS was hosting an SS related meeting in DC. The Working Group members who were hosting the lunch, agreed to host our meeting also. Following the lunch. The SFS was founded in 1983 by a patient, with the mission to be a voice for patients while educating physicians and increasing awareness of SS worldwide. The ACR-EULAR Working Group exploratory meeting was introduced by the SFS CEO and VP for Research (important, politically because the SFS is highly respected by the international SS scientific community)

- Xavier Mariette and I-Co-Chaired the meeting representing EULAR and ACR, respectively. We invited the lead author of the AECG classification paper and other members of the European SS research group, the SICCA PI, and the SICCA statistician to present a potential analysis plan for external validation and AECG-ACR comparison. Overall, the meeting went well despite strong opposition to the new criteria being raised by some European members who would have preferred to keep using AECG criteria, although now sub-optimal since they have not been ACR endorsed. I found that using empathy-active listening and focusing on the data-driven aspect of the project were very helpful in leading the discussion and steering the process forward.

The meeting was concluded with a general consensus that this project was worth pursuing.

5) Wrote a detailed AECG-ACR report of the meeting, and circulated it to the larger ACR-EULAR Working Group

6) ACR-EULAR proposal was reviewed, but not funded. Currently exploring creative solutions to organize virtual meetings of the ACR-EULAR working group and a web-based consensus methodology voting process, although the 12th International Symposium on SS will be held in Kyoto in October 2013, and will be another opportunity for meeting as many Working Group members will attend.

7) Statistical cut-point performing exploratory analyses to compare AECG and ACR within SICCA data as a first step

Conclusions

First phase of this project has been accomplished. Next phase is to complete the analyses and consensus methodology to arrive to the final consensus classification. Would be ideal for performing randomised clinical trials testing new therapies for SS. It would benefit the UCSF School of Dentistry by raising our profile as a leader in a multidisciplinary project with global health significance.