EUSTAR research grant
(Revised version after the comments of EULAR Referees)
2007-2010

Applicant Prof Marco Matucci-Cerinic on behalf of EUSTAR members*
Department of Biomedicine,
Division of Rheumatology, University of Florence
cerinic@unifi.it

revised and approved by the chairman of ESCISIT, prof Maxime Dougados

Summary
In the last three years (2004-2007), thanks to an EULAR research grant, EUSTAR has achieved the tracking of more than 5064 scleroderma patients through the Minimal essential data set from 115 centres throughout Europe (105), USA (4), Asia (4), Africa (1), and Australia (1). The Essential data set: (EDS) has been developed and need now to refined and used for further development of clinical studies and for clinical practice. EUSTAR Working groups have also achieved clinical, educational and basic research tasks as demonstrated by publications, congress participation and courses organised. EUSTAR has indeed fostered the creation of FESCA (Federation of European Scleroderma Associations) founded in Brussels in November 2006. With the further help of EULAR Recommendations on treatment of systemic sclerosis are in preparation.

The task of EUSTAR for the future is to raise at European level the awareness through a careful planning of new initiatives on different levels, educational, social and scientific. For the next three years, the main objectives are to develop MEDS and EDS on line in order to strengthen the activity of member centres, to create a bio-bank where samples from whole Europe can be stored, to launch a campaign to achieve early diagnosis of systemic sclerosis and to further foster and develop education. The budget requested will cover all the main activities and will help in giving stability to the group.

Outline of the grant:

Background (EUSTAR achievements)
Projects:
1. Minimal Essential data set and Essential Data set go on line
2. Bio-bank
3. Very Early Diagnosis Of Systemic sclerosis (VEDOS)
4. Educational Courses

Budget

Member Centres*

Background

During the EULAR congress 2004 in Berlin, EUSTAR has been founded under the auspices of the ESCISIT committee. The mission statement comprised:

- Foster co-operation between different countries and geographical areas
- Encourage and assist the foundation of national organizations
- Promote educational programs
- Sponsor or organize international congresses on scleroderma
- Supervise the scientific activities of all meetings organized with the EUSTAR patronage
- Encourage the publication of scientific proceedings of such meetings
- Stimulate scientific research on scleroderma
- Establish contacts with all other specialties interested in scleroderma: dermatology, cardiology, respiratory medicine, radiology, vascular medicine, internal medicine, etc.
- Encourage cooperation with other scientific associations in other continents and with patient organizations in Europe and worldwide.

Along these guidelines, the group has developed in these three years thanks to a research grant that has been generously funded by EULAR. The following points have been achieved:

- Minimal essential data set (MEDS) has been the main form used to enrol patients (5064) from 115 centres throughout Europe (105), USA (4), Asia (4), Africa (1), and Australia (1).
- Essential data set: (EDS) has been developed: This more detailed and organ directed data set is designed as a permanent and prospective record of individual patients from which direct clinical research questions may be answered. Being more extensive, data entry would be an issue and therefore EDS may be more applicable to major centres with appropriate resources. This part is still waiting to be finalised
• **Working groups:** Three working groups, clinical, educational and basic research, have achieved the following, respectively:

  1. **EULAR/EUSTAR Course on Systemic Sclerosis:** The first in Budapest (2005, 93 students, 40 teachers) is online on the EUSTAR web site, the second will take place in Giessen, January 2007 (90 students, 35 teachers),

  2. Publication of 2 papers in Ann. Rheum. Dis. (VEGF, Fibrillin) and another one in press (anti-Ku antibodies)

  3. Publication of 2 papers in ARD (Skin score and MEDS papers),


• **Creation of FESCA (Federation of European Scleroderma Associations):** EUSTAR has fostered the creation of the federation between European scleroderma patient associations. It has been founded in Brussels in November 2006. Two representatives are now part of EUSTAR and contribute to all activities inside EUSTAR

• **Recommendations on treatment of systemic sclerosis:** Through an additional EULAR funding, the ad hoc committee is now preparing the final draft of the recommendations.

After a considerable effort to achieve all the above mentioned items, now EUSTAR is facing a new triennium where all the work done must be eventually finalised and in particular the awareness of the disease must be fully developed in all European countries. This may be achieved only through a careful planning of new initiatives on different levels, educational, social and scientific.

**Aim of the grant proposal:** To stabilise, further develop and disseminate the EUSTAR methodology throughout Europe in the next three years.

**Objectives:**

1. To develop MEDS and EDS on line
2. To create a bio-bank
3. To further foster and develop education
4. To launch a campaign to achieve early diagnosis of systemic sclerosis

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Projects
**I°. EUSTAR minimal essential data set and essential data set go on line**

**Background:** Systemic sclerosis (SSc) is a multi-system autoimmune disease involving three overlapping processes; vascular, inflammatory/ immunological and fibrotic. Comprehensive, reliable, prospective data are lacking but are needed to better subgroup SSc and guide early aggressive and/or expensive treatment. The EULAR Scleroderma Trials And Research (EUSTAR) collection of a Minimal Essential Data Set (MEDS) of all patients seen in participating centres has been created to define more clearly disease subgroups, establishing reliable factors predictive of outcome and providing a platform on which further in depth studies will be performed. As of July 2006 (after about 3 years), 4,405 patients from 104 centres in 35 countries (including the US, Asia and South Africa) were registered. This is now the largest SSc data base in the world and expanding.

The data base has been in part funded by EULAR, and until now patient registration has been through paper forms, which has been transcribed into the central data base. It is now essential to convert the data entry to an **electronic web-based system**, one of the subjects of this application.

For the continued success of the now unique EUSTAR MEDS data base, a conversion to a web-based electronic system is essential. This was not possible at the onset three years ago due to lack of resources and unpredictability of participation.

A web-based system will ensure more accurate and complete data collection, as built-in stop points will block non-sense answers (e.g. date of birth being after date of disease onset), and will only allow patient entry if all domains are complete. In addition, automatic or optional pop-ups will be available to explain some domains e.g. ACR definition of SSc, EULAR activity score criteria, definition of pulmonary artery hypertension etc. This and an additional monitoring tool will increase the quality of data. In addition, the limited resources now expanded on data entry and on “missing data” queries at the study centre will be available for more productive activities such as ensuring follow up entry and co-ordinating studies of subgroups e.g. deaths. **In particular, MEDS on line will be designed, with the help of EUSTAR centres and subspecialty committees, to capture intercurrent events, disease evolution, patient and medication outcome, and complications. This should help not only in getting raw data about the disease but also will serve as a basis, in particular with EDS on line, to monitor patients in the office of every physician member of EUSTAR. This will allow any center to use MEDS and EDS to follow their own patients collective without overloading the central MEDS/EDS data base. This issue will be addressed at the next EUSTAR business meeting Saturday June the 16th, 2007.**

After ethics committee approval and informed patient consent, sera and DNA will also be systematically stored. The database will also establish the nucleus for web-based EULAR trials for
select patients in this cohort. The EUSTAR group, through EULAR, will continue maintenance of the database. A domain concerning pharmacovigilance and potential patient target groups for new pharmaceutical agents is planned to introduce industry based funding. Such access and funding will be strictly controlled through already existing EUSTAR guidelines.

**Plan:** Realization of an internet-based multinational scleroderma database with the following features

**Software**
- Internet-based relational data base
- Centralized storage of pseudonymized data
- Encrypted (128 bit) data transfer according to international safety standards
- Compliance with centre-specific data-safety guidelines
- Remote date entry by standard web browser ("thin client")
- Data output importable into excel-spreadsheet
- Context sensitive help and hints“.
- Monitoring tool (queries about number and quality of data)
- Data feedback to submitting centre - Definition of default values and plausibility checks for all parameters
- Automated recall reminders“ when individuals are due for follow-up
- Complex, online-administered, user-role management“
- Data entry sheets and data model rapidly and easily extensible by XML-programming
- Software used: mySQL MaxDB with JAVA-Technology, Sun-Solaris application server

**Physical resources**
- Server response time 1 second maximally, even during simultaneous usage by multiple clients
- System requirement of clients: PC, Windows 95, 98, 2000, ME, NT, TCP/IP and standard web browser
- 4 Gigabit Ethernet connections
- At least double redundancy of all hardware resources (including hard drives, internet connections and power supply
- System availability at least 99.5 % of time
- Servers and back-up data are hosted securely with regard to non-authorized third party
- Complete data back-up at least weekly
- Daily incremental or differential back-up of database logs

**Timeline / milestones:** As soon as the grant is approved, a data set for the entry module will be elaborated. An ad hoc committee with representatives from FESCA and other specialties (dermatology, pneumology,
cardiology and gastroenterology) will be created. The data set derived will be discussed with EUSTAR members and finalised after 2 months. During the same time interval, programming and hosting will be contracted. Programming will take 6 weeks (based on previous experience of the applicant). Testing and bug-fixing of the database will take 4 weeks. Import of previous electronic data will take 1 week. Thus, the database will be online approximately 6 months after grant approval.

Focus on the Follow-Ups: As already more than 5000 patients have been entered in the data base, the main focus of EUSTAR will be on short and long term follow-ups (disease evolution, deaths etc). The addition of new cases will mainly be due to recruitment of new centres members joining EUSTAR in Europe and in other continents (see below).

Contribution of centres to the data base: in the first triennium 2004-2007, some centers have contributed significantly providing a large number of patients that are now followed up yearly. The recently enrolled centers, in particular in eastern Europe, will be asked to enroll more patients in order to have a more balanced and homogeneous distribution of the cases population into the data base.

Expected results: MEDS and EDS should allow to speed up recruitment of patients and in particular allow the follow up evaluation of patients. This will lead to a study of follow up after the first MEDS paper and to a comparison between the European and American cohorts.

II°. Generation of an EUSTAR bio-bank for patients with systemic sclerosis

Systemic sclerosis (SSc) is a chronic fibrotic disorder with unknown etiology that affects the skin and a variety of internal organs including the heart, lungs and gastrointestinal tract. Histopathological hallmarks of early stages of SSc are perivascular inflammatory infiltrates and a reduced capillary density. Later stages of the disease are characterized by an excessive accumulation of extracellular matrix (ECM) components. The resulting fibrosis disrupts the physiological structure of the affected tissues and leads frequently to dysfunction of the affected organs. Tissue fibrosis causes not only significant morbidity, but is also the major cause of death in SSc patients.

Unfortunately, validated biomarkers to assess disease activity and severity for the three main pathways of the SSc pathogenesis are lacking. These biomarkers are of crucial importance to guide early aggressive and/or expensive treatment. Using the EUSTAR data base, built up in the past 3 years as described above and currently the largest SSc data base in the world, the aim of the EUSTAR basic science working group is to link clinically-related basic science projects in the SSc field with the well-documented clinical characterization of patients in the EUSTAR databank. In the two years of its existence the working group has stimulated and initiated several projects, which
already lead to first publications in high-ranked journals in the field (see below). The EUSTAR group can overcome the problem of low patient numbers in many studies on biomarkers in a heterogenic disease such as SSc by having access to an extremely large number of patient samples at the individual EUSTAR centres.

**Objective:** To establish an EUSTAR bio-bank consisting of sera, plasma, cells, DNA and skin biopsies of patients with systemic sclerosis following the European regulation for biobanking, in conjunction with the clinical characterization of patients according the MEDS guidelines of EUSTAR to allow the prospective validation of biomarkers for activity and severity of the disease. Control samples will be also gathered.

**Work plan** Study population: The study population consists currently of the more than 5064 patients with SSc in the EUSTAR database. Considering the relative low incidence of the disease, this number can only be achieved in a multi-centre approach, such as the EUSTAR initiative. These patients are fully characterized clinically according to gold-standard methods as established in the guidelines for clinical examinations for the minimal essential dataset (MEDS) of EUSTAR. In addition, the leading physicians of participating centres were trained in the assessment of SSc patients in two large EULAR/EUSTAR-initiated training courses.

Interventions (if relevant):

Interventions besides the routine state of the art clinical assessment includes the generation of samples for the EUSTAR biobank, in particular serum, plasma, and skin biopsies. As mentioned above, the EUSTAR basic science working group has already established guidelines to define “good laboratory practice” in obtaining and handling biological samples of systemic sclerosis patients. These guidelines are published on the EUSTAR website (www.eustar.org) Interventions, handling and storage will be performed according to these guidelines in accordance with European regulation.

Outcome parameters and assessment procedures:

To establish biomarkers as potential outcome parameters for clinical studies as well as for clinical follow-up of patients, they need to be validated according to the OMERACT criteria of truth (face, content, construct, and criterion validity), discrimination (reliability/reproducibility and sensitivity to change), and feasibility. Serum and plasma samples as well as skin biopsies (were applicable) obtained from the participating centres will be used for the validation according to the OMERACT filter. The techniques required for the assessment of the above mentioned biomarkers in serum and/or plasma samples will be performed according to standard protocols and are all available and
established in certain member centres. The specific outcome parameters of non-organ-based laboratory markers that are promising, but need further validation were defined in a recent consensus conference on the core set assessment of patients with SSc. Core set variables recommended by the subcommittee on non-organ-based outcome markers for further validation were divided according to the three main pathways in the pathogenesis of SSc. This includes endothelial markers (von Willebrand Factor, VCAM, E-selectin), autoimmune and inflammatory markers (sIL-2R, erythrocyte sedimentation rate, anti-centromere antibodies, anti-topoisomerase I antibodies, anti-RNA polymerase I-II antibodies) and fibroblast/fibrosis markers (Procollage III NPP) as well as histological evaluation of the degree of fibrosis immunohistochemistry and in situ hybridization techniques.

Data analysis:
For the validation of the above mentioned biomarkers, a cross-sectional as well as longitudinal analysis will be necessary. Correlations of the values of the biomarkers in serum/plasma samples as well as in the histological parameters used for skin biopsies analysis with the clinical data and the particular organ system will be performed according to standard statistical tests.

III°. Educational Courses:
Courses will be organized by EUSTAR mainly with two modalities:
1. **Biannual course (2007-2009)** on SSc for the education of young rheumatologists for the assessment of SSc patients. General and specific aspects of the disease and organ involvement are considered and the integration with the management of the disease in a biomedical social context presented. In 2007 the course will be partly interactive but already in 2009 it will become fully interactive and will be designed also for HPs.

2. **Regional Courses:** These courses will be organized in different European regions for the education of young rheumatologists and GP about early SSc and for the achievement for the homogenization of standardization of diagnosis and maximal care of SSc patients independent from regional influences.

These courses will be propedeutic to develop the knowledge of SSc throughout Europe in order to foster and support the realization of the VEDOS project (presented below).

IV°. Very Early Diagnosis Of Systemic sclerosis (VEDOS)

**Background**
The cost of the management of systemic sclerosis (SSc) increases enormously with the increase of disease duration and the damage that the disease provokes to cutaneous, renal, cardiovascular, pulmonary and GI systems. Indeed, the goal of the treatment is now to block the progression of the
disease, maintain quality of life and prevent organ damage. Therefore, the early diagnosis is mandatory to achieve these tasks. Unfortunately, the late diagnosis of SSc allows, in the majority of cases, the evolution and the spreading of organ damage that leads potentially to functional failure.

Early SSc has recently become the main target of care and treatment. The recognition of the disease and its early symptoms is therefore of paramount importance to reach an early diagnosis and to fight appropriately the disease. Raynaud’s phenomenon (RP) is the earliest sign of SSc suggesting an underlying endothelial and microvascular dysfunction. RP can precede the disease onset and spreading from months to years. Therefore, a program designed to increase the awareness and further investigation of RP by primary care physicians is essential. The identification of early microvascular changes is nowadays possible using nailfold capillaroscopic patterns. Indeed, autoantibodies (ANA, anti CENP, anti topoisomerase I) are very helpful serological signs as they are frequently present in the earliest prescleroderma
tous phase.

Thus, in presence of a RP, a careful clinical assessment together with the presence of an altered capillaroscopic pattern and the antibody positivity may allow a diagnosis of very early SSc.

**Aims**

- To increase awareness of the disease in Europe
- To create a strategy to achieve an early diagnosis

**Objectives:**

1. Track SSc through the identification of patients with Raynaud’s phenomenon
2. Develop regional networks to disseminate and implement the awareness of systemic sclerosis and its early diagnosis and classification in Europe
3. Develop the clinics methodology to detect Raynaud’s phenomenon in order to identify SSc early
4. Develop computer systems to facilitate and support the early diagnosis and treatment of the disease
5. Develop postgraduate education programmes to support the above objectives

To achieve these objectives the following is proposed:

**Plan:**

**First step** characterised by the following points

1. Start regional courses to raise the awareness of SSc and educate young rheumatologists to understand SSc, track RP and use the handy capillaroscope correctly.
2. Develop informatic systems (soft and hardware) to support the clinics in their effort to track and diagnose RP and early SSc
Second Step: characterised by the following points
1. Start regional networks for the creation of clinics devoted to the diagnosis of SSc and RP
2. Organise the EUSTAR centres to launch a capillary campaign to track RP patients and identify early SSc

Third step: characterised by the following points
1. Analyse and exploit the data emerged from the work of the regional networks
2. Stabilise the networks of clinics

Assessment procedures: To achieve an early diagnosis of SSc a filter procedure will be used to identify those RP patients who are most likely suspect to be secondary to a connective tissue disease. Only RP patients with the following items will be considered eligible for further diagnostic procedure:
   - Swollen hands ndn/or feet/legs
   - Carpal tunnel syndrome
   - Arthritis or arthralgias
   - Mono-polyneuropathy
   - Dysfagia

In these patients the following diagnostic procedures will be performed:
1. Differential diagnosis: exclusion of other causes of RP
2. Capillaroscopy: identification of a SSc pattern
3. Autoantibodies: ANA, ENA( Scl70/topo I), centromere

Timeline and milestones:
First milestones 2007 EULAR congress Barcelona - 2008 EULAR congress Paris:
1. EUSTAR centres will start to organise regional courses to raise the awareness of SSc and educate young rheumatologists to understand SSc and GPs to track RP with the inclusion characteristics.
2. EUSTAR centres must be progressively involved in campaigning with authorities and GP to launch an initiative to identify RP patients and start organising their centres to identify early SSc.
3. Development of informatic systems to facilitate and support the early diagnosis and treatment of the disease
4. Implementation of the EUSTAR MEDS data base to support the work of the regional networks

Second milestones 2008 EULAR congress Paris -2009 EULAR congress Copenhagen:
1. Further development of regional courses
2. Creation of clinics devoted to the diagnosis of SSc and RP
3. Application of the criteria defined for early SSc

Third milestones 2009 EULAR congress Copenhagen -2010 EULAR congress Rome:

1. Analysis of the data obtained from the work of the regional networks
2. Publication and dissemination of the results and further implementation of the clinics devoted to early diagnosis of SSc

Budget: The cost of the grant may be divided as follows

1st year, 2007-2008
1. Meds online 20.000
2. Bio-bank 25.000
3. Vedos 20.000
4. Secretariat 15.000
5. Web site 5.000
6. BM and overhead 15.000
Total per year 100.000

2nd year, 2008-2009
1. Meds online 5.000
2. Bio-bank 20.000
3. Vedos 15.000
4. Secretariat 15.000
5. Web site 5.000
6. BM and Overhead 10.000
7. Course 30.000
Total per year 100.000

3rd year, 2009-2010
1. Meds online 10.000
2. Biobank 20.000
3. Vedos 20.000
4. Secretariat 15.000
5. Web site 5.000
6. BM and Overhead 10.000
7. Course 20.000
Total per year 100.000

Grand total 2007-2010 euro 300.000
## Members

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<thead>
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<th>CENTRE</th>
<th>STATE</th>
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<tbody>
<tr>
<td>001</td>
<td>Dept of internal Medicine, Section of Rheumatology, University of Florence</td>
<td>Italy</td>
</tr>
<tr>
<td>002</td>
<td>Rheumatologische Universitätsklinik Felix Platter Spital Burgfelderstr.101</td>
<td>Switzerland</td>
</tr>
<tr>
<td>003</td>
<td>University of Regensburg,</td>
<td>Germany</td>
</tr>
</tbody>
</table>
Department of Internal Medicine-I
FJS-Allee II
D-93042 Regensburg
Germany

004 U.O. Reumatologia Università degli studi di Bari
Az. Ospedaliera Policlinico Padiglione V. Chini
di Bari
Piazza G. Cesare, 11
70124 Bari
Italy

Insegnamento di Reumatologia
Servizio per lo Studio, diagnosi e cura delle malattie immunologiche
Univ. di L’Aquila
Blocco 11
P.za Tommasi, 1
67100 L’Aquila
Italy

006 Department of Rheumatology University Hospital Zurich
Gloriast, 25
CH-8032 Zuerich
Switzerland

007 Institute of Rheumatology, 1st Medical School, Charles University,
Na slupi 4, Praha 2
CZ-12850 Czech Rep
Czech Republic

008 Department of Rheumatology and Internal Diseases,
Medical University of Bialystok
M M Sklodowskiej-Curie 24-A
15-276 Bialystok
Poland

009 Instituto portugues de Reumatologia, Rua D. Estefania, 187-189
Apartado 13051
1000-154 Lisboa
Portugal

010 Service de Médecine Interne Pavillon Horloge 2° Hopital Saint Antoine
184 Faubourg Saint Antoine
75571
Paris cedex 12 France
<table>
<thead>
<tr>
<th>No.</th>
<th>Institution</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>011</td>
<td>Research Laboratory and Division of Rheumatology Department of Internal Medicine University of Genova Viale Benedetto XV, 6 16132 Genova</td>
<td>Italy</td>
</tr>
<tr>
<td>012</td>
<td>Center for Autoimmune Diseases, Department of Medicine B, Sakler Faculty of Medicine, Tel-Aviv University</td>
<td>Israel</td>
</tr>
<tr>
<td>013</td>
<td>Dipartimento Medicina Clinica e Sperimentale “F. Magrassi” II Policlinico U.O. Reumatologia Via Pansini, 5 I-80131 Napoli</td>
<td>Italy</td>
</tr>
<tr>
<td>014</td>
<td>Institute of Rheumatic Diseases, Piestany Národný ústav Reumatických Chorôb Nábřeží I. Krasku 4782/4 921 12 PIEŠŤANY</td>
<td>Slovak Republic</td>
</tr>
<tr>
<td>015</td>
<td>Department of Rheumatology-Charité University Hospital, Schumannstr.20/21 D- 10117 Berlin</td>
<td>Germany</td>
</tr>
<tr>
<td>016</td>
<td>Clinica Reumatologie – Medicală II University of Medicine &amp; Pharmacy Cluj Str. Clinicilor nr. 2-4 400006 Cluj-Napoca</td>
<td>Romania</td>
</tr>
<tr>
<td>017</td>
<td>Groupe Hospitalier Cochin Saint-Vincent-De-Paul La Roche-Guyon 27, rue du Fg Saint-Jacques 75679 Paris Cedex 14</td>
<td>France</td>
</tr>
<tr>
<td>018</td>
<td>Department of Pathopysiology Medical School, National University of Athens 75 M. Asias str, Goudi 11527 Athens</td>
<td>Greece</td>
</tr>
<tr>
<td>019</td>
<td>Unità Operativa e Cattedra di Reumatologia (Dir. Prof. C. Montecucco) IRCCS Policlinico S. Matteo 27100 Pavia</td>
<td>Italy</td>
</tr>
<tr>
<td>020</td>
<td>Department of Dermatology</td>
<td>Czech Rep</td>
</tr>
</tbody>
</table>
the 1st Faculty of Medicine, Charles University, Prague
U nemocnice 2, 128 00 Praha
2, Czech Rep

Istanbul Medical Faculty
Department of Internal Medicine
Division of Rheumatology
34390, Capa, Istanbul
Turkey

Department of Rheumatology and Rehabilitation
Karol Marcinkowski
University of Medical Sciences in Poznan
61-545 Poznan
Ul. 28 Czerwca 1956 r.
135/147
Poland

Hospital Universitario
12 de Octubre
Servicio de Reumatología
Avda. De Córdoba, s/n
28041 Madrid
Spain

Dep. of rheumatology and Clinical Immunology, Internal medicine
KBC Rijeka, Croatia

Hungarian Brothers of St. John of God and University of Pécs
Faculty of Medicine
Department of Immunology and Rheumatology
Hungary

Department of Rheumatology
Hospital Santa Maria
Av Prof. Egas Moniz
1600 Lisbon
(R.Virgilio Correia,51 5° Drto
1600-222 Lisbon)
Portugal

Rheumatologische Ambulanz
Medizinische Klinik I
Universitätskliniken des Saarlandes
D-66421 Homburg/Saar
Germany

Immunology and Allergy
University Hospital
1211 Geneva 14
Switzerland

Department of Internal Medicine
Karol Marcinkowski
University of Medical Sciences in Poznan
61-545 Poznan
Ul. 28 Czerwca 1956 r.
135/147
Poland
030 Dept.Rheumatology, Medicine and Rheumatology, Medical University of Silesia, ul. Ziołowa 45/47, PL 40-634 Katowice, Poland
031 Division of Rheumatology, Heinrich-Heine University Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany
032 University Medical Center Ljubljiana, Division of Internal Medicine, Department of Rheumatology, Vodnikova 62, 1000 Ljubljana, Slovenia
033 “Stella Maris”, 7 Kannizzata Street, Balzan, BZN 07-MALTA, Malta
034 Istituto di Clinica Medica Generale, Ematologia ed Immunologia Clinica Polo Didattico Università Politecnica delle Marche, Via Tronto,10, 60020 Ancona, Italy
035 Department of Internal Medicine, Hopital Saint Louis, 1 avenue Claude Vellefaux, 75 010 PARIS, France
036 Department of Rheumatology, Internal Medicin III, University of Vienna, AKH, Währinger Gürtel 18-20 A-1090 Wien, Austria
037 Westpfalz-KliniKum Dep. Rheumatology, Westpfalz-KliniKum Dep. Rheumatology, Düsseldorf, Germany
<table>
<thead>
<tr>
<th>Code</th>
<th>Location</th>
<th>Details</th>
</tr>
</thead>
</table>
| 038  | Italy    | Spedali Civili di Brescia  
Servizio di Reumatologia  
Allergologia e Immunologia Clinica  
P.le Spedali Civili, 1  
25123 Brescia |
| 039  | Germany  | Klinik für Dermatologie,  
Venerologie und Allergologie  
Universitätsklinikum Leipzig  
Stephanstraße 11  
D-04103 Leipzig |
| 040  | Sweden   | Department of Rheumatology  
Lund University Hospital  
S-22185 Lund |
| 041  | Croatia  | Rheumatology Department of  
Internal Clinic. Clinical Hospital of Split  
Spinčiceva 1  
21000 Split |
| 042  | Israel   | Rheumatology department  
Rambam Medical Center  
Haifa BatGalim 31096  
Israel |
| 043  | Italy    | Dept. Of Clinical and Experimental Medicine  
Section of Rheumatology  
University of Ferrara  
Arcispedale S. Anna  
Corso Giovecca 203  
44100 Ferrara |
| 044  | Germany  | Universitätshautklinik Köln  
Joseph.Stelzmann Str.9  
D-50924 Köln |
| 045  | Poland   | Department of Dermatology  
02-008 Warsaw  
Ul. Koszykowa 82-a |
| 046  | Germany  | Department of Dermatology  
Georg-August-University Göttingen  
Von-Siebold-Str. 3  
D-37075 Göttingen |
| 047  | Italy    | Dept of internal Medicine,  
Rheumatology Unit,  
University of Pisa, Santa Chiara |
Via Roma 67
56126 Pisa
048 General Hospital “Ag. Pavlos”
Department of Rheumatology
Eth. Antistaseos 161
55134 Thessaloniki

049 Ospedale Mauriziano
Centro di Reumatologia
Largo Turati 62
10128 Torino

050 Università degli Studi di Verona
Dipartimento di Medicina Clinica e Sperimentale
Reumatologia-Medicina Interna B
Policlinico GB Rossi
Piazzale LA Scuro 10
37134 Verona

051 Division of Clinical Immunology and Rheumatology, Dep. Of Internal Medicine Dubrava University Hospital Av. G. Šuška, 5
10000 Zagreb

052 Centre for Rheumatology, Royal Free and University College London Medical School
Royal Free Campus
Rowland Hill Street
London NW3 2PF

053 Klinik für Dermatologie und Allergologie
Universität Ulm
Maienweg 12
D-89081 Ulm (Germany)

054 Universitair Medisch Centrum St Radboud
Secretariat reumatologie
Huispost 546
PB 9101
6500 HB Nijmegen

055 INSTITUTE OF RHEUMATOLOGY – BELGRADE
Resavska 69., 11000 BELGRADE

048 Greece
049 Italy
050 Italy
051 Croatia
052 United Kingdom
053 Germany
054 The Netherlands
055 SERBIA & MONTENEGRO
056  Universitätsklinikum Tübingen
    Medizinische Klinik und Poliklinik
    Internal Medicine/Rheumatology/
    Haematology/Oncology
    Otfried-Müller-Straße 10
    D-72076 Tübingen

057  Rheumatology Granollers
    General Hospital
    Avgda Francesc Ribas, s/n
    08400 Granollers (Barcelona)

058  Department of Rheumatology
    Marienhospital Stuttgart
    Böheimstraße 37
    D-70199 Stuttgart

059  Department of Dermatology
    Medical University of Lublin
    20-080 Lublin,
    Radziwiłłowska Str 13

060  Medizinische Universitäts-
    Poliklinik
    Dep. Of Rheumatology
    Wilhelmstr. 35-37
    D-53111 Bonn
    Bonn

061  Kantonsspital Aarau
    Rheumaklinik und Institut für
    Physikalische Medizin und
    Rehabilitation
    Kantonsspital Aarau
    Tellstrasse
    5001 Aarau

062  Leiden University Medical Center,
    Dept. of Rheumatology
    Albinusdreef 2
    2333 ZA Leiden

063  Klinikum der Johan Wolfgang Goethe – Universität
    Medizinische Klinik III,
    Rheumatologische Ambulanz,
    Theodor-Stern-Kai 7 60590
    Frankfurt am Main

064  Pediatric Rheumatology Clinic
    Germany
Friedrichsberger Str. 60
D-22081 Hamburg
065 Hospital son llàtzer
cta./ Manacor Km 4
07198. Palma de Mallorca
066 Arcispedale Santa Maria
Nuova
Dipartimento Area Medica 1
UO di Reumatologia, Pad
Spallanzani
Viale Umberto I°, 50
42100 Reggio Emilia
067 Department of Rheumatology
Central Clinical Hospital
MSW I A
Wołoska 137 Warsaw
068 Reumatologia, Hospitais da
Universidade
3000-075 Coimbra
069 Department of Rheumatology
Rigshospitalet, University of
Copenhagen
Blegdamsvej 9
2100 Copenhagen
070 Charité – Universitätsmedizin
Berlin
Department of Dermatology
and Allergy
Schumannstr. 20/21
10117 Berlin
071 Medizinische Universität Graz
Medizinische
Universitätsklinik - Abteilung
für Rheumatologie
Auenbruggerplatz 15
8052 Graz
072 Dept. Of Dermatology
University of Düsseldorf
Moorenstrasse 5
D-40225 Düsseldorf
073 Institute for prevention,
treatment and rehabilitation
rheumatic and cardiovascular
disease Niska Banja
Srpskih Junaka 2
18205 Niska Banja
074 Rheumatology Unit -
Humanitas Clinical Institute
Via Manzoni, 56
20089 - Rozzano (Milan)
075 Department of Reumatology
Poland
and Connective Tissue Diseases, Medical University of Lublin
20-090 Lublin, Jaczewskiego 8

076 Clinical Center Skopje, FYR Macedonia
Rheumatology Clinic "Dr Dimitar Arsov", University "St. Cyril and Methodius"
Vodnjanska 17
1000 Skopje

077 Rheumatology Unit, South Africa
Department of Medicine
Chris Hani Baragwanath Hospital and University of the Witwatersrand
P.O. Bertsham 2013
Johannesburg

078 Institute of Rheumatology, Russian
Russian Academy of Medical Science
Kashirskoye shosse, 34 A
115522 Moscow

079 Department of Dermatology, Germany
University of Mainz
Langenbeckstr. 1
D-55131 Mainz

080 Hope Hospital/University of Manchester, United Kingdom
Rheumatic Diseases Centre,
Clinical Sciences Building,
Stott Lane, Salford M6 8HD

081 Lehrstuhl für Innere Medizin mit Schwerpunkt Rheumatologie der Justus-Liebig-Universität Giessen
Abteilung für Rheumatologie und Klinische Immunologie
Kerckhoff-Klinik Bad Nauheim
Benekestr. 2-8
D-61231 Bad Nauheim

082 Gulhane Military Medical Academy Division of Rheumatology, Turkey
GATA Romatoloji Bilim Dali
06018- Etilik
Ankara

083 UO Immunologia Clinica-, Italy
Centro di Riferimento per le Malattie Autoimmuni Sistemiche
Via Pace 9 - 20122 Milano

084 Aarhus University Hospital, Department of Rheumatology
Noerrebrogade 44
8000 Aarhus, C

085 Clinica di medicina interna ad orientamento immunologico
Università di Genova
c/o Azienda Ospedale-Università San Martino
Viale Benedetto XV, 6 16132 Genova

086 Dept of Rheumatology and Endocrinology, Herlev

087 Third Department of Medicine
Rheumatology Division
University of Debrecen Medical Center
22 Moricz street
H-4004 Debrecen

088 Division of Rheumatology & Immunology
96 Jonathan Lucas Street,
Suite 912
P.O. Box 250637
Charleston, South Carolina

089 Ospedale L. Sacco - Azienda Ospedaliera-Polo Universitario
Unità Operativa di Reumatologia
Via G.B. Grassi 74
20157 Milano

090 Consulta Reumatologia Hospital deMendaro
BºMendarozabal s/n. 20850 Mendaro Guipuzcoa

091 Servicio de Reumatología
Hospital Ramon Y Cajal
Carretera de Colmenar, km.9,100
28034 Madrid

092 Dep. of Rheumatology, Rikshospitalet, Oslo, Norway
Rikshospitalet
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<td>DIVISIONE DI REUMATOLOGIA - UNIVERSITA' DI ROMA LA SAPIENZA DIPARTIMENTO DI CLINICA E TERAPIA MEDICA APPLICATA, POLICLINICO UMBERTO I VIALE DEL POLICLINICO 155, 00161 ROMA, Italy</td>
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111 Rheumatology Research Unit
Post Office Box 368
Maroochy waters
Sunshine coast 4558
Queensland, Australia

112 Department of Internal Medicine of Pr Loïc Guillevin
Hôpital Cochin
27 rue du Faubourg Saint jacques
75014 Paris

113 University of Ghent
Department of rheumatology
de pintelaan 185
9000 Ghent

114 Celal Bayar University
Medical School
PM&R department
Manisa

115 U.O. Reumatologia - Università degli Studi di Foggia
Ospedale "Col. D'Avanzo"
Viale degli Aviatori – 71100
Foggia

116 Reumatologia, Università degli Studi di Milano
Istituto Ortopedico Gaetano Pini
Piazza Cardinal Ferrari, 1
20122 Milano

117 Department of Internal Medicine of Pr Loïc Guillevin
Hôpital Cochin
27 rue du Faubourg Saint jacques
75014 Paris

118 University of Ghent
Department of rheumatology
de pintelaan 185
9000 Ghent

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PM&R department
Manisa

120 U.O. Reumatologia - Università degli Studi di Foggia
Ospedale "Col. D'Avanzo"
Viale degli Aviatori – 71100
Foggia