European Reference Network
for rare or low prevalence complex diseases
Network Vascular Diseases (VASCERN)

VASCERN (March 2017-February 2018) – CONTINUOUS REPORTING

WP6 – Clinical Trials

DELIVERABLE 6 – Clinical Trials and Research studies

WP6 – Description

WP6	Clinical trials
WHO	RDWGs, cooperation with Patient Group
HOW	Monthly RDWG meetings to discuss new protocols, research projects and clinical trials , Information on publication, research and clinical trials will be regularly updated in the website, Newsletter for calls, promotion by patient representatives, Annual Report a report on VASCERN Research Projects and Clinical Trials, Encourage and promotion of EU H2020 projects
DESCRIPTION	All the clinical trials running through VASCERN will be listed on the website, with contact information, so that additional HCPs outside VASCERN can participate as appropriate (including cooperating and affiliated HCPs not yet included as full members). Some clinical trials are already ongoing in VASCERN. Information on publication, research and clinical trials will be regularly updated in the website. newsletter for calls for research collaboration or clinical trials in order to promote clinical trials. Monthly meeting of RDWG (including patient representative co-chair) will discuss new protocols, research projects and clinical trials within the area of the RDWG. Patient representatives will also have the role to promote clinical trials among the patient community.VASCERN also plan to include in its Annual Report a report on VASCERN Research Projects and Clinical Trials as requested in the ERN call, as well as publications report as appendix
OBJECTIVES	promote the design and help in the realisation of international clinical trials in as many diseases included in VASCERN as possible demonstrate the benefit of a new treatment, mode of follow-up and diagnostic strategy. improve care and research
MILESTONES	Inclusion of calls for clinical trials in monthly newsletters and updates Monthly RDWG meeting: point on clinical trials Mid-term report draft (M6-7) on clinical trials, research collaboration, publications in view of the annual report Completion of 1 clinical trial (M12) as an important milestone Annual report on clinical trials and research collaborations to be included in general VASCERN annual report
INDICATORS	number of studies, number of patients included in studies, newsletters, report), completion of 1 clinical trial
TARGETS	number of patients included in clinical trial/HCPs (1/month), completed clinical trials (1/year), improved research/ publication (1/clinical trial)
TIMELINE	M1-M12: Newsletter including a part on research collaboration and clinical trials, regular updates on the website on call for research/ clinical trials; Collect data on research projects, clinical trials and their findings among HCPs,; M1-M12: RDWG discussion including about new protocols, research projects and clinical trials; M5-M7: Mid-term annual report draft; M10-12: review of annual reports drafts to be included in Year 1 annual report, M12: completion of 1 clinical trial
DELIVERABLES	**M6 mid report of ongoing and completed trials** **M12 annual report on clinical trials, research projects, publications** **Completion of 1 clinical trial**

Implementation

1) Monthly RDWG Meetings

In order to discuss the implementation of **WP6** all rare disease working groups (RDWGs) have held monthly virtual conference calls. During these calls ongoing, completed and future clinical trials and research studies are discussed between members.

The VASCERN 2 day 1st Annual seminar, which enabled all of the 5 RDWGs, the 2 active transversal WGs and the Patient Group to meet **face to face,** in addition to specific face to face meetings held in parallel to Scientific Congresses (HHT international Congress in Dubrovnik, ESC Congress in Barcelona, etc.), as well as the regular VASCERN Council meetings (every 4 months) were also important milestones in order to progress on the implementation of this WP.

Minutes of all VASCERN Meetings are available on our ERN Collaborative Platform.

2) Dissemination

VASCERN communicates on the networks clinical trials, research studies and notable publications via the VASCERN Website (in the news section, via our monthly newsletters) and social media channels. We mainly try to focus on collaborative (involving more than 1 HCP) publications, such as The Lung in Hereditary Hemorrhagic Telangiectasia by HHT-WG members Dr Sophie Dupuis-Girod (FR) and Prof Claire Shovlin (UK) or Blue Rubber Bleb Nevus (BRBN) Syndrome Is Caused by Somatic TEK (TIE2) Mutations by a number of VASCA-WG members, including VASCA-WG Chair, Prof Miikka Vikkula (BE), Prof Laurence Boon (BE), and Prof Alan Irvine (IE).

In addition, we equally have a dedicated section on “Calls for clinical trials” in order to keep our members updated on any relevant calls for projects/recruitment/funding. For example: Call for recruitment for the European Fibromuscular dysplasia (FMD) initiative was posted in this section of our website.

3) Highlights

VASCERN has completed at least one clinical trial (in the HHT-WG; monocentric trial) and have been very active as a group in regards to research studies and publications.

We have lots of research studies currently underway, many of them involving multiple HCPs.

Multinational clinical trials however are limited at the moment due to the cost and ethical/legal issues involved in these ambitious projects. We hope to be able to extend local clinical trials to other HCPs if we can find proper funding opportunities.

Co-funded by the Health Programme of the European Union

As a possible source of funding for research in rare diseases, VASCERN and the ERNs have been directly involved in the elaboration of the future European Joint Programme (EJP) on Rare Diseases.

4) Clinical trials and Research Studies

Please note that the following lists of clinical trials, research studies and publications may not be exhaustive for each RDWG.

HHT-WG, chaired by Prof Claire Shovlin and co-chaired by Dr Sophie Dupuis-Girod and Prof Elisabetta Buscarini

Clinical trials during the last 12 months:

It was noted that the Working Definition of a Clinical Trial from UK MHRA and NIH "Research studies that explore whether a medical strategy, treatment, or device is safe and effective for humans" excludes observational studies of an existing treatment. Most HHT Research is currently at an Observational Stage.

Trials completed:

1. DUPUIS GIROD (F): NCT02484716: EFFICACY OF A TIMOLOL NASAL SPRAY AS A TREATMENT FOR EPISTAXIS IN HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT) - (TEMPO) (TEMPO)

Trials ongoing:

2. DUPUIS GIROD (F): NCT03152019: EFFICACY AND SAFETY OF A 0.1% TACROLIMUS NASAL OINTMENT AS A TREATMENT FOR EPISTAXIS IN HEMORRHAGIC HEREDITARY TELANGIECTASIA (HHT) (TACRO)
3. DUPUIS GIROD (F): NCT03227263 EFFICACY AND SAFETY OF BEVACIZUMAB ON SEVERE BLEEDINGS ASSOCIATED WITH HEMORRHAGIC HEREDITARY TELANGIECTASIA (HHT). (BABH)

Trials receiving funding to commence 2018:

4. SHOVLIN (UK): NONSENSE READ-THROUGH THERAPIES FOR PATIENTS WITH INHERITED GENETIC DISEASES: PROOF OF CONCEPT STUDIES IN HEREDITARY HAEMORRHAGIC TELANGIECTASIA. NCT/ETHICS IN PROGRESS 5

Calls for clinical trials to be published in the monthly newsletters

1. Results will be presented in the newsletters.

2. Recruitment adverts were not part of the Ethical Approved pathways for M1-6 clinical trials but are being incorporated into the Ethical Approval pathways for (4).

Research projects ongoing within the RDWGs (with several HCP members)

1. SHOVLIN (UK), DUPUIS GIROD (F) BUSCARINI (I), KJELDSEN (DK), MAGER (NL), SABBA(I), GEISTHOFF (D), PAGELLA (F), BOTELLA (E), CROCIONE (I), FEDERICI (I) AND MEMBERS OF HHT WG HCPS:
ESTABLISHING RESEARCH PRIORITIES FOR VASCERN HHT.
COMPLETED, AND PRESENTED AT THE 12TH INTERNATIONAL HHT SCIENTIFIC CONFERENCE, JUNE 2017

2. BUSCARINI (IT), DUPUIS GIROD (FR), SHOVLIN (UK), KJELDSEN (DK), MAGER (NL), SABBA(IT), GEISTHOFF (DE), PAGELLA (IT), BOTELLA (E), CROCIONE (IT), FEDERICI (IT) AND MEMBERS OF HHT WG HCPS:

ESTABLISHING AN HHT DRUG REGISTRY.
COMPLETED, AND PRESENTED AT THE 12TH INTERNATIONAL HHT SCIENTIFIC CONFERENCE, JUNE 2017

3. SHOVLIN (UK), BUSCARINI (I), AND COLLEAGUES: LONG-TERM OUTCOMES OF PATIENTS WITH **PULMONARY ARTERIOVENOUS MALFORMATIONS CONSIDERED FOR LUNG TRANSPLANTATION, COMPARED TO SIMILARLY HYPOXEMIC COHORTS.** COMPLETED, AND ACCEPTED BY BMJ OPEN RESPIR RES 2017

4. BUSCARINI (I), DUPUIS-GIROD (F) **BEVACIZUMAB FOR THE TREATMENT OF RENDU-OSLER DISEASE**
COMPLETED, AND PUBLISHED IN LIVER INT., 2017

5. BUSCARINI (I), DUPUIS-G IROD (F) **LIVER TRANSPLANTATION FOR HHT**
COMPLETED, AND PUBLISHED IN LIVER INT., 2016

6. SHOVLIN (UK), DUPUIS GIROD (F) BUSCARINI (I), MAGER (NL), SABBA (I), CROCIONE (I), FEDERICI (I), KJELDSEN (AK), AND COLLEAGUES: **OPTIMISATION OF IRON TREATMENTS IN HHT PATIENTS**
FUNDING APPLICATION IN PROGRESS

7. SHOVLIN (UK), DUPUIS GIROD (F) BUSCARINI (I), MAGER (NL), KJELDSEN (DK), BOTELLA (E) AND THE HHT GECIP SUBDOMAIN:
HHT IN THE 100,000 GENOMES PROJECT
IN PROGRESS

Additionally, and in keeping with the Strategic Research Plan, VASCERN HHT WG have:

- Reviewed the existing literature to optimize up to date guidance
- Moved towards the development of a database of patients with clinical and genetic data, with UK platforms of Open Clinica, Genie and PowerChart considered as potential options, already containing HHT Data Models and being populated with HHT data
- Initiated a Quarterly Research Forum through which to date 5 new concepts have been presented including paediatric cerebral AVM screening.

Research projects ongoing within the RDWG (individual HCPs):

More than 40 different research projects are currently ongoing in individual HCPs, with currently no second ERN HCP participating. These will continue to be developed, and if second HCPs are included in the study, will become part of the M24 Report.

Publications:

The following list of publications is not exhaustive. We have tried to search for the most relevant publications to include in this report.

Collaborative publications (2017):

Executive summary of the 12th HHT international scientific conference.Andrejecsk JW, Hosman AE, **Botella LM**, **Shovlin CL**, Arthur HM, **Dupuis-Girod S**, **Buscarini E**, Hughes CCW, Lebrin F, Mummery CL, Post MC, **Mager JJ**. Angiogenesis.2017 Nov 16.doi: 10.1007/s10456-017-9585-2. [Epub ahead of print] PMID: 29147802

Long-term outcomes of patients with pulmonary arteriovenous malformations considered for lung transplantation, compared with similarly hypoxaemic cohorts.**Shovlin CL, Buscarini E**, Hughes JMB, Allison DJ, Jackson JE. BMJ Open Respir Res. 2017 Oct 13;4(1):e000198. doi: 10.1136/bmjresp-2017-000198. eCollection 2017.PMID: 29071074

The Lung in Hereditary Hemorrhagic Telangiectasia.**Dupuis-Girod S**, Cottin V, **Shovlin CL**. Respiration. 2017;94(4):315-330. doi: 10.1159/000479632. Epub 2017 Aug 30. PMID: 28850955

Response to Bevacizumab for the treatment of Rendu-Osler disease-A note of caution.**Dupuis-Girod S**, **Buscarini E.**Liver Int. 2017 Jun;37(6):928. doi: 10.1111/liv.13385. No abstract available. PMID: 28544692

HCP individual publications (2017):

1) **Hammersmith Hospital, Imperial College Healthcare NHS Trust, UK:**

British Thoracic Society Clinical Statement on Pulmonary Arteriovenous Malformations.**Shovlin CL,** Condliffe R, Donaldson JW, Kiely DG, Wort SJ; British Thoracic Society.Thorax. 2017 Dec;72(12):1154-1163. doi: 10.1136/thoraxjnl-2017-210764. PMID: 29141890

Pulmonary arteriovenous malformations emerge from the shadows.**Shovlin CL**, Condliffe R, Donaldson JW, Kiely DG, Wort SJ. Thorax. 2017 Dec;72(12):1071-1073. doi: 10.1136/thoraxjnl-2017-211072. No abstract available. PMID: 29141889

Cerebral Abscess Associated With Odontogenic Bacteremias, Hypoxemia, and Iron Loading in Immunocompetent Patients With Right-to-Left Shunting Through Pulmonary Arteriovenous Malformations.Boother EJ, Brownlow S, Tighe HC, Bamford KB, Jackson JE, **Shovlin CL**. Clin Infect Dis. 2017 Aug 15;65(4):595-603. doi: 10.1093/cid/cix373. PMID: 28430880

Pulmonary arteriovenous malformations: evidence of physician under-education.**Shovlin CL**, Gossage JR.ERJ Open Res. 2017 Apr 12;3(2). pii: 00104-2016. doi: 10.1183/23120541.00104-2016. eCollection 2017 Apr. PMID: 28421188

7-day weighed food diaries suggest patients with hereditary hemorrhagic telangiectasia may spontaneously modify their diet to avoid nosebleed precipitants.Finnamore H, Silva BM, Hickson BM, Whelan K, **Shovlin CL**. Orphanet J Rare Dis. 2017 Mar 28;12(1):60. doi: 10.1186/s13023-017-0576-6. PMID: 28347346

Hemoglobin Is a Vital Determinant of Arterial Oxygen Content in Hypoxemic Patients with Pulmonary Arteriovenous Malformations.Rizvi A, Macedo P, Babawale L, Tighe HC, Hughes JMB, Jackson JE, **Shovlin CL**. Ann Am Thorac Soc. 2017 Jun;14(6):903-911. doi: 10.1513/AnnalsATS.201611-872OC. PMID: 28267932

Cancer and hereditary haemorrhagic telangiectasia.Hosman AE, **Shovlin CL**. J Cancer Res ClinOncol. 2017 Feb;143(2):369-370. doi: 10.1007/s00432-016-2298-x. Epub 2016 Nov 11. PMID: 27837281

2) **CHU de Lyon HCL, France**

Pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia: Correlations between computed tomography findings and cerebral complications. Etievant J, Si-Mohamed S, Vinurel N, **Dupuis-Girod S**, Decullier E, Gamondes D, Khouatra C, CottinV, Revel D. EurRadiol. 2017 Oct 10.doi: 10.1007/s00330-017-5047-x. [Epub ahead of print]PMID: 29018941

Pulmonary hypertension subtypes associated with hereditary haemorrhagic telangiectasia: Haemodynamic profiles and survival probability.Revuz S, Decullier E, Ginon I, Lamblin N, Hatron PY, Kaminsky P, Carette MF, Lacombe P, Simon AC, Rivière S, Harlé JR, Fraisse A, Lavigne C, Leguy-Seguin V, Chaouat A, Khouatra C, **Dupuis-Girod S**, Hachulla E. PLoS One. 2017 Oct 5;12(10):e0184227. doi: 10.1371/journal.pone.0184227. eCollection 2017.PMID: 28981519

3) Maggiore Hospital, ASST Crema, Italy

No additional HHT-related publications in 2017 (see 3 joint publications above)

4) Odense University Hospital, Denmark:

Familial cerebral abscesses caused by hereditary hemorrhagic telangiectasia.**Tørring PM**, Lauridsen MF, I Dali C, Andersen PE, Ousager LB, Brusgaard K, **Kjeldsen A.**Clin Case Rep. 2017 Apr 13;5(6):805-808. doi: 10.1002/ccr3.785. eCollection 2017 Jun. PMID: 28588815

Prevalence of hereditary hemorrhagic telangiectasia in patients operated for cerebral abscess: a retrospective cohort analysis.Larsen L, Marker CR, **Kjeldsen AD**, Poulsen FR. Eur J ClinMicrobiol Infect Dis. 2017 Oct;36(10):1975-1980. doi: 10.1007/s10096-017-3023-7. Epub 2017 Jun 3. PMID: 28578477

5) Essen University Hospital, Germany:

Emerging role of bevacizumab in management of patients with symptomatic hepatic involvement in Hereditary Hemorrhagic Telangiectasia.Chavan A, Schumann-Binarsch S, Schmuck B, Oltmer F, **Geisthoff U**, Hoppe F, Wirsching K, Klempnauer J, Manns M, Philip Thomas R, Köhne CH. Am J Hematol. 2017 Nov;92(11):E641-E644. doi: 10.1002/ajh.24878. Epub 2017 Aug 24. No abstract available. PMID: 28776732

6) Fondazione IRCCS Policlinico San Matteo, Pavia, Italy:

No HHT-related publications in 2017.

7) AziendaOspedaliero-UniversitariaConsorziale di Bari Policlinico-Giovanni XXIII, Italy

Hepatic angiodynamic profile in paediatric patients with hereditary haemorrhagic telangiectasia type 1 and type 2.Giordano P, Francavilla M, Buonamico P, Suppressa P, Lastella P, Sangerardi M, MinielloVL, Scardapane A, **Lenato GM**, **Sabbà C.** Vasa. 2017 May;46(3):195-202. doi: 10.1024/0301-1526/a000616. Epub 2017 Mar 1. PMID: 28248153

8) St. Antonius Hospital, Nieuwegein, The Netherlands

SMAD4 gene mutation increases the risk of aortic dilation in patients with hereditary haemorrhagic telangiectasia.Vorselaars VMM, Diederik A, Prabhudesai V, Velthuis S, Vos JA, Snijder RJ,

Westermann CJJ, Mulder BJ, Ploos van Amstel JK, **Mager JJ**, Faughnan ME, Post MC. Int J Cardiol. 2017 Oct 15;245:114-118. doi: 10.1016/j.ijcard.2017.06.059.PMID:28874282

Screening children for pulmonary arteriovenous malformations: Evaluation of 18 years of experience. Hosman AE, de Gussem EM, Balemans WAF, Gauthier A, Westermann CJJ, Snijder RJ, Post MC, Mager JJ.Pediatr Pulmonol. 2017 Sep;52(9):1206-1211. doi: 10.1002/ppul.23704. Epub 2017 Apr 13. PMID:28407366

HTAD-WG, chaired by Prof Julie De Backer and co-chaired by Prof Guillaume Jondeau

Clinical trials:

The HTAD-WG does not have any clinical trials underway at the moment as they have chosen to focus on other work packages such as patient pathways and clinical guidelines. They have however been very busy with research studies and have authored many scientific publications.

A Resveratrol trial in adult Marfan patients is currently in its initial phases (finalization of protocol) and will involve two HCPs from the HTAD WG, **Academic Medical Center (NL), Radboud University Medical Center (NL).**

Research projects ongoing within the RDWG (with several HCP members):

ROPAC III registry; organized by the European Society of Cardiology, that will follow pregnant women with thoracic aortic diseases, is currently in the development phase (the Case Report Forms are being prepared) but the inclusion of patients could start as early as in May-June 2018. Both our coordinator Prof Guillaume Jondeau (**Hôpital Bichat (FR)**) and HTAD-WG Chair, Prof Julie De Backer (**Ghent University (BE)**) are executive committee members of this registry.

Montalcino Aortic Consortium (MAC) registry; which is an international registry on HTADs, with the European part of the project centralized in Paris, and that involves numerous HCP representatives from the HTAD-WG including those from **Ghent University (BE), Hôpital Bichat (FR), University Medical Center Hamburg-Eppendorf (DE), Semmelweis University (HU), Academic Medical Center (Netherlands), IRCCS Foundation Policlino San Matteo (IT) and Azienda Socio Sanitaria Territoriale Fatebenefratelli – Sacco (IT).**

The Rotterdam Bicuspid Aortic Valve (BAV) study, together with **Radboud University Medical Center (NL**) and **University of Antwerp (BE).**

Marfan cardiomyopathy study; with collaboration between **Ghent University (BE) and Semmelweis University (HU).**

Research projects ongoing within the RDWG (individual HCPs):

Ghent University (BE) is involved in several studies including, ClinGen Aortopathy Gene Curation, From gene to aortic dissection, a detailed study of the etiology, pathogenesis and cardiovascular characteristics of heritable thoracic aortic aneurysms and dissections, and a Study of the influence of sex and pregnancy on progression of aortic disease in Marfan syndrome.

Azienda Socio Sanitaria Territoriale Fatebenefratelli – Sacco (IT) are currently working on 14 different Research Projects.

Publications:

The following list of publications is not exhaustive. We have tried to search for the most relevant publications to include in this report.

Collaborative publications (2017):

Arterial tortuosity syndrome: 40 new families and literature review.Beyens A, Albuisson J, Boel A, Al-Essa M, Al-Manea W, Bonnet D, Bostan O, Boute O, Busa T, Canham N, Cil E, Coucke PJ, Cousin MA, Dasouki M, **De Backer J**, De Paepe A, De Schepper S, De Silva D, Devriendt K, De Wandele I, Deyle DR, Dietz H, **Dupuis-Girod S**, Fontenot E, Fischer-Zirnsak B, Gezdirici A, Ghoumid J, Giuliano F, Diéz NB, Haider MZ, Hardin JS, **Jeunemaitre X**, Klee EW, Kornak U, Landecho MF, Legrand A, **Loeys B**, Lyonnet S, Michael H, Moceri P, Mohammed S, Muiño-Mosquera L, Nampoothiri S, Pichler K, Prescott K, Rajeb A, Ramos-Arroyo M, Rossi M, Salih M, Seidahmed MZ, Schaefer E, Steichen-Gersdorf E, Temel S, Uysal F, Vanhomwegen M, Van Laer L, Van Maldergem L, Warner D, Willaert A, Collins TR, Taylor A, Davis EC, Zarate Y, CallewaertB.Genet Med. 2018 Jan 11. doi: 10.1038/gim.2017.253. [Epub ahead of print] PMID: 29323665

Pregnancy in Women With SMAD3 Mutation.van Hagen IM, van der Linde D, **van de Laar IM**, MuiñoMosquera L, **De Backer J**, **Roos-Hesselink JW**. J Am CollCardiol. 2017 Mar 14;69(10):1356-1358. doi: 10.1016/j.jacc.2016.12.029. No abstract available. PMID: 28279300

Organisation of care for pregnancy in patients with congenital heart disease. Roos-Hesselink JW1, Budts W2, Walker F3, De Backer JFA4, Swan L5, Stones W6,7, Kranke P8,9, Sliwa-Hahnle K10,11, Johnson MR12. Heart. 2017 Dec;103(23):1854-1859. doi: 10.1136/heartjnl-2017-311758. Epub 2017 Jul 24. PMID: 28739807

Homozygous and compound heterozygous mutations in the FBN1 gene: unexpected findings in molecular diagnosis of Marfan syndrome.Arnaud P, Hanna N, Aubart M, Leheup B**, Dupuis-Girod S,** Naudion S, Lacombe D**, Milleron O**, Odent S, Faivre L, Bal L, Edouard T, Collod-Beroud G, Langeois M, Spentchian M, Gouya L**, Jondeau** G, **Boileau C**.J Med Genet. 2017 Feb;54(2):100-103. doi: 10.1136/jmedgenet-2016-103996. Epub 2016 Aug 31. PMID: 27582083

A mutation update on the LDS associated genes TGFB2/3 and SMAD2/3. Schepers D, Tortora G, Morisaki H, MacCarrick G, Lindsay M, Liang D, Mehta SG, Hague J, Verhagen J, **van de Laar I**, Wessels M, Detisch Y, van Haelst M, Baas A, Lichtenbelt K, Braun K, van der Linde D, **Roos-Hesselink J**, McGillivray G, Meester J, Maystadt I, Coucke P, El-Khoury E, Parkash S, Diness B, Risom L, Scurr I, Hilhorst-Hofstee Y, Morisaki T, Richer J, Désir J, **Kempers M**, Rideout AL, Horne G, Bennett C, Rahikkala E, Vandeweyer G, Alaerts M, Verstraeten A, Dietz H, Van Laer L, **Loeys B**. Hum Mutat. 2018 Feb 1. doi: 10.1002/humu.23407. [Epub ahead of print]

HCP individual publications (2017):

1) **Center for Medical Genetics Ghent, Ghent University, Ghent, Belgium**:

Clinical history and management recommendations of the smooth muscle dysfunction syndrome due to ACTA2 arginine 179 alterations.Regalado ES, Mellor-Crummey L, De Backer J, Braverman AC, Ades L, Benedict S, Bradley TJ, Brickner ME, Chatfield KC, Child A, Feist C, Holmes KW, Iannucci G, Lorenz B, Mark P, Morisaki T, Morisaki H, Morris SA, Mitchell AL, Ostergaard JR, Richer J, Sallee D, Shalhub S, Tekin M; Montalcino Aortic Consortium, Estrera A, Musolino P, Yetman A, Pyeritz R, Milewicz DM. Genet Med. 2018 Jan 4. doi: 10.1038/gim.2017.245. [Epub ahead of print] PMID: 29300374

Sex, pregnancy and aortic disease in Marfan syndrome.Renard M, Muiño-Mosquera L, Manalo EC, Tufa S, Carlson EJ, Keene DR, **De Backer J**, Sakai LY. PLoS One. 2017 Jul 14;12(7):e0181166. doi: 10.1371/journal.pone.0181166. eCollection 2017.PMID: 28708846 Free PMC Article

Efficacy of losartan as add-on therapy to prevent aortic growth and ventricular dysfunction in patients with Marfan syndrome: a randomized, double-blind clinical trial.Muiño-Mosquera L, De Nobele S, Devos D, Campens L, De Paepe A, **De Backer J**. ActaCardiol. 2017 Jun 28:1-9. doi: 10.1080/00015385.2017.1314134. [Epub ahead of print]PMID: 28657492

The spectrum of spontaneous coronary artery dissection: illustrated review of the literature. Vandamme M, De Backer J, De Backer T, Drieghe B, Devos D, Gevaert S. Acta Cardiol. 2017 Dec;72(6):599-609. doi: 10.1080/00015385.2017.1309095. Epub 2017 Jun 28. PMID: 28657457

Nitric oxide mediates aortic disease in mice deficient in the metalloprotease Adamts1 and in a mouse model of Marfan syndrome.Oller J, Méndez-Barbero N, Ruiz EJ, Villahoz S, Renard M, Canelas LI, Briones AM, Alberca R, Lozano-Vidal N, Hurlé MA, Milewicz D, Evangelista A, Salaices M, Nistal JF, Jiménez-Borreguero LJ, De Backer J, Campanero MR, Redondo JM. Nat Med. 2017 Feb;23(2):200-212. doi: 10.1038/nm.4266. Epub 2017 Jan 9. PMID: 28067899

Propagation-based phase-contrast synchrotron imaging of aortic dissection in mice: from individual elastic lamella to 3D analysis. Logghe G, Trachet B, Aslanidou L, Villaneuva-Perez P, **De Backer J**, Stergiopulos N, Stampanoni M, Aoki H, Segers P. Sci Rep. 2018 Feb 2;8(1):2223. doi: 10.1038/s41598-018-20673-x. PMID: 29396472

2) Centre national de Référence pour le Syndrome de Marfan et apparentés, Hôpital Bichat-Claude Bernard, APHP, Paris

From genetics to response to injury: vascular smooth muscle cells in aneurysms and dissections of the ascending aorta.Michel JB, **Jondeau** G, Milewicz DM. Cardiovasc Res. 2018 Jan 17. doi: 10.1093/cvr/cvy006. [Epub ahead of print] PMID: 29360940

Clearance of plasmin-PN-1 complexes by vascular smooth muscle cells in human aneurysm of the ascending aorta.Boukais K, Borges LF, Venisse L, Touat Z, François D, Arocas V, **Jondeau** G, Declerck P, Bouton MC, Michel JB. CardiovascPathol. 2018 Jan - Feb;32:15-25. doi: 10.1016/j.carpath.2017.10.002. Epub 2017 Oct 24. PMID: 29149696

Skeletal evolution in Marfan syndrome: Growth curves from French national cohort.Benoist G, Tubach F, Roy C, Rioux S, Michelon-Jouneaux M, Chevallier B, **Jondeau G**, Stheneur C. PediatrRes. 2017 Aug 28. doi: 10.1038/pr.2017.210. [Epub ahead of print] PMID: 28846673

Marfan Syndrome: Always Evolving. **Jondeau G, Boileau C, Milleron O**. CircCardiovasc Genet. 2017 Jun;10(3). pii: e001785. doi: 10.1161/CIRCGENETICS.117.001785. No abstract available. PMID: 28600389

3) University Hospital of Antwerp, Belgium

Differences in manifestations of Marfan syndrome, Ehlers-Danlos syndrome, and Loeys-Dietz syndrome.Meester JAN, Verstraeten A, Schepers D, Alaerts M, Van Laer L, Loeys BL. Ann Cardiothorac Surg. 2017 Nov;6(6):582-594. doi: 10.21037/acs.2017.11.03. Review.PMID: 29270370

NGS panel analysis in 24 ectopialentis patients; a clinically relevant test with a high diagnostic yield.Overwater E, Floor K, van Beek D, de Boer K, van Dijk T, Hilhorst-Hofstee Y, Hoogeboom AJM, van Kaam KJ, van de Kamp JM, Kempers M, Krapels IPC, Kroes HY, **Loeys B**, Salemink S, Stumpel CTRM, Verhoeven VJM, Wijnands-van den Berg E, Cobben JM, van Tintelen JP, Weiss MM, Houweling AC, Maugeri A. Eur J Med Genet. 2017 Sep;60(9):465-473. doi: 10.1016/j.ejmg.2017.06.005. Epub 2017 Jun 19. PMID: 28642162

Two novel MYLK nonsense mutations causing thoracic aortic aneurysms/dissections in patients without apparent family history.Luyckx I, Proost D, Hendriks JMH, Saenen J, Van Craenenbroeck EM, Vermeulen T, Peeters N, Wuyts W, Rodrigus I, Verstraeten A, Van Laer L, **Loeys BL**. Clin Genet. 2017 Oct;92(4):444-446. doi: 10.1111/cge.13000. Epub 2017 Apr 12. No abstract available. PMID: 28401540

Aetiology and management of hereditary aortopathy.
Verstraeten A, Luyckx I, **Loeys B**.Nat Rev Cardiol. 2017 Apr;14(4):197-208. doi: 10.1038/nrcardio.2016.211. Epub 2017 Jan 19. Review.PMID:28102232

Loss-of-function mutations in the X-linked biglycan gene cause a severe syndromic form of thoracic aortic aneurysms and dissections.Meester JA, Vandeweyer G, Pintelon I, Lammens M, Van Hoorick L, De Belder S, Waitzman K, YoungL, Markham LW, Vogt J, Richer J, Beauchesne LM, Unger S, Superti-Furga A, Prsa M, Dhillon R, Reyniers E, Dietz HC, Wuyts W, Mortier G, Verstraeten A, Van Laer L**, Loeys BL**. Genet Med. 2017 Apr;19(4):386-395. doi: 10.1038/gim.2016.126. Epub 2016 Sep 15. PMID: 27632686 Free PMC Article

4) University Medical Center Hamburg-Eppendorf, Germany

Non-contrast MR angiography at 1.5 Tesla for aortic monitoring in Marfan patients after aortic root surgery.Veldhoen S, Behzadi C, Lenz A, Henes FO, Rybczynski M, **von Kodolitsch Y**, Bley TA, Adam G, Bannas P. J CardiovascMagnReson. 2017 Oct 30;19(1):82. doi: 10.1186/s12968-017-0394-y. PMID: 29084542

Inpatient rehabilitation for adult patients with Marfan syndrome: an observational pilot study.Benninghoven D, Hamann D, **von Kodolitsch Y**, Rybczynski M, Lechinger J, Schroeder F, Vogler M, Hoberg E. Orphanet J Rare Dis. 2017 Jul 12;12(1):127. doi: 10.1186/s13023-017-0679-0. PMID: 28701211 Free PMC Article

Genetic diagnostics of inherited aortic diseases : Medical strategy analysis. **vonKodolitsch Y**, Kutsche K. Herz. 2017 Aug;42(5):459-467. doi: 10.1007/s00059-017-4577-y. PMID: 28555287

Evaluating the quality of Marfan genotype-phenotype correlations in existing FBN1 databases.Groth KA, **Von Kodolitsch Y**, Kutsche K, Gaustadnes M, Thorsen K, Andersen NH, Gravholt CH.Genet Med. 2017 Jul;19(7):772-777. doi: 10.1038/gim.2016.181. Epub 2016 Dec 1. PMID: 27906200

5) Semmelweis University, Budapest, Hungary

The effects of acute and elective cardiac surgery on the anxiety traits of patients with Marfan syndrome.**Benke K**, Ágg B, Pólos M, Sayour AA, Radovits T, Bartha E, Nagy P, Rákóczi B, Koller Á, Szokolai V, Hedberg J, Merkely B, Nagy ZB, **Szabolcs Z**. BMC Psychiatry. 2017 Jul 17;17(1):253. doi: 10.1186/s12888-017-1417-9. PMID: 28716062

6) IRCCS Foundation Policlino San Matteo, Italy

No additional HTAD-related publications in 2017.

7) Careggi Hospital, University of Florence, Italy

Genetic Bases of Bicuspid Aortic Valve: The Contribution of Traditional and High-Throughput Sequencing Approaches on Research and Diagnosis.**Giusti B**, Sticchi E, De Cario R, Magi A, Nistri S, **Pepe G**. Front Physiol. 2017 Aug 24;8:612. doi: 10.3389/fphys.2017.00612. eCollection 2017. Review. PMID: 28883797

Role of TGFBR1 and TGFBR2 genetic variants in Marfan syndrome. De Cario R, Sticchi E, Lucarini L, Attanasio M, Nistri S, Marcucci R, **Pepe G, Giusti B**. J Vasc Surg. 2017 Aug 25. pii: S0741-5214(17)31587-2. doi: 10.1016/j.jvs.2017.04.071. [Epub ahead of print] PMID: 28847661

8) Azienda Socio Sanitaria Territoriale Fatebenefratelli – Sacco, Milan, Italy

The face in marfan syndrome: A 3D quantitative approach for a better definition of dysmorphic features.Dolci C, Pucciarelli V, Gibelli DM, Codari M, Marelli S, Trifirò G, **Pini A**, Sforza C. Clin Anat. 2017 Dec 11. doi: 10.1002/ca.23034. [Epub ahead of print] PMID: 29226593

Aortic dilatation in Marfan syndrome: role of arterial stiffness and fibrillin-1 variants.Salvi P, Grillo A, Marelli S, Gao L, Salvi L, Viecca M, Di Blasio AM, Carretta R, **Pini A**, Parati G. J Hypertens. 2018 Jan;36(1):77-84. doi: 10.1097/HJH.0000000000001512. PMID: 29210860

Impaired Central Pulsatile Hemodynamics in Children and Adolescents With MarfanSyndrome. Grillo A, Salvi P, Marelli S, Gao L, Salvi L, Faini A, Trifirò G, Carretta R, **Pini A**, Parati G. J Am Heart Assoc. 2017 Nov 7;6(11). pii: e006815. doi: 10.1161/JAHA.117.006815. PMID: 29114001

Vascular smooth muscle cells in Marfan syndrome aneurysm: the broken bricks in the aortic wall.Perrucci GL, Rurali E, Gowran A, **Pini A**, Antona C,Chiesa R, Pompilio G, Nigro P. Cell Mol Life Sci. 2017 Jan;74(2):267-277. doi: 10.1007/s00018-016-2324-9. Epub 2016 Aug 17. Review.PMID: 27535662

9) Academic Medical Center, The Netherlands

Surgical treatment of Marfan syndrome and related disorders is all about dealing with uncertainties.**Groenink M**, Koolbergen DR. Heart. 2017 Aug 16.pii: heartjnl-2017-312081. doi: 10.1136/heartjnl-2017-312081. [Epub ahead of print] No abstract available. PMID: 28814491

Aortic microcalcification is associated with elastin fragmentation in Marfan syndrome.Wanga S, Hibender S, Ridwan Y, van Roomen C, Vos M, van der Made I, van Vliet N, Franken R, van Riel LA, **Groenink M**, Zwinderman AH, Mulder BJ, de Vries CJ, Essers J, de Waard V. J Pathol. 2017 Nov;243(3):294-306. doi: 10.1002/path.4949. Epub 2017 Sep 21. PMID: 28727149

10) Radboud university medical center, Nijmegen, The Netherlands

NGS panel analysis in 24 ectopia lentis patients; a clinically relevant test with a high diagnostic yield. Overwater E, Floor K, van Beek D, de Boer K, van Dijk T, Hilhorst-Hofstee Y, Hoogeboom AJM, van Kaam KJ, van de Kamp JM, **Kempers M**, Krapels IPC, Kroes HY, Loeys B, Salemink S, Stumpel CTRM, Verhoeven VJM, Wijnands-van den Berg E, Cobben JM, van Tintelen JP, Weiss MM, Houweling AC, Maugeri A. Eur J Med Genet. 2017 Sep;60(9):465-473. doi: 10.1016/j.ejmg.2017.06.005. Epub 2017 Jun 19. PMID:28642162

Candidate Gene Resequencing in a Large Bicuspid Aortic Valve-Associated Thoracic Aortic Aneurysm Cohort: *SMAD6* as an Important Contributor.Gillis E, Kumar AA, Luyckx I, Preuss C, Cannaerts E, van de Beek G, Wieschendorf B, Alaerts M, Bolar N, Vandeweyer G, Meester J, Wünnemann F, Gould RA, Zhurayev R, Zerbino D, Mohamed SA, Mital S, Mertens L, Björck HM, Franco-Cereceda A, McCallion AS, Van Laer L, Verhagen JMA, van de Laar IMBH, Wessels MW, Messas E, Goudot G, Nemcikova M, Krebsova A, **Kempers M**, Salemink S, Duijnhouwer T, Jeunemaitre X, Albuisson J, Eriksson P, Andelfinger G, Dietz HC, Verstraeten A, Loeys BL; Mibava Leducq Consortium. Front Physiol. 2017 Jun 13;8:400. doi: 10.3389/fphys.2017.00400. eCollection 2017. Erratum in: Front Physiol. 2017 Sep 25;8:730. PMID:28659821

11) Erasmus Medical Center, Rotterdam, The Netherlands

Aortic Diameter Growth in Children With a Bicuspid Aortic Valve. Merkx R, Duijnhouwer AL, Vink E, **Roos-Hesselink JW**, Schokking M. Am J Cardiol. 2017 Jul 1;120(1):131-136. doi: 10.1016/j.amjcard.2017.03.245. Epub 2017 Apr 12. PMID:28483205

Pregnancy, Marfan syndrome, and type-B aortic dissection. Johnson MR, Roos Hesselink JW. BJOG. 2017 Jun 10. doi: 10.1111/1471-0528.14781. [Epub ahead of print] No abstract available. PMID: 28600893

12) Karolinska University Hospital, Sweden

No additional HTAD-related publications in 2017

13) Guy's Hospital, London, UK

See this HCP's publications in MSA-WG

MSA-WG, chaired by Dr. Leema Robert and co-chaired by Prof Xavier Jeunemaître

Clinical Trials:

The French **ARCADE (Angiotensin II Receptor Blockade in Vascular Ehlers Danlos Syndrome)** trial is a double blind, randomized, placebo controlled, and multicenter trial that has the possibility of being extended to other HCPs in the MSA-WG to make it a multinational trial.

The aim of this study is to see if angiotensin II receptor blockade by irbesartan, administered alone or in addition to celiprolol (vEDS reference therapy), reduces the rate of onset of asymptomatic and symptomatic cardiovascular events over 24 months compared to placebo.

Many questions have been brought up including how long it will take to set up in other countries, the cost and availability of randomisation for irbesartan and placebo, the imaging studies mentioned in the protocol, as well as various funding and ethical/regulatory approval issues. The feasibility of extending this trial is still ongoing in the MSA-WG.

Research projects ongoing within the RDWG (with several HCP members):

The RaDiCo SEDvasc (REDCap) registry is a cohort of patients with vascular Ehler's Danlos Syndrome which is currently underway in 16 centers in France. The MSA-WG wishes to extend this cohort to include patients from the other HCPs of the MSA-WG, thereby increasing the number of patients in the cohort. The Rare Disease Cohorts Programme « RaDiCo » is coordinated by « Inserm », the French Institut of Health and Medical Research. Currently involving the **HEGP Hôpital Européen Georges Pompidou,** it will soon have other HCP centers from the MSA-WG participating as the various study documents have now been translated (see VASCERN-WP11-D13-Translation).

Research projects ongoing within the RDWG (individual HCPs):

There are various research projects currently ongoing in individual HCPs, with currently no second ERN HCP participating. These will continue to be developed.

Publications:

The following list of publications is not exhaustive. We have tried to search for the most relevant publications to include in this report.

Collaborative publications (2017):

Diagnosis, natural history, and management in **vascular Ehlers-Danlos syndrome**.
Byers PH, Belmont J, Black J, **De Backer J**, **Frank M**, **Jeunemaitre X**, Johnson D, Pepin M, **Robert L**, Sanders L, Wheeldon N.
Am J Med Genet C Semin Med Genet. 2017 Mar;175(1):40-47. doi: 10.1002/ajmg.c.31553. Review.
PMID: 28306228

The 2017 international classification of the Ehlers-Danlos syndromes.
Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, Bloom L, Bowen JM, Brady AF, Burrows NP, Castori M, Cohen H, Colombi M, Demirdas S, **De Backer J**, De Paepe A, Fournel-Gigleux S, **Frank M**, Ghali N, Giunta C, Grahame R, Hakim A, **Jeunemaitre X**, Johnson D, Juul-Kristensen B, Kapferer-Seebacher I, Kazkaz H, Kosho T, Lavallee ME, Levy H, Mendoza-Londono R, Pepin M, Pope FM, Reinstein E, **Robert L**, Rohrbach M, Sanders L, Sobey GJ, Van Damme T, Vandersteen A, van Mourik C, Voermans N, Wheeldon N, Zschocke J, Tinkle B.
Am J Med Genet C Semin Med Genet. 2017 Mar;175(1):8-26. doi: 10.1002/ajmg.c.31552.
PMID: 28306229

Recognizing the tenascin-X deficient type of Ehlers-Danlos syndrome: a cross-sectional study in 17 patients.
Demirdas S, Dulfer E, **Robert L**, **Kempers M**, van Beek D, Micha D, van Engelen BG, Hamel B, Schalkwijk J, **Loeys B**, Maugeri A, Voermans NC.
Clin Genet. 2017 Mar;91(3):411-425. doi: 10.1111/cge.12853. Epub 2016 Nov 4.
PMID: 27582382

HCP individual publications (2017) :

1) **Guy'sHospital, London UK**

No additional MSA-related publications in 2017

2) **HEGP Hôpital Européen Georges Pompidou, Paris, France**

Phenotypic variability and diffuse arterial lesions in a family with Loeys-Dietz syndrome type 4. Mazzella JM, **Frank M**, Collignon P, **Langeois M**, Legrand A, **Jeunemaitre X**, Albuisson J. Clin Genet. 2017 Mar;91(3):458-462. doi: 10.1111/cge.12838. Epub 2016 Sep 13. PMID:27440102

3) **Ghent University Hospital, Belgium**

See this HCP's publications in HTAD-WG

4) **University Hospital of Antwerp, Belgium**

See this HCP's publications in HTAD-WG

5) **IRCCS Foundation Policlino San Matteo, Italy**

See this HCP's publications in HTAD-WG

6) **Azienda Socio Sanitaria Territoriale Fatebenefratelli – Sacco, Itlay**

See this HCP's publications in HTAD-WG

7) **Erasmus Medical Center, The Netherlands**

See this HCP's publications in HTAD-WG

PPL-WG, chaired by Dr. Robert Damstra and co-chaired by Prof Sahar Mansour

Clinical trials:

There are currently no collaborative clinical trials underway in the PPL-WG.

Research projects ongoing within the RDWGs (with several HCP members):

There is a collaborative PPL-WG research project currently underway on the genetics of primary lymphoedema. This research study is based at **St George's University Hospitals** and **Derby Teaching Hospitals NHSF Trust** is also a recruiting center involved. Together data will be used for phenotyping and genetic testing.

These two centers are equally participating in the 100,000 Genomes Project, an ambitious genomics project hoping to sequence 100,000 genomes from around 70,000 patients with rare disease (and their families) and cancer. **St George's University Hospitals** and **Derby Teaching Hospitals NHSF Trust** are contributing data to the lymphoedema group.

Research projects ongoing within the RDWG (individual HCPs):

Derby Teaching Hospitals NHSF Trust; Analysis of genes and their functions in patients with primary lymphedema study currently underway, as well as CCRN 2359 (Lymphoedema compression programs).

HEGP Hôpital Européen Georges Pompidou is conducting the LYMPHADEX research study which is an exploration study of the tissue of patients with primary lymphedema of the lower limbs. This study is interested in body composition measured by biphotonic absorptiometry.

University Hospitals Leuven are involved in several studies including the following: Exploring the potential of cell therapy and study the role of Notch/BMP signaling in models of lymphatic regeneration in the mouse (ongoing), Efficacy of MLD in the treatment of sec BCRL: multicentre, randomized trial supported by IWT (national) research grant (IWT project accepted in June 2015, 150178), Efficacy of velcro bandages in the treatment of LO of lower limb (starting in 2018), Compression questionnaire: validity (finished, currently writing paper), Lymphofluoroscopy: validity, comparability with clinical aspect/measurements (finished, writing paper), Determining pre-excisting factors in the development of BCRL (started in 2017 and is ongoing), and Lymphovenous anastomosis for treatment of unstable lymphoedema: a feasability study (started in 2017 and is ongoing).

Helsinki University Hospital is currently undergoing a long term efficacy of microvascular lymphonode transfer in the lower extremity

Publications

The following list of publications is not exhaustive. We have tried to search for the most relevant publications to include in this report.

Collaborative Publications (2017):

No collaborative publications for this group.

HCP individual publications (2017):

1) **NijSmellinghe hospital, Drachten, The Netherlands**

The Dutch lymphedema guidelines based on the International Classification of Functioning, Disability, and Health and the chronic care model. **Damstra RJ,** Halk AB; Dutch Working Group on Lymphedema. J Vasc Surg Venous Lymphat Disord. 2017 Sep;5(5):756-765. doi: 10.1016/j.jvsv.2017.04.012. Epub 2017 Jun 30. PMID: 28818234

Circumferential suction-assisted lipectomy in the treatment of primary and secondary end-stage lymphoedema of the leg. Lamprou DA, Voesten HG, **Damstra RJ**, Wikkeling OR. Br J Surg. 2017 Jan;104(1):84-89. doi: 10.1002/bjs.10325. Epub 2016 Nov 3. PMID:27809337

First Dutch guidelines on lipedema using the international classification of functioning, disability and health. Halk AB, **Damstra RJ**. Phlebology. 2017 Apr;32(3):152-159. doi: 10.1177/0268355516639421. Epub 2016 Jul 9. Review. PMID: 27075680

2) **St George's University Hospitals, London**

An approach to familial lymphoedema. Jones GE, **Mansour S**. Clin Med (Lond). 2017 Dec;17(6):552-557. doi: 10.7861/clinmedicine.17-6-552. PMID: 29196357

Human phenotypes caused by PIEZO1 mutations; one gene, two overlapping phenotypes? Martin-Almedina S, **Mansour S**, Ostergaard P.J Physiol. 2018 Jan 13. doi: 10.1113/JP275718. [Epub ahead of print] PMID: 29331020

VIPAR, a quantitative approach to 3D histopathology applied to lymphatic malformations. Hägerling R, Drees D, Scherzinger A, Dierkes C, Martin-Almedina S, Butz S, Gordon K, Schäfers M, Hinrichs K, Ostergaard P, Vestweber D, Goerge T, **Mansour S**, Jiang X, Mortimer PS, Kiefer F. JCI Insight. 2017 Aug 17;2(16). pii: 93424. doi: 10.1172/jci.insight.93424. [Epub ahead of print] PMID:28814672

Renal anomalies and lymphedema distichiasis syndrome. A rare association? Jones GE, Richmond AK, Navti O, Mousa HA, Abbs S, Thompson E, **Mansour S**, Vasudevan PC. Am J Med Genet A. 2017 Aug;173(8):2251-2256. doi: 10.1002/ajmg.a.38293. Epub 2017 May 23. PMID: 28544699

3) **AZ Sint-Maarten, Belgium**

Intraoperative imaging of lymphatic vessel using ultra high-frequency ultrasound. Hayashi A, Visconti G, Yamamoto T, **Giacalone G**, Hayashi N, Handa M, Yoshimatsu H, Salgarello M. J Plast Reconstr Aesthet Surg. 2018 Feb 1. pii: S1748-6815(18)30025-1. doi: 10.1016/j.bjps.2018.01.013. [Epub ahead of print] No abstract available. PMID:29398613

4) **University Hospitals Leuven, Belgium**

The discovery of the lymphatic system in the seventeenth century. Part IV: the controversy. Suy R, **Thomis S**, Fourneau I. Acta Chir Belg. 2017 Aug;117(4):270-278. doi: 10.1080/00015458.2017.1326658. Epub 2017 May 19. PMID: 28521639

5) **Helsinki University Hospital, Finland**

No additional PPL publications in 2017

6) **Primary Lymphedema Expert Unit of CRMR Rare Vascular Diseases (HEGP Hôpital Européen Georges Pompidou), France**

[Primary lymphedema in childhood]. **Vignes S**, Vidal F, Arrault M, Boccara O. Arch Pediatr. 2017 Aug;24(8):766-776. doi: 10.1016/j.arcped.2017.05.002. Epub 2017 Jun 23. French. PMID:28651791

Specialized consultations in a hospital-based referral center for patients suspected of having limb lymphedema: Impact on diagnosis. **Vignes S**, Vidal F, Arrault M. Vasc Med. 2017 Aug;22(4):331-336. doi: 10.1177/1358863X17714884. Epub 2017 Jun 20. PMID:28633618

[Abnormal nails and chronic cough].**Vignes S**, Simon L, Vidal F, Arrault M. Rev Med Interne. 2017 Jun 1. pii: S0248-8663(17)30519-2. doi: 10.1016/j.revmed.2017.05.002. [Epub ahead of print] French. No abstract available. PMID:28579108

Yellow nail syndrome: a review. **Vignes S**, Baran R. Orphanet J Rare Dis. 2017 Feb 27;12(1):42. doi: 10.1186/s13023-017-0594-4. Review. PMID:28241848

[Commentaries on the article: "Algorithm for surgical treatment of limb lymphedema"]. **Vignes S**.Ann Chir Plast Esthet. 2017 Feb;62(1):113-114. doi: 10.1016/j.anplas.2016.11.001. Epub 2016 Nov 28. French. No abstract available. PMID:27908557

[Lymphedema: From diagnosis to treatment].**Vignes S**.Rev Med Interne. 2017 Feb;38(2):97-105. doi: 10.1016/j.revmed.2016.07.005. Epub 2016 Aug 31. Review. French. PMID:27591818

7) University Medical Center Freiburg, Germany

See this HCP's publications in VASCA-WG.

8) Derby Teaching Hospitals NHSF Trust, U.K.

Advances in understanding and management of lymphoedema (cancer, primary). **Keeley V**. Curr Opin Support Palliat Care. 2017 Dec;11(4):355-360. doi: 10.1097/SPC.0000000000000311. PMID: 28984676

Identifying priority areas for research into the diagnosis, treatment and prevention of cellulitis (erysipelas): results of a James Lind Alliance Priority Setting Partnership. Thomas KS, Brindle R, Chalmers JR, Gamble B, Francis NA, Hardy D, Hooper J, **Keeley V**, Levell NJ, McPhee M, Metcalf L, Santer M, Tarpey M, Smart P, Wallace A, Wilkes S. Br J Dermatol. 2017 Aug;177(2):541-543. doi: 10.1111/bjd.15634. Epub 2017 Jun 14. No abstract available. PMID: 28477399

Future Research Priorities for Morbidity Control of Lymphedema. Narahari SR, Aggithaya MG, Moffatt C, Ryan TJ, **Keeley V**, Vijaya B, Rajendran P, Karalam SB, Rajagopala S, Kumar NK, Bose KS, Sushma KV. Indian J Dermatol. 2017 Jan-Feb;62(1):33-40. doi: 10.4103/0019-5154.198039. PMID:28216723

Chronic oedema: a prevalent health care problem for UK health services. Moffatt CJ, **Keeley V**, Franks PJ, Rich A, Pinnington LL. Int Wound J. 2017 Oct;14(5):772-781. doi: 10.1111/iwj.12694. Epub 2016 Dec 4. PMID: 27917617

VASCA-WG, chaired by Prof Miikka Vikkula and co-chaired by Prof Leo Schultze Kool

Clinical Trials:

The VASCA-WG currently has one clinical trial underway: **The VASE (Vascular Anomaly-Sirolimus-Europe)** ongoing in Brussels (Cliniques Universitaires Saint-Luc) and activated in France (Caen, Amiens and Montpellier) in May 2017. It is now a VASCERN collaborative project with two other HCPs from the VASCA-WG participating (**University Medical Center Freiburg** and **Helsinki University Hospital** (FI), both in preparation stage). A similar trial is ongoing at the **Radboud University Medical Center** in the Netherlands.

University Medical Center Freiburg is in the preparation phase of the SIPA-SOS trial (study of Sirolimus in patients with segmental overgrowth syndrome).

Research projects ongoing within the RDWGs (with several HCP members):

A research study on the genetic basis of **Generalized Lymphatic Anomaly/Gorham-Stout Disease (GLA/GSD)** with collaboration between two HCPs from the VASCA WG (**Cliniques Universitaires Saint-Luc (BE) and University Medical Center Freiburg (DE**)).

A research study of the genotype-phenotype in **Verrucous Venous Malformation/ Hyperkeratotic Cutaneous Capillary-Venous Malformation (VVM/HCCVM)** with collaboration between two HCPs from the VASCA-WG (**Cliniques Universitaires Saint-Luc (BE) and Our Lady's Children's Hospital Crumlin (IE))**

Research projects ongoing within the RDWGs (individual HCP members):

Bambino Gesù Children's Hospital is currently performing research in Hemangioma sequela after propranolol, Cutaneous and hepatic hemangiomas, and Ultrasound in hemangiomas treated with propranolol.

Publications:

The following list of publications is not exhaustive. We have tried to search for the most relevant publications to include in this report.

Collaborative publications (2017):

Blue Rubber Bleb Nevus (BRBN) Syndrome Is Caused by Somatic TEK (TIE2) Mutations.Soblet J, Kangas J, Nätynki M, Mendola A, Helaers R, Uebelhoer M, Kaakinen M, Cordisco M, Dompmartin A, Enjolras O, Holden S, **Irvine AD,** Kangesu L, Léauté-Labrèze C, Lanoel A, Lokmic Z, Maas S, McAleer MA, Penington A, Rieu P, Syed S, **van der Vleuten C**, Watson R, Fishman SJ, Mulliken JB, Eklund L, Limaye N, **Boon LM, Vikkula M**. J Invest Dermatol. 2017 Jan;137(1):207-216. doi: 10.1016/j.jid.2016.07.034. Epub 2016 Aug 9. PMID:27519652

Development of an international core outcome set for peripheral vascular malformations: the OVAMA project. Horbach SER, van der Horst CMAM, Blei F, **van der Vleuten CJM**, Frieden IJ, Richter GT, Tan ST, Muir T, Penington AJ, **Boon LM**, Spuls PI; OVAMA Consensus Group Br J Dermatol. 2017 Oct 7. doi: 10.1111/bjd.16029. [Epub ahead of print] PMID: 28986976

HCP individual publications (2017):

1) **Cliniques Universitaires Saint-Luc, Belgium**

Etiology and Genetics of Congenital Vascular Lesions. Queisser A, **Boon LM, Vikkula M.** Otolaryngol Clin North Am. 2018 Feb;51(1):41-53. doi: 10.1016/j.otc.2017.09.006. Review. PMID:29217067

Venous Malformations of the Head and Neck. Seront E, **Vikkula M, Boon LM**. Otolaryngol Clin North Am. 2018 Feb;51(1):173-184. doi: 10.1016/j.otc.2017.09.003. Review.PMID:29217061

Loss of ADAMTS3 activity causes Hennekam lymphangiectasia-lymphedema syndrome 3. Brouillard P, Dupont L, Helaers R, Coulie R, Tiller GE, Peeden J, Colige A, **Vikkula M.**
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