

BACKGROUND:

Multiple sclerosis (MS) is considered an autoimmune disease of the Central Nervous System (CNS) characterized by inflammation, demyelination, and neurodegeneration. Recently the possible pathogenetic role of functional and structural abnormalities of cervical and intracranial veins has been postulated (1,2). Such a condition, called chronic cerebrospinal venous insufficiency has been initially reported to occur in 100% of MS patients and very rarely in normal controls (3). Subsequent studies failed to confirm the association between CCSVI and MS (4,5). To help addressing the conflicting reports and provide answers to MS patients the Italian MS Society, through its Foundation (FISM), has promoted and financed the CoSMo study: a large multicenter observational study.

INCLUSION CRITERIA

Individuals of either gender aged between 18 and 55 who gave written informed consent.

Subjects with Multiple Sclerosis (MS)

- Individuals with a diagnosis of MS according to McDonald criteria and revisions
- Clinical course of disease: RR - SP - PP – CIS
- Duration of disease: from 1 month to 25 years (RR and SP and PP); up to 5 years (CIS)
- Subjects treated or not treated with immunomodulating and immunosuppressive drugs

Other Neurodegenerative Disorders (OND)

- Subjects with inflammatory neurodegenerative diseases
- Subjects with other non-inflammatory neurodegenerative diseases

Healthy Subjects (HS)

- Absence of major diseases and no family history of MS

EXCLUSION CRITERIA

- Any acute or chronic debilitating illness which may interfere with the design and objectives of the study;
- Cardiac dysfunction (≥ NYHA Class I);
- Previous episodes of venous thromboembolism (including deep vein thrombosis and pulmonary embolism);
- Neoplasms; Thrombophilia; Diabetes; Primary or secondary pulmonary hypertension and any treatment for it;
- Systemic treatment with steroid concomitant or in the past 30 days;
- Cerebrovascular disorders past or current; Episodes of transient global amnesia.

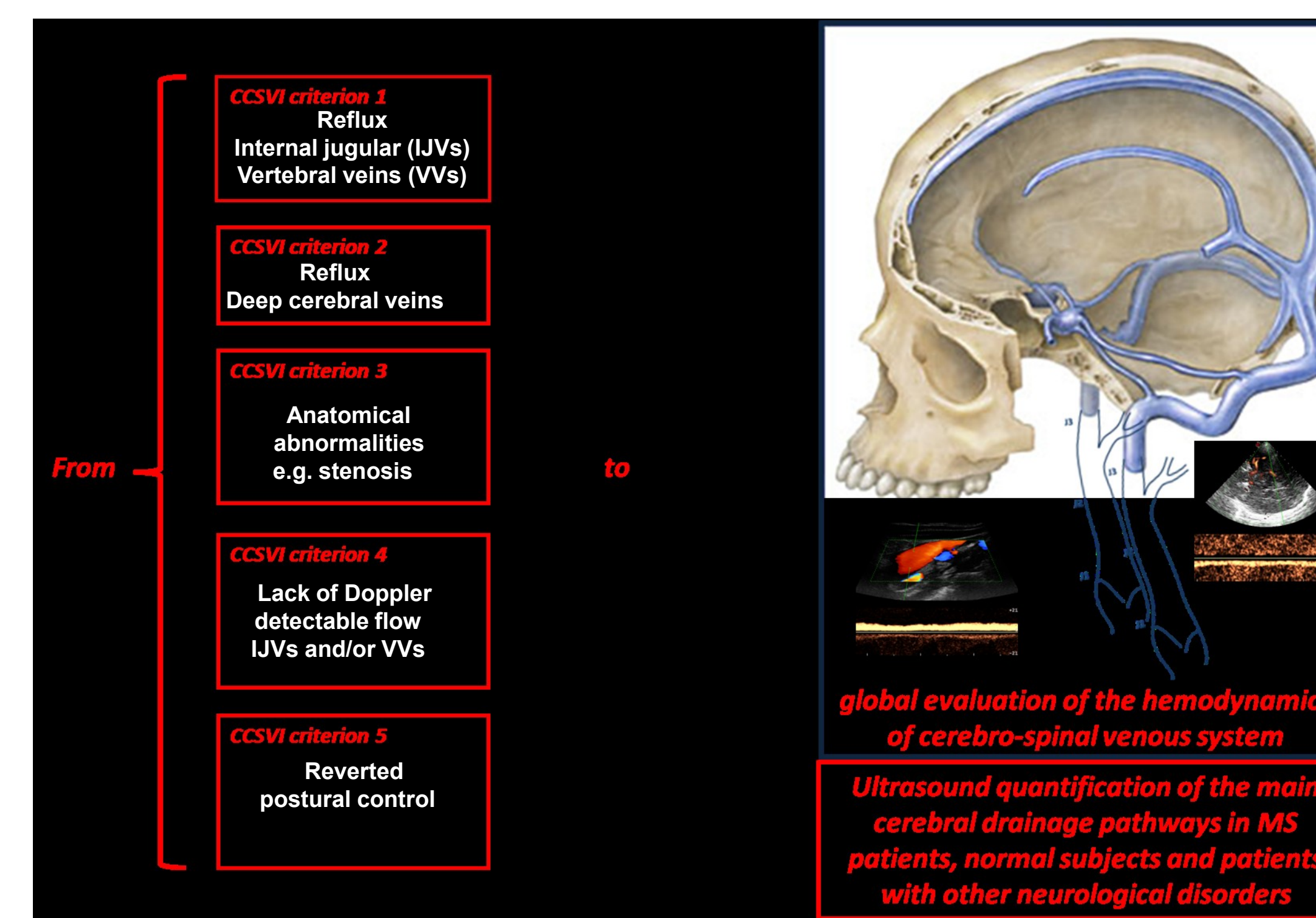
OBJECTIVE:

To compare the prevalence of CCSVI and other anomalies of the cerebrospinal venous haemodynamics in patients with Multiple Sclerosis (MS), with the prevalence in patients affected by other neurodegenerative disorders and in healthy subjects.

FEATURES OF THE STUDY:

- **Observational Multicenter Study conducted in 43 Italian clinical sites (38 active)**
- **Sample size: 2000 subjects. 1200 MS subjects versus 400 subjects with other neurodegenerative disorders and 400 healthy controls**
- **Echo Color Doppler (ECD) analysis to evaluate standardized criteria for study of venous function in MS: global evaluation of the hemodynamic of cerebro-spinal venous system parameters in addition to the five CCSVI criteria**
- **Blind ECD analysis performed by local and central sonologists**
- **Data monitoring managed by an independent CRO (Opera CRO-Genoa)**

EVALUATION OF THE VENOUS FUNCTION

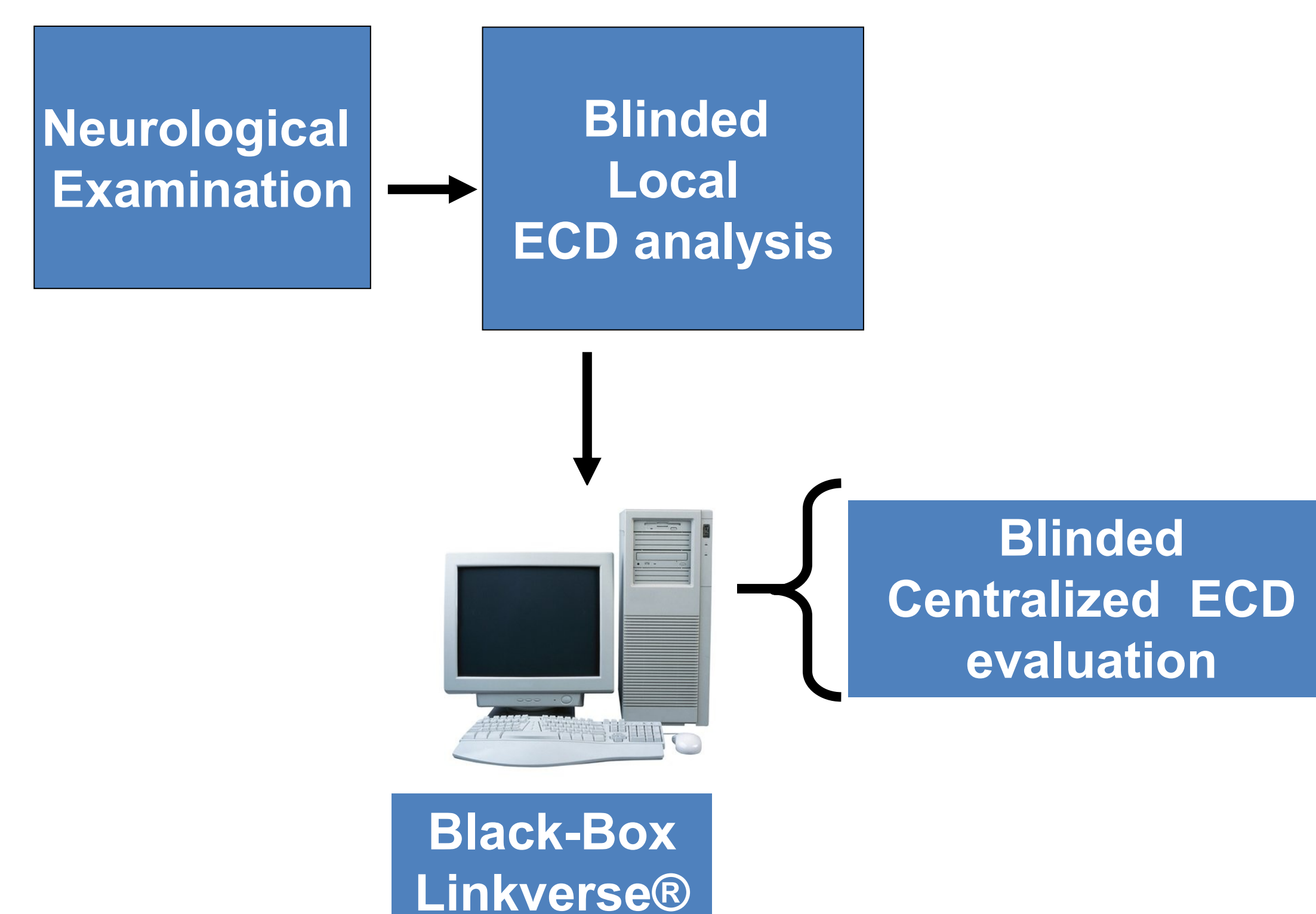


- Diagnosis of CCSVI: 2 out the 5 criteria described in the literature have to be met (1, 2).

- Global evaluation of the hemodynamic of cerebro-spinal venous system parameters in addition to the 5 CCSVI criteria.

- The evaluation of the ECD examination made by the independent sonologist is compared with the one made at the clinical site, if the two evaluations are matching a final report is issued. If the two evaluations do not match, the image is sent to the other two independent sonologists. The evaluation shared by two out of three independent sonologists is considered as final

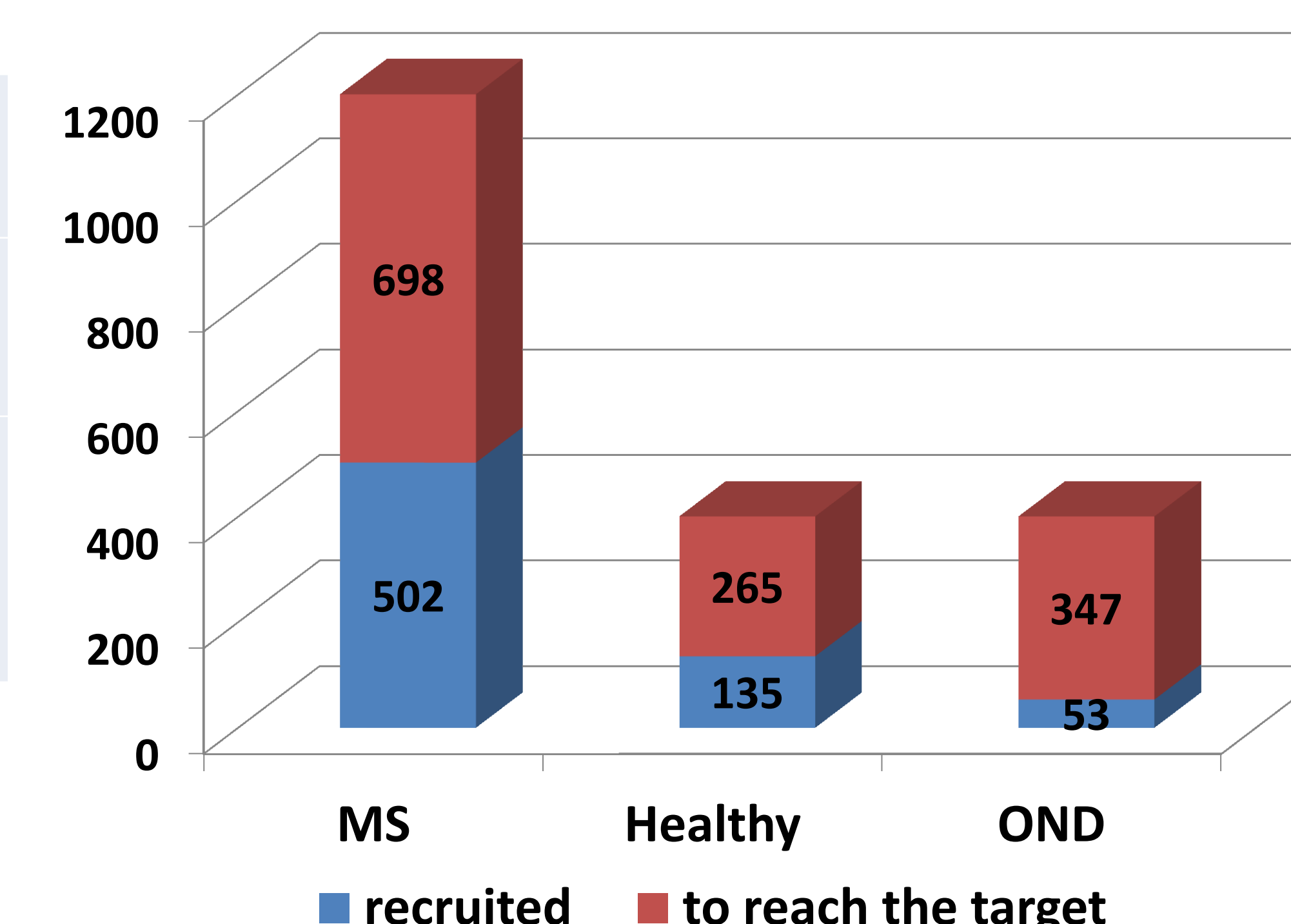
STUDY WORK FLOW



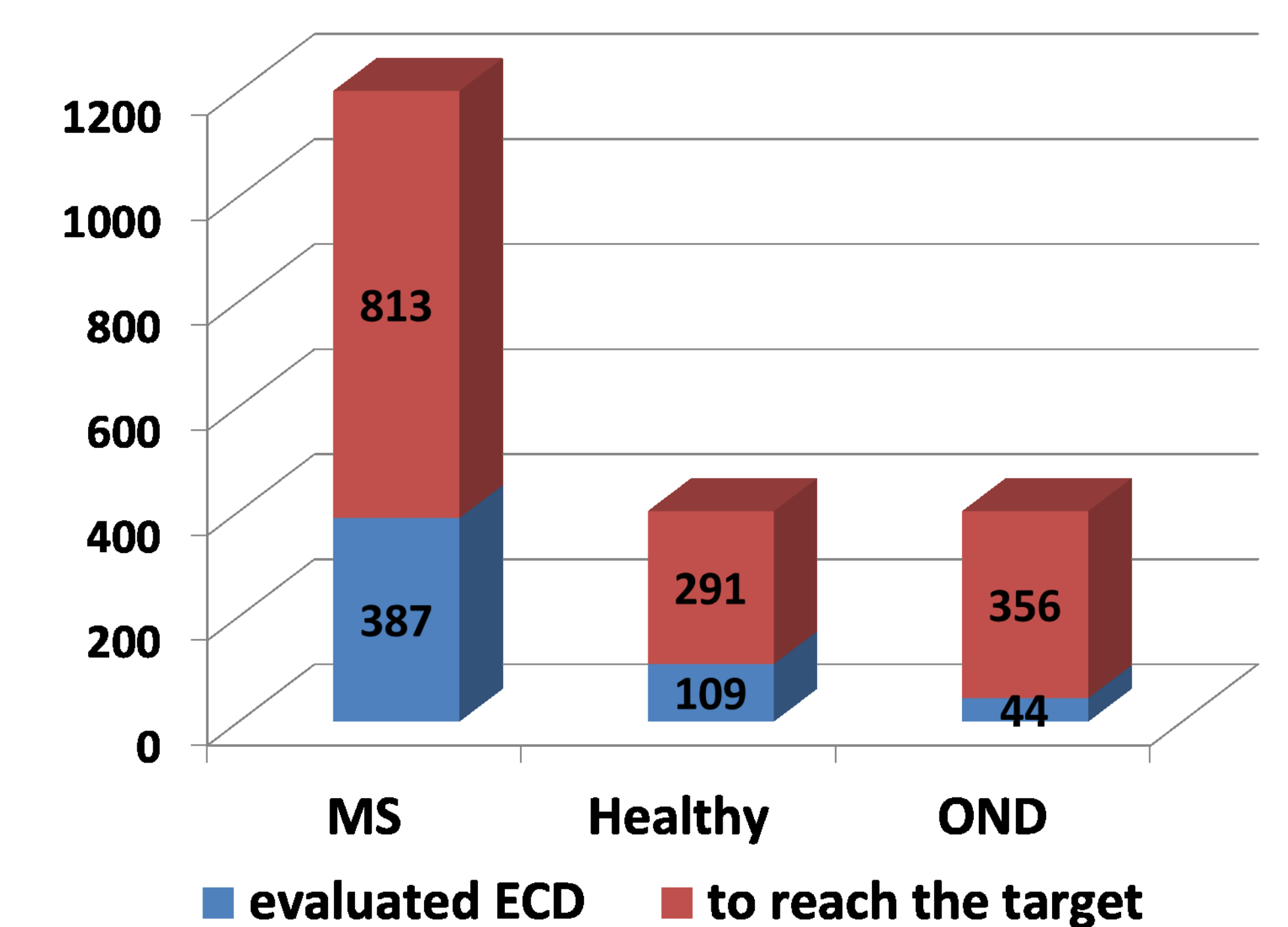
CONCLUSIONS

- The CoSMo study is the largest study performed so far aiming at comparing the prevalence of anomalies of the cerebrospinal venous haemodynamics and CCSVI in patients with Multiple Sclerosis (MS), with the prevalence in patients affected by other neurodegenerative disorders and in healthy subjects.
- The Italian MS Foundation funded the training on a large scale of sonologists to use standardized ECD criteria for studying the hemodynamics of cerebro-spinal venous system and the results of the CoSMo study may provide insights into the use of Echo Color Doppler as a new diagnostic tool to evaluate venous functions in MS and in other neurodegenerative disorders.
- In line with the features of the CoSMo study, the Steering Committee has decided to complete the blind ECD analysis in 2000 subjects.

DISTRIBUTION of RECRUITED POPULATION



DISTRIBUTION of ECD EVALUATED POPULATION



REFERENCES

1. Zamboni P et al. Eur J Vasc Endovasc Surg. 2011
2. Zamboni P et al. J Vasc Surg. 2009
3. Zamboni P et al. J Neurol Sci. 2009
4. Doepp F, et al. Ann Neurol. 2010
5. Krogias C, et al. Nervenarzt. 2010.

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DISCLOSURES: Prof. Battaglia has no conflicts of interest to declare. Dr A. Bertolotto has been on steering committees in clinical trials sponsored by Biogen Idec, Roche, and has received speaker honoraria from Biogen Idec, Merck Serono, TEVA, Bayer Schering, Sanofi-aventis, and Novartis; and has received research support from Biogen Idec, Bayer Schering, Merck Serono, Sanofi-Aventis, from the Italian Multiple Sclerosis Society, and the European Union Sixth Framework Programme. Prof. Comi has received consulting fees for participating on advisory boards from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Merck Serono, and Bayer Schering; lecture fees from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Merck Serono, Biogen Dompè, Bayer Schering and Serono Symposia International Foundation. He is member of the Board of Governors of the Italian Foundation for Multiple Sclerosis. Dr. M. Del Sette has no conflicts of interest to declare. Dr A. Ghezzi received honoraria for speaking from Bayer-Schering, Biogen-Dompè, Merck-Serono, Novartis, Sanofi-Aventis, Allergan, for consultancy from Actelion, Merck-Serono, Teva and Novartis, received support for participation to National and International Congresses from Bayer-Schering, Biogen-Dompè, Merck-Serono, Novartis, Sanofi-Aventis. Dr G. Malferrari has no conflicts of interest to declare. Prof. GL Mancardi received honoraria for lecturing, travel expenses for attending meetings, and financial support for research from Bayer Schering, Biogen Idec, Sanofi-Aventis, Novartis and Merck Serono Pharmaceuticals. He is member of the Board of Governors of the Italian Foundation for Multiple Sclerosis. Dr. M Salvetti declares grant support from Bayer-Schering, Merck-Serono, Sanofi-Aventis. Dr. MP Sormani has received consulting fee or honoraria from Biogen IDEC, Merck Serono, Actelion, Synthon, TEVA. Prof. E. Stolz has no conflicts of interest to declare. Prof. L. Tesio is member of the Board of Governors of the Italian Foundation for Multiple Sclerosis