RESEARCH PROTOCOL

RESVcue Marfan

(February 2019)

Resveratrol as potential aortic growth inhibitor in patients with Marfan Syndrome.

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EudraCT number	Not applicable
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Laboratory sites	Local laboratories will provide routine assessments.
Pharmacy	Not applicable

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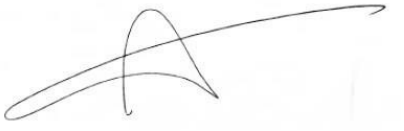
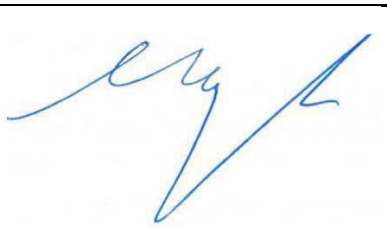
Sponsor or legal representative: Amsterdam UMC – location AMC Meibergdreef 9 1105 AZ Amsterdam **Head of Department:** Prof. Dr. Y. Pinto, Academic Medical Center Amsterdam Dept. of Cardiology 1105 AZ, Amsterdam The Netherlands		
Principal Investigator: Dr. Maarten Groenink Amsterdam UMC – location AMC Meibergdreef 9 1105 AZ, Amsterdam The Netherlands Dept. of Cardiology		

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: We have shown that the food supplement Resveratrol inhibits aortic growth and promotes aortic repair in Marfan Syndrome mice (doi:10.1161/ATVBAHA.116.307841). The hypothesis is that Resveratrol treatment will also be protective against aortic dilatation and functional deterioration in humans with Marfan syndrome.

Objective: The aim of the study is to obtain sufficient data on beneficial effects of Resveratrol on aortic aneurysm expansion rate, aortic functional properties, endothelial function and biomarkers in patients with Marfan syndrome to justify a phase IIb or a phase III randomized trial.

Study design: A pre-post observational design with evaluation of cardiovascular parameters (primary and secondary outcomes) before and after one year of Resveratrol treatment.

Study population: 100 Marfan patients (50 patients with native aorta and 50 patients with a history of aortic root replacement surgery) with a known Fibrillin-1 gene (*FBN1*) mutation, between 18-40 years of age, of whom at least two echocardiography and one magnetic resonance imaging (MRI) measurements are available prior to Resveratrol treatment.

Intervention (if applicable): Resveratrol 500 mg/day for one year.

Main study parameters/endpoints:

There are three main study parameters/endpoints:

1. A decrease in aortic aneurysm expansion rate in > 90% of the study subjects as measured by echocardiography between baseline (at timepoint of inclusion in the study) and after one year of follow-up (after Resveratrol treatment).
2. Any statistical significant beneficial change in aortic elasticity or aortic wall shear rate as measured by MRI between baseline (at timepoint of inclusion in the study) and after one year of follow-up (after Resveratrol treatment).
3. Any statistical significant beneficial change in endothelial function as measured by Flow Mediated Dilatation (FMD) between baseline (at timepoint of inclusion in the study) and after one year of follow-up (after Resveratrol treatment).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Study subjects will be evaluated before and after one year of Resveratrol treatment (2x) with various measurements. They will undergo echocardiography, MRI, FMD, blood sampling and skin biopsy. Furthermore, patients will complete a Well-being questionnaire before and after one year of treatment. The risks of participation are in general limited.

1. INTRODUCTION AND RATIONALE

Treatment of aortic degenerative disease in Marfan patients with Resveratrol

Marfan syndrome is a heritable connective tissue disease characterized by mutations in the Fibrillin-1 gene (FBN1) located on chromosome 15. The most important manifestation is progressive enlargement of the proximal aorta, ultimately leading to aortic dissection and sudden death. Standard management is to surgically resect the enlarged part of the aorta, which is then replaced by a synthetic graft (with or without an artificial aortic valve) when the aneurysm has reached certain dimensions. Although this strategy has increased survival in Marfan syndrome significantly, many patients are referred for open heart surgery at relatively young age (20-50 years). Many of them will also need anticoagulant therapy for the rest of their lives when the aortic valve has to be replaced. Moreover, prophylactic surgery of the proximal aorta may progress aneurysm formation and aortic dissection in the more distal aorta.

Ideally, aneurysm formation and the need for prophylactic surgery would be prevented in known patients with Marfan syndrome. However, we do not exactly know how the FBN1 gene defect results in aortic disease and we can not explain the extreme heterogeneity in expression of aortic manifestations, even within families with the same FBN1 mutation. We do however know multiple mechanisms play a role in this process.

Among the possible mechanisms that lead to aortic disease in Marfan syndrome, smooth muscle cell (SMC) contractile function in the vessel wall of the aorta seem to play an important role. Recently, we have shown that premature aging and cell death of SMCs are present in an animal model of Marfan syndrome.(1) This process of premature aging is called 'senescence' and it negatively affects the regenerative capacity (after aortic damage). Figure 1A shows that aortic senescence (green) was mainly seen in the enlarged ascending aorta of MFS mice. In the microscopic photograph below a senescence area can be seen. The fibers in this area are interrupted, where you would expect a regular build-up of elastic fibers (white lines) in a healthy aorta. Therefore, this figure implies vascular wall damage.

Present day pharmacological treatment is based on blood pressure lowering drugs, using mostly B-blockers and Losartan. Unfortunately, this is not sufficient for most patients and surgical treatment is still necessary. Inhibiting senescence is a potential treatment approach to combat aneurysm development. Resveratrol, a dietary supplement that intervenes in cellular metabolism, appears to have a favorable effect on the degree of aortic damage and aortic dilatation in MFS mice. A graphical display of this effect is shown below. Figure 1B shows a strong positive correlation between the aortic root dilatation rate and aortic senescence.
Resveratrol significantly reduced the aortic root dilatation rate and shows a decrease in elastic fiber breaks (Figure 1C).

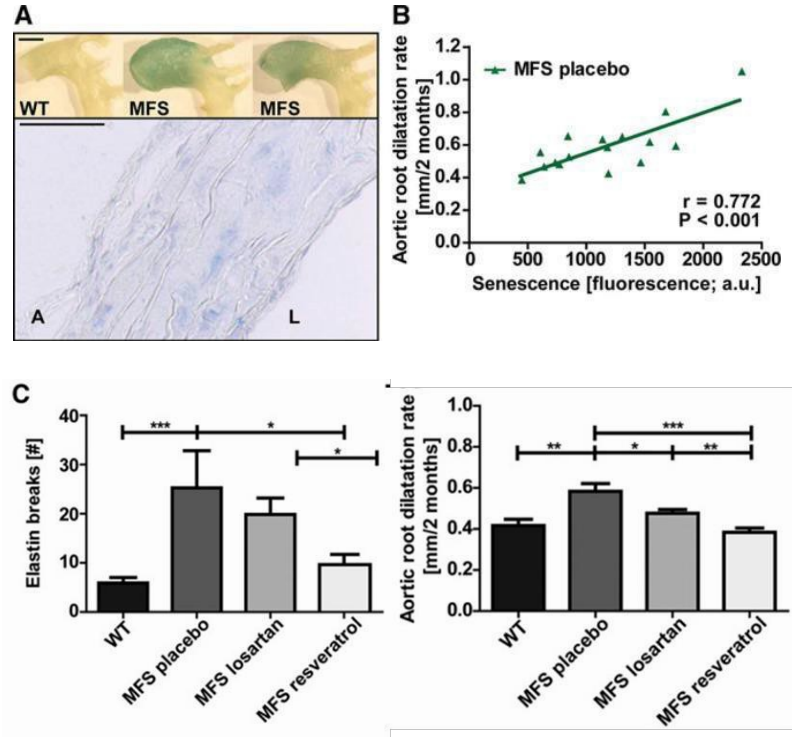


Figure 1. *Aortic root dilatation correlates with senescence.* ***A****. Representative macroscopic photographs of senescence-associated (cytoplasmic) β-galactosidase-stained aortic arches from wild-type (WT) and Marfan syndrome (MFS) mice (top; x6.5; scale bar, 1mm) and a microscopic photograph of a cross section of a MFS mouse ascending aorta (bottom; x200; scale bar, 50 μm). Blue cells are senescent cells.* ***B****. Correlation between aortic root dilatation rate and senescence in MFS mice.* ***C.*** *MFS placebo mice show more elastin breaks and enhanced aortic root dilatation rate when compared with WT mice. Resveratrol treatment results in a decrease in elastin breaks and reduced aortic dilatation. Losartan was used in the MFS model as positive control. (ref 1: doi: 10.1161/ATVBAHA.116.307841)*

There are no established direct methods available to determine senescence in the aorta in humans. Therefore we aim to measure the indirect effect of senescence, namely decreased regenerative capacity, in the aortic wall, and the effect of Resveratrol on these features. There are two levels of measurements; namely in tissue samples or by advanced imaging techniques. In tissue samples biomarkers of abnormal function or enhanced tissue degradation will be studied. By advanced imaging techniques, the functional performance of the aorta/vasculature (such as elasticity and endothelial cell function) is visualized and thus examined.

A) In tissue samples:

1. Blood samples (determining degradation products of SMCs)
2. Skin biopsy (analyzing extracellular matrix abnormalities)

B) By advanced imaging techniques:

1. Ultrasound (echocardiography)
2. Magnetic resonance imaging

In Marfan syndrome, aortic elasticity is affected by aortic disease, partly through broken elastic fibers, which are not repaired efficiently due to senescence. This reduction in aortic elasticity causes enhanced dilatation of the aorta and altered blood flow patterns. Agents that reduce senescence, such as Resveratrol, could potentially have a beneficial effect on these aortic abnormalities. Improved arterial elasticity with Resveratrol has already been demonstrated in Type II Diabetic patients.(2)

Besides a reduction in aortic elasticity, a reduction in energy levels have also been reported in Marfan patients.(3) Resveratrol provides an improved energy mechanism in human muscles (4-6), which may also apply to the SMCs in the aorta, and potentially enhance SMC survival.

Lastly, SMC behavior in the aortic wall is intricately regulated by cellular communication with endothelial cells, which separate the SMC from the blood and form the inner lining of the aorta. Since endothelial cells are connected to the bloodstream, they sense substances in the circulation, such as drugs, first. Patients with Marfan syndrome have a disturbed endothelial function, which strongly correlates with the aortic diameter.(7) Resveratrol has been described as having a beneficial effect on the endothelial function in arteriosclerosis patients, patients with kidney failure and obese patients. (8-10)

In conclusion, the beneficial effect of Resveratrol on aneurysm formation has been described in four different aortic aneurysm studies in animal models (1, 11-13), including our study in the Marfan mouse model. Thereby, Resveratrol has a possible beneficial effect on aortic elasticity, energy levels in SMCs and on endothelial function. However, the effect of Resveratrol in Marfan patient is still unknown. With this study we aim to analyze whether treatment with Resveratrol could be beneficial in Marfan patients.

2. OBJECTIVES

2.1 Aim

To obtain sufficient data with a one year study on the expansion rate of thoracic aortic aneurysms and functional vascular parameters in 100 patients (50 pts with native aorta and 50 pts with a history of aortic root replacement surgery) with Marfan syndrome (with a known FBN1 mutation) treated with Resveratrol, so that a reliable estimate of the effect of Resveratrol is obtained with which a phase IIb or a phase III randomized trial can be designed to measure the effect of Resveratrol on aortic aneurysm expansion rate and aortic functional properties in a 3-year randomized study.

2.2 Primary Objective(s)

To evaluate potential beneficial effects of the food supplement Resveratrol on aortic degenerative disease in patients with Marfan syndrome. More in detail:

1) Morphologically: on aneurysm expansion rate as measured by echocardiography and MRI.
2) Functionally: on aortic elastic properties and wall shear rate as measured by MRI.
3) Biochemically: on the levels of smooth muscle cell degradation products in plasma and in skin biopsies.

2.3 Secondary Objective(s)

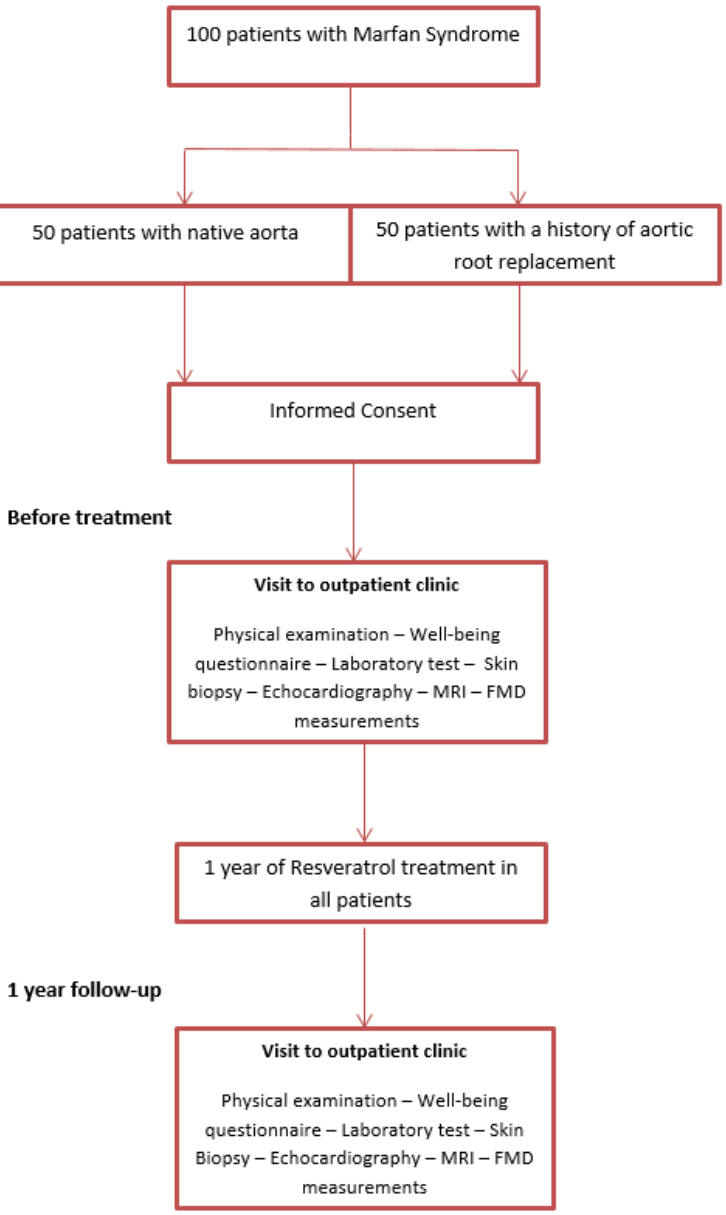
1. To evaluate functional cardiac parameters by echocardiography in Marfan patients upon treatment with Resveratrol.
2. To evaluate changes in blood pressure/heart rate in patients with Marfan syndrome treated with Resveratrol.
3. To evaluate changes in endothelial cell function in patients with Marfan syndrome treated with Resveratrol by flow mediated dilation measurement (FMD).
4. To evaluate differences between Marfan patients who have had aortic replacement and Marfan patients with a native aorta, before or after Resveratrol.
5. To evaluate differences between Marfan patients who have a haploinsufficient (HI) *FBN1* mutation or a dominant negative (DN) *FBN1* mutation. Geneticists determine the HI or DN status, however, skin cultures may provide conclusive results when the mutation effect is unpredictable.

2.4 Other Objective(s)

1. To evaluate patients well-being before and after one year of Resveratrol treatment via a Well-being questionnaire.

3. STUDY DESIGN

The study is a phase IIa study with the food supplement Resveratrol, with the primary aim to obtain a sufficiently reliable estimate of the effect of Resveratrol on growth of thoracic aortic dimensions, and aortic elasticity and wall shear stress in patients with Marfan syndrome. The study uses a pre-post design with evaluation of cardiovascular parameters (i.e. the primary and secondary outcomes) before and after one year of Resveratrol treatment.



4. STUDY POPULATION

4.1 Population (base)

All patient known with Marfan Syndrome between the age of 18-40 years old, are eligible for this study. Potential candidates are identified through the CONgenital CORvitia (CONCOR) registry, the Dutch national database and DNA-bank of adult CHD. Only patients who are currently seen at the outpatient clinic of the department of cardiology in one of the participating medical centers are approached. Patients will be recruited from all Marfan Centers in the Netherlands, even when they are not known in the CONCOR database.
Patients are selected and approached by the research fellow, in consultation with the treating physician. A total of 100 patients will be included.

Patients will receive a letter informing them on the study and requesting their participation. One week after receiving the letter, patients will be contacted by telephone to give additional information, answer potential questions and again request participation. The information is sufficient to give each participant a thorough understanding of the purpose and the nature of the study, the cooperation required and the anticipated benefits and potential hazards of the study. Special emphasis is made to the fact that informed consent is given for treatment with the trial food supplement (Resveratrol).
The research fellow also stresses that the patient is completely free to refuse participation or to withdraw from the trial at any time, without consequences for his/her treatment, and that the physician or investigator can decide to withdraw a patient from the study for urgent medical reasons.
The informed consent form is signed on the day of the inclusion. In all cases it is the responsibility of the research fellow to obtain written informed consent.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Marfan patient with a known *FBN1* mutation
- Between 18-50 years of age
- A maximum of 1 vascular prosthesis
- At least 2 echocardiography measurements prior to study
- At least 1 MRI measurement prior to study
- Stable blood pressure before entering study

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- More than one vascular prosthesis
- Aortic root diameter > 45 mm
- Aortic surgery likely within 6 months of inclusion
- Aortic surgery in the last 6 months prior to inclusion
- Aortic dissection
- Contraindication for MR imaging
- Mental retardation
- Pregnancy, or planned pregnancy during study period

4.4 Sample size calculation

We will include 100 patients in the study. Measured by MRI, the average annual growth of the aortic root in patients with Marfan syndrome is approximately 0.35 mm/year with standard deviation 0.49 (Groenink *et al.* 2013, doi: 10.1093/eurheartj/eht334). With 100 patients the width of the 95% confidence interval of the average annual growth rate with Resveratrol treatment is therefore about 0.2 (4*0.49/10), which we judge to be sufficient to be used as a basis for decision making for a randomized phase IIb or Phase III study. With 100 patients there will be 80% power to find a statistically significant effect size of about 0.3 or more. Such large effect has not been observed so far with pharmacological interventions in Marfan patients, but the effect size of 0.3 is still considered to be moderate. The effect size used is a Cohen's effect size. A Cohen's effect size at a SD of 0.49 mm is equal to an (additional) aortic diameter change of 0.147 mm, which is the mean difference between baseline and 1 year follow up in the COMPARE trial (Groenink *et al.* 2013, doi: 10.1093/eurheartj/eht334).

5. TREATMENT OF SUBJECTS

To study the effect of food supplement Resveratrol on top of the ongoing medicinal regime in Marfan patients on cardiovascular biomarkers and function.

5.1 Investigational product/treatment

Intervention: Resveratrol 500 mg/day on top of existing medicinal regime Duration of intervention: one year

Comparator of placebo: none

We will compare cardiovascular parameters before and after one year of Resveratrol treatment.

5.2 Use of co-intervention (if applicable)

The use of other cardiac medication is recorded. No changes will be made to the already existing, patient-specific, treatment.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Resveratrol purified from polygonum cuspidatum root extract (98% pure) and capsulated by EHF-group; 500 mg Resveratrol/capsule.

6.2 Summary of findings from non-clinical studies

There are 4 manuscript on the beneficial role of Resveratrol in animal models of aortic aneurysm disease:

1. **Resveratrol Inhibits Aortic Root Dilatation in the Fbn1C1039G/+ Marfan Mouse Model.** Hibender S, et al., Arterioscler Thromb Vasc Biol. 2016 Aug;36(8):1618-26. doi: 10.1161/ATVBAHA.116.307841.
2. **Resveratrol inhibits growth of experimental abdominal aortic aneurysm associated with upregulation of angiotensin converting enzyme 2**. Corey Moran, et al., Arterioscler Thromb Vasc Biol. 2017 Nov;37(11):2195-2203. doi:10.1161/ATVBAHA.117.310129.
3. **Resveratrol counteracts systemic and local inflammation involved in early abdominal aortic aneurysm development.** Palmieri D, et al., J Surg Res. 2011 Dec;171(2):e237-46. doi: 10.1016/j.jss.2011.07.041.
4. **Resveratrol prevents the development of abdominal aortic aneurysm through attenuation of inflammation, oxidative stress, and neovascularization.** Kaneko H, et al., Atherosclerosis. 2011 Aug;217(2):350-7. doi: 10.1016/j.atherosclerosis.2011.03.042.

There is a comprehensive review on the (beneficial) effects of Resveratrol on cardiac disease in animal models:

1. **Therapeutic potential of Resveratrol in heart failure.** Sung MM, Dyck JR. Ann N Y Acad Sci. 2015 Aug;1348(1):32-45. doi: 10.1111/nyas.12839. Review.

6.3 Summary of findings from clinical studies

Relevant human studies on the effect of Resveratrol on (cardiovascular) parameters are:

- Resveratrol has been shown to improve arterial elasticity (ref 1).
- Resveratrol improves endothelial function (ref 2-4).
- Resveratrol improves muscle metabolism (ref 5-7).

References:

1. **Resveratrol Ameliorates Arterial Stiffness Assessed by Cardio-Ankle Vascular Index in Patients With Type 2 Diabetes Mellitus.** Imamura H, et al., Int Heart J. 2017 Aug 3;58(4):577-583. doi: 10.1536/ihj.16-373.
2. **Resveratrol for primary prevention of atherosclerosis: clinical trial evidence for improved gene expression in vascular endothelium.** Agarwal B, et al., Int J Cardiol. 2013 Jun 5;166(1):246-8.doi:10.1016/j.ijcard.2012.09.027.
3. **Supplementation with high-dose trans-resveratrol improves ultrafiltration in peritoneal dialysis patients: a prospective, randomized, double-blind study**. Lin CT, et al., Ren Fail. 2016;38(2):214-21. doi: 10.3109/ 0886022X.2015.1128236.
4. **Chronic Resveratrol consumption improves brachial flow-mediated dilatation in healthy**

obese adults. Wong RH, et al., J Hypertens. 2013 Sep;31(9):1819-27. doi: 10.1097/HJH.0b013e328362b9d6.

5. **Resveratrol Enhances Exercise-Induced Cellular and Functional Adaptations of Skeletal Muscle in Older Men and Women.** Alway SE, et al., J Gerontol A Biol Sci Med Sci. 2017 Nov 9;72(12):1595-1606.doi:10.1093/gerona/glx089.
6. **Resveratrol Improves Vascular Function and Mitochondrial Number but Not Glucose Metabolism in Older Adults.** Pollack RM, et al., J Gerontol A Biol Sci Med Sci. 2017 Nov 9;72(12):1703-1709.doi:10.1093/gerona/glx041.
7. **Resveratrol as Add-on Therapy in Subjects With Well-Controlled Type 2 Diabetes: A Randomized Controlled Trial.** Timmers S, et al., Diabetes Care. 2016 Dec;39(12):2211-2217. doi:10.2337/dc16-0499.

6.4 Summary of known and potential risks and benefits

No harmful effects were reported when using concentrations of Resveratrol 500 mg/day in human studies published since 2015.

In the meta-analysis of 21 studies in obese patients (reference indicated below) a small reduction in blood pressure was observed upon Resveratrol treatment (-2.26 mmHg; 95% CI, -4.82 to -0.49; P = 0.02).

The effects of Resveratrol intervention on risk markers of cardiovascular health in overweight and obese subjects: a pooled analysis of randomized controlled trials. Huang H. et al., Obes Rev. 2016Dec;17(12):1329-1340.doi:10.1111/obr.12458.

Marfan patients are mostly on blood pressure lowering medication to protect their aorta and may experience dizziness due to additional blood pressure lowering, which should therefore be monitored upon Resveratrol treatment.

6.5 Description and justification of route of administration and dosage

In 18 (non-cancer related) human Resveratrol studies published since 2015 (Pubmed), 24 dosages were used, of which the median dosage was 500 mg/day (orally) and the median time of treatment 3 months. Therefore, we will use 500 mg/day (for one year).

This dosage has been chosen, because this is a safe and widely used dose of Resveratrol in (non-cancer) patients.

This following study shows that trans-resveratrol is a substance of low oral toxicity. Human clinical studies have been performed with dosages up to 5g/day for 28 days and generally support the expectation of safety at the ADI defined for resVida(®).

Safety of resveratrol with examples for high purity, trans-resveratrol, resVida((R)). Edwards JA, Beck M, Riegger C, Bausch J. Ann N Y Acad Sci 2011 Jan;1215:131-137.

6.6 Dosages, dosage modifications and method of administration

Resveratrol 500 mg/day (1 capsule/day), orally.

6.7 Preparation and labelling of Investigational Medicinal Product

European Health & Fitness Group (EHF Group) will be responsible for the distribution of the Resveratrol.

EHF Group is a member of the Natuur- en gezondheidsproducten Nederland (NPN) sector association and produces by Hazard Analysis and Critical Control Points (HACCP) guidelines in the form of ISO22000 for food safety and FSCC22000 for basic conditions and hygienic.

6.8 Drug accountability

Drug accountability will be recorded to current Good Clinical Practice (GCP) guidelines. All local hospital pharmacies will store the Resveratrol and perform the administration of the drug accountability according to their local procedures

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The main study endpoints are the change in aortic dimension at any aortic level, and aortic elasticity and wall shear stress, as measured by MRI, between baseline (at time point of inclusion) and after one year of follow-up, upon Resveratrol treatment.

7.1.2 Secondary study parameters/endpoints (if applicable)

1. Changes in functional cardiac parameters by echocardiography in Marfan patients upon treatment with Resveratrol.
2. Changes in blood pressure/heart rate in patients with Marfan syndrome treated with Resveratrol.
3. Changes in endothelial cell function in patients with Marfan syndrome treated with Resveratrol by flow mediated dilation measurement (FMD).
4. Changes in biomarkers in blood and skin biopsies in patients with Marfan syndrome treated with Resveratrol.
5. Differences between Marfan patients who have had aortic replacement and Marfan patients with a native aorta, before or after Resveratrol.
6. Differences between Marfan patients who have a haploinsufficient (HI) FBN1 mutation or a dominant negative (DN) FBN1 mutation.

7.1.3 Other study parameters (if applicable)

1. Change in patients well-being as measured by a Well-being questionnaire, before and after Resveratrol treatment.

7.2 Study procedures

Patients are requested to visit the outpatient clinic to undergo various measurements at baseline and after one year of Resveratrol use. During the 12 months of Resveratrol use patients do not have to undergo any other investigations. According to the wishes of the patient it is always possible to have intermediate contact, most likely by phone. Thereby, the research fellow will contact patients included in the study by telephone, every three months, to detect any complications. After one year they visit the outpatient clinic again. During these visits (at baseline and after one year), patients undergo the following investigations:

7.2.1 Medical history

Details of the medical history are taken at baseline and follow-up. The following data are recorded. Medical history of: echocardiography, MRI, aortic surgery. Risk factors for cardiac disorders are recorded (i.e. smoking, drinking, family history of heart disease, hypertension, hypercholesterolemia, diabetes mellitus). Patient files are checked at baseline, and follow-up, to provide information on changes in medication, presentations to the cardiac emergency department and admissions to hospital.

7.2.2 Physical examination

Careful physical examination is performed at each visit, especially focusing on (decrease in) blood pressure and presence of heart valve regurgitation.

7.2.3 Medication

The use of any medication is recorded.

7.2.4 Well-being Questionnaire (SF-12)

This questionnaire is designed to measure general well-being, including negative well- being, energy and positive well-being. The questionnaire, as will be presented to the patient, has been added as an attachment to this protocol. It will take the patients approximately 10 to 15 minutes to finish the questionnaire.

7.2.5 Hospital Depression and Anxiety Scales (HADS)

The HADS questionnaire measures core complaints of anxiety and depression. It is a short questionnaire, which is easy to use, consisting of an anxiety and a depression scale, both containing seven items. The questionnaire, as will be presented to the patient, has been added as an attachment to this protocol. It will take the patients approximately 10 minutes to finish the questionnaire.

7.2.6 Checklist Individuele Spankracht (CIS)

The CIS questionnaire measures fatigue and behavioural aspects related to this in a subjective manner. The CIS consists of 20 statements that examine how the patient has felt in the past two weeks. The patient has to indicate in what extend the statement applies to him/her. The CIS questionnaire measures an image of fatigue in which fluctuations over time are taken into account. The questionnaire, as will be presented to the patients, has been added as an attachment to this protocol. It will take the patients approximately 10 minutes to finish the questionnaire.

7.2.7 Blood analysis

Routine and extended laboratory measurements will be performed at baseline and after one year of Resveratrol use. Concentration of the following parameters are recorded: transforming growth factor betas (TFG-beta), microfibrillar associated protein 4 (MFAP-4) and aortic (smooth muscle cell) markers.
Patients do not need to fast before samples are taken. All blood samples are drawn and analysed locally.

7.2.8 Skin Biopsy

Marfan Syndrome affects the aorta, which is not easily accessible for a biopsy to study an effect of Resveratrol. Skin is a connective tissue, as is the aorta, and thus in a skin biopsy the biochemical effect of Resveratrol can be evaluated as surrogate for aortic tissue in Marfan patients.

Furthermore, by culturing the fibroblasts from the biopsy, the true mutation effect of the FBN1 mutation on production of the extracellular matrix can be accessed, to provide in depth understanding beyond the predictions of the geneticists, to identify different subtypes of Marfan patients.
For this reason patients will undergo a punch skin biopsy at baseline and after one year of

Resveratrol use. The punch biopsy specimens will be 4 mm in diameter and will be taken from the front side of the upper leg. 1 or 2% lidocaine will be used as local anesthesia. Punch biopsies can heal by secondary intention, when needed the wound can be closed with one or two sutures.

7.2.9 Echocardiography

Echocardiography is performed in all patients as standard clinical care at baseline and after one year of Resveratrol use. The VIVID 7 (GE Medical Systems) is used for echocardiography. Echocardiograms are performed and analysed locally. All echocardiogram are digitally stored.

7.2.10 Magnetic Resonance Imaging

Study subjects will be examined supine in a 3Tesla MR scanner using a high power gradient system (Ingenia, Philips, Best, The Netherlands) at baseline and after one year of Resveratrol use.

Protocol:

1. Localisation of the aorta by balanced TFE sequences (1-2 minutes)
2. The entire aorta will then be visualized using a mDixon 3D sequence with specific read- outs for water, fat, in phase and out phase MR signals and with an isotropic (or near isotropic) resolution of 1x1x1 mm. (5 minutes)
3. A 4D-Flow phase contrast sequence (Turbo Field echo) will be applied to the thoracic aorta as visualized at 2). This sequence will yield time resolved images of 3D aortic strain and 3D aortic luminal velocities with a temporal resolution of approximately 30 ms and an isotropic or near isotropic spatial resolution of approximately 2.5x2.5x2.5 mm. (5-10 minutes)
4. A stack of gradient echo CINE images, encompassing the entire heart, will be acquired by balanced TFE to yield standard cardiac parameters: End diastolic volume, end systolic volume, ejection fraction and stroke volume.

7.2.11 Flow-mediated Dilation measurements

Measuring the FMD will be done of the right brachial artery. Ultrasound imaging of the brachial artery will be performed using a 5- to 13-MHz linear transducer with a VIVID 7 USG machine. With the patient in a relaxed supine position, the transducer will be placed on the right brachial artery trace at 4 to 5 cm above the right elbow. First the baseline diameter will be recorded. After that, a sphygmomanometer cuff will be put around the forearm, and will inflate to 50 mm Hg higher than the baseline systolic BP. This pressure will be kept for 5 minutes. After 5 minutes, the sphygmomanometer cuff will be deflated suddenly, and measurements of the brachial artery diameter will be taken again. FMD will be calculated utilizing the following equation:

$$\text{FMD (\%)} = \frac{(\text{Peak diameter} - \text{Baseline diamter})}{\text{Baseline diameter}}$$

7.3 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.4 Replacement of individual subjects after withdrawal

Subjects who are withdrawn from the study for whatever reason, will not be replaced.

7.5 Follow-up of subjects withdrawn from treatment

Subjects who are withdrawn will be followed according to routine care that is provided for Marfan patients at the participating hospitals.

7.6 Premature termination of the study

The study will not be prematurely stopped.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs:
The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

8.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

8.5 Data Safety Monitoring Board (DSMB) / Safety Committee

No data safety monitoring board will be installed.

9. STATISTICAL ANALYSIS

Primary aims of the study are exploratory and no specific comparison of effects is planned. When calculating summary statistics we will calculate 95% confidence intervals for all statistics.

9.1 Primary study parameter(s)

Primary outcomes of the study are quantified with the average change of the aortic diameters, aortic elasticity and wall stress, together with the associated standard deviation and 95% confidence interval.

9.2 Secondary study parameter(s)

Depending on whether secondary outcomes are of a quantitative or categorical nature, other outcomes of the study are summarized either with mean change values and associated 95% confidence intervals or category-specific percentages and associated 95% confidence intervals.

9.3 Other study parameters

Depending on whether other outcomes are of a quantitative or categorical nature, other outcomes of the study are summarized either with mean change values and associated 95% confidence intervals or category-specific percentages and associated 95% confidence intervals.

In an exploratory fashion, the primary, secondary and other outcomes of patients will be associated using (generalized) linear models with baseline clinical characteristics (such as baseline aorta dimensions, age, sex, Marfan-mutation, concurrent Marfan medication).

The rate of patients who drop-out or withdraw from the study as well as the (serious) adverse event rates will be quantified using proportions and associated 95% confidence intervals. To assess whether drop-out is ignorable for the estimation of the average change levels of the outcome parameters, we will compare baseline characteristics of patients who complete the study with those of patients who drop-out.

9.4 Interim analysis (if applicable)

No interim analysis will be performed.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

This study will be conducted in full accordance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, and Johannesburg) and with the laws and regulations of the Netherlands. The complete text of the Declaration of Helsinki is available to the investigators upon request.

10.2 Recruitment and consent

For detailed information on recruitment and consent we refer to Chapter 4.1 ("Population") of this protocol. All adult patients known with Marfan Syndrome are potentially eligible for this study. Only patients who are treated in one of the participating medical centers are approached. Patients are selected and approached by the research fellow. Patients receive a letter (in Dutch or English) from the research fellow with information informing them on the study and requesting their participation. One week after receiving the letter, patients will be contacted by telephone to give additional information, answer potential questions and again request participation. The information is sufficient to give each participant a thorough understanding of the purpose and the nature of the study, the cooperation required and the anticipated benefits and potential hazards of the study. The research fellow also stresses that the patient is completely free to refuse participation or to withdraw from the trial at any time, without consequences for his/her treatment, and that the physician or investigator can decide to withdraw a patient from the study for urgent medical reasons.

The informed consent form is signed on the day of the inclusion. In all cases it is the responsibility of the research fellow to obtain written informed consent.

10.3 Benefits and risks assessment, group relatedness

The research product (Resveratrol) has not yet shown a beneficial effect in patients familiar with Marfan Syndrome. However, the use of Resveratrol may reduce aortic growth, as previously mentioned positive effects were shown in MFS mice.

Disadvantages of participating in the research can be

- Potential side effects of Resveratrol use.
- Potential inconveniences of the various measurements.

Potential complaints will be monitored (3 monthly), patients can contact the research fellow at any time with questions or notice of any complication. Thereby it is stressed in patients that quitting the research is possible at any moment.

The risks of participation are in general limited. When the research product (Resveratrol) shows a beneficial effect, this on the other hand can be a major breakthrough in the treatment of aortic growth in Marfan patients.

10.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

The investigator ensures that patient anonymity is maintained, according to the General Data Protection Regulation (GDPR). On CRF's and other documents, patients are not identified by their names or dates of births but by randomly assigned identification codes. The investigator keeps a separate log of patient's codes, names and addresses, where only the research fellow will have excess to. The investigator maintains all documents in strict confidence.

11.2 Monitoring and Quality Assurance

No monitoring of the conduct of the study will take place.

11.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

11.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.
In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

11.6 Public disclosure and publication policy

The Investigators are entitled to disseminate the findings of the trial via publications in reputable scientific journals and via presentations at seminars or scientific conferences. The Investigators carry final responsibility for the scientific content of the publication on the main findings of the study. No limitations to the disclosure and publication of the findings have been imposed by the sponsor.

12. STRUCTURED RISK ANALYSIS

12.1 Synthesis

This study focuses on the effect of Resveratrol on the expansion rate of thoracic aortic aneurysms and functional vascular parameters. Previous research on the effect of Resveratrol on (cardiovascular) parameters demonstrated improved arterial elasticity, improved endothelial function and improved muscle metabolism (see chapter 6.3). No harmful effects were reported in human studies with Resveratrol 500mg/day.

Patients will most likely endure no risk during the study. The only side effect described is a possible small reduction in blood pressure. Patients with Marfan Syndrome are mostly on blood pressure lowering medication, patients will therefore be alerted to contact the research fellow in case of complaints of dizziness or fainting. Thereby, the research fellow will contact patients included in the study by telephone, every three months, to detect any complications.

All the investigations are part of regular medical care according to international guidelines and no risks are expected from these investigations, except for the blood withdrawal, when bruising or hemorrhages can occur.

In general, the overall risk of the patients participating in this study is limited.

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14. APPENDIX

14.1 Well-being Questionnaire

SF-12 Gezondheidstoestand vragenlijst

INSTRUCTIE: Deze vragenlijst gaat over uw standpunten t.a.v. uw gezondheid. Met behulp van deze gegevens kan worden bijgehouden hoe u zich voelt en hoe goed u in staat bent uw gebruikelijke bezigheden uit te voeren.

Beantwoord elke vraag door één hokje aan te kruisen. Als u niet zeker weet hoe u een vraag moet beantwoorden, geef dan het best mogelijke antwoord.

1. Hoe zou u, over het algemeen genomen, uw gezondheid noemen?
   - ☐ Uitstekend
   - ☐ Zeer goed
   - ☐ Goed
   - ☐ Matig
   - ☐ Slecht

2. De volgende vragen gaan over bezigheden die u misschien doet op een doorsnee dag. Wordt u door uw gezondheid op dit moment beperkt bij deze bezigheden? Zo ja, in welke mate?

   2a. **Matige inspanning** zoals het verplaatsen van een tafel, stofzuigen, zwemmen of fietsen
   - ☐ Ja, ernstig beperkt
   - ☐ Ja, een beetje beperkt
   - ☐ Nee, helemaal niet beperkt

   2b. **Een paar** trappen oplopen
   - ☐ Ja, ernstig beperkt
   - ☐ Ja, een beetje beperkt
   - ☐ Nee, helemaal niet beperkt

3. Heeft u in de afgelopen 4 weken één van de volgende problemen bij uw werk of andere dagelijkse bezigheden gehad, ten gevolge van uw lichamelijke gezondheid?

   3a. U heeft **minder bereikt** dan u zou willen
   - ☐ Ja
   - ☐ Nee

   3b. U was beperkt in het **soort** werk of andere bezigheden
   - ☐ Ja
   - ☐ Nee

4. Heeft u in de afgelopen 4 weken één van de volgende problemen ondervonden bij uw werk of andere dagelijkse bezigheden ten gevolge van emotionele problemen (zoals depressieve of angstige gevoelens)?

4a. U heeft **minder bereikt** dan u zou willen
- ☐ Ja
- ☐ Nee

4b. U deed uw werk of andere bezigheden niet zo **zorgvuldig** als gewoonlijk
- ☐ Ja
- ☐ Nee

5. In welke mate bent u de afgelopen 4 weken door pijn gehinderd bij uw normale werk (zowel werk buitenshuis als huishoudelijk werk)?
- ☐ Helemaal niet
- ☐ Een klein beetje
- ☐ Nogal
- ☐ Veel
- ☐ Heel erg veel

6. Deze vragen gaan hoe u zich voelt en hoe het met u ging in de afgelopen 4 weken. Wilt u a.u.b. bij elke vraag het antwoord geven dat het best benadert hoe u zich voelde? Hoe vaak gedurende de afgelopen 4 weken

6a. Voelde u zich rustig en tevreden?
- ☐ Altijd
- ☐ Meestal
- ☐ Vaak
- ☐ Soms
- ☐ Zelden
- ☐ Nooit

6b. Had u veel energie?
- ☐ Voortdurend
- ☐ Meestal
- ☐ Vaak
- ☐ Soms
- ☐ Zelden
- ☐ Nooit

6c. Voelde u zich somber en neerslachtig?
- ☐ Voortdurend
- ☐ Meestal
- ☐ Vaak
- ☐ Soms
- ☐ Zelden
- ☐ Nooit

7. Hoe vaak hebben uw lichamelijke gezondheid of emotionele problemen u gedurende de afgelopen 4 weken gehinderd bij uw sociale activiteiten (zoals vrienden of familie bezoeken, etc)?
- ☐ Voortdurend
- ☐ Meestal
- ☐ Vaak
- ☐ Soms
- ☐ Zelden
- ☐ Nooit

14.2 Hospital Depression and Anxiety Scales

HADS

Vragen over uw stemming

De volgende vragen dienen als hulpmiddel om te weten hoe u zich voelt. Wilt u met een kruisje aangegeven welk antwoord het beste weergeeft hoe u zich de afgelopen week gevoeld heeft?

1. Ik voel me gespannen:

   ☐ Meestal

   ☐ Vaak

   ☐ Af en toe, soms

   ☐ Helemaal niet

2. Ik geniet nog steeds van de dingen waar ik vroeger van genoot:

   ☐ Zeker zo veel
   ☐ Niet zoveel als vroeger
   ☐ Weinig
   ☐ Haast helemaal niet

3. Ik krijg een soort angstgevoel alsof er elk moment iets vreselijks zal gebeuren:

   ☐ Heel zeker en vrij erg
   ☐ Ja, maar niet zo erg
   ☐ Een beetje, maar ik maak me er geen zorgen over
   ☐ Helemaal niet

4. Ik kan lachen en de dingen van de vrolijke kant zien:

   ☐ Net zoveel als vroeger
   ☐ Niet zo goed als vroeger
   ☐ Beslist niet zoveel als vroeger
   ☐ Helemaal niet

5. Ik maak me ongerust:

   ☐ Heel erg vaak
   ☐ Vaak
   ☐ Af en toe maar niet te vaak
   ☐ Alleen soms

6. Ik voel me opgewekt:

   ☐ Helemaal niet
   ☐ Niet vaak
   ☐ Soms
   ☐ Meestal

7. Ik kan rustig zitten en ontspannen:

   - ☐ Zeker
   - ☐ Meestal
   - ☐ Niet vaak
   - ☐ Helemaal niet

8. Ik voel me alsof alles moeizamer gaat:

   - ☐ Bijna altijd
   - ☐ Heel vaak
   - ☐ Soms
   - ☐ Helemaal niet

9. Ik krijg een soort benauwd, gespannen gevoel in mijn maag:

   - ☐ Helemaal niet
   - ☐ Soms
   - ☐ Vrij vaak
   - ☐ Heel vaak

10. Ik heb geen interesse meer in mijn uiterlijk:

    - ☐ Zeker
    - ☐ Niet meer zoveel als ik zou moeten
    - ☐ Waarschijnlijk niet zoveel
    - ☐ Evenveel interesse als vroeger

11. Ik voel me rusteloos en voel dat ik iets te doen moet hebben:

    - ☐ Heel erg
    - ☐ Tamelijk veel
    - ☐ Niet erg veel
    - ☐ Helemaal niet

12. Ik verheug me van te voren al op dingen:

    - ☐ Net zoveel als vroeger
    - ☐ Een beetje minder dan vroeger
    - ☐ Zeker minder dan vroeger
    - ☐ Bijna nooit

13. Ik krijg plotseling gevoelens van panische angst:

    - ☐ Zeer vaak
    - ☐ Tamelijk vaak
    - ☐ Niet erg vaak
    - ☐ Helemaal niet

14. Ik kan van een goed boek genieten, of van een radio- of televisieprogramma:

    - ☐ Vaak
    - ☐ Soms
    - ☐ Niet vaak
    - ☐ Heel zelden

14.3 Checklist Individuele Spankracht

CIS

Checklist Individuele Spankracht

Instructie:

Op de volgende pagina staan 20 uitspraken. Met behulp van deze uitspraken willen wij een indruk krijgen van hoe u zich de laatste twee weken heeft gevoeld. Er staat bijvoorbeeld de uitspraak:

Ik voel me ontspannen

Wanneer u vindt dat het helemaal klopt dat u zich de laatste twee weken ontspannen heeft gevoeld, plaatst u een kruisje in het linker hokje; dus zo

Ik voel me ontspannen

Wanneer u vindt dat het helemaal niet klopt dat u zich de laatste twee weken ontspannen heeft gevoeld, plaatst u een kruisje in het rechter hokje, dus zo:

ja, dat klopt								nee, dat klopt niet
	X							

Ik voel me ontspannen

Wanneer u vindt dat het antwoord niet "ja, dat klopt", maar ook niet "nee, dat klopt niet" is, zet dan een kruisje in het hokje dat het meest overeenkomt met uw gevoel.

ja, dat klopt								nee, dat klopt niet
							X	

Bijvoorbeeld als u zich wel wat ontspannen voelt, maar niet zo erg ontspannen, kunt u het kruisje in een van de hokjes zetten die in de buurt staan van de antwoordmogelijkheid "ja, dat klopt". Dus bijvoorbeeld als volgt:

Ik voel me ontspannen

Sla geen uitspraak over en plaats telkens één kruisje bij iedere uitspraak.

ja, dat klopt								nee, dat klopt niet
			X					

1. Ik voel me moe	Ja, dat klopt								Nee, dat klopt niet
2. Ik zit vol activiteit	Ja, dat klopt								Nee, dat klopt niet
3. Nadenken kost me moeite	Ja, dat klopt								Nee, dat klopt niet
4. Lichamelijk voel ik me uitgeput	Ja, dat klopt								Nee, dat klopt niet
5. Ik heb zin om allerlei leuke dingen te gaan doen	Ja, dat klopt								Nee, dat klopt niet
6. Ik voel me fit	Ja, dat klopt								Nee, dat klopt niet
7. Ik ben lichamelijk erg actief	Ja, dat klopt								Nee, dat klopt niet
8. Als ik ergens mee bezig ben, kan ik mijn gedachten er goed bijhouden	Ja, dat klopt								Nee, dat klopt niet
9. Ik voel me slap	Ja, dat klopt								Nee, dat klopt niet
10. Ik ben lichamelijk weinig actief	Ja, dat klopt								Nee, dat klopt niet
11. Ik kan me goed concentreren	Ja, dat klopt								Nee, dat klopt niet
12. Ik voel me uitgerust	Ja, dat klopt								Nee, dat klopt niet
13. Het kost me moeite ergens mijn aandacht bij te houden	Ja, dat klopt								Nee, dat klopt niet
14. Lichamelijk voel ik me in een slechte conditie	Ja, dat klopt								Nee, dat klopt niet
15. Ik zit vol plannen	Ja, dat klopt								Nee, dat klopt niet
16. Ik ben gauw moe	Ja, dat klopt								Nee, dat klopt niet
17. Mijn lichamelijk activiteitenniveau ligt laag	Ja, dat klopt								Nee, dat klopt niet
18. De zin om dingen te ondernemen ontbreekt mij	Ja, dat klopt								Nee, dat klopt niet
19. Mijn gedachten dwalen gemakkelijk af	Ja, dat klopt								Nee, dat klopt niet
20. Lichamelijk voel ik me in een uitstekende conditie	Ja, dat klopt								Nee, dat klopt niet