Pedersen MF (2003). VONOD Vocal Nodules project. A multicentre 2x2 factorial designed observer blinded randomised clinical trial (vocal nodules (VONOD)). *Approved by The Research Committee.*

Forskningsstyrelsen
Ministeriet for Videnskab Teknologi og Udvikling

Danish Research Agency
Ministry of Science Technology and Innovation

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26. november 2003

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The Research Committee has reviewed your application of 29th September 2003 in support of your project:

A multicentre 2x2 factorial designed observer blinded randomised clinical trial (vocal nodules (VONOD)).

The committee regrets to inform you that the request could not be met.

The Research Committee regrets that the request could not be met, the Committee finds that the project is **worthy of support** due to following criteria:

- The quality and originality of the project, comprising its scientific and societal perspectives.
- The projects' problem formulation, theoretical application and the suggested methods appropriateness.
- The projects' feasibility (timetable, work location, access to scientific guidelines and facilities etc.)
- The applicant'/applicants' scientific qualifications.
- The project's ethical aspects.

The Committee's funds are too limited to accommodate all the qualified applications. SSVS can only finance 14% of the requested means. In this situation the Committee regrets to inform you that other applications have a higher priority.

Best regards

Signature

Mette Pedersen
Administrative officer

The decision is made according to § 4 b, section 1, No 1 and section 2 in Law of Research Counselling etc (Law No 120 of 4 March 1996 as altered by Law No 390 of 10 June 1997).

Complaints about judicial matter in relation to this decision can cf. the Law § 4 m be filed to the Minister for Science, Technology and Innovation.

The government Research Councils' professional decision cannot be presented to other administrative authorities.

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Forskningsrådet har behandlet Deres ansøgning af 29. september 2003 om støtte til projektet:

Et multicenter 2x2 faktorielt designet observatør blindet randomiseret klinik forsøg (vocal nodules (VONOD)).

Rådet beklager at måtte meddele, at ansøgningen ikke har kunnet imødekommes.

Forskningsrådet har beklageligvis ikke kunnet imødekomme ansøgningen, selvom rådet ud fra følgende kriterier finder det beskrevne projekt **støtteværdigt**:

- Forskningens kvalitet og originalitet, herunder dens videnskabelige og samfundsmæssige perspektiver.
- Projektets problemformulering, teoridannelse og de foreslåede metoders egnethed.
- Projektets gennemførlighed (tidsplan, arbejdssted, adgang til videnskabelig vejledning og faciliteter i øvrigt).
- Ansøgerens/ansøgernes videnskabelige kvalifikationer.
- Projektets etiske aspekter.

Rådets midler er ikke tilstrækkelige til, at rådet kan imødekomme alle kvalificerede ansøgninger. SSVF har ved denne uddeling kun haft midler, der svarer til ca. 14% af de ansøgte midler. I denne situation har rådet vurderet, at Deres ansøgning ikke har kunnet opnå en tilstrækkelig høj prioritering til, at den har kunnet imødekommes.

Med venlig hilsen

Mette Pedersen
Kontorfuldmægtig

Afgørelsen er truffet i henhold til § 4 b, stk. 1, nr. 1 og stk. 2 i lov om forskningsrådgivning m.v. (lov nr. 120 af 4. marts 1996 som ændret ved lov nr. 390 af 10. juni 1997).

Klager over retlige spørgsmål i forbindelse med denne afgørelse kan jf. lovens § 4 m indgives til Videnskabsministeren.

De statslige forskningsråds faglige afgørelser kan ikke indbringes for anden administrativ myndighed.

Statens
Sundhedsvidenskabelige
Forskningsråd

Forskningsstyrelsen

A multi -centre 2x2 factorial designed observer -blinded, randomised clinical trial (vocal nodules (VONOD))

Purpose of the project

Vocal nodules are of the most frequent causes to chronic dysphonia (hoarseness).
The illness is estimated to affect 5000 perso ns in Denmark annually. Vocal nodules can result in considerable reduction of life quality. Within some professions the illness can result in loss of working capacity. Despite research during the years, the most optimal treatment is still controversial through out the world. There is being advocated for treatment of possible underlying medical diseases, logopedic techniques (speech therapy), surgical removal of the nodules, or a combining of the two. The pros and cons of these treatments have never been sys tematically tested in randomised clinical trials. We are yet to discover for certain which treatment or combining are the most effective.

The VONOD group finds it to be of greatest importance to examine the effect of the different treatment possibilities. It is necessary to complete a randomised clinical trial, in which the 4 most applied treatments are being tested and compared. A successful trial could make basis for future recommendations of which treatment to offer the patients. The purpose of VONOD tr ial is to establish whether the four treatments are different with regard to reducing the nodules and normalising the voice.

Background and status on current knowledge

To bring clarity over the current knowledge, the initiators of VONOD have conducted a C ochrane Review on the subject (1). In the review no randomised studies were found, but instead used 20 only observatory epidemiological studies (n = 2004). These studies evaluated the effect of treatment on vocal nodules. All studies were conducted without a control group. The 20 studies can roughly be divided into 3 main groups

- Microsurgery without logopedic treatment
- Logopedic treatment without surgery
- Logopedic treatment combined though the with microsurgery whenever estimated as indicated, indications were vague.

Due to the way the studies were designed, the effect of the treatments cannot be concluded on.
Sufficient follow -up is needed in most of the studies (15/20).
There has recently been conducted a randomised clinical trial on 204 patient s with dysphonia, 16% of them suffered from vocal nodules. The effect of 6 weeks logopedic treatment (speech therapy) vs. non logopedic treatment, were evaluated with 12 -14 weeks of follow -up. These trials did not show any significant difference with regar ds to the effect of the treatment (2).
Therefore no results from a well designed randomised trial has been published, which patients with vocal cord nodules are a part of, and in which the most applied treatments are being tested and compared. This is the trial that VONOD group wish to conduct.

VONOD trial

VONOD trial is an international, Danish initiated and conducted, medical science project. A cohort on approximately 2000 patients with symptomatic vocal cord nodules, undergo careful examination based on international recommendations. The patients are first offered medical treatment for three months. The treatment is customized to the individual based on the results of a series of trials. The patients who do not achieve contraction of symptoms and/or voca l cord nodules during the three

months period – estimated to be 700 patients – will in VONOD trial be offered a randomized selection of following treatments:

- Continuing medical treatment
- Speech therapy and continuing medical treatment
- Microsurgery to remov e the nodules and continuing medical treatment
- Combined speech therapy with microsurgery and medical treatment

Measuring procedure
The following procedures are international recognized means for measurement of vocal cord nodules, dysphonia, voice quality and quality of life. They will be referred to in abbreviated form in the text:

GRBAS overall severity score: Consensus Auditory Perceptual Evaluation of Voice
Video-stroboscopy: Laryngo -stroboscopy images
VHI: Voice Handicap Index
Quality of Life: Voice -related Quality of Life (V -RQOL)
Short Form 36 Quality of Life measure (SF 36)

Purpose of effect
Patients will after ended, randomized, treatment be observed for an additional six months period. Patients whom at that point have experienced reduction of vocal cord nodules and a normalization of the voice, will be considered cured (primary target of effect).

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The **primary target of effect** will be evaluated through use of digital images obtained from video stroboscopy, where the vocal cord nodules will be ca tegorized as: unchanged, decreased or cured. On top of that there is being recorded a digital tape of their sound for measurement of dysphonia GRBAS. Images and voice recordings are being evaluated by an external committee, blinded for the chosen charac ter of treatment.
There is also a series of **secondary targets of effect** which concern the patient's own evaluation of the treatments effect and life quality, the practitioner's evaluation of the patient's voice quality and job situation and finally possibl e side effects to the treatment are evaluated.

Patient material
An estimate of 2000 patients included in phase 1, are expected.

Inclusion criteria for phase 1 (for initial medical treatment and instruction on voice hygiene):

- Dysphonia according to the pa tient, meaning VHI Total Score > 10
- Vocal cord nodules diagnosed as a result of centralized blinded on laryngo -stroboscopical image of the vocal cords during phonation and respiration
- GRBAS Overall Severity Score >33% by a centralized blinded evaluation of a digital voice recording on at least 600 Kilobytes recorded on the terms provided by the GRBAS instructions
- Age ≥ 18 year
- Signed informed declaration of consent on participation in both phase 1 and phase 2.

Exclusion criteria for phase 1 (for initial me dical treatment and instruction on voice hygiene):

- Earlier surgical treatment of vocal cord nodules
- Neurological diseases including upper airways
- Malignant diseases in larynx

- Notable communication difficulties
- Notable difficulties participating in the tria l
- Professional user of the voice, demanding acute intervention
- Participation in clinical trials on vocal cord nodules within the last six months
- Lack of informed consent.

Patients suffering from dysphonia (VHI >10) and vocal cord nodules GRBAS Severity Score >33%) diagnosed with a new video -stroboscopy after the three months period will be offered randomization providing that they fulfil following inclusion criteria and none of the exclusion criteria

Inclusion criteria for phase 2:

- Dysphonia and reduced voice function for more than three months despite optimal medical treatment
- Vocal cord nodules diagnosed by a centralized blinded evaluation of a laryngo –strobosopical image of the vocal cords during phonation and respiration
- GRBAS Overall Severity Score >33% by a centralized blinded evaluation of a digital voice recording on at least 600 Kilobytes recorded on the terms provided by the GRBAS instructions
- Signed informed consent

Exclusion criteria for phase 2:

- Same as for phase 1 only including not "Par ticipation in clinical trials on vocal cord nodules within the last six months"

Clinical centres

29 clinical centres from Europe are expected to participate in the trial. A list of possible centres is not attached (appendix to be required). Every centre i s expected to include approx. 70 patients a month – or 3-4 patients a month during the inclusion period.

Research plan

Inclusion of 2000 patients for phase 1 of which 700 patients will continue to phase 2

Follow up on the last patients.

Data processi ng and assembling

Hypothesis

Zero-hypothesis is, there will be no difference between treatments (Speech therapy and/or microsurgery) on the vocal cord nodules (evaluated with video -stroboscopy) and the voice quality (measured with GRBAS Overall Severity S core).

Statistical calculations
It is expected that an estimate of 60% will respond positively on medical treatment and advice on voice hygiene after phase 1 (no vocal cord nodules and/or GRBAS Overall Severity Score <34%). A minimum of 1630 patients m ust be included in the VONOD trial phase 1. Earlier trial shows that the offered treatment in phase 1 can expect a drop -out on 20%, therefore a minimum of 2000 patients must be included in phase 1 to reach a basis on 700 patients for phase 2: Based on foll owing assumption: a minimal difference between the four intervention groups on 20% and an expected recovery rate (no vocal cord nodules and no GRBAS Overall Severity Score >33%) on 20% with patients in the continued randomised treatment in one of the four intervention groups, a type I error on 1% and a type II error on 10% (power 90%) at least 163 patients must be included in each intervention group. There are being calculated with a 10% dropout during test period, therefore a minimum of 700 patients must be randomised.

Randomization
This multi -centre 2x2 factor designed, observatory -blinded, randomized clinical trial establishes the effect of speech therapy and/or microsurgery. The included patients from each participating centre will be stratified accord ing to centre and duration of symptoms (less than six months; equals or more than six months) and random distribution to one of the four intervention groups. Copenhagen Trial Unit will conduct the randomization.

Ethical considerations
Patients in the tria l will be randomized after an oral and written informed consent.
At current point in time there is no knowledge on which treatment is the most effective in curing vocal cord nodules and dysphonia. There is no data suggesting that medical and microsurgery interacts. The VONOD group judges that the unethical part consists in offering continuing different treatments to patients where the actual effect is unknown.
The participating centres will within 24 hours report serious incidents to Copenhagen Trial Unit, which will forward the report to the Independent Safety and Data committee. The committee will following evaluate these incidents.
If a significant difference between the treatments ($p < 0,001$) occurs in one of the four groups during the trial, an independ ent Data Monitoring and Safety committee will stop the trial (or a certain group of the trial) before all patients are included. Therefore it is evaluated that the trial can be conducted without any ethical issues.

The trials feasibility and economy
The V ONOD group consists of a series of leading international scientists. We can therefore with certainty assure that the VONOD trial will be carried out according to the best techniques on all areas. The VONOD trial is designed after a thorough international c ooperation. The coordination and randomization in VONOD will be conducted by Copenhagen Trial Unit, Centre for Clinical intervention research, H:S University Hospital of Copenhagen.

The VONOD trial is developed with the effort of the, volunteer, M Pedersen together with the Copenhagen Hospital Corporations' investment in Copenhagen Trial Unit at the Copenhagen University Hospital. The fact that the VONOD trial is conducted as a joint collaboration on international research will have great significance and assertiveness on an international level. The results will be achieved faster not only in the trial but in clinical practice later on as well.
There exist no sufficient public funds to carry out a project of the character and extend of VONOD.

Therefore we apply private and public funds for coverage of the expenses for the project.
The economy of VONOD will be managed on public accounts by H:S University Hospital of Copenhagen which are subordinated the public revision (Copenhagen Hospital Corporation and t he National Audit Office).

References

1. Pedersen M, McGlashan J. Surgical versus non -surgical intervention for vocal cord nodules (Cochrane Review). The Cochrane Library, Issue 2, 2001.

   Pedersen M, McGlashan J, Surgical versus non -surgical intervention for vocal cord nodules (Updated Cochrane Review). 2003 (posted)

2. MacKenzie K, Millar A, Wilson J, Sellars C, Deary IJ. Is voice therapy an effective treatment for dysphonia. A randomised controlled trial. BMJ 2001; 323: 658 -61.