# Protocol

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| Project Name | Chinese：口腔舌咽肌肉功能訓練介入達文西手術後之阻塞性睡眠呼吸中止症患者之成效<br>English：Efficacy of oropharyngeal myofunctional therapeutic training for obstructive sleep apnea patients after transoral robotic surgery<br>NCT number: NCT04876482 |
| Project Director | Lin Cheng-Yu |
| Research Period | Approval Date of Human Research Ethics to December 31, 2022 |
| Collaborating Institutions | ENT and Sleep Medicine Center, National Cheng Kung University Hospital |
| Project Description | **Abstract:**<br>Obstructive sleep apnea syndrome (OSA) is caused by the complete or partial obstruction of the upper airway, leading to repeated episodes of apnea or hypoventilation during sleep, accompanied by uncoordinated chest and abdominal movements, excessive intrathoracic negative pressure, intermittent hypoxia, and decreased blood oxygen levels, potentially even sudden death. This condition is common among the middle-aged population, though its prevalence is often underestimated due to underdiagnosis. In Taiwan, the prevalence among adult men is 4%, and among women, it is 2%. The progression of the disease involves both structural and non-structural predisposing factors, making clinical symptoms varied and complex. The intermittent hypoxia associated with OSA can lead to systemic oxidative stress and a series of oxidative reactions, making it a risk factor for cardiovascular disease, which explains why cardiovascular disease is the most prevalent comorbidity in the OSA population. Other studies have found a strong correlation between daytime sleepiness and emotional states in OSA patients. Previous generational studies using drug-induced sleep endoscopy have shown that the upper airway of OSA patients is more prone to collapse during the sleep cycle, with 81% of collapses occurring behind the soft palate, 46.6% behind the tongue base, and 38.7% in the hypopharynx. In normal individuals, the driving ability of the respiratory center weakens during the sleep cycle, leading to a narrowing of the upper airway. However, OSA patients often experience insufficient muscle responsiveness of the pharyngeal |

dilators or issues with fat accumulation due to aging, particularly during the REM stage and in the supine position when muscle tone is at its lowest, making their upper airway more prone to collapse. Therefore, sleep cycles and sleep positions affect muscle tone and muscle responsiveness. Treatment options for OSA patients include sleep surgery, continuous positive airway pressure (CPAP), mandibular advancement devices, weight loss, and oropharyngeal muscle training.

**Aim:**

This project is an extension of Professor Hung Ching-Hsia's related project on the same topic from 2014 (original project approval certification number: A-ER-103-168) in the Department of Physical Therapy at National Cheng Kung University. Based on the 2014 research outcomes, this extension aims to integrate sleep surgery and multifocal interventions for neuromuscular re-education of the pharyngeal dilator muscles to explore the individuality and specificity of clinical symptoms in patients. Therefore, this study will be a controlled clinical trial.

**Controlled Clinical Trial:**

The study includes two aspects: clinical research and biomarker research, with the objectives outlined as follows (Figure 1):

**Clinical Research:**

According to clinical examination of upper airway collapse sites, multiple interventions, including surgery and neuromuscular re-education training of the pharyngeal dilator muscles, will be implemented. The treatment modalities include sleep surgery and orofacial myofunctional therapy, to investigate their clinical efficacy for OSA. Using G power analysis, with a power level set at 80% and an alpha level at 0.05, the effective sample size is estimated to be about 28 subjects per group. The planned number of subjects for the experiment is 35 per group. The experiment is divided into two groups: the experimental group and the control group. The experimental group includes (1) a post-upper airway surgery group undergoing 12 weeks of orofacial myofunctional therapy (n=35) and (2) an upper airway surgery group (n=35). The control group consists of patients undergoing self-directed weight loss, using CPAP, and waiting for mandibular advancement devices (n=35). Given that the fabrication of mandibular advancement devices takes approximately 3-4 months, relevant measurements will be taken during the waiting period. For patients attempting self-directed weight loss, the principal investigator will inquire in the clinic if they are willing to receive professional weight loss consultation. (1) If the patient is willing, they will be referred to Dr. Chang Chin-Sung's weight loss clinic in the Family Medicine Department. (2) If the patient is unwilling, they will receive self-directed weight loss education materials, and a follow-up appointment will be scheduled 6 weeks later in the ENT clinic to check the weight loss status. If weight

loss is unsatisfactory, research assistant (physical therapist Lai Yi-Ju) will arrange bi-weekly visits to measure weight and inquire about dietary status, providing food diaries, weight control diaries from the Family Medicine Department, and exercise diaries to ensure accurate recording and monitoring of weight loss. After 12 weeks, a follow-up appointment in the ENT clinic will confirm the weight loss status. All three groups will undergo pre- and post-intervention measurements and follow-up tests in a longitudinal study design to assess the effectiveness of functional training in physical therapy for post-surgical OSA patients.

**Objective 1:** Compare the different clinical outcomes between the two experimental groups to evaluate the clinical benefits of surgery combined with orofacial myofunctional therapy.
**Objective 2:** Based on drug-induced sleep endoscopy and CT scans, divide the experimental group into three subgroups: soft palate collapse, tongue base collapse, and hypopharyngeal collapse, and compare which subgroup shows the best clinical benefits from the exercise training.
**Objective 3:** According to sleep study reports, conduct a 2x2 factorial analysis of the experimental group based on sleep cycle (REM and non-REM) and sleep position (supine and non-supine) to compare which subgroup shows the best clinical benefits from the exercise training.

- **Biomarker Research:**

This study will measure biomarkers including 8-hydroxy-2-deoxyguanosine (8-OHdG), malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), nuclear factor kappa B (NF-κB), tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and matrix metalloproteinase 9 (MMP-9). Previous literature indicates that the repetitive ischemia and reperfusion injuries associated with OSA lead to excessive production of reactive oxygen species (ROS), oxidative stress substances (such as 8-OHdG and MDA), and inflammatory precursors (such as TNF-α and IL-6), which damage antioxidant capabilities. Oxidative stress substances can increase ROS levels, which activate NF-κB, a transcription factor that stimulates the production of inflammatory precursors and regulates the transcription of MMPs. The activation of TNF-α, IL-6, and MMP-9 can impair endothelial cell function, potentially leading to cardiovascular disease. Research has shown significant increases in serum levels of 8-OHdG, MDA, NF-κB, TNF-α, IL-6, and MMP-9 in OSA patients, while antioxidant stress substances (SOD and CAT) show significant decreases. MDA, NF-κB, and MMP-9 levels are highly positively correlated with the duration of nocturnal oxygen saturation below 85%, and negatively correlated with the average blood oxygen saturation. Additionally, MMP-9 levels are positively correlated with plasma IL-6 and TNF-α levels. This study aims to understand the correlation between the severity of OSA and cardiovascular disease risk factors and to explore whether surgical and

exercise interventions improve these risk factors.

Objective 4: Investigate the correlation between the severity of OSA and cardiovascular disease risk factors.
Objective 5: Examine whether exercise intervention improves cardiovascular disease risk factors and mental state.

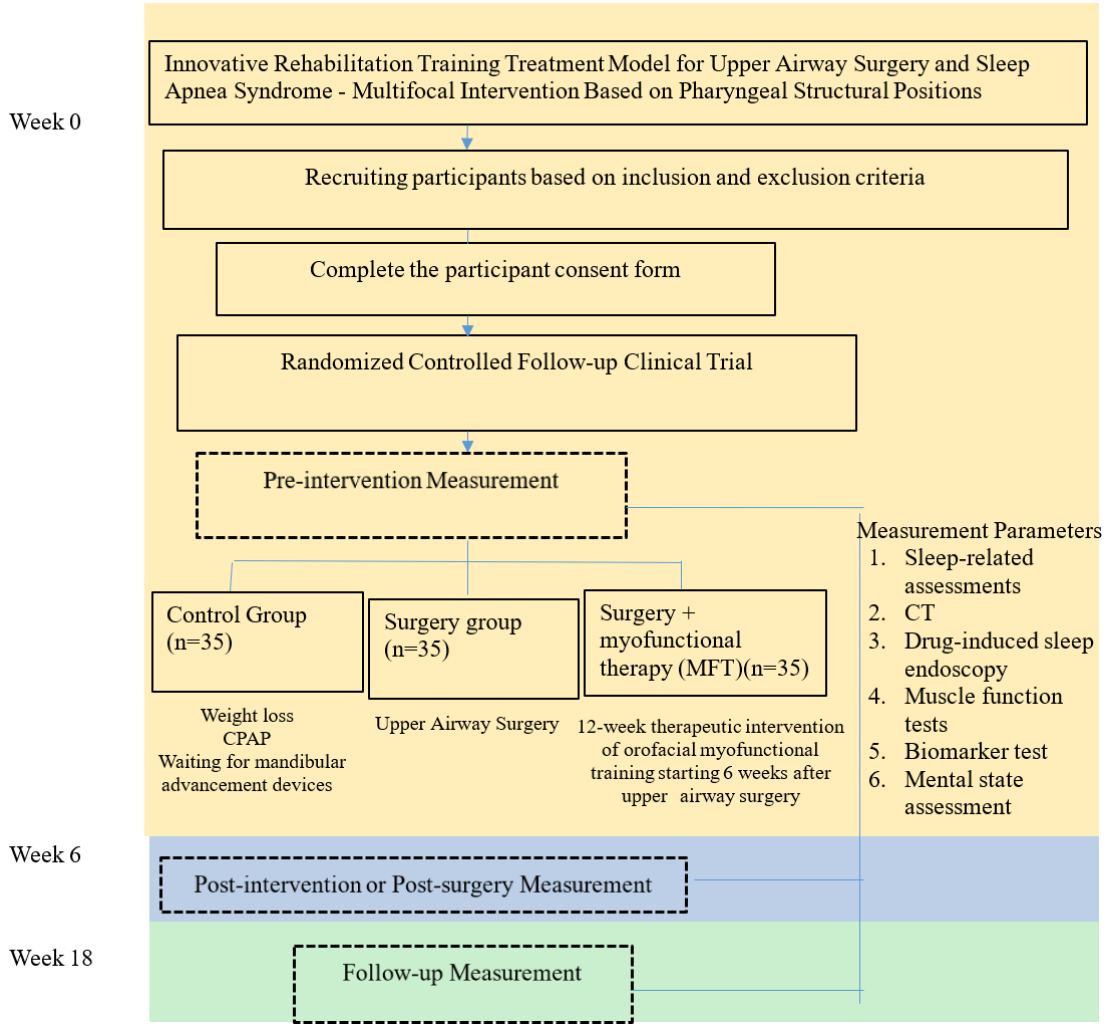



**Figure 1. Experimental Flow Diagram**

Experimental Equipment: Figure 2, Table 1

A) Primary Outcome Measurements:

- Sleep-related assessments:

i. PSG (Polysomnography) including sleep quality questionnaires: ESS (Epworth Sleepiness Scale), PSQI (Pittsburgh Sleep Quality Index)

ii. Drug-induced sleep endoscope examination (DISE)

- Computed Tomography (CT)

B) Secondary Outcome Measurements:

- Respiratory-related muscle function tests:

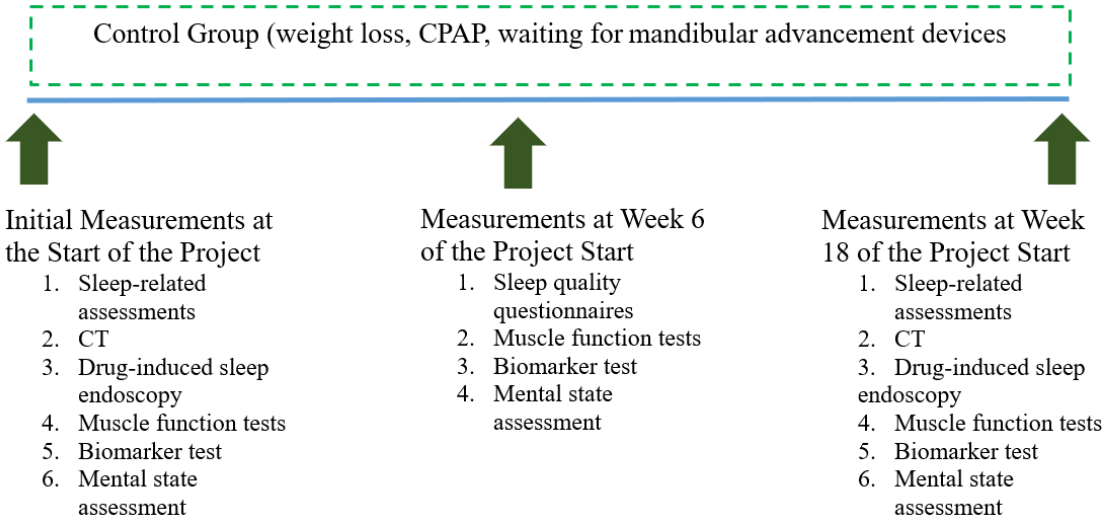
i. Tongue muscle (Genioglossus): Iowa Oral Performance Instrument (Medical LLC, Carnation, WA)

ii. Masticatory muscle function: Dynamometer

- Mental state assessment: Using the Hospital Anxiety and Depression Scale (HADS) to understand the participant's mood status over the past week.

The Hospital Anxiety and Depression Scale (HADS), developed by Zigmond and Snaith (1983) for outpatient patients with physical illnesses, is a tool for measuring anxiety and depression in patients with physical diseases. The scale has been translated into multiple languages and widely used in clinical and research settings (Quintana et al., 2003). The HADS consists of 14 items: 7 items for anxiety (HAD-A) and 7 items for depression (HAD-D). Each item is scored on a four-point scale (0-3), with separate scores for each subscale. Each subscale has a total score of 21, with higher scores indicating higher levels of anxiety or depression. Scores of 0-7 are considered normal, 8-10 indicate mild, 11-14 indicate moderate, and 15-21 indicate severe anxiety or depression. For each subscale, scores of 0-7 indicate no anxiety or depression, 8-10 indicate mild anxiety or depression, and scores of 11 or more indicate the presence of anxiety or depression (Zigmond & Snaith, 1983).

- Molecular biology tests: Analyzing biomarkers in patient serum and cell experiments, including Flow Cytometry, Western Blot, and Enzyme-Linked Immunosorbent Assay (ELISA).



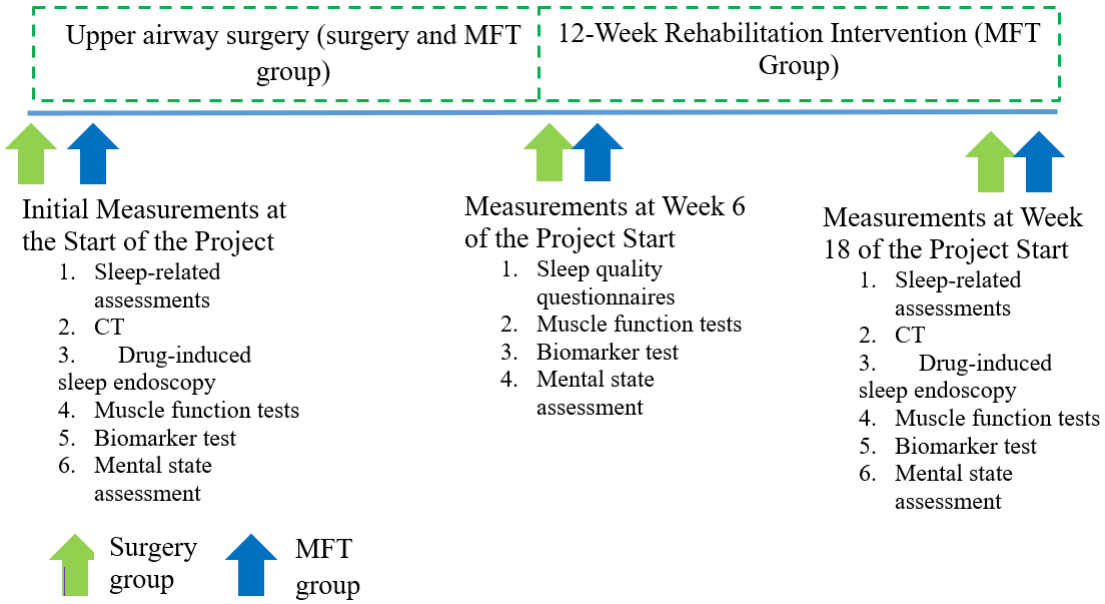



**Figure 2. Sampling Procedure Description**

**Table 1. Detailed Sampling Description**

| MFT: Y/Surgery: Z/Control: O | Week 0 | Week 6 | Week 18 |
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| **Basic Data Collection** | | | |
| Age, Gender, and Volumetric Parameters | Y/Z/O | Y/Z/O | Y/Z/O |
| **Confounding Variables** | | | |
| Medical History Record | Y/Z/O | Y/Z/O | Y/Z/O |
| Medication Record | Y/Z/O | Y/Z/O | Y/Z/O |
| Craniofacial Abnormality Examination Record | Y/Z/O | Y/Z/O | Y/Z/O |
| Sleep Clinical Symptoms Record | Y/Z/O | Y/Z/O | Y/Z/O |
| **CT** | Y/Z/O | | Y/Z/O |
| **Sleep-related Assessments** | | | |
| Polysomnography | Y/Z/O | | Y/Z/O |
| Drug-induced sleep endoscopy | Y/Z/O | | Y/Z/O |
| **Mental state assessment** | | | |
| HADS | Y/Z/O | Y/Z/O | Y/Z/O |
| **Muscle function tests** | | | |
| Tongue | Y/Z/O | Y/Z/O | Y/Z/O |
| Pharyngeal Lateral Wall Muscles | Y/Z/O | Y/Z/O | Y/Z/O |
| Masticatory Muscles | Y/Z/O | Y/Z/O | Y/Z/O |
| Others | Y/Z/O | Y/Z/O | Y/Z/O |
| **Biomarker test** | Y/Z/O | Y/Z/O | Y/Z/O |

## Experimental Procedures and Methods:

### (1) Assessment Process:

- **Experimental Procedures and Testing Items:** The experimental steps primarily

follow standard clinical procedures, detailed as follows:

i. Screening through the sleep clinic to determine if further sleep-related assessments are needed (current clinical procedures).
ii. Establishing the diagnosis of obstructive sleep apnea syndrome through sleep examinations (current clinical procedures, requiring overnight sleep studies at a sleep center).
iii. Participants agree to self-weight management, use CPAP, await the fabrication of an anti-snoring dental appliance, or undergo sleep surgery.
iv. Recruiting clinical participants based on inclusion and exclusion criteria, providing comprehensive study information, and informing participants of their right to withdraw from the study at any time. Participants will complete the consent form and will be orally introduced to the study grouping method during the clinic visit. Participants will choose their group based on personal preference and officially enter the clinical research study.
v. Using computed tomography (CT) and drug-induced sleep endoscope examination to understand the pre-surgical pharyngeal anatomy.
vi. Performing tongue muscle function tests, recording the results to understand pre-intervention functional indicators (approximately half an hour).
vii. Conducting biomarker tests to understand pre-intervention biomarker indicators.
viii. As detailed in Table 1, measurement parameters include sleep-related assessments, mental state assessments, drug-induced sleep endoscope examination, CT scans, respiratory-related muscle function tests, and biomarker tests. Pre- and post-surgical measurements, as well as follow-up measurements, will be conducted and repeated.

- **Assessment Location:** NCKU Hospital Physical Therapy Center

(2) **Research Procedures and Participant Cooperation:**

Collect basic participant information (body mass index, body fat, etc.), followed by muscle function tests (muscle strength parameters, posture assessment) conducted by a physical therapist. The treatment plan includes 12 weeks of post-surgical or post-intervention orofacial myofunctional training, with pre- and post-surgical measurements and follow-up tests (Figure 2). Measurement items include drug-induced sleep endoscope examination and CT scans performed by a sleep specialist, sleep assessments conducted by a sleep technologist, tongue muscle function tests performed by a professional physical therapist, and blood collection by a professional nurse. Blood samples (20 cc each) will be collected at Week 0, Week 6 after the start of the project or post-surgery, and Week 18 after the start of the project

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| | or post-surgery, totaling three blood collections.<br><br>Expected Results:<br>For obstructive sleep apnea syndrome (OSA), this study proposes invasive upper airway surgery and non-invasive rehabilitation training. The invasive surgery targets common upper airway collapse sites based on the pathological development mechanisms of the condition, and post-surgery intervention involves muscle re-education for pharyngeal dilators through exercise therapy. This approach is expected to improve clinical symptoms of sleep apnea. Currently, sleep clinics provide home-based education by specialized nurses, but lack professional physical therapists for exercise training. This study aims to monitor and confirm the accuracy and effectiveness of exercise training through continuous and regular therapy. Additionally, the study will investigate the correlation between biomarkers and clinical symptoms, and the relationship between OSA severity and cardiovascular disease risk factors. The experimental design as a controlled study represents a significant milestone in the development of interdisciplinary teamwork and will serve as an important guideline for future clinical practice.<br><br>**Statistical analysis:**<br>Continuous variables are presented as mean and standard deviation (SD), whereas categorical variable is presented as numbers and percentages. Kolmogorov-Smirnov test was used to analyze the normal distribution of the variables. Due to the non-normal distribution, Kruskal–Wallis test and Fisher's exact test was used for continuous and categorical data to compare baseline characteristics among the study groups. Besides, the Wilcoxon signed-rank test was used to compare the pre- and post-differences in demographic characteristics, questionnaire, sleep parameters and the data of CT image. Linear regression model with generalized estimating equations (GEE) was used to estimate (1) the difference in differences and the corresponding 95% confidence intervals (CIs) of pre-treatment to post-treatment changes between the 3 groups and (2) multivariate adjusted effects of time in muscle strengths and biomarkers. The working correlation matrix was defined as unstructured. $P < .05$ was defined as statistically significant. All the statistical analyses were conducted by using SPSS 17.0. |

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| Participant Description | A) **Participant or Sample Description:**<br>• **Study Duration:** From the date of ethical approval until December 31, 2022.<br>• **Type of Participants (e.g., normal controls or patients with specific diseases):** Please specify: Diagnosed with obstructive sleep apnea syndrome (OSA).<br>• **Estimated Number of Participants or Samples:** 105; Age range: 20–65 years.<br>• **Are participants selected by gender?** □ Yes: □ Male □ Female ■ No<br>• **If there is a possibility of pregnancy among participants, does the study include pregnancy testing?** □ Yes ■ No<br>• **If participants are children or disabled individuals, please explain the need for such participants:**<br>• **Describe the relationship between the principal investigator and the participants:** □ Teacher/Student ■ Researcher/Participant □ Healthcare Provider/Patient □ Employer/Employee<br>□ Friend □ Other, please specify:<br>• **Describe the recruitment method for participants:** Participants will be recruited from the ENT and sleep clinics at Cheng Kung University Hospital. After diagnosis and evaluation, patients with obstructive sleep apnea syndrome who consent to weight loss, use of CPAP, waiting for anti-snoring appliance production, or undergoing sleep surgery will be approached by the principal investigator, co-investigators, and research team. They will be given detailed information about the research intervention, procedures, and risks, and will be asked to sign a consent form. This will be a controlled experiment.<br>B) **Main Inclusion and Exclusion Criteria:**<br>1. **Inclusion Criteria:**<br>o Age between 20 and 65 years.<br>o Diagnosed with mild to severe pure obstructive sleep apnea syndrome by PSG sleep study.<br>o Epworth Sleepiness Scale score ≧10.<br>o Agreement to weight loss, use CPAP, wait for anti-snoring appliance production, or undergo sleep surgery.<br>2. **Exclusion Criteria:**<br>o Smoking, alcohol, or drug abuse within the past year.<br>o Pregnancy.<br>o Severe obstructive or restrictive pulmonary disease.<br>o High-risk cardiovascular disease.<br>o History of central or peripheral neurological disorders that prevents participation in exercise prescriptions.<br>o Musculoskeletal or psychological disorders that prevent participation in |

exercise prescriptions.
    - Other non-respiratory sleep disorders.
    - Coexisting central or mixed sleep apnea disorders.

C) **Funding:** The study will be funded by internal grants covering one CT scan, two drug-induced sleep endoscopy examinations, and three blood sampling costs. Follow-up visits, outpatient consultations, and surgical costs will be borne by the patients.

D) **Methods for Ensuring Confidentiality of Participant or Sample Data:**

- **During the Study:** ■ Use codes instead of participant names □ Other, please specify:
- **After the Study:** ■ Research results and published articles will not include identifiable participant information □ Other, please specify:

# 臨床試驗計畫書簽名:

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| 計畫名稱 | 中文：口腔舌咽肌肉功能訓練介入達文西手術後之阻塞性睡眠呼吸中止症患者之成效<br>英文：Efficacy of oropharyngeal myofunctional therapeutic training for obstructive sleep apnea patients after transoral robotic surgery<br>NCT編號: NCT04876482 |
| 計畫主持人 | 林政佑 |
| 研究期間 | 人體研究倫理審查通過日至 111年12月31日 |
| 合作機構 | 成大醫院耳鼻喉科與睡眠醫學中心 |
| 計畫內容 | **計畫摘要：**<br>阻塞性睡眠呼吸中止症候群（Obstructive sleep apnea syndrome, OSA）乃因為上呼吸道完全或部分阻塞，而在睡眠過程反覆發生呼吸中止或換氣不足的現象，合併不協調的胸腹運動，過度的胸內負壓，間歇性缺氧以及血氧濃度下降，甚至猝死，為中年族群常見的疾病，盛行率卻因為沒有被診斷出來常被低估，在台灣成年人男性盛行率 4%，女性 2%。其病程發展同時具有結構性以及非結構性相關的前置因子(predisposing factors)，使得臨床症狀變得多變而複雜。OSA 間歇性的缺氧問題，會導致系統性的氧化壓力以及一連串的氧化反應，是心血管疾病的危險因子之一，這也解釋了為什麼心血管疾病是 OSA 族群中最高盛行率的共病症。另有研究發現 OSA 患者白天嗜睡狀況與情緒狀態有高度相關性。在過去世代研究中，根據藥物誘導式的睡眠內視鏡檢查發現，OSA 患者其上呼吸道於睡眠週期較容易發生坍陷的問題，發生坍陷的位置 81%為軟顎後方坍陷，46.6%為舌根後方坍陷，而 38.7%為下咽坍陷。正常人體的呼吸中樞的驅動能力在睡眠週期，會有減弱的現象，導致上呼吸道變窄，但是 OSA 患者常因為咽部擴張肌(pharyngeal dilators)肌肉活動反應不足(insufficient muscle responsiveness)或老化脂肪堆積的問題，尤其在肌肉張力活動最低的快速動眼時期以及仰躺的姿勢，使其上呼吸道會更容易發生坍陷的問題，所以睡眠週期以及睡眠姿勢會影響肌肉張力以及肌肉反應能力的表現。阻塞性睡眠呼吸中止症候群的患者，其治療方式包含睡眠外科手術、連續正壓呼吸輔助器(CPAP)、止鼾牙套、減重及口咽肌肉訓練。<br>**目的：** |

本計畫乃成大物理治療系洪菁霞教授 103 年相關主題計畫之延伸計畫（原計畫審查核准認證編號：A-ER-103-168），根據 103 年研究成果，此次延伸發展整合睡眠外科手術及多處介入咽部擴張肌的肌肉再教育之運動治療，探討臨床患者其症狀的個別性以及特異性。故而本研究將為對照臨床試驗。

**對照臨床試驗**

包含臨床研究以及生物標記研究兩個層面，其目的分述如下：（圖一）

- **臨床研究**

依臨床檢查上呼吸道癱陷位置多處介入手術及咽部擴張肌之肌肉再教育訓練（neuromuscular re-education training），治療模式為睡眠外科手術及口腔舌咽肌肉功能訓練（orofacial myofunctional therapy），探討其對於 OSA 的臨床成效。利用 G power 檢定估算，設定 power level 為 80%，α level 為 0.05，有效樣本數約為 28 名/組，經估算實驗預定收案人數為 35 名/組，實驗分成兩組實驗組和控制組，實驗組分別為上呼吸道手術後進行 12 週口腔舌咽肌肉功能訓練(運動)組(n=35)及上呼吸道手術組(n=35)，控制組為自行減重、使用 CPAP 及等待配戴止鼾牙套之患者(n=35)，因止鼾牙套製作時間約需 3-4 個月，將於患者等待期間進行相關測量，而自行減重患者，主持人於診間會詢問自行減重患者是否願意接受減重門診專業諮詢。(1)若患者願意，將轉介至家醫科張秦松醫師之減重門診治療；(2)若患者不願意，將於診間給予自行減重衛教單張，如附件，並於 6 周後安排回耳鼻喉科門診，以確認患者減重狀況，若減重情形不理想，將請研究助理(物理治療師賴奕儒)安排每 2 周回院一次，測量體重並詢問飲食狀況，且給予飲食日記、成大醫院家庭醫學部體重控制門診體重日記及運動日記，如附件，要求患者確實記錄，以監控減重情形。持續 12 周後，將再次安排回耳鼻喉科門診，確認患者減重狀況。三組皆會進行介入前後量測以及追蹤量測等重複測試的縱向研究設計，探討物理治療的功能性訓練對於手術後 OSA 病人的成效。

**目的（一）**比較兩組實驗組其不同臨床成效，檢視手術輔以口腔舌咽肌肉功能訓練的臨床效益。

**目的（二）**根據藥物誘導式的睡眠內視鏡檢查、電腦斷層掃描，將實驗組分為軟顎後方坍陷、舌根後方坍陷、以及下咽坍陷三組，比較運動訓練對於哪一組具有較好的臨床效益。

**目的（三）**根據睡眠檢查報告，將實驗組依照睡眠週期：快速動眼以及非快速動眼，以及睡眠姿勢：仰躺及非仰躺，進行 2*2 因素分析，比較運動訓練對於哪一組具有較好的臨床效益。

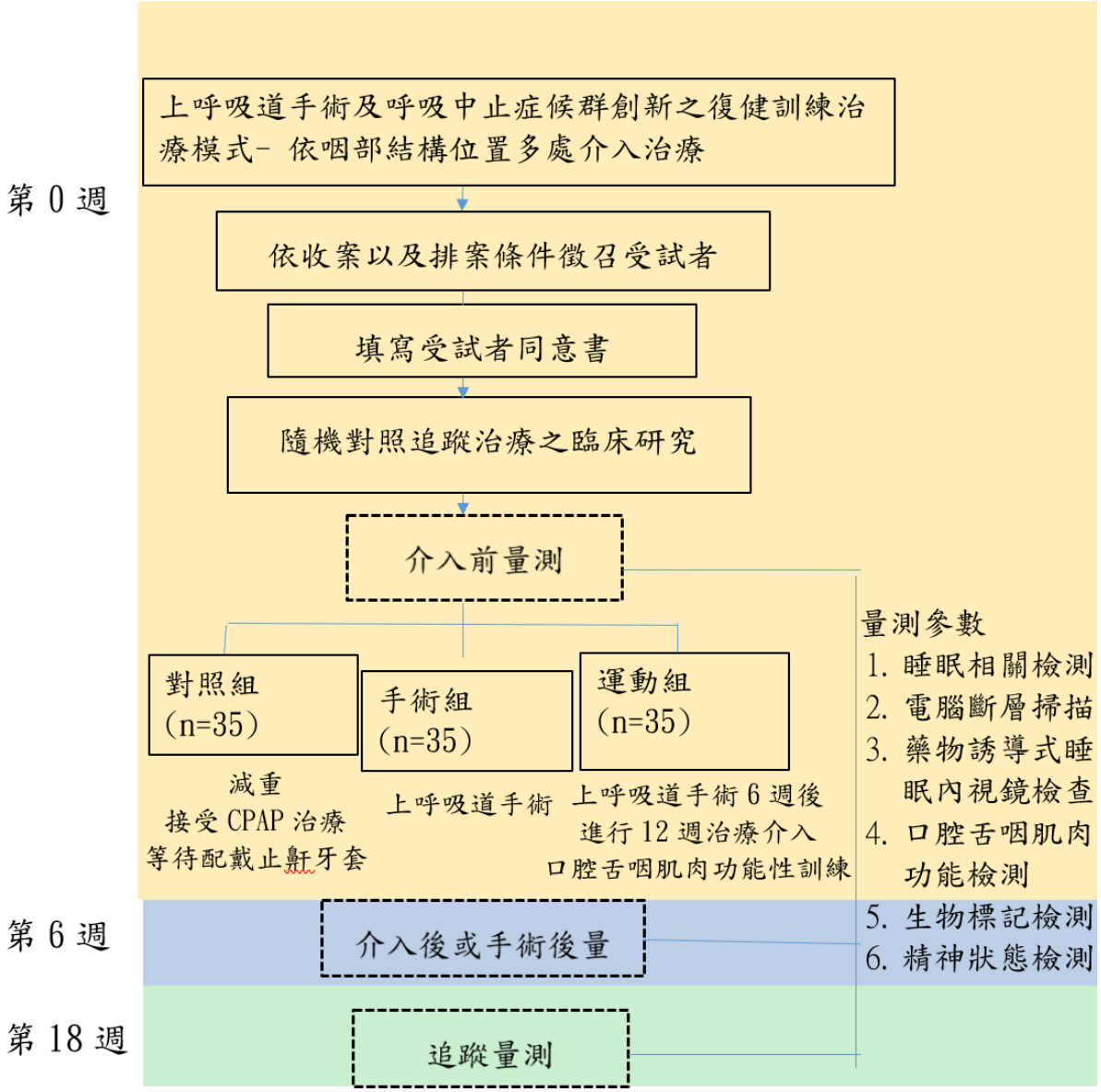
- **生物標記研究**

本研究將檢測之生物標記包含 8-羥基-2´-脫氧鳥苷(8-hydroxy-2-deoxyguanosine, 8-OHdG)、丙二醛(Malondialdehyde, MDA)、超氧化物歧化酶(superoxidase dismutase, SOD)、過氧化氫酶(catalase, CAT)、細胞核因子-κB(nuclear factor kappa B, NF-κB)、腫瘤壞死因子-α(tumor necrosis factor-α, TNF-α)、介白質 6(interleukin 6, IL-6)及基質金屬蛋白酶 9(Matrix metalloproteinases, MMP-9)。過去文獻顯示 OSA 產生的反覆性缺血及再灌流損傷，將造成活性氧化物(Reactive oxygen specie, ROS)、氧化壓力物質(如: 8-OHdG 及 MDA)及發炎前驅物質(如：TNF-α、IL-6) 過度產生，並損傷抗氧化能力。氧化壓力物質會造成 ROS 濃度上升，ROS 會活化 NF-κB，NF-κB 會刺激產生發炎前驅物質，並同時

調節 MMPs 的轉錄，TNF-α、IL-6 及 MMP9 的活化會造成內皮細胞失能，進而造成心血管疾病，已有研究發現阻塞性睡眠呼吸中止症患者血清中之 8-OHdG、MDA、NF-κB、TNF-α、IL-6 及 MMP-9 濃度有顯著性上升之情況，而抗氧化壓力物質(SOD 及 CAT)濃度有顯著性下降之情況，MDA、NF-κB 及 MMP-9 濃度與夜間氧氣飽和濃度低於 85%持續時間呈高度正相關性，而與平均血氧飽和濃度呈負相關性，另 MMP-9 又與血漿中 IL-6 和 TNF-α 呈正相關性。希望藉由此研究了解瞭解 OSA 嚴重程度與心血管疾病危險因子之相關性，並探討手術及運動介入是否改善心血管疾病發生的危險因子。

**目的（四）**探討 OSA 嚴重程度，與心血管疾病危險因子之相關性

**目的（五）**探討運動介入是否改善心血管疾病發生的危險因子及精神狀態




**圖（一）實驗流程圖**

**實驗設備：**圖（二）表（一）

A）主要結果量測（primary outcome）

- 睡眠相關檢查：

  i. PSG(polysomnography)包含睡眠品質相關問卷量表：ESS(Epworth Sleepiness Scale), PSQI(Pittsburgh Sleep Quality Index)

ii. 藥物誘導式睡眠內視鏡 Drug induced sleep endoscope examination (DISE)

- 電腦斷層掃描(Computed tomography, CT)

B) 次要結果量測 (secondary outcome)

- 呼吸相關肌肉功能性檢測

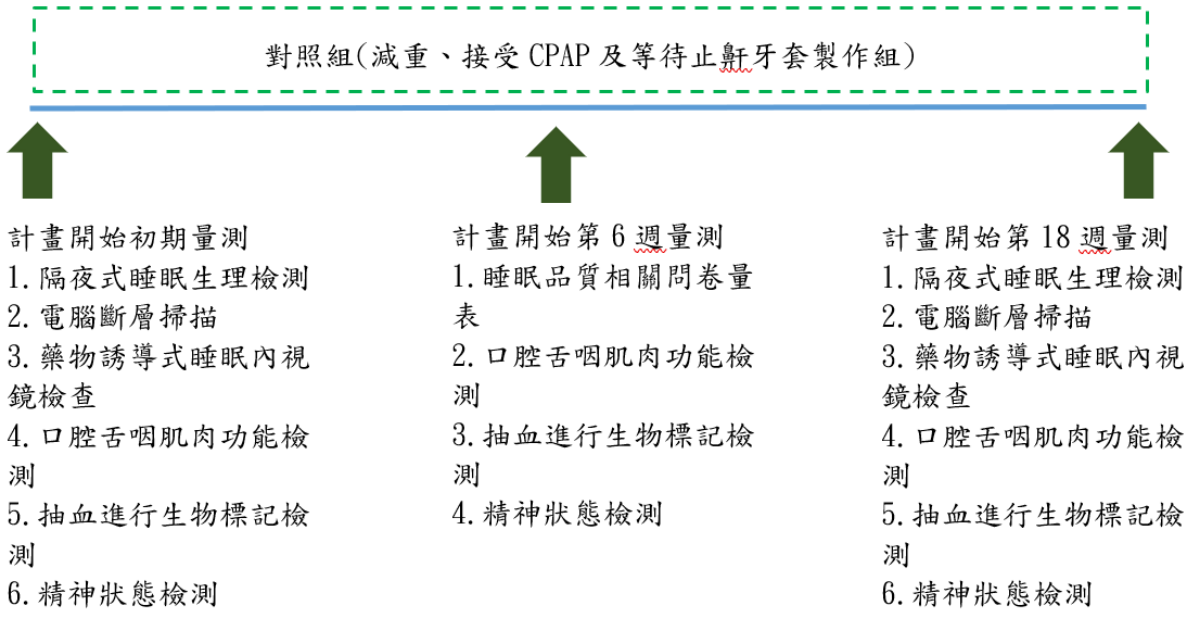
i. 舌肌(Genioglossus)：Iowa Oral Performance Instrument (Medical LLC, Carnation, WA)

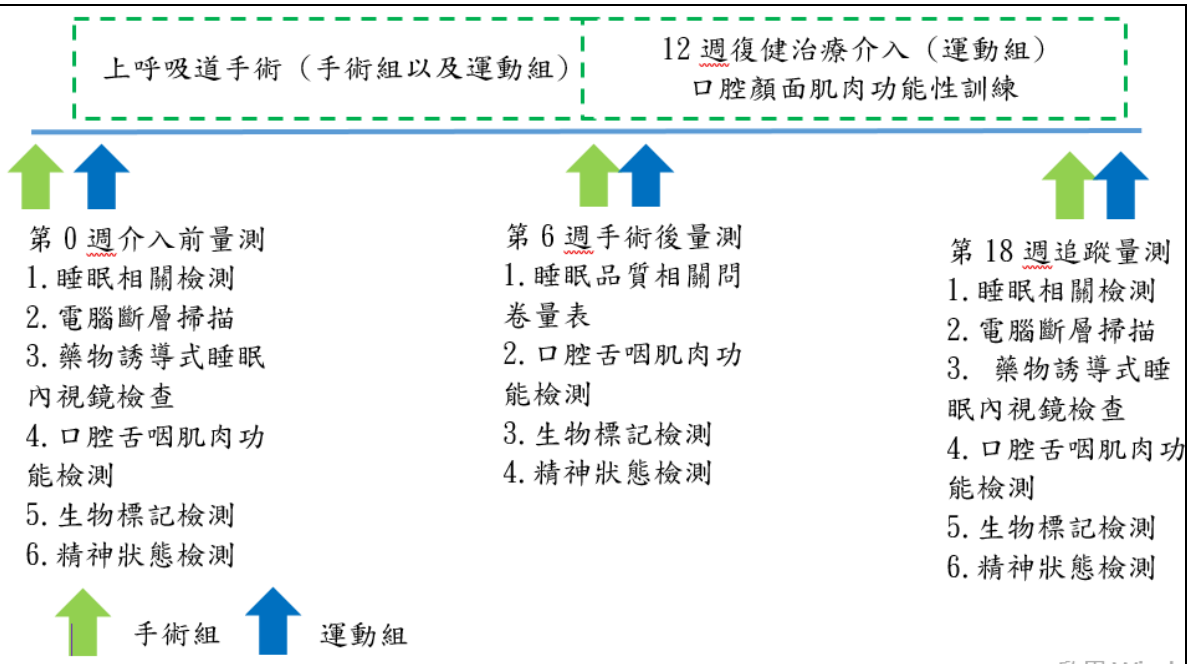
ii. 咀嚼相關肌群(Masticatory muscle function)：dynamometer

- 精神狀態檢測:利用醫院焦慮與憂鬱量表(HADS)了解受試者最近 1 周之心情狀況

醫院焦慮憂鬱量表(Hospital Anxiety and Depression Scale, HADS)，由 Zigmond 與 Snaith (1983) 針對醫院非精神疾病的門診病患，發展出合併焦慮與憂鬱疾病的身體疾病患者之測量工具。此量表被翻譯成多國語言，並廣泛運用於臨床與研究上(Quintana et al., 2003)。HADS 量表共有 14 題：包含 7 題測試焦慮 (HAD-A) 與 7 題測試憂鬱 (HAD-D)。每一題採四點計分法 (0-3 分)，兩個量表分別計分，各量表總分 21 分，分數越高，表焦慮或憂鬱程度越高；總分 0-7 分表示正常，8-10 分表示輕度，11-14 分表示中度，15-21 分表示嚴重；分量表總分 0-7 分表示無焦慮或憂鬱問題，8-10 分表示有輕度焦慮或憂鬱情況，各分量表總分≧11 分則為確定有焦慮與憂鬱之狀況 (Zigmond & Snaith, 1983)。

- 分子生物學檢查：利用病人血清與細胞實驗分析生物標記(biomarker) 包括：流式細胞儀(FLOW)、 西方墨點法(western blot) 、酵素免疫分析法(ELASA)等。






**圖（二）採樣流程說明**

**表（一）採樣細項說明**

| 運動組:Y/手術組 Z/對照組:0 | 第 0 週 | 第 6 週 | 第 18 週 |
|---|---|---|---|
| **基本資料收集** | | | |
| 年齡、性別、體積描記參數 | Y/Z/0 | Y/Z/0 | Y/Z/0 |
| **干擾變項** | | | |
| 病史記錄 | Y/Z/0 | Y/Z/0 | Y/Z/0 |
| 用藥記錄 | Y/Z/0 | Y/Z/0 | Y/Z/0 |
| 顱顏異常檢查記錄 | Y/Z/0 | Y/Z/0 | Y/Z/0 |
| 睡眠臨床症狀記錄 | Y/Z/0 | Y/Z/0 | Y/Z/0 |
| **電腦斷層掃描** | Y/Z/0 | | Y/Z/0 |
| **睡眠相關檢測** | | | |
| 睡眠檢查 | Y/Z/0 | | Y/Z/0 |
| 藥物誘導式的睡眠內視鏡檢查 | Y/Z/0 | | Y/Z/0 |
| **精神狀態檢測** | | | |
| 醫院焦慮與憂鬱量表 | Y/Z/0 | Y/Z/0 | Y/Z/0 |
| **呼吸相關肌肉功能檢查** | | | |
| 舌肌 | Y/Z/0 | Y/Z/0 | Y/Z/0 |
| 咽部外側壁肌群 | Y/Z/0 | Y/Z/0 | Y/Z/0 |
| 咀嚼相關肌群 | Y/Z/0 | Y/Z/0 | Y/Z/0 |
| 其他 | Y/Z/0 | Y/Z/0 | Y/Z/0 |
| **生物標記檢測** | Y/Z/0 | Y/Z/0 | Y/Z/0 |

**實驗流程及方法：**

(1) 評估流程：

- 實驗流程及檢測項目：

  實驗執行步驟多屬臨床處置標準流程，其細節如下說明：

  i. 透過睡眠門診篩檢是否需要進一步的睡眠相關檢測（現行臨床處置流程）
  ii. 透過睡眠檢查確立阻塞性呼吸中止症候群診斷（現行臨床處置流程，需要在睡眠中心進行過夜睡眠檢查）
  iii. 受試者同意自行減重、使用 CPAP 及等待止鼾牙套製作或進行睡眠外科手術
  iv. 依照收案以及排案條件徵收臨床受試者，提供完整詳細的研究說明，並告知受試者有權利隨時終止參與計畫，完成受試者同意書填寫，此外也會在門診時口頭介紹計畫分組方式，受試者將以自身意願決定進入之組別，正式進入臨床人體研究計畫。
  v. 透過電腦斷層掃描及藥物誘導式睡眠內視鏡檢查，瞭解手術前口咽部解剖結構
  vi. 透過舌肌肌肉檢測，紀錄檢測結果，瞭解受試者介入前功能指標（約需半個小時左右完成）
  vii. 透過生物標記檢測，瞭解受試者介入前生物標記指標
  viii. 如（表一）說明量測參數包含睡眠相關檢測、精神狀態檢測、藥物誘導式睡眠內視鏡檢查、電腦斷層掃描、呼吸相關肌肉功能性檢測以及生物標記檢測，並依進行手術前後量測以及追蹤量測等重複測試。

- 評估地點：成大醫院物理治療中心。

(2) 研究程序及受試者應配合事項：蒐集受試者的基本資料（身體質量指數、體脂肪）等，再由物理治療師施行實驗相關之肌肉功能性測試（肌力參數、姿勢評估）等等，治療計畫分別為手術及術後介入口腔舌咽肌肉功能訓練12週，並進行手術前後量測以及追蹤量測等重複測試（圖二）。其量測項目包含睡眠專科醫師進行藥物誘導式的睡眠內視鏡檢查及電腦斷層掃描，睡眠專科技師進行睡眠檢查，專業物理治療師進行舌肌肌肉功能檢查，以及專業護理人員血液採集，分別在第0週、計畫開始後或術後第6週和計畫開始後或術後第18週採血，一次採血20c.c，總共採血3次。

**預期結果：**

故此，針對阻塞性睡眠呼吸中止症候群，本研究所提出的侵入性上呼吸道手術及非侵入性復健訓練，依照該族群病理發展機轉及其常發生的上呼吸道癱陷位置進行侵入性上呼吸道手術，並於術後介入咽部擴張肌的肌肉再教育之運動治療，預期可以改善睡眠 OSA 的臨床症狀，目前睡眠門診乃由診間專科護士進行相關居家介入之衛教，缺乏專業物理治療師執行運動訓練實務，希望藉由連續性的定期療程，追蹤並確認病患執行運動訓練的正確性以及有效性。此外，本實驗將透過生物標記的研究，進一步探討生物標記與臨床症狀的相關性，瞭解 OSA 嚴重程度與心血管疾病危險因子之相關性。故本研究以對照研究之實驗設計，從復健運動治療介入睡眠醫學，將是跨專業團隊合作發展的重大里程碑，同時也是未來臨床實務發展的重要指導守則。

| | |
|---|---|
| | **統計分析：**<br>連續變數以均值和標準差（SD）表示，而分類變數以數量和百分比表示。使用 Kolmogorov-Smirnov 檢驗來分析變數的正態分布。由於分布不符合正態分布，對於連續數據和分類數據，分別使用 Kruskal – Wallis 檢驗和 Fisher 精確檢驗來比較研究組之間的基線特徵。此外，使用 Wilcoxon 符號秩檢驗比較人口特徵、問卷、睡眠參數和 CT 圖像數據的前後差異。使用帶有廣義估計方程（GEE）的線性回歸模型來估計（1）治療前後三組間差異的差異及其對應的 95%置信區間（CIs），以及（2）時間對肌肉力量和生物標誌物的多變量調整效果。工作相關矩陣定義為非結構化。$P < 0.05$ 被定義為統計學上顯著。所有統計分析均使用 SPSS 17.0 進行。 |
| 受試者<br><br>描述 | 一、受試者或樣本資料：<br>• 研究期間：人體研究倫理審查通過日至 111 年 12 月 31 日<br>• 受試者型態（如：normal controls，或罹患特殊疾病之病患）<br>請說明：患有阻塞性睡眠呼吸中止症確立診斷<br>• 受試者或樣本之估計數量：105 人；年齡範圍：20~65 歲<br>• 是否有依性別選擇受試者或樣本？ □是： □男性 □女性■否<br>• 如受試者有懷孕之可能，此研究是否包括懷孕檢測？□是 ■否<br>• 如受試者為孩童或殘障人士，請說明需要此類受試者之原因：<br>• 請說明計畫主持人與受試者之關係？<br>□老師／學生 ■研究者／受試者 □醫療人員／病人 □雇主／職員<br>□朋友 □其它，請說明：<br>• 請說明受試者招募方式？<br>本研究將從成大醫院經耳鼻喉科及睡眠門診收案，門診醫師經診斷評估後為阻塞性睡眠呼吸中止症個案，個案同意自行減重、使用 CPAP、等待止鼾牙套製作或進行睡眠外科手術，由計畫主持人、共/協同主持人及協同研究員親自向符合收案條件的病患說明研究介入方式、實驗流程與風險後，經個案同意簽訂參與計畫同意書。為對照實驗。<br>二、研究之主要納入與排除條件：<br>(1) 收案條件: 年紀介於 20~65 歲，已用 PSG 睡眠檢查新診斷為輕度到重度純粹阻塞性睡眠呼吸中止症病人， 愛普渥斯嗜睡度量表 ≧10，且已同意自行減重、使用 CPAP、等待止鼾牙套製作或接受睡眠外科手術治療者。<br>(2) 排除條件：<br>• 一年內有抽菸、酒精和藥物濫用者<br>• 懷孕<br>• 嚴重阻塞性或限制性肺部疾病<br>• 運動高風險心血管疾病<br>• 中樞或周邊神經疾病病史導致無法執行運動處方<br>• 肌肉骨骼或心理障礙導致無法執行運動處方<br>• 其他非呼吸相關的睡眠疾患<br>• 合併中樞型或混合型睡眠呼吸中止症的睡眠疾患<br>三、經費補助<br>由院內計畫補助 1 次電腦斷層、2 次藥物誘導式睡眠內視鏡檢查費用及 3 次採血費 |

| | |
|---|---|
| | 用。回診/門診及手術費用將由病人自行支付。<br>四、使用何種方法確保受試者或樣品資料之機密性？（請說明研究中及研究完成後受試者或樣品資料、錄音帶、圖片等之處理方式）<br>研究中：■以編碼代替受試者姓名 □ 其它，請說明：<br>研究完成後：■研究成果及其刊登出來的文章不會出現可資辨認受試者之資訊 □ 其它，請說明： |

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# *Human Study Approval*

*Date: 2019.11.29*

**Title:** Efficacy of oropharyngeal myofunctional therapeutic training for obstructive sleep apnea patients after transoral robotic surgery
**Protocol No/ IRB No:** -- / A-BR-108-059
**Period of Project:** From 2019.11.28 to 2022.12.31
**Period of Approval:** From 2019.11.28 to 2020.11.27
**Content/Version:**
1. Protocol: Version: 3, Date: 2019/11/18
2. Informed Consent Form: Version 3, Date: 2019/11/18
3. Education Sheet: Version: 1, Date: 2019/9/6

**Institute:** National Cheng Kung University Hospital
**Investigator:** Dr. Cheng-Yu Lin (Department of Otolaryngology)
**Co-Investigator:** Professor Ching-Hsia Hung
**Co-Researcher:** Yi-Ju Lai

**Approved Number of Participants:** NCKUH: 105 persons. If the number of participants enrolled exceeds the approved number, please submit an application for amendment and approval.

The Institutional Review Board of National Cheng Kung University Hospital (NCKUH) is organized and operated according to the laws and regulations of ICH-GCP and of Central Competent Authorities.

This project is reviewed and approved by NCKUH IRB in **2019.11.28.** The period of approval is granted until **2020.11.27.**

Regarding multi-period project, please submit the Interim Report before **2020.10.27.** If the approval of the interim report is not granted on its expiry date, except safeguarding the health of the participants, the research is suspended.

Regarding completed project, the Final Report shall be submitted within three months of its approved expiry date. Except for the health of the participants, all the procedures of the project shall be terminated on its approved stated deadline.

If PI does not submit the Interim/Final Report on time, he/she will be recorded in the overdue list and received the suspension/ termination notice from NCKUH IRB. The overdue list will be reported to the IRB. After the resolution of the board meeting, NCKUH IRB will suspend all the new projects applied by PI until the Interim/Final Report is submitted.

Please submit the Interim/Final Report in written form and send to NCKUH IRB office. The lastest application forms can be downloaded in its website (http：// www.ncku.edu.tw/ ~nckuhirb)

Any changes or amendments to the project (including the project period), please submit an amendment application to NCKUH IRB within its approved period. Any changes or amendments in any other way will not be accepted. Before the approval of the amendment application, the project is carried out according to its previously approved plan.

For some reasons projects granted approval by NCKUH IRB couldn't be implemented, PI shall apply for suspension/termination.

During or after the project is completed, please report any unfavorable occurrence in a human study particant according to GCP.

Yours sincerely,
Ting-Tsung Chang M.D.
Chairman

Institutional Review Board
National Cheng Kung University Hospital

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# *Human Study Amendment Approval*

*Date: 2020.07.03*

**Title:** Efficacy of oropharyngeal myofunctional therapeutic training for obstructive sleep apnea patients after transoral robotic surgery

**Protocol No/ IRB No:** -- / A-BR-108-059

**Period of Project:** From 2019.11.28 to 2022.12.31

**Period of Approval:** From 2019.11.28 to 2020.11.27

**Content/Version:**

1. Protocol: Version: 6, Date:2020.06.09
2. Informed Consent Form: Version 6, Date: 2020.06.09
3. Add Diet Diary: Version: 1, Date:2020.06.09
4. Add Weight loss Education Sheet: Version: 1, Date:2020.06.03
5. Add Weight Management and Exercise Diary: Version: 1, Date:2020.06.09

**Institute:** National Cheng Kung University Hospital

**Investigator:** Dr. Cheng-Yu Lin (Department of Otolaryngology)

**Co-Investigator:** Professor Ching-Hsia Hung

**Co-Researcher:** Yi-Ju Lai



The Institutional Review Board of National Cheng Kung University Hospital (NCKUH) is organized and operated according to the laws and regulations of ICH-GCP and of Central Competent Authorities.

This project is reviewed and approved by NCKUH IRB in **2020.07.02**. The period of approval is granted until **2020.11.27.**

Regarding completed project, the Final Report shall be submitted within three months of its approved expiry date. Except for the health of the participants, all the procedures of the project shall be terminated on its approved stated deadline.

If PI does not submit the Interim/Final Report on time, he/she will be recorded in the overdue list and received the suspension/ termination notice from NCKUH IRB. The overdue list will be reported to the IRB. After the resolution of the board meeting, NCKUH IRB will suspend all the new projects applied by PI until the Interim/Final Report is submitted.

Please submit the Interim/Final Report in written form and send to NCKUH IRB office. The lastest application forms can be downloaded in its website (http://nckuhirb.med.ncku.edu.tw/)

Any changes or amendments to the project (including the project period), please submit an amendment application to NCKUH IRB within its approved period. Any changes or amendments in any other way will not be accepted. Before the approval of the amendment application, the project is carried out according to its previously approved plan.

For some reasons projects granted approval by NCKUH IRB couldn't be implemented, PI shall apply for suspension/termination.

During or after the project is completed, please report any unfavorable occurrence in a human study particant according to GCP.

Yours sincerely,
Ting-Tsung Chang M.D.
Chairman

Institutional Review Board
National Cheng Kung University Hospital

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# *Interim Report Approval*

*Date: 2020.10.27*

**Title:** Efficacy of oropharyngeal myofunctional therapeutic training for obstructive sleep apnea patients after transoral robotic surgery

**Protocol No/ IRB No:** NCKUH-10902002/ A-BR-108-059

**Period of Project:** From 2019.11.28 to 2022.12.31

**Period of Approval:** From 2019.11.28 to 2021.11.27

**Institute:** National Cheng Kung University Hospital

**Investigator:** Dr. Cheng-Yu Lin (Department of Otolaryngology)

The Institutional Review Board of National Cheng Kung University Hospital (NCKUH) is organized and operated according to the laws and regulations of ICH-GCP and of Central Competent Authorities.

This project is reviewed and approved by NCKUH IRB in 2020.10.27. The period of approval is granted until 2021.11.27.

Regarding multi-period project, please submit the Interim Report before 2021.10.27. If the approval of the interim report is not granted on its expiry date, except safeguarding the health of the participants, the research is suspended.

Regarding completed project, the Final Report shall be submitted within three months of its approved expiry date. Except for the health of the participants, all the procedures of the project shall be terminated on its approved stated deadline.

If PI does not submit the Interim/Final Report on time, he/she will be recorded in the overdue list and received the suspension/ termination notice from NCKUH IRB. The overdue list will be reported to the IRB. After the resolution of the board meeting, NCKUH IRB will suspend all the new projects applied by PI until the Interim/Final Report is submitted.

Please submit the Interim/Final Report in written form and send to NCKUH IRB office. The lastest application forms can be downloaded in its website (http：// www.ncku.edu.tw/ ~nckuhirb)

Any changes or amendments to the project (including the project period), please submit an amendment application to NCKUH IRB within its approved period. Any changes or amendments in any other way will not be accepted. Before the approval of the amendment application, the project is carried out according to its previously approved plan.

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During or after the project is completed, please report any unfavorable occurrence in a human study particant according to GCP.

國立成功大學醫學院附設醫院 第一人體研究倫理審查委員會

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# *Interim Report Approval*

*Date: 2021.10.26*

**Title:** Efficacy of oropharyngeal myofunctional therapeutic training for obstructive sleep apnea patients after transoral robotic surgery

**Protocol No/ IRB No:** NCKUH-10902002/ A-BR-108-059

**Period of Project:** From 2019.11.28 to 2022.12.31

**Period of Approval:** From 2019.11.28 to 2022.11.27

**Institute:** National Cheng Kung University Hospital

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