Impact of intra nasal administration of Ayurveda Medicine in apparently Healthy individuals on neuro-physiological variables and functional connectivity in Brain-Study protocol of an Exploratory Randomized Controlled Trial using f-MRI

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Table of Contents

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Abstract

Background: Nasya karma, Ayurveda nasal drug delivery system, is considered as one of the potent therapeutic modalities among Panchakarma. The uniqueness of the procedure lies in the fact that nasal drug delivery can bypass normal liver metabolism and BBB (Blood Brain Barrier), opening up a faster drug-delivery pathway. Available studies on 'Nasya' focus mainly on the efficacy of the same. This pioneering study aims to explore the mechanisms of nasya karma on brain function and neurophysiology, investigating its potential to modulate activity in specific brain regions and affect the functional connectivity between these regions using functional MRI.

Objective: The study aims to map the neuro-physiological response of brain to Nasya using BOLD functional MRI in both rest and task phases and to assess its impact on quality of life, cognition, sleep, and psychological well-being in healthy volunteers.

Methods: 60 healthy volunteers, in the age group of 20-40 years fulfilling the selection criteria will be recruited for this RCT from National Ayurveda Institute of Panchakarma, Kerala, India and randomized in 1:1 ratio to either the intervention group, n=30 (Group I receiving Nasya with Anu Taila for a period of 14 days) or the Control Group, n=30 (Group II), not receiving any intervention. The participants will undergo task based and resting f-MRI on day 1(twice on day 1, before administration and 15 minutes after Nasya for participants in Group I) and day 14 to map the neuro-physiological response of Nasya on brain. A comprehensive neuroimaging protocol using structural and functional magnetic resonance imaging will be employed in the study.Effect of Nasyain sleep, psychological domain, cognitive function, quality of life domain will be assessed on 1st day and 30th day in both the groups.

Results: This study will investigate the neurophysiological mechanisms of Nasya by examining clinical, neuropsychological, and neuroimaging variables to identify associated neural patterns to develop therapeutic protocols for manu diseases. The findings will also provide evidence for future research, supporting the use of Nasya as a practical and noninvasive therapeutic modality for treating cerebrovascular, behavioral, and neurological disorders, as indicated in Ayurveda.

Conclusions: The study will propel innovative research focusing on the neural mechanisms responsible for the delivery of central nervous system therapeutics to the brain and thereby bypassing BBB and generating favorable outcomes in CNS diseases Clinical Trial: Trial has been registered prospectively in Clinical Trial Registry of India with registration number

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Key words: Nasya, Healthy individuals, neurophysiology, Functional MRI, BOLD, Intranasal nasya, Functional MRI

Background:

In Ayurveda, Nasya karma, is one among the Panchakarma procedures, a set of five therapeutic modalities for body purification, involving nasal administration of medicine, and is regarded as a potent approach for promotive, preventive and therapeutic arenas. The therapeutic applications of Nasya span a wide clinical spectrum, addressing conditions such as chronic sinusitis, cervical spondylosis, as well as various neurological and psychiatric disorders.). Nasya is the only procedure that employs the nasal route for medicine administration to deliver therapeutic agents directly to the central nervous system, bypassing the digestive tract and potentially enhancing the efficacy of treatment owing to its faster absorption.

Intranasal drug administration has gained considerable traction since many decades as a non-invasive route for delivering medications targeting local, systemic, and central nervous system (CNS) effects. The leaky intercellular junctions of the nasal mucosa and the extensive vascularity of lamina propria and nasal mucosa facilitate optimal drug absorption, positioned intranasal delivery as a highly effective and versatile method for a wide range of therapeutic applications[1,2] . In the context of neurological disorders, intranasal drug delivery is advantageous due to its ability to achieve high drug levels in the brain, providing a direct pathway that bypasses the blood-brain barrier more effectively than traditional parenteral and oral routes., especially considering that the anatomical features allow for rapid drug absorption, a minimally invasive administration method, and the avoidance of hepatic first-pass metabolism, leading to faster therapeutic effects [3]. Direct absorption of molecules through the trigeminal and olfactory pathways provides a direct route to the brain, resulting in a favorable pharmacokinetic/pharmacodynamic (PK/PD) profile by bypassing major physiological barriers, such as the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (B-CSF-B) [4].

The unique relationship exists between nasal cavity and cranial cavity tissues makes intranasal drug delivery to the brain more feasible and effective. The intranasal delivery provides drugs with short channels to bypass the blood-brain barrier (BBB), greatly enhancing the therapeutic effect on neurological disease spectrum[5].

Panchakarma encompasses a comprehensive set of Ayurvedic detoxification procedures including vamana (emesis), virechana (purgation), nasya (nasal administration of herbal oils/powders), basti or vasti (herbal enema), and raktamokshana (bloodletting) [6] Panchakarma is a mainstay of Ayurveda

clinical practice, where the physician can choose any of the five set of therapeutic modalities to bring about a homeostatic equilibrium in the body, tailored per individual depending upon the intended purpose of use (promotive, preventive, therapeutic, rehabilitative), body constitution, Dosha (the body humors/functional principles that govern physiological and psychological processes), status of health/disease, age, fitness to undergo Panchakarma procedure, etc.

Anutaila is an oil-based formulation manufactured using a paste and decoction of herbal medicines, with oils as the base material. The ingredients are combined in specific proportions as highlighted in classical Ayurvedic texts and subjected to unique heating process to meet certain pharmaceutical parameters, ensuring the retention of both water-soluble and lipid-soluble principles at optimal levels. Anutaila can be likened to liposomes, where nanoparticles comprise lipid bilayer membranes surrounding an aqueous interior. The higher viscosity of this formulation increases contact time between the drug and the nasal mucosa, thereby enhancing permeation and the viscosity may influence mucociliary clearance, potentially reducing it and thus prolonging the formulation's retention time in the nasal cavity, which can lead to increased drug absorption [7,8]

Despite its extensive use as a therapeutic modality in clinical practice across a wide range of conditions and in healthy individuals to maintain health and homeostasis, the exact mechanism of action of Nasya remains obscure and mysterious, primarily due to a lack of physiological or mechanistic studies in this area. Given the paucity of research on the neurophysiological mechanisms underlying Nasya, the present study aims to utilize functional MRI (fMRI) to investigate its potential to modulate activity in specific brain regions and affect the functional connectivity between these regions. Understanding these neuro-physiological correlates is crucial, as it will elucidate whether Nasya exerts targeted effects or has more widespread, non-specific impacts on the brain's intrinsic functioning. This knowledge will benefit stakeholders by providing a scientific basis for conceptualizing future research, potentially leading to optimized therapeutic protocols, improved clinical outcomes, and enhanced integration of Nasya into modern medical practice. By establishing clear spatial and temporal patterns of brain activity associated with Nasya, this study could pave the way for more precise and effective applications of this traditional Ayurvedic practice in contemporary healthcare. This may also propel innovative research focusing on the neural mechanisms responsible for the delivery of central nervous system therapeutics to the brain and thereby bypassing BBB and generating favorable outcomes in CNS diseases.

Objectives:

The primary objective of the study is to investigate the neuro-physiological activity of the brain induced by the Nasya procedure utilizing Blood Oxygen Level Dependent (BOLD) functional MRI

to elucidate the comprehensive neural response to Nasya both in rest and task phase. The secondary objective is to examine the impact of the Marsa Nasya procedure on health parameters such as quality of life, cognitive, sleep and psychological in apparently healthy volunteers, such as quality of life, cognitive, sleep and psychological wellbeing through anxiety, stress and cognitive health.

Methods:

The present study is structured as an exploratory randomized controlled clinical trial. with participants allocated in a 1:1 ratio, matched for age and sex to comprehensively assess and evaluate the neuro-physiological and holistic health effects of the Marsa Nasya procedure in comparison to a control group. Settings of the study include National Ayurveda Research Institute for Panchakarma, Cheruthuruthy, Thrissur, Kerala, India and Amrita Institute of Medical Sciences, Kochi, Kerala, India.

Study setting:

Participants will be screened and enrolled at the National Ayurveda Research Institute for Panchakarma in Cheruthuruthy, Thrissur, an institute under the Central Council for Research in Ayurvedic Sciences, Ministry of Ayush, Government of India.The institute is well-equipped for comprehensive Ayurvedic assessments and interventions, ensuring a high standard of participant care and protocol adherence during the Nasyaprocedure. Functional MRI assessments will be carried out at the Amrita Institute of Medical Sciences in Kochi, which is equipped with state-of-the-art imaging technology and experienced radiologists, providing the advanced neuroimaging capabilities necessary for detailed BOLD (Blood Oxygen Level Dependent) functional MRI studies. The study will strictly adhere to the principles outlined in the Declaration of Helsinki (World Medical Association version, 2013). Prior to enrollment in this trial, all participants will be required to provide informed consent by signing the consent form. The protocol has undergone rigorous ethical review and received approval from the Institutional Ethics Committee and the study is registered with the Clinical Trials Registry of India

Sample size: Since this study is designed as an exploratory study, aiming to gather preliminary data on the neuro-physiological effects of the Nasya procedure and its impact on various health parameters, a sample size of 60 (30 per group)is considered to achieve the study objectives and provide valuable insights that will inform the design of future, larger-scale clinical trials. Feasibility is a critical consideration, as recruiting a larger sample of participants willing to undergo both the Nasya procedure and twice-repeated fMRI assessments may be challenging, particularly among healthy volunteers. However, the expected variation in response to the interventions is likely to be lower than in a patient population, which would allow for meaningful conclusions to be drawn from

a smaller sample size. Likewise, a sample size of 60 balances the need for preliminary data with the practical constraints of logistical and financial resources in the study.

Eligibility criteria:

Apparently healthy volunteers aged 20-40, physically independent, ambulatory, and right-handed,BMI of 17.5 to 30.5 kg/m2who are willing to participate and provide written informed consent were included for the study. Only those who agree to abstain from beverages such as coffee, tea, energy drinks, or other stimulants beginning 12 hours prior to undergoing fMRI, would be considered for recruitment. The healthy status of volunteers will be confirmed through the absence of any active or chronic disease, as determined by a comprehensive medical evaluation that includes a detailed medical history, complete physical examination (including vital signs), 12-lead ECG, hematology, blood chemistry, serology, psychological assessment, urinalysis, etc.

Presence of any disease/ symptom, individuals with a history of psychiatric disorders, as assessed by the Mini International Neuropsychiatric Interview, or those with psychosomatic disorders,use of psychotropic medications known to interfere with the dopaminergic system or sedatives within the last six months,or with a family history of psychiatric diseases, past or current abuse of psychoactive drugs, alcohol use, and smoking will be excluded. Individuals contraindicated for MRI, such as those with medical implants, retained wires (e.g., temporary pacing), an increased risk of heart attack or other cardiac problems, known pregnancy, nausea (due to aspiration risk), metallic dental work, cochlear implants, body jewelry, and other metallic foreign objects implanted in the body, also will not be eligible.Individuals with cognitive impairment, women in the menstrual phase, intracranial abnormalities that could adversely affect the interpretation of brain scans, and those who self-identify as claustrophobic are also not eligible for participation in the study. In addition to this, the participants deemed unfit for Nasyatherapy[9] such as those with fever, rhinitis, cough, or other inflammatory conditions, as indicated in the Ayurveda treatises will be excluded.

Interventions:

The participants in the intervention group would be administered Nasya (nasal instillation) with Anutaila in the dose of 3 ml per nostril for 07 days (on every alternate day for 14 days) as indicated by Ayurveda treatises for healthy individuals. Prior to Nasya, local oleation and sudation of the head region will be administered for approximately ten minutes. Following the Nasya procedure, participants will inhale medicated smoke and rinse their mouths with lukewarm water. The control group, consisting of healthy individuals, will not undergo any interventions. The participants in the control group would not receive any intervention to facilitate assessment of the specific effects attributed to Nasya in the intervention group when compared to baseline measures in healthy

individuals.

Nasya will be administered by the investigator at the hospital's Panchakarma unit, except on assessment days where it will be conducted at the Ayurveda unit of Amrita Institute of Medical Sciences. Each participant will be closely monitored for 30 minutes following the procedure to observe any immediate effects or reactions. Vital signs, such as heart rate, blood pressure, and respiratory rate, will be monitored and recorded before and after every session. Participants reporting any adverse symptoms experienced after each session would be recorded through a standardized format designed to capture a wide range of potential side effects, including nasal irritation, headache, dizziness, nausea, or any other discomfort. Any serious adverse event (SAE) will be reported immediately to the institutional ethics committee, and causality assessment would also be made. All adverse events (AEs), requiring medical intervention would be provided appropriate care and will be followed up until resolution or stabilization.

If a participant experiences significant adverse effects such as severe nasal irritation, fever, sinusitis or any other serious discomfort that impacts their well-being, the intervention will be immediately halted and the participants would be withdrawn. Discontinuation will also occur in cases of non-compliance with the treatment regimen, if the participant wishes to withdraw for any reason, or if the participant meets any exclusion criteria during the study. Since the trial involves healthy volunteers, administration of concomitant medication is prohibited during the trial period of 30 days.

Randomization and Allocation: Eligible participants in this study will undergo random allocation to either the intervention or control group using a computer-generated random sequence prepared by an independent statistician, ensuring an unbiased approach to treatment assignment. Each random sequence number will be securely sealed in opaque envelopes, with the enrollment ID on the outside. Prior to enrollment, participants will open these envelopes to determine their allocated group, to minimize bias.

Outcomes:

The primary outcome measure for this study is the Blood Oxygen Level Dependent (BOLD) signal detected via functional Magnetic Resonance Imaging (fMRI) in specific brain regionswhich are associated with motor, sensory, memory, and cognitive circuits elicited during both rest and task phases. A 3 Tesla (3T) MRI scanner will be used to assess the brain's response to different stimuli at multiple time points: before the Nasya procedure, immediately before the Nasya procedure, immediately after (within 15 minutes) the Nasya procedure, and on the 14th day of the Nasya therapy.

The secondary outcome measures includes the therapeutic effects of Marsa Nasya on cognitive

function assessed via Montreal Cognitive Assessment Scale (MocA)[10], perceived stress assessed with Perceived Stress Scale (PSS)[11], anxiety Hamilton Anxiety Scale (HAM-A)[12], and health-related quality of life assessed using SF-36[13]. The secondary outcomes would be assessed before the intervention, on the 1st day, and on the 30th day following the Nasya therapy.

The primary outcome of the study encompasses two key components:

1. Assessing the immediate neurophysiological response elicited by Nasya during both resting and task phases using MRI.

2. Evaluating the neurophysiological response elicited by Nasya after 14 days (following 7 days of Nasya) during both resting and task phases using MRI. Functional neuroimages will be collected using a 3.0 Tesla GE Medical Systems, Discovery MR 750w. Rs-fMRI data will include three-dimensional T1 weighted structural imaging with a Fast Spin Echo sequence and BOLD imaging with a Spin Echo-Gradient Echo-Echo Planar Imaging (SE-GRE-EPI) sequence for 40 minutes, covering the whole brain. The parameters for 3D-T1 imaging will include a slice thickness of 1 mm, a TR/TE of 8.5 ms/3.2 ms, an FOV of 256× 256 × 142 mm3, a flip angle of 12°, a matrix of 256 × 256, an in-plane resolution of 1 × 1 × 1 mm3, and 142 layers. The parameters for BOLD imaging will include a slice thickness of 3.2 mm, a TR/TE of 3,000 ms/30 ms, a flip angle of 80°, a matrix of 64 × 64, an FOV of 256 × 256 × 142 mm3, 35 layers, and 150 time points. Participants have a four-button fiber optic response box with their right hand, which is used to record behavioral responses. To examine the tasks specifically, participants wear earplugs to reduce the scanner noise. Head motion is minimized using foam pads and a headband.

Preparatory phase:

Participants undergo a robust screening interview to ensure understanding and absence of contraindications for MRI scanning. Before task phase fMRI, participants are thoroughly informed and trained. Communication with the operator is maintained throughout the scan. Incidental findings requiring medical intervention will be disclosed, and participant comfort is ensured during scanning. Verbal communication is limited due to MRI noise; and the participants will utilize a four-button fiber optic response box positioned for use with their right hand to communicate and to record behavioral responses during tasks. To mitigate the effects of scanner noise, participants will wear earplugs. Head motion will be minimized using foam pads and a headband to ensure stable positioning throughout the MRI scans. Metallic items would be removed, and participants wear MRI-compatible attire. Participants in the trial group would be directed to avoid heavy meals within 2 hours before and 1 hour after Nasya karma, with no dietary restrictions for the control group. Both groups refrain from consuming coffee, tea or caffeinated drinks for 12 hours preceding functional

MRI.In contrast, the control group will undergo resting state mapping on both the first and fourteenth day. While the participants in the intervention group would undergo procedure lasts approximately 30-45 minutes, after which participants proceed to the MRI room. Participants in the control group will proceed directly to MRI without any intervention.

Data collection:

A. Resting phase functional MRI:

In this study, a block design paradigm will be employed during task phases before and after Marsha Nasya Karma, where stimuli are presented continuously within specific blocks alternated with rest periods to elicit and distinguish brain responses. Resting state fMRI, on the other hand, captures spontaneous brain activity without external stimuli, allowing for the correlation of signal fluctuations among functionally related brain regions [13]. Pan-brain activation mapping will be conducted during the resting phase before and immediately after Nasya therapy (within 15 minutes) in the trial group. Functional MRI will be done prior to the procedure of Nasya and then again, after the complete procedure is over. Participants in the control group will proceed directly to MRI without any intervention. During scanning, participants would be instructed to remain still with eyes closed for 15 minutes to avoid motion artifacts. Any head movement necessitates repeat mapping. The resting state fMRI paradigm will map spontaneous brain activity across visual, auditory, motor (left and right), memory, and language domains before and after Marsha Nasya Karma.

Task Based fMRI:

The task paradigms in this study are designed to effectively stimulate relevant brain areas while ensuring participant performance remains accurate. Rest blocks are strategically interspersed between active blocks to establish baseline fMRI signals and allow participant rest. Each domain collects sufficient data through a structured design featuring at least four blocks per task. Task durations are optimized to maintain participant concentration without inducing fatigue; breaks are included if needed due to head movements, ensuring image consistency.

A. Visual fMRI:

The study employs a checkerboard method with 8Hz flickering alternating with 30-second rest blocks in a sequence of 1 REST plus 4 cycles (B AB ABAB AB). Participants receive prior education and training to understand their tasks, viewing a flickering checkerboard followed by a fixation cross during rest periods. The paradigm runs for 4 minutes and 30 seconds, minimizing eye movements while allowing effective scene categorization.

B. Auditory fMRI:

Auditory tones (1000 Hz:2000 Hz, ratio 4:1) alternate with 20-second veena sounds in a sequence of

ABABABABABAB. Participants, relaxed with eyes closed, hear alternating tones during rest periods, with more frequent standard tones. Each auditory block is followed by a 20-second veena sound. The paradigm duration is 4 minutes.

C. Motor fMRI (Right and Left):

Right and left motor areas are separately mapped using hand movements. Participants perform finger movements indicated by a flashing green dot on the screen, alternating with 30-second rest blocks (1 OFF plus 4 cycles BABABABAB). They synchronize opening and closing fist movements with the dot, followed by rest periods focusing on a fixation cross. Each motor task runs for 4 minutes and 30 seconds per hand.

D. Memory fMRI:

The working memory attention task lasts 6 minutes and 45 seconds, presenting numbers for 0.5 seconds with 2.5 seconds of black screen. Blocks of 51 seconds feature numbers with 30-second rest periods in between. Participants press a button when presented with identical numbers, with task initiation and closure including 15-second rest blocks. This paradigm effectively tests working memory under fMRI conditions.

The response to nasya karma will be assessed by considering the 3 principles,firstly, neural activity correlates with changes in local blood oxygen levels. Secondly, oxygenated blood exhibits different magnetic properties compared to deoxygenated blood. Thirdly, alterations in the ratio of oxygenated to deoxygenated blood, known as the hemodynamic response function, can be inferred using fMRI through the measurement of the BOLD response.

Data management:

Data pertaining to the study including the screening, recruitment, baseline information, daily nasya procedure assessments, lab investigation reports, and secondary outcome measures assessed with scaleswill comprehensively documented in Case Report Forms (CRF) within 24 hours and electronic CRF (eCRF) will be completed within 07 days. Only the study personnel or individuals delegated with the task for data entry or the statisticians will have access to the data. The imaging data generated from fMRIwill be stored in hard disks at AIMS, Kochi, and will undergo further analysis after completion of the study. All study documents will be securely stored for five years following study completion.

Statistical Analysis:

The modified intention-to-treat (mITT) principle will guide the analysis for all outcomes within the full analysis set. Quantitative data will be summarized using mean, standard deviation (SD), minimum (min), maximum (max), and median values. Enumeration data will be presented as

frequency (n) and corresponding percentage (%). Intra-group comparisons will utilize Student's paired t-test or Wilcoxon signed rank test for continuous variables, and the chi-squared test for categorical variables. Inter-group comparisons will be conducted using independent-sample T-test or Mann–Whitney U test. Significance thresholds will be set at $p<0.05$ for all two-tailed tests.

fMRI data analysis:

The fMRI data will undergo preprocessing using either DPABI or CONN toolkit, which will encompass essential steps such as slice timing correction, realignment for motion correction, regression to remove confounding effects, normalization to a standard template, smoothing to enhance signal-to-noise ratio, detrending to remove low-frequency drifts, and filtering to focus on relevant frequency bands, aligning with established practices in the field. After data preprocessing, amplitude of low-frequency fluctuation (ALFF), functional connectivity (FC), and large-scale functional brain network analysis, etc. will be conducted to investigate the difference of neuro-physiological responses between the groups. The results will be interpreted in the context of the experimental paradigm to elucidate neural correlates of the studied phenomena, providing insights into the effects of nasya on brain function. Voxels exhibiting expected time-course correlations (30-second periods) will receive high activation scores, while those showing no correlation or deactivation will receive lower or negative scores, respectively. MRI data analysis will employ general linear models via statistical parametric mapping (SPM). fMRI data will be processed using MATLAB 2023 (MathWorks Inc., Natick, MA, USA).

Resting phase MRI data will be analyzed using software tools like SPM, Conn toolbox, and FSL, while task phase functional MRI will specifically employ SPM. Given the focus on group data in this study, complex patterns of brain activation will be interpreted collectively rather than individually. For voxel-based analysis, a significance threshold of $p<0.01$ at the voxel-level and $p<0.05$ corrected for false discovery rate at the cluster-level will be applied. Connectome-based analysis will utilize a threshold of $p<0.05$ corrected for false discovery rate. Additionally, Pearson correlation analysis will be performed to explore potential associations between clinical outcomes and fMRI findings, examining changes in brain activity following different interventions.

Discussion:

As a basic research work conducting in the field of nasya research, the study tries to get the evidence of neurological response evoked by nasya procedure in brain, which can act as a lead to further upcoming research works to better utilize the procedure in neurological disease spectrum. Since

nasya karma is a procedure recommended by Ayurveda to include in daily regimen, the mapping of neuro-physiological response of specific brain areas will shed new light on the aspects of utilizing nasya procedure in preventive medicine against a huge spectrum of neurological diseases.

Additionally, the study maps the neuronal response of different brain areas like visual, auditory, motor and cognitive domains separately in task phase for nasya procedure. This will help to generate preliminary data on the differential response of various brain areas to nasya. Also, the study focuses on the immediate and cumulative impact of nasya in brain by mapping the brain response within 15 minutes and 14th day of nasya. This will further guide the clinicians and researchers to get a preliminary idea on the time required by the nasya procedure to produce a neurological response in a specific brain area.

The study comes with its own limitations like minimum sample size of 30 kept in each group due to the feasibility issues study will be facing in the recruitment of healthy volunteers to a radiological technique. Also, the nasya proceure is administered in the OPD level, the investigator team will be having less control over patient's adherence to nasya procedure protocol.

Conclusion:

The study will serve as a primary data source providing evidence for the action of Ayurveda procedure, nasya karma in brain. The study will propel innovative research focusing on the neural mechanisms responsible for the delivery of central nervous system therapeutics to the brain and thereby bypassing BBB and generating favorable outcomes in CNS diseases.

Ethical considerations:

The study will be initiated only after getting ethical approval from Scientific Review Board and Institutional Ethics Committee at AIMS, Kochi and Institutional Ethics Committee at NARIP, Cheruthuruthy. Protocol amendments if any needed in the whole course of the trial will be communicated to both IECs at AIMS and NARIP, Cheruthuruthy. Personal information about potential and enrolled participants will be collected, shared, and maintained in a confidential manner before, during, and after the trial unless subjected to judiciary. Access to trial data will be made only to the research team involved at NARIP and AIMS, Kochi. There will be no public access to trial data set. Dissemination policy includes publication of study findings in peer reviewed indexed international journal.

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Conflicts of interest: None declared

Roles and responsibilities of authors:

Author 1 and 3 drafted the manuscript. Author 2 extended all technical support in drafting radiodiagnosis part of the manuscript. Author 3, 4 and 6 reviewed and made necessary corrections in the manuscript. Authors 5,7,8,9,10 extended the technical advice regarding the framing of whole protocol.

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Figure 01: Schematic diagram of study plan

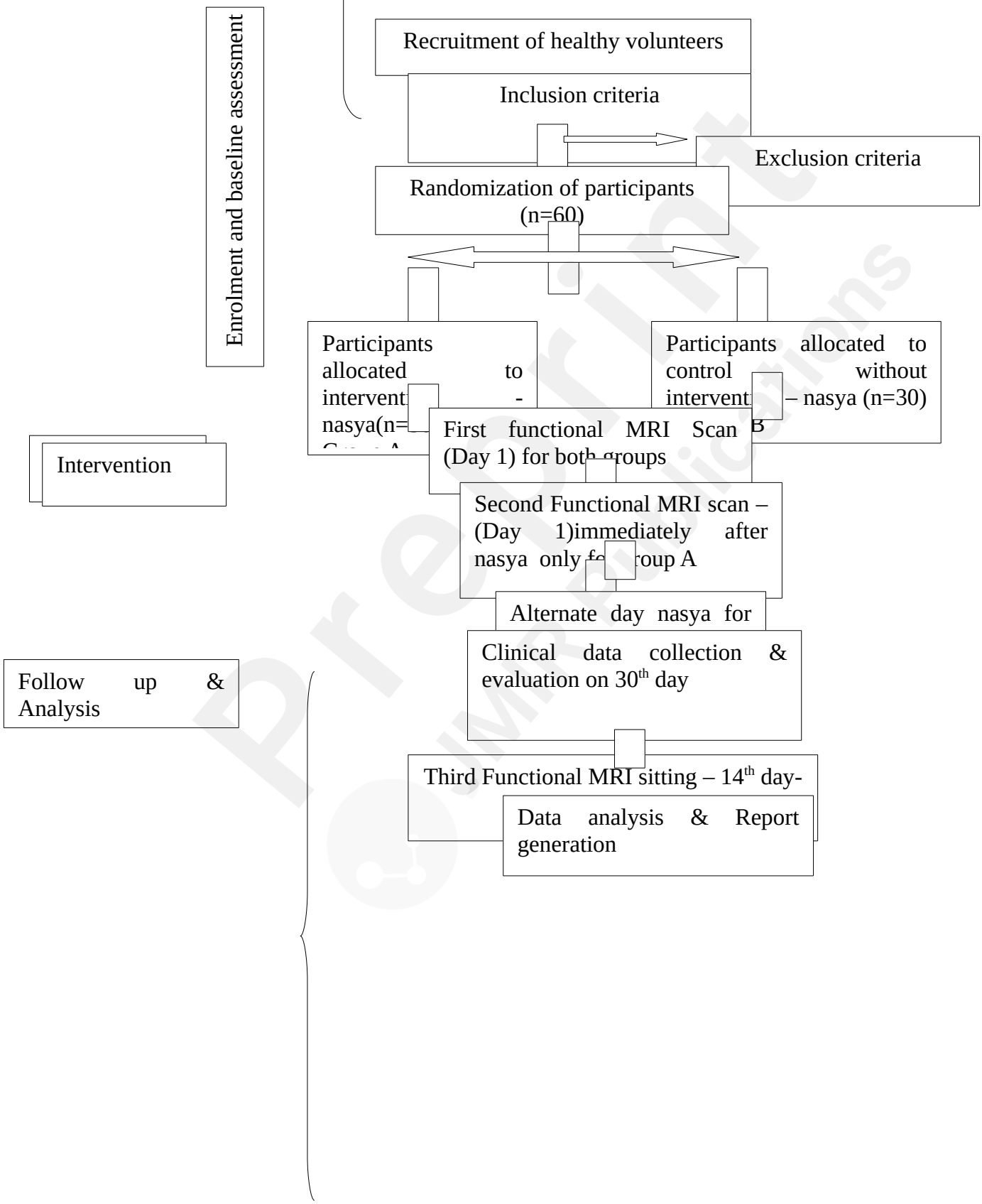

Figure 02: GANT Chart

Study period week		Baseline		Intervention period	Follow up	
Time point	0^{th} week	1^{st} day	1^{st} day (immediately after nasya)	1^{st}-13^{th} day	14^{th} day	30^{th} day
Patient screening including lab test	★					
Informed consent	★					
Randomization	★					
Intervention Group A		★		★		
Group B						
fMRI Scan						
Group A		★	★		★	
Group B		★			★	
Clinical assessment						
Group A						★
Group B						★