Cover Page – Study Protocol with SAP and ICF

Official Title: Exploring effects of probiotic formulation (resB® Lung Support) on gut- lung axis in elderly pneumonia patients: a randomized controlled trial

ClinicalTrials.gov Identifier (NCT Number): yet not assigned

Document Type: Study Protocol with Statistical Analysis Plan and Informed Consent Form

Document Date: 02 February 2022

Principal Investigator: Dr. Jayanta Kumar Mitra, MD Additional Professor, Department of Anesthesiology & Critical Care All India Institute of Medical Sciences (AIIMS), Bhubaneswar, Odisha, India

Co- Principal Investigator: Dr. Balamurugan Ramadass, PhD Additional Professor, Department of Biochemistry AIIMS, Bhubaneswar, Odisha, India

Collaborating Institution: Institute of Life Sciences (ILS), Bhubaneswar

All India Institute of Medical Sciences, Bhubaneswar-751 019

RESEARCH CELL

SUBMISSION & APPROVAL OF INTRAMURAL, EXTRAMURAL & COLLABORATIVE PROJECTS AT AIIMS BHUBANESWAR

PROCEDURE OF SUBMISSION & APPROVAL OF EXTRAMURAL/COLLABORATIVE PROJECTS

Principal investigator (PI) submits Concept proposal to funding agency (if applicable) and also informs the research cell.



After acceptance of Concept proposal by funding agency, PI submits the complete Extramural/Collaborative Project proposal along with Informed Consent Documents (in case of human studies) to Research Cell. The PI is also required to submit the filled Project information form (given below).



After receiving hard and soft copies of the documents, the Research Cell provides a Provisional Project code and forwards to Scientific Advisory Committee (SAC) for review (The PI will have to make a presentation of their project before SAC).



After SAC approval, the Research Cell forwards the documents along with SAC approval letter to the Institute Ethics Committee (IEC) for review.



After IEC approval, the PI provides SAC and IEC approval letters and other relevant documents and obtains permission from Head of Institute (including signing of MOU in case of collaborative projects).



Submission of project proposal to funding agency for review and approval



Following acceptance of the project, the PI provides sanction letter from funding agency to Research Cell for issuance of a Permanent Project code, and the Research Cell notifies Accounts Section for disbursement of funds.

PROCEDURE OF SUBMISSION & APPROVAL OF INTRAMURAL PROJECTS (FUNDED)

Call for intramural projects notified by Research Cell to Faculty members



Interested Faculty member (i.e. Principal Investigator [PI]) submits complete Intramural Project proposal in the prescribed format along with Informed Consent Documents (in case of human studies) to Research Cell. The PI is also required to submit the filled Project information form (given below).



After receiving hard and soft copies of the documents, the Research Cell provides a Provisional Project code and forwards to Scientific Advisory Committee (SAC) for review (The PI will have to make a presentation of their project before SAC).



After SAC approval, the Research Cell forwards the documents along with SAC approval letter to the Institute Ethics Committee (IEC) for review.



After IEC approval the Research Cell facilitates the short-listing of projects for institute research grant



After IEC approval, the PI provides SAC and IEC approval letters and other relevant documents and obtains permission from Head of Institute



After permission from Head of the institute, PI informs the Research Cell which issues a Permanent Project code and notifies Accounts Section for disbursement of the grant.

APPROVED VERSION-1.1 Dated 15.04.2014

PROCEDURE OF SUBMISSION & APPROVAL OF NON-FUNDED PROJECTS

Principal Investigator [PI]) submits complete Intramural Project proposal along with Informed Consent Documents (in case of human studies) to Research Cell. The PI is also required to submit the filled Project information form (given below).



After receiving hard and soft copies of the documents, the research cell provides a Provisional project code and forwards to Scientific Advisory Committee (SAC) for review (The PI will have to make a presentation of their project before SAC).



After SAC approval, the research cell forwards the documents along with SAC approval letter to the Institute Ethics Committee (IEC) for review.



After IEC approval, the PI provides SAC and IEC approval letters and other relevant documents and obtains permission from Head of Institute.



After permission from Head of the institute, PI informs the Research Cell which issues a Permanent Project code for the record.

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, BHUBANESWAR
SIJUA, DUMUDUMA, BHUBANESWAR, ODISHA, PIN-751019

SECTION-A: FOR INFORMATION OF THE RESEARCH CELL

01. Title of the Research Project :

Exploring effects of probiotic formulation (resB® Lung Support) on gut-lung axis in elderly pneumonia patients: an RCT

02. Type of Project : Extramural
(Intramural/Extramural/Collaborative)

03. Name, Designation & Address of the :
Principal Investigator with email & Mobile number

Principal Investigator:

Dr. Jayanta Kumar Mitra

Additional Professor,

Department of Anaesthesiology

AIIMS-Bhubaneswar

Co-Principal Investigator:

Dr. Ramadass Balamurugan

Additional Professor,

Department of Biochemistry,

AIIMS-Bhubaneswar

Dr. Prasanta Kumar Sahoo

Senior Medical Officer (Ayurveda)

Department of AYUSH

AIIMS-Bhubaneswar

Address:

Sijua, Patrapada, Bhubaneswar, Odisha, India - 751019

Email:

Dr. Jayanta Kumar Mitra: mitra.jayanta@gmail.com

Dr. Ramadass Balamurugan: balaramadass1@gmail.com

Dr. Prasanta Kumar Sahoo: ayush_prasanta@aiimsbhubaneswar.edu.in

Phone Number:

Dr. Jayanta Kumar Mitra: 9433798583

Dr. Ramadass Balamurugan: 8547805341

Dr. Prasanta Kumar Sahoo: 72407 34331

04. Is the study interventional? : Yes

05. Background Information & Justification (100-200 words). :

(State the reasons for undertaking the study & include

06-10 relevant references)

In view of the recent CoVID-19 pandemic, there has been renewed interest in further probing this gut- lung axis. Though the novel Coronavirus (SARS-CoV-2) primarily infects the lungs, gastro-intestinal symptoms like diarrhoea, nausea, vomiting and abdominal pain have been early/ presenting complaints in a sizeable proportion of the cases. While this has been variously ascribed to secondary bacterial infections as a consequence of antibiotic use, the finding that the SARS-CoV-2 can infect and multiply in the gut is particularly interesting. Viral RNA has been isolated from stool specimen of infected patients and also, the receptor that SARS-CoV-2 uses to invade cells have been reported to be expressed in the mucosal cells of the GI tract. Alongside, in a small cohort of these patients it has been shown that the resident gut flora has been significantly altered. The immune system is a double-edged sword. It has to provide a pro- inflammatory response towards undesirable pathogens and environmental (e.g. food derived) antigens, while maintaining tolerance to self-antigens. The pathophysiology of many chronic as well as acute disease processes have implicated a tipping over of this delicate balance towards a more exaggerated pro- inflammatory response. As an example, one might cite the cytokine storm and excessive immune response that cause extensive tissue damage secondary to CoVID-19 infections. This has been associated with a depletion/ exhaustion of the anti-viral CD8+ T cells in the circulation, that promote immune tolerance. The gut microbiota is known to moderate the balance between pro- and anti-inflammatory host responses both locally and also via inter-compartment and systemic cross-talks. This is the rationale behind targeting the gut microbiome homeostasis in respiratory tract infections.

Various randomized controlled trials designed to study the protective effects of probiotic supplementation in respiratory tract infections and subsequent meta-analyses on these have demonstrated a reduction in incidences of respiratory tract infections without any mortality benefit or reduction in length of hospital/ICU stay. However, majority of these studies are in children and young healthy adults and have heterogenous primary outcomes including both upper and lower respiratory tract infections. The elderly population, in whom, pneumonia is a significant cause of mortality and morbidity has not been adequately addressed.

The current treatment strategies for pneumonia are appropriate antibiotics, with oxygen therapy and ventilatory support, if required. This approach has its origin in the widespread misconception that the lungs are a sterile compartment and any infection is exogenous. Since the work of Dickson in 2016, this concept has been brought to test. The current understanding is that there is a resident flora in the lungs also, in a much lower density as compared to the

other mucosa-lined passages like the gastro-intestinal tract (10^{3-5} bacteria per gram of tissue in the lungs as compared to 10^{11-12} in the intestines). In the past, this had led to the failure of conventional culture-dependent microbiological techniques to demonstrate the presence of resident microbial flora in the lungs. With the advent of Next Generation Sequencing, and the ambitious Human Microbiome project, it is now known that the respiratory tract is colonized by a diverse set of microbes, ranging from bacteria to fungi and there exists a topographical variation in their distribution along the respiratory tree. Our present understanding of the resident lung flora is that its composition depends on the balance between the inoculation via micro-aspirations from the GI tract and the muco-ciliary clearance functions of the respiratory tract.

Our current study proposes to address the present gap in knowledge in the literature about whether probiotic formulation (resB® Lung Support) supplementation helps to reduce the incidence and severity of lower respiratory tract infections in the elderly population in an acute care setting. Given the current pandemic of CoVID-19, an RNA virus that shows tropism to both the lung and the gut and has been implicated in resident flora dysbiosis, this study seems more necessary now than ever before. We know that the novel Corona virus also exerts its deleterious effects by mounting a cytokine storm, which shows a response to immune-suppressant therapy. Furthermore, we want to substantiate our findings by microbiome analysis of the lungs using next- generation sequencing both before and after the intervention, something which has not been done in this subset of patients in the Indian scenario, to the best of our knowledge.

06. Research Questions; Hypotheses :

Whether the dietary supplementation of Probiotic formulation can improve host immunity by altering the gut-lung axis in elderly patients with pneumonia and improve clinical outcomes

07. Objectives

Primary Objective

To compare the incidence and prognosis of pneumonia in elderly patients admitted to an acute-care set-up with and without dietary supplementation of probiotic formulation (resB® Lung Support) for 14 days.

Secondary Objectives

1. To compare the changes in the microbial composition and the levels of secretory IgA in the bronchopulmonary aspirate with and without dietary supplementation of probiotic formulation (resB® Lung Support) in these patients.

2. To compare the changes in the microbial composition and the levels of total small chain fatty acids (SCFAs) in the stool sample with and without dietary supplementation of probiotic formulation (resB® Lung Support) in these patients.

08. Was statistical expert consulted? If yes, Name, Designation : no

09. Material and Methods

(a) Whether the study involves humans animals or both? : Humans

(b) Type of study : Randomized controlled trial
(Randomized controlled trial/cohort
study/case control study/record review/
prospective clinical study/others)

(c) In case of human study mention the
(Randomized controlled trial/cohort
study/case control study/record review/
prospective clinical study/others) :

Inclusion Criteria:
1. Elderly patients (age > 60 years) admitted to the various ICUs / Emergency Department of AIIMS, Bhubaneswar who provide a valid informed consent for participation in the trial.

Exclusion Criteria:
1. Any contraindications for enteral feeding during the proposed study period
2. Any contraindications for broncho-alveolar lavage
3. Patients with intestinal diversions and stoma and diagnosed anatomical abnormalities of the GI tract like muco-cutaneous fistulae, etc.
4. Patients with hematological malignancies, infected with hemo-parasites or lymphotropic organisms.
5. Patients with chest trauma.

(d) Number of groups to be studied, :
their names and definitions
(Name the groups as control, treatment I,
treatment II, etc.)

Upon receiving an informed and voluntary consent, the patients will be randomized into either of the two study groups using a computer-generated randomization scheme and serially numbered sealed opaque envelopes for allocation concealment. The process of allocation as per the randomization codes will be done by a staff nurse, who will not be part of the investigating team. The two groups will be as follows-

- Study Group (S): Receiving resB® Lung Support capsule twice daily for 14 days from enrolment.
- Control Group (C): Receiving placebo capsules twice daily for 14 days from recruitment.

(e) Sample size in each group and sample :
size determination methods
(Sample size must be estimated using

standard scientific/statistical methods)

We propose to enrol 60 patients into this study over a period of 1 years and randomize them into treat and control group with 1:1 allocation.

(f) Interventions (including drugs) to be used, if any :

resB® Lung Support
Twice a day capsule for 14 days Orally

10. Are the drugs and doses to be used, approved for these indications by Drugs Controller General of India (DCG-I)? (Enclose the approval letter from DCG-I for the trial on humans) : Not applicable
11. Methodology (include sampling method, randomization technique, interventions and their standardizations, variables to be studied, proposed statistical methods, etc.) :

Study Population

Elderly patients (age > 60 years) admitted to the various ICUs / Emergency Department of AIIMS, Bhubaneswar who provide a valid informed consent for participation in the trial.

Study Design

The study is designed as a randomized, placebo-controlled, double-blinded clinical trial.

Sites Enrolling Subjects

The study will be conducted in the various ICUs and Emergency Department of AIIMS Bhubaneswar, under the Department of Anesthesiology & Critical Care and the patients will be followed up till discharge in their respective wards. The biochemical and immuno-microbiological studies will be conducted in the Department of Biochemistry, AIIMS Bhubaneswar in collaboration with ILS, Bhubaneswar for technological support.

Number of Subjects

We propose to enrol 60 patients into this study over a period of 1 years and randomize them into treat and control group with 1:1 allocation.

Test product, Dose and Mode of Administration

resB® Lung Support
Twice a day capsule for 14 days Orally

Proposed Duration of Study

1 year

Subject Population

Inclusion Criteria:
1. Elderly patients (age > 60 years) admitted to the various ICUs / Emergency Department of AIIMS, Bhubaneswar who provide a valid informed consent for participation in the trial.

Exclusion Criteria:
1. Any contraindications for enteral feeding during the proposed study period
2. Any contraindications for broncho-alveolar lavage
3. Patients with intestinal diversions and stoma and diagnosed anatomical abnormalities of the GI tract like muco-cutaneous fistulae, etc.
4. Patients with hematological malignancies, infected with hemo-parasites or lymphotropic organisms.
5. Patients with chest trauma.

Study Procedures:

Screening:

Elderly patients admitted to the acute care units (ICUs and the Emergency Department of AIIMS Bhubaneswar) during the study enrolment period and meeting all the study criteria will be eligible for participation. They/their relatives will be approached with an information brochure containing the detailed description of the study and will be encouraged to volunteer for the study.

Upon receiving an informed and voluntary consent, the patients will be randomized into either of the two study groups using a computer-generated randomization scheme and serially numbered sealed opaque envelopes for allocation concealment. The process of allocation as per the randomization codes will be done by a staff nurse, who will not be part of the investigating team. The two groups will be as follows-

- Study Group (S): Receiving resB® Lung Support capsule twice daily for 14 days from enrolment.
- Control Group (C): Receiving placebo capsules twice daily for 14 days from recruitment.

Baseline (Day 0):

Within 24 hours of enrolment and admission into the acute care unit and after collection of the baseline samples of blood, stool and respiratory aspirate, the patients in both the groups will be started on an enteral feeding regimen provided by the hospital Nutrition Team.

Study Drug Administration:

- Study Group (S): Receiving resB Lung Support capsule twice daily orally for 14 days from enrolment.

- Control Group (C): Receiving placebo capsules twice daily orally for 14 days from recruitment

Samples of venous blood, stool and respiratory aspirate will be collected from the patients at each of the following three (3) defined time points –

- Within 24 hours of admission and enrolment
- After 14 completed days of interventional supplementation
- After 30 completed days since initiation of interventional supplementation/ hospital discharge – whichever is earlier

Respiratory aspirates will be performed as per the standard described procedure

10 ml of venous blood will be aspirated under all aseptic precautions via a fresh ante-cubital vene-puncture and collected in two sterile vacutainers of 5 ml each – one containing EDTA as the anti- coagulant and the other without any anticoagulants.

Stool samples (about 10-20g) will also be collected using appropriate methods to avoid contamination, in sterile containers, designated for the same.

The collected samples will be appropriately labelled and sent off to the CCMR laboratory, where they will be appropriately processed, aliquoted and preserved in - 80°C freezer till analysis.

Rescue Treatment:

Not specifically planned. Symptomatic management of the patients will be done with supportive care in case of any study drug elated adverse effects.

Criteria for Evaluation of Endpoints

Diagnosis of pneumonia and its incidence:

This will be done using pre-designed proforma and will include the patient's demographics, past medical, surgical and treatment history, course of the present disease, biochemical, hematological, radiological and microbiological investigation parameters, antibiotic therapy and other relevant treatment details curetted from a thorough review of the patient's daily clinical notes, vitals chart and investigation records.

Human Secretory IgA:

Isolated serum and fecal sample will be used to measure human secretory IgA using commercially available indirect immunoassay kits.

Respiratory aspirates and fecal samples collected will be processed for DNA extraction using DNeasy PowerLyzer PowerSoil kits. The hypervariable V4 region of the 16S rRNA gene will

be amplified using appropriate primers and PCR conditions. PCR will be performed using Illumina barcoded adapters to prepare sequencing libraries and sequenced using Illumina MiSeq to generate 2x300 base pair (bp) reads. Sequence data quality will be assessed, adapters removed, and bio-informatics analysis performed. De novo assembly of contigs of at least 900 bp will be done, and gene prediction will be performed after discarding genes less than 100 bp. A non- redundant gene catalogue will be constructed and annotated to the KEGG database using BLASTP with e-values = 1 × 10-5. Relative gene abundances will be estimated by dividing gene- length normalized read counts by total sample mapped reads. The taxonomic characterization of each sample will be determined by mapping high-quality reads from each sample to appropriate genes databases. Data analysis will attempt to correlate lung infection category to markers of intestinal dysfunction using standard statistical analysis. Associations of lung infection status with gut microbial composition will be determined using appropriate software.

Short-chain fatty acid (SCFA) estimation:

5g of fecal sample will be used for the free and total SCFA analysis. The collected fecal sample will be diluted to 20% using 0.9% sodium chloride solution. 2ml 20% fecal sample will be added to 2ml of internal acid mixture. This sample will be stored in -80°C freezer for the estimation. The samples to be analysed will be taken out and allowed to thaw for room temperature. Sample will be divided into three portions and used for free and total SCFA and dry weight measure using GC MS machine. Internal standard method will be used for the calibration. 0.5 mM concentration will be used for the internal acids (isobutyric and isovaleric acid). For estimating free SCFA, the sample will be adjusted to pH 2-3 using 20% ortho phosphoric acid. After pH adjustment sample will be centrifuged for 10 minutes at 2000 rcf. The supernatant will be taken for GCMS injection. For estimating total SCFA, 1 ml of the sample will be digested using 150 ul of 6M sodium hydroxide for 2 hours with 30 minutes' interval shaking. After 2 hours' sample will be adjusted to pH 2-3 using 40% ortho phosphoric acid. After pH adjustment sample will be centrifuged for 10 minutes at 2000 rcf. The supernatant will be taken for GCMS injection.

Immunophenotyping:

a)Peripheral blood mononuclear cells (PBMCs) will be directly isolated by Ficoll-Hypaque gradient.

b)Immune profiling: Single-cell suspension of cells will be stained with the following antibodies: CD3 (UCHT1), CD4 (RPA-T4; VIT4), CD8 (RPA-T8; OKT8), CD19 (HIB19), CD56 (B159,), CD127 (eBioRDR5), CD25 (M-A251 BD; BC96), ICOS (ISA-3), CXCR5 (51505), CCR6 (11A9), CCR5 (27D/CCR5).

c) Samples will be processed and passed on a flow-cytometer.

d) $CD4^+$ T-cell subsets will be gated according to well-established phenotypic markers.

e) Data will be analyzed using FlowJo software.

f) PBMC culture and CyTOF based immune profiling:

Immunophenotyping of the participants will be performed by particularly estimating CD4, CD8 T Cells and cytokines IL-6, IL-10, TNFα, an extensive approach will be taken on a sub-cohort.

Statistical Analysis:

The primary outcome data is the incidence of pneumonia between the two groups of elderly population receiving probiotics and placebo. This will be compared by the Chi- squared test for statistical significance.

The Next Generation Sequence data will be analyzed using the software named QIIME. This platform evaluates alpha and beta diversity, generates core microbiome. Principal co-ordinate analysis will be used to reveal association between lung infection severity of the patients. We will compare the microbiome composition at baseline and after intervention in all patients using ANOVA or Kruskal Wallis test to determine the differences between the two study groups.

We will assess for the correlation between microbiome composition and other study parameters like demography, socioeconomic status, medical history, nutritional parameters, secretory IgA levels and cytokine profiles.

Statistical significance of the immune profile will be calculated using two-tailed Student t test in the case of a Gaussian distribution (determined by the use of SPSS software, IBM); otherwise, the Mann-Whitney test will be used for unmatched groups and the Wilcoxon test will be used for paired groups. P values <0.05 will be regarded as statistically significant.

12. (a) If the study is institutional, state whether it is intra-departmental or inter-departmental. : Inter-departmental

b) If the study is inter-departmental, :

(i) State the names of collaborating departments :

Department of Anesthesiology & Critical Care and Department of Biochemistry

(ii) State whether consent/administrative sanction has been obtained from them : Yes

13. (a) If the study is inter-institutional, whether it is national or international. : National

(b) State the names of collaborating institutions. : ILS Bhubaneswar

© State whether consent/administrative sanction has been obtained from collaborating institutions. Enclose copies of the same. : Yes

(d) State whether you have enclosed a copy of the original research protocol submitted by the coordinating institution. : Yes

e) State the responsibilities of each collaborating institution. :

The Clinical and biochemical work will be conducted at AIIMS Bhubaneswar. The genome sequencing will be done at ILS Bhubaneswar.

14. Total funds required for the study (in rupees). : Rs. 33, 12, 000

15. Justification for required funds. :

(a) Non-recurring requirements and their costs :

(b) Recurring requirements and their costs :

(c) Research project staff requirements & their expenditures :

(d) Overhead charges :

(e) Others (specify) :

Man power (Medical Officer) (32,000/- Consolidated)	Rs.3,84,000	Recruitment of study subjects and collection of Biological samples
Laboratory Technician (24,000/-)	Rs.2,88,000	Processing Samples and to perform laboratory assays.
Sequencing	Rs.15,00,000	Viral genome, metagenome sequencing and immune phenotyping
Consumables	Rs.7,40,000	DNA and RNA extraction kits and cytokine assay kits.
Bioinformatics analysis	Rs.2,50,000	Bioinformatics analysis for study data will be performed by OUAT
Contingency	Rs.2,00,000	For sample collection containers, Dry Ice, incidentals, proforma printing, stationary etc.
Travel	Rs.1,50,000	For the sample collection from rural and urban areas, project meetings and subject related conference.

16. (a) Source of funding (intramural or extramural) : Extra-mural

(b) If extramural, state the name of funding agency. : ResBiotic Nutrition

18. Duration of the study : 1 year

19. Approval by Institute Ethics committee obtained : No

(Also enclose approvals from other IECs for multicentre studies) :

20. The principal investigator should state

(a) The number of ongoing research projects as principal investigator : 1

(b) Source and amount of funds in each of his/her research project : 3,58,800 (intra-mural)

21. Enclosures :

SECTION-B: DISCLOSURE FOR ETHICAL REVIEW

Serial No of IEC Management Office :

- To be filled by IEC secretariat

1. Type of Study	Cross sectional		Case Control		Cohort		Clinical Trial		Review		
Participating Centre	Single center		Multi-centric		Others (Specify)						

Whether any work on this project has started or not?		(mark √if yes, X if no)
	(Please enclose a separate certificate to this effect).	

2. TYPE OF REVIEW:

Initial Review	
Resubmission Review	
Amendment Review	
Expedited Review	
Emergency Review	
Continuing Review	
Report Review	
Protocol Termination	

3. Sponsor Information:										
1. Indian	a.	Government		Central		State		Institutional		
	b.	Private					c.	Self- Funded		
2. International		Government		Private				UN agencies		
3. Industry		National				Multinational				
Contact Address of Sponsor:										
Financial Disclosure:			Yes (provide break-up)			NO, Why not? ……				
Who will bear the cost of investigation / implants drugs / contrasts?			1. Patient		2. Project		3. Exempted			
							4. Other Agencies (Name)			

- Has the principal investigator ever been involved in or convicted of a crime, disciplined by a public or private medical organization, or by a licensing authority?
  No Yes, explain.....
- Does the PI, the study colleagues or their families have any financial relationship with the sponsor other than payment for the conduct of the study?
  No Yes, describe the relationship.....

Note: Financial disclosure includes speaking fees, consultation fees, stock ownership or other equity interest, patents, trademarks, copyrights, licensing agreements. Report interests valuing over $10,000 and interests representing a greater than 5% ownership in an enterprise.

- For this study, how many of the following will the PI supervise? Sub-investigators.....Study. sites .....
- How many (in total) of the following does the PI currently supervise? Open studies ..... Location..... Sub-investigators..... . Study staff .....

Essential Enclosures based on standard formats

Item	Status	Page no.

	(encircle right response)	
Informed Consent Form Provide Informed consent form (clearly identified and dated) in the language(s) understood by the potential research participants and, when required, in other languages too.	Yes/No/NA	

Consent:	Written		Oral		Audio-visual	

i. Consent form: (tick the included elements)		Alternatives to participation	
Understandable language		Confidentiality of records	
Statement that study involves research		Contact information	
Purpose and procedures		Statement that consent is voluntary	
Risks & Discomforts		Right to withdraw	
Benefits		Consent for future use of biological material	
Compensation for participation		Benefits if any on future commercialization eg. genetic basis for drug development	
Compensation for study related injury			
*If written consent is not obtained, give reasons:			

Who will obtain consent?	PI/ Co-PI Research staff	Nurse/Counsellor Any other (specify)
Participant Information Sheet Written and other forms of information for potential research participants (clearly identified and dated) in the language(s) understood by the potential research participants and, when required, in other languages too.	**Yes / No / NA**	
Case report forms, diary cards, and other questionnaires intended for research participants;	**Yes / No / NA**	
Study budget and budget justification	**Yes / No / NA**	
A statement of agreement to comply with ethical principles set out in relevant guidelines, Good Clinical Practices (GCP) protocols for clinical trials.	**Yes / No / NA**	
Curriculum Vitae (CV) of investigators (updated, signed, and dated)	**Yes / No / NA**	
Investigators' Brochure*	**Yes / No / NA**	
* when the research involves a study product (such as a pharmaceutical or device under investigation), an adequate summary of all safety, pharmacological, pharmaceutical, and toxicological data available on the study product, together with a summary of clinical experience with the study product to date (e.g., recent investigator's brochure, published data, a summary of the product's characteristics etc.) has to be provided. For any drug / device trial, all relevant pre-clinical animal data and clinical trial data from other centres within the country / other countries, if available should be provided.		
Material to be used (including advertisements) for the recruitment of potential research participants	**Yes / No / NA**	
All significant previous decisions (e.g., those leading to a negative decision or modified protocol) by other ECs or regulatory authorities for the proposed study (whether in the same location or elsewhere) and an indication of modification(s) to the protocol made on that account. The reasons for previous negative decisions should be provided.	**Yes / No / NA**	

CPCSEA clearance, if any	**Yes / No / NA**	
HMSC/DCGI/DBT/BARC clearance if obtained	**Yes / No / NA**	
In case of multi-centric study, IEC clearance of other centres must be provided	**Yes / No / NA**	
In case an insurance cover is intended, Insurance certificate must be provided (as per ICMR guidelines)	**Yes / No / NA**	
Permission to use copyrighted Questionnaire/ proforma	**Yes / No / NA**	
Definite undertaking as to who will bear the expenditure of injury related to the project	**Yes / No / NA**	
Institutional Animal Ethics Committee clearance	**Yes / No / NA**	
Agreement to report all Serious Adverse Events (SAE) to AIIMS BBSR -IEC.	**Yes / No / NA**	

Essential Descriptions

A. Provide a description of the ethical considerations involved in the research and plan to address this issue.

Also include information on following items as mentioned in the box below

Subject selection:		
i. Number of Subjects :		
ii. Duration of study :		
iii. Will subjects from both sexes be recruited	Yes	No
iv. Inclusion / exclusion criteria given	Yes	No

v. Type of subjects	Volunteers		Patients	

vi. Vulnerable subjects (Tick the appropriate boxes)		Yes		No	
pregnant women		children		elderly	
fetus		illiterate		handicapped	
terminally ill		seriously ill		mentally challenged	
economically & socially backward		any other			

vii. Special group subjects s (Tick the appropriate boxes)		Yes		No	
captives		institutionalized		employees	
students		nurses/dependent		armed	
any other		staff		forces	

Privacy and confidentiality			
i. Study involves -	Direct Identifiers		
	Indirect Identifiers/coded		
	Completely anonymised/ delinked		

ii. Confidential handling of data by staff	Yes	No
Use of biological/ hazardous materials i. Use of fetal tissue or abortus	Yes	No
ii. Use of organs or body fluids	Yes	No
iii. Use of recombinant/gene therapy **If yes**, has Department of Biotechnology (DBT) approval for rDNA products been obtained? **If Yes**, the study has been reviewed by ….. ¡ None ¡ Bio-safety ¡ Recombinant DNA Advisory Committees	Yes Yes	No No
iv. Use of pre-existing/stored/left over samples	Yes	No
v. Collection for banking/future research	Yes	No
vi. Use of ionizing radiation/radioisotopes **If yes**, has Bhaba Atomic Research Centre (BARC) approval for Radioactive Isotopes been obtained?	Yes	No
vii. Use of Infectious/bio hazardous specimens	Yes	No
viii. Proper disposal of material	Yes	No
ix. Will any sample collected from the patients be sent abroad? **If Yes, justify with details of collaborators**	Yes	No
a) Is the proposal being submitted for clearance from Health Ministry's Screening Committee (HMSC) for International collaboration?	Yes	No

b) Sample will be sent abroad because (Tick appropriate box):

Facility not available in India		
Facility in India inaccessible		
Facility available but not being accessed.		
If so, reasons…		

Risks & Benefits: i. Is the risk reasonable compared to the anticipated benefits to subjects / community / country?	Yes	No

ii. Is there physical / social / psychological risk / discomfort?		Yes	No
If Yes, Minimal or no risk			
More than minimum risk			
High risk			

iii. Is there a benefit a) to the subject ?				
Direct		Indirect		
b) Benefit to society				

Is there compensation for participation? (including expenses and access to medical care)				Yes	No
If Yes, Monetary		In kind			
Specify amount and type:					

Is there compensation for injury?				Yes	No
If Yes, by Sponsor		by Investigator			
by insurance company		by any other (give details)			

14. Do you have conflict of interest? (financial/nonfinancial) If Yes, specify :	Yes	No

Conflict of interest for any other investigator(s) (if yes, please explain in brief	1.	Yes		No	
	2.				
	3.				
	4.				

B. Provide a description of the process used to obtain and document consent

C. A description of the arrangements for indemnity, if applicable.

D. A description of the arrangements for insurance coverage for research participants, if applicable.

E. Explain all anticipated 'risks' (adverse events, injury, discomfort) of the project. Efforts taken to minimize the 'risks'. Proposed compensation and reimbursement of incidental expenses and management of research related and unrelated injury/ illness during and after research period.

F. How long will the research data be stored by the PI? …….years after closing the study

G. **What kind of means will be used to recruit subjects for the study?** (All recruitment materials [copy to be enclosed] must be approved by IRB before use.)

	Personal contact
	Referrals
	From database other than the PI's list
	Advertising
	Other, specify……

H. Investigator should provide undertaking what they will do with the leftover sample tissue?

I. For international collaborative study details about foreign collaborators and documents for review of Health Ministry's Screening Committee(HMSC) or appropriate Committees under other agencies/ authority like Drug Controller General of India (DCGI)

J. For exchange of biological material in international collaborative study a MoU/ Material Transfer Agreement between the collaborating partners. **(Enclose copy and indicate the enclosure no. and page no. in this document)**

K. Plans for publication of results / positive or negative / while maintaining the privacy and confidentiality of the study participants.

L. Any other information relevant to the study.

Additional Information for Clinical Trials / Experimental Studies

Clinical Trials: **Drug /Vaccines/Device/Herbal Remedies :**						
i. Does the study involve use of :						
Drug		Devices		Vaccines		
Indian Systems of Medicine/		Any other		NA		
Alternate System of Medicine						

Is it approved and marketed					
In India		UK & Europe		USA	
		Other countries, specify			

iii. Does it involve a change in use, dosage, route of administration? If yes, whether DCGI's /Any other Regulatory authority's Permission is obtained? If yes, Date of permission :	Yes Yes	No No
iv. Is it an Investigational New Drug? If yes, IND/ FDA No: Name of IND: Sponsor: Holder:	Yes	No
v. Is it an Investigational New Device? If yes, INE/ FDA No: Name of IDE: Sponsor: Holder:	Yes	No
Procedure used:	Invasive	Non-invasive
a). Investigator's Brochure submitted	Yes	No
b). In vitro studies data	Yes	No
c). Preclinical Studies done	Yes	No

d) Clinical Study is :	Phase I		Phase II		Phase III		Phase IV	

e). Are you aware if this study/similar study is being done elswhere ? If Yes, attach details and give enclosure no. ____ & Page no.____	Yes	No
Data Monitoring i. Is there a data & safety monitoring committee/ Board (DSMB)?	Yes	No

ii. Is there a plan for reporting of adverse events? If Yes, reporting is done to :	Sponsor		Ethics Committee		DSMB		Yes	No

iii. Is there a plan for interim analysis of data?	Yes	No

vi. Are there plans for storage and maintenance of all trial database? If Yes, for how long ?	Yes	No

In case of clinical trials CTRI status Other relevant details	Registered / Not registered No……

	Name, Designation, Department & Qualifications	Address Tel & Fax Nos. Email ID	No of projects already with Investigator	Signature
PI	**Dr. Jayanta Kumar Mitra** **Additional Professor** **Department of Anesthesiology & Critical Care** **AIIMS Bhubaneswar**	**Sijua, Patrapada, Bhubaneswar, Odisha 751019** 9433798583 mitra.jayanta@gmail.com	4	Dr. Jayanta Kumar Mitra Additional Professor Dept. of Anesthesiolog AIIMS,Bhubaneswar-75101
Co-PI / Collaborators 1.	Dr. Ramadass Balamurugan Additional Professor, Department of Biochemistry, AIIMS-Bhubaneswar	**Sijua, Patrapada, Bhubaneswar, Odisha 751019** 8547805341 balaramadass1@gmail.com		3/2/22 Dr. Balamurugan Ramadass Additional Professor Department of Biochemistry Head Centre For Clinical Microbiome Research (CCMR) AIIMS, Bhubaneswar-751019
2.	Dr. Prasanta Kumar Sahoo	Dept. of AYUSH Mob: 7240734331 Sahooprasanta78@gmail.com		Prasanta 3/2/2022 Dr. Prasanta Ku... MS (Ay) Senior Medical ... (Ayurveda) Department ... AYUSH AIIMS, Bh... ...war
3.				
4.				

Signature of the Principal Investigator
(Name & Designation)

Dr. Jayanta Kumar
Additional Profess
Dept. of Anesthesiolc
AIIMS, Bhubaneswar-751

Dr. Jayanta Kumar Mitra

Additional Professor

Department of Anesthesiology & Critical Care

AIIMS Bhubaneswar

Signature of Head of the Department
of the Principal Investigator 3/2/22
(Name & Designation)

Dr. Satyajeet Misra

Professor and Head,

Department of Anesthesiology & Critical Care

AIIMS Bhubaneswar

Signature(s) of the Co-Investigator(1)
(Name & Designation)

Dr. Ramadass Balamurugan

Additional Professor

Department of Biochemistry

AIIMS-Bhubaneswar

3/2/22

Dr. Balamurugan Ramadass
Additional Professor
Department of Biochemistry
Head Centre For Clinical
Microbiome Research (CCMR)
AIIMS, Bhubaneswar-751019

Signature(s) of the Co-Investigator(2)
(Name & Designation)

Signature(s) of the Co-Investigator(2)
(Name & Designation)

3/2/2022

Dr. Prasanta Kumar Sahoo
SMO, Dept. of AYUSH
Dr. Prasanta Kr. Sahoo, MS (Ay)
Senior Medical Officer (Ayurveda)
Department of AYUSH
AIIMS, Bhubaneswar

Signature(s) of the Co-Investigator(3)
(Name & Designation)

To be filled by Research cell, AIIMS Bhubaneswar only

Checklist:

1. Complete information provided as per format (Yes/ No / Any deficiencies…….)

2. Copy of complete project proposal with signatures of PI, co-PIs and HoD and required documents received (Yes/ No / Any deficiencies…….)

3. Copy of project in digital format (CD/ DVD/ pen drive/email) received (Yes / No / Any deficiencies…….)

4. Category of research project (please tick □)

a. Intramural

b. Extramural
   - Concept proposal
   - Final proposal

c. Collaborative with other institute

Project received on date_____

Provisional project code assigned: _____

Acknowledgement

Received copy of project proposal titled "……" from Dr.
…… Department of……..,……,
AIIMS Bhubaneswar on Date……..
Provisional project code assigned……..

Signature of Member Secretary, Research cell Date:

PARTICIPANT INFORMED COSENT FORM (PICF)

Participant identification number for this study: _____

Title of the study:

Exploring effects of probiotic formulation (resB® Lung Support) on gut-lung axis in elderly pneumonia patients: an RCT

Name of Principal Investigator:

Dr. Jayanta Kumar Mitra, Addl. Professor, Department of Anesthesiology & Critical Care, AIIMS, Bhubaneswar.

The contents of the information sheet dated …… that was provided have been read carefully by me / explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions.

The nature and purpose of the study and its potential risks / benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected.

I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible individuals from AIIMS, Bhubaneswar. I give permission for these individuals to have access to my records.

I agree to take part in the above study.

---------- Date:

(Signatures / Left Thumb Impression) Place:

Name of the Participant: _____

Son / Daughter / Spouse of: _____

Complete postal address: _____

This is to certify that the above consent has been obtained in my presence.

Signatures of the Principal Investigator Date:

Place:

1) Witness – 1

Signature

Name:

Address:

2) Witness – 2

Signature

Name:

Address: