Trials

STUDY PROTOCOL

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A phase II, randomized, open-labeled study to evaluate low-dose pembrolizumab in addition to neoadjuvant chemotherapy for triple-negative breast cancer (TNBC)

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Abstract

Background Breast cancer is the most common malignancy diagnosed in women worldwide. Triple-negative breast cancer (TNBC) is the most aggressive subtype, accounting for nearly one third of all breast cancers in India. The addition of pembrolizumab to neoadjuvant chemotherapy improved the pathological response and event free survival in patients with TNBC. However, for most patients in low- and middle-income countries, immunotherapy remains inaccessible due to its high cost. Pharmacological and early clinical data suggest that a lower dose of pembrolizumab may be effective. However, there are no prospective clinical trials in patients with TNBC.

Methods This is a single-site phase II, randomized, open-labeled, parallel-group trial. Eligible patients will be randomized (1:1) to either of the two treatment groups. Patients in the control arm will be administered standard of care chemotherapy [4 cycles of dose-dense doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2), followed by 4 cycles of dose-dense paclitaxel (175 mg/m^2)]. Patients in the experimental arm will receive 3 doses of pembrolizumab 50 mg every 6 weeks along with neoadjuvant dose-dense chemotherapy. The primary objective of the study is to compare the pathological complete response with the addition of low-dose pembrolizumab to neoadjuvant chemotherapy in patients with TNBC. Secondary objectives include invasive disease-free survival and quality of life assessment.

Discussion The PLANeT trial aims to establish the efficacy of low-dose pembrolizumab in addition to neoadjuvant chemotherapy in patients with triple-negative breast cancer patients. This strategy, if found effective, will help improve the outcomes of women with TNBC who currently have limited access to pembrolizumab.

Trial registration Clinical Trials Registry of India—CTRI/2024/01/062088.

Keywords Triple negative, Breast cancer, Immunotherapy, Low dose, Pembrolizumab, Non-metastatic

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Introduction

Background and rationale {6a}

Triple-negative breast cancer (TNBC) accounts for 12–13% of all breast cancers in the Western population [1]. The prevalence of TNBC varies considerably globally, with it being more frequent in young women and in African-American women compared to white women [2] The risk of TNBC is more is 2.7 times higher in black women compared to whites [3]. It is the most aggressive subtype of breast cancer, associated with poorer outcomes when compared with other subtypes, even when adjusted for stage and other prognostic factors [3]. The prevalence of TNBC is lower in the Asian population; however, in India, the proportion of patients with TNBC has been reported to be as high as 31% [4, 5], likely due to the younger average population in India. There is a higher prevalence in premenopausal women, and patients with TNBC are more likely to present with larger tumor size and metastatic disease as compared with other subtypes [6]. The maximum chance of cure for patients with TNBC is at an early stage, and once metastatic, the prognosis remains poor, with a median overall survival of approximately 15 months [7]. Even at an earlier stage, the risk of metastatic recurrence is higher compared to other subtypes of breast cancer [8].

The management of early TNBC has witnessed a paradigm shift to neoadjuvant chemotherapy in the early stage [9]. This approach provides an opportunity to assess the in vivo pathological response to neoadjuvant chemotherapy. In patients where a pathological complete response is observed, the prognosis is significantly better than that of those with residual disease [10]. Additional systemic treatment with capecitabine for 6 months in patients with residual disease showed significant improvement in overall survival [11]. Furthermore, adding pembrolizumab, an immune checkpoint inhibitor, also improved the pathological complete response and disease-free survival in these patients.

In the Keynote 522 trial, patients with stage I-III TNBC were randomized in a 2:1 ratio to receive pembrolizumab or placebo in addition to 8 cycles of neoadjuvant chemotherapy (4 cycles of carboplatin and paclitaxel followed by 4 cycles of epirubicin/docetaxel and cyclophosphamide). These patients then underwent surgery, followed by pembrolizumab or placebo every 3 weeks for up to nine cycles. This trial demonstrated increased pathological complete response and event-free survival at 3 years by adding pembrolizumab to neoadjuvant chemotherapy [12].

After this landmark trial, pembrolizumab with neoadjuvant chemotherapy is considered the new standard of care for patients with TNBC [9]. However, the cost of pembrolizumab is prohibitive; therefore, it remains inaccessible for more than 95% of patients in low- and middle-income countries (LMICs) [13, 14].

Lower doses of immune checkpoint inhibitors (nivolumab and pembrolizumab) have been shown to be effective in several cancers, including head and neck cancers and Hodgkin's lymphoma [15, 16]. Ex vivo IL2 stimulation for the purpose of evaluating PD-1 receptor modulation revealed total peripheral target engagement beginning at 1 mg/kg and lasting for at least 21 days, with no discernible difference between 1, 3, and 10 mg/kg [17]. Evaluation of low-dose immunotherapy in breast cancer has not been done so far.

Testing low-dose pembrolizumab could have significant implications for society, healthcare professionals, and the healthcare system as a whole.

Full-dose immunotherapy is inaccessible for most patients in low- and middle-income countries due to its high cost [18]. If this study proves that adding low-dose pembrolizumab to neoadjuvant chemotherapy is effective, it could establish this as a new standard of care, making it accessible to a wider population across the globe. Healthcare professionals will have more options to tailor treatments to individual patient needs, potentially improving outcomes while decreasing financial toxicity. Reducing the dose will also lower overall treatment costs in publicly funded healthcare systems, reducing the financial burden.

Therefore, we designed this study to evaluate a lower dose of pembrolizumab in addition to neoadjuvant chemotherapy in patients with TNBC as a cost-effective intervention.

Objectives {7}

Primary objective (endpoint):

The primary objective is to compare the pathological response with the addition of low-dose pembrolizumab in addition to NACT in patients with TNBC (proportion of patients with pathological complete response in two arms).

Secondary objectives (endpoint):

1. To compare invasive disease-free survival in two arms (invasive disease-free survival rate at 3 years)
2. Quality of life assessment in both arms (EORTC QLQ30 at baseline, with the 4.th cycle of neoadjuvant therapy and at the end of neoadjuvant therapy)

Trial design {8}

This is a single-center randomized, open-labeled, parallel-group trial. Patients will be randomized at the All India Institute of Medical Sciences, New Delhi, and the

National Cancer Institute, Jhajjar. They will be allocated to the two treatment groups in a ratio of 1:1.

Methods: participants, interventions, and outcomes

Study setting {9}

Adult patients diagnosed with non-metastatic triple-negative breast cancer (stages I–III) will be invited to participate in the study. Patients will be recruited from the two cancer blocks of the All India Institute of Medical Sciences, a central government-funded tertiary care hospital.

1) Dr BR Ambedkar Institute Rotary Cancer Hospital (IRCH), New Delhi, India
2) National Cancer Institute, Jhajjar, Haryana, India

The IRCH and National Cancer Institute cater to a large population (over 20 million) in Delhi and its neighboring states and registers over 15,000 patients with cancer annually.

All patients shall be enrolled within 2 years. All the patients shall be followed up to 5 years after surgery.

Eligibility criteria {10}

Patients meeting the following criteria will be enrolled in the trial.

Inclusion criteria:

1. Age ≥ 18 years
2. Confirmed TNBC
3. Eastern cooperative oncology group performance status 0 or 1
4. Left ventricular ejection fraction ≥ 50%
5. Nonmetastatic disease with a primary tumor size of more than 1 cm in the absence of axillary lymph nodal involvement or any size with axillary lymph nodal involvement
6. Adequate organ functions, defined as
    a. Serum creatinine ≤ 1.5 mg or creatinine clearance ≥ 50 ml/min
    b. Serum bilirubin < 1.5 UNL, alanine aminotransferase/aspartate aminotransferase < 3 UNL
    c. Hemoglobulin > 9.0 gm/dl, platelet count > 100,000, and absolute neutrophil count > 1500/μL
7. Subjects must have a left ventricular ejection fraction (LVEF) of ≥ 50%, assessed via echocardiogram (ECHO) or multigated acquisition (MUGA) scan during screening.
8. Male and female subjects of childbearing potential must agree to use effective contraception methods, including:
    a. Intrauterine device (IUD)
    b. Vasectomy of the female subject's male partner
    c. Contraceptive rod implanted under the skin
    d. Diaphragm with spermicide (not to be used with a cervical cap/spermicide)
    e. Contraceptive sponge (for nulliparous women only)
    f. Male or female condom (not to be used simultaneously)
    g. Hormonal contraceptives: oral pills (either estrogen/progestin or progestin-only), skin patches, vaginal rings, or subcutaneous injections

The following patients will be excluded from the trial:

1. ECOG performance status of ≥ 2
2. Preexisting autoimmune condition requiring systemic immunosuppression, including steroids (> 10 mg prednisolone or equivalent)
3. Acquired immunosuppression (e.g., HIV, systemic immunosuppression)
4. Recipient of hematopoietic or organ transplant
5. History of any synchronous malignancy or having a synchronous malignancy
6. History of invasive malignancy ≤ 5 years before signing informed consent
7. Previous therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or another co-inhibitory T cell receptor agent
8. Received a live vaccine within 30 days before the first dose of study treatment
9. Known active hepatitis B (e.g., HBsAg reactive) or hepatitis C (e.g., HCV RNA [qualitative] detected)
10. History of (non-infectious) pneumonitis that required steroids or current pneumonitis
11. Active infection requiring systemic therapy
12. Significant cardiovascular disease, such as a history of myocardial infarction, acute coronary syndrome, or coronary angioplasty/stenting/bypass grafting within the past 6 months, or congestive heart failure (CHF) classified as New York Heart Association (NYHA) Class II-IV or history of CHF NYHA Class III or IV
13. History or current evidence of any condition, therapy, laboratory abnormality, or other circumstances that might expose the subject to risk by participating in the trial, confound the trial results, or interfere with participation for the full duration of the trial
14. Known psychiatric or substance abuse disorders that would interfere with adherence to trial requirements
15. Pregnant or breastfeeding or planning to conceive children within the trial duration, starting from

screening through 12 months after the last dose of trial treatment for those who received cyclophosphamide, and for 6 months after the last dose of study medication for those who did not
16. Known hypersensitivity to the study therapy components or their analogs
17. Active tuberculosis (*Bacillus tuberculosis*)

Who will take informed consent? {26a}

Informed written consent shall be taken by one of the study investigators prior to enrolment into clinical trial. The potential risks and benefits of participating in the study will be discussed with the patient and caretakers in their native language (Hindi or English) so that the patient can easily comprehend. Consent will be entirely voluntary and free from any coercion. Written informed consent will be obtained from all subjects, and the investigator will countersign and date it before any study-specific screening investigations are performed.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable.

Interventions

Explanation for the choice of comparators {6b}

Not applicable.

Intervention description {11a}

The experimental arm will be given pembrolizumab 50 mg thrice (with 1st, 4th, and 8th cycles) with dose-dense AC chemotherapy (4 cycles), followed by 4 cycles of two weekly single-agent paclitaxel.

The control arm will be given dose dense AC chemotherapy (4 cycles), followed by 4 cycles of two weekly single-agent paclitaxel (Table 1).

Criteria for discontinuing or modifying allocated interventions {11b}

In case of grade 3 or grade 4 immune-related adverse events, pembrolizumab will be discontinued. For grade 1 or 2 toxicity, drug rechallenge shall be done after recovery.

Pembrolizumab shall be stopped upon withdrawal of consent from the patient.

Management shall be done for chemotherapy-related adverse events as per institutional protocol. For grade 3 or 4 adverse events, dose reduction will be done as per the treating physician's discretion.

Table 1 Drug, drug potency, dose frequency, route of administration, and dosing time of each cycle

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Dosing Time of each cycle
Pembrolizumab	50mg	Every six weeks: with cycles 1 and 4 of ddAC and cycle 3 of single-agent paclitaxel	IV infusion	Day 1 of 1st and 4th cycle of ddAC and cycle 3 of single-agent paclitaxel.
Doxorubicin	60 mg/m2	Every 2 weeks, cycle 1-4	IV infusion	Day 1 of Cycles 1-4 of ddAC
Cyclophosphamide	600 mg/m^2	Every 2 weeks, cycle 1-4	IV Infusion	Day 1 of Cycles 1-4 of ddAC
Paclitaxel	175 mg/m^2	Every 2 weeks, cycle 5-8	IV Infusion	Day 1 of Cycles 5-8 of single-agent paclitaxel

Strategies to improve adherence to interventions {11c}
Not applicable.

Relevant concomitant care permitted or prohibited during the trial {11d}
Permitted: The investigator may administer any treatments deemed essential for the patient's well-being, adhering to the community standards of medical care. All accompanying medications, including prescriptions, over-the-counter drugs, herbal supplements, and intravenous treatments, will be documented in the case report form (CRF).

Prohibited: Subjects are prohibited from receiving the following therapies from the time of screening until completion of all study therapy:

- Immunotherapy other than that in this protocol
- Chemotherapy other than that in this protocol
- Live vaccines within 30 days before the first dose of trial treatment and while participating in the trial
- Glucocorticoids are used for any purpose other than to modulate symptoms from an immune-related adverse event of suspected immunologic etiology or for use as a premedication for chemotherapeutic agents specified in the protocol.

Provisions for post-trial care {30}
All patients will receive standard post-trial care that will include capecitabine or olaparib for residual disease and radiotherapy as per the discussion with the treating physician. Continuation of pembrolizumab after surgery will not be covered in the current clinical trial; however, the patient may receive further immunotherapy, if accessible. All post-trial interventions will be documented in the study.

Outcomes {12}
Primary objective:

The primary objective is to compare the pathological complete response rates with the addition of low-dose pembrolizumab in addition to NACT in patients with TNBC.

Secondary objectives:

1. To compare radiological response with mammograms performed at baseline and at completion of NACT
2. To compare invasive disease-free survival in the two arms

Pathological complete response is defined as the absence of residual cancer in the resected specimen after complete resection of the primary lesion and all sampled regional lymph nodes at the end of neoadjuvant therapy.

Disease-free survival is the duration between the point of randomization to disease recurrence or death. Invasive disease-free survival is the time from randomization to invasive disease recurrence or death due to any cause.

Participant timeline {13}

	Screening Within 14 days prior to registration	Baseline Within 3 days prior to day 1 of cycle 1	On treatment Within 3 days prior to day 1 of chemotherapy ± pembrolizumab	End of study After surgery
Informed consent	X			
Clinical assessment		X	X	X
Concomitant medications		X	X	
Routine Blood investigations		X		
2D ECHO/MUGA		X		
ECG		X		
Adverse events assessment including iRAE			X	
Pathological response assessment				X
Quality of life assessments/PRO		X	X* (4th cycle)	X

Sample size {14}
From prior institutional experience and published literature, approximately 40% of patients receiving the standard chemotherapy group will have a pathological complete response (pCR) [12].

The KEYNOTE 522 reported PCR in 64% of patients. Assuming the PCR rate will be 60% in the experimental arm and 40% in the control arm, 160 patients will be randomized in a 1:1 ratio. This will provide 80% power to detect a difference of 20% in the pathological complete response rates, with a one-sided alpha error of 0.05 and an attrition rate of 5%.

Recruitment {15}
This trial will enroll patients with TNBC breast cancer who attend outpatient services in the Department of Medical Oncology, Dr BR Ambedkar Institute Rotary Cancer Hospital, Department of Surgical Oncology, and the Department of Surgical Disciplines of All India Institute of Medical Sciences, New Delhi, India. Eligible subjects will also be enrolled at the National Cancer Institute, Jajjhar, Haryana, the second oncology block of All India Institute of Medical Sciences, New Delhi.

Assignment of interventions: allocation

Sequence generation {16a}

Subjects will be registered and subsequently randomized by research staff who will not participate in data collection and analysis. An independent statistician generated a computer-generated permuted block random number sequence stratified for the involvement of axillary lymph nodes.

Concealment mechanism {16b}

Allocation concealment will be ensured by using opaque, sealed, and sequentially numbered envelopes. The envelopes will be numbered in advance and opened only after the participant's name and date of randomization are written on them.

Implementation {16c}

Research staff, who are not involved in treatment, follow-up of data collection will generate allocation sequence. Envelopes will be numbered in advance by them and will be opened only after writing the participant's name on the envelope. Patients will be allocated to treatment groups in a ratio of 1:1. Treatment should be planned to start within 14 days after randomization.

Assignment of interventions: blinding

Who will be blinded {17a}

Not applicable.

Procedure for unblinding if needed {17b}

Not applicable.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Data shall be captured on each visit and telephonically also. The data shall be entered in Redcap eCRF forms. All required data entry fields will be completed.

Plans to promote participant retention and complete follow-up {18b}

Not applicable.

Data management {19}

The investigator will verify and sign key case report forms (CRFs) to confirm their accuracy. Source documents related to the trial will be kept at the investigational site under the principal investigator's supervision. All documents will be stored for 10 years following the study's completion.

i) Data cleaning

(1) Data validation—automated checks will be implemented to detect errors, inconsistencies, and missing information
(2) Query management—queries will be generated for any data inconsistencies or errors identified during the data validation process. The site investigators will respond to the queries, providing necessary corrections or clarifications
The clinical data management (CDM) team will review and resolve all queries.
(3) Data review—CDM will conduct periodic reviews to monitor data quality and ensure consistency

ii) Database lock

(1) Lock criteria

(a) All data must be complete and accurate
(b) All queries must be resolved
(c) All discrepancies must be addressed

(2) The CDM team, along with the principal investigator (PI) and other relevant stakeholders, will conduct a thorough review to confirm that the data meets all lock criteria. Any outstanding issues will be addressed before proceeding to the final lock

The locked database will be used for statistical analysis and regulatory submission. Any data changes required post-lock will follow a formal process involving documentation and justification.

Confidentiality {27}

All data generated in this study will remain confidential. All information will be stored securely at the All India Institute of Medical Sciences, New Delhi, and will only be available to people directly involved directly with the study.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The primary endpoint, pathological complete response (pCR) [19], will be compared between the two groups using the chi-squared test, which evaluates the association

between categorical variables. To assess correlations, linear regression analysis will examine relationships between predictor and response variables, while multivariate analysis will control for potential confounding factors. For invasive disease-free survival, the Kaplan–Meier method will be employed to generate survival curves over time, providing a visual representation of survival probabilities. The log-rank test will then compare these survival curves between the two groups, determining if there are statistically significant differences in survival rates. This comprehensive approach ensures that both the effectiveness of the treatment and survival outcomes are rigorously analyzed.

From prior institutional experience and published literature [12], approximately 40% of patients receiving standard chemotherapy arm will have a pathological complete response (PCR). The KEYNOTE 522 reported PCR in 64% of patients, with the assumption that the PCR rate will be 60% in the experimental arm and 40% in the control arm, 204 patients will be randomized in a 1:1 ratio. This will provide a power of 80% to detect a difference of 20% in the pathological complete response rates, with an alpha error of 0.1 and an attrition rate of 5%.

Interim analyses {21b}

No interim analysis is planned as the primary outcome of the study is PathCR and not survival. Interim analysis will not change the management in any manner. The safety of pembrolizumab has already been established [12]. No increased toxicity is expected by giving lower doses of pembrolizumab.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Not applicable.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Not applicable.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

Not applicable.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

An independent Data Safety Monitoring Board (DSMB) will be established, comprising experts from various fields. The DSMB will be informed of all serious adverse events (SAEs) and any grade 3 or 4 non-hematological toxicities within 72 h of notification by the principal investigator. The DSMB will convene every 6 months to review all adverse event data and perform causality assessments. Based on the information provided, the DSMB will offer timely recommendations to the investigators.

All support staff, clinicians, investigators, and trial coordinators will undergo regular quality assurance training related to trial procedures. This training will occur at frequent intervals.

Key quality metrics will be tracked, reported, and reviewed throughout the trial. All protocol deviations will be documented and assessed for severity. Any major protocol deviations will be reported to the principal investigator and DSMB, followed by corrective and preventive actions to prevent recurrence.

The trial nurse shall screen the eligible patients, counsel, and explain about the benefits and risks involved. The PI shall review and finalize enrollment and obtain consent. Randomization will be blinded, done by trial coordinator. Ensuring uninterrupted supply of drugs and other materials shall be ensured by the coordinator. The PI and trial nurse shall monitor for toxicity. The coinvestigators shall ensure that the trial proceeds smoothly.

Composition of the data monitoring committee, its role and reporting structure {21a}

A Safety and Data Monitoring Committee has been constituted. It will be independent of the sponsor and without any competing interests. The committee shall include 3 medical oncologists and a biostatistician.

Adverse event reporting and harms {22}

Adverse events will be closely monitored and documented to evaluate the treatment regimen's safety profile.

Rigorous monitoring protocols, including regular blood tests, clinical assessments, and patient-reported outcomes, will be implemented to ensure patient safety. Severe or life-threatening adverse events were promptly managed with appropriate medical interventions.

The investigator will report all serious adverse events (SAE) to the Institute Ethics Committee (IEC) within 1 working day of the investigator becoming aware of the event using the Serious Adverse Events form. SAEs will be reported up to 30 days from the end of the study intervention.

Frequency and plans for auditing trial conduct {23}

Not applicable.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Changes and amendments to the protocol can only be made by the principal investigator. In case of any amendment, the principal investigator shall inform the institutional ethics committee and, also, the funding agency

(ICMR). Approval of amendments by the Institutional Ethics Committee is required before their implementation. The amendment shall be notified to Clinical Trials Registry of India (CTRI) as well. No protocol amendments have been done to date.

Dissemination plans {31a}

The principal investigator and all co-investigators will prepare the draft to be submitted to a peer-reviewed journal(s). The first publication will be the report of the full trial results based on the main protocol using the study group name, with subsequent publications of data subsets in individual names based on contribution. All publications must receive prior approval from the co-investigators before submission.

Discussion

Not applicable.

Trial status

Recruitment of the first participant occurred on February 07, 2024, and 136 patients have been recruited by 1 January 2025. No protocol amendments have been made to date.

Name of the registry: Clinical Trials Registry-India (CTRI).

Trial registration number: CTRI/2024/01/062088.

Date of registration: 23 January 24.

URL of trial registry record: https://ctri.nic.in/Clinicaltrials/login.php

Abbreviations

TNBC	Triple-negative breast cancer
CTRI	Clinical Trial Registry of India
ICMR	Indian Council of Medical Research
PD	Program death
NACT	Neoadjuvant chemotherapy
EORTC	European Organisation for Research and Treatment of Cancer
UNL	Upper normal limit
AC	Adriamycin and cyclophosphamide
CRF	Case report form
OTC	Over the counter
ECG	Electrocardiogram
PRO	Patient-reported outcomes
PCR	Pathological complete response
DSMB	Data safety and monitoring board
SAE	Serious adverse events
IEC	Institutional ethics committee

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08726-9.

Supplementary Material 1.

Acknowledgements

Not applicable.

Authors' contributions {31b}

Adhip Arora is the principal investigator. Atul Batra is the chief moderator and guide. He is the corresponding author. V Seenu, Rajinder Parshad, VK Bansal, Anita Dhar, Piyush Mishra, Kamal Kataria, Suhani, Brijesh Kumar, Om Prakash, Ashutosh Mishra, Babul Bansal, Jyoti Sharma, and Jyoutishman Saikia are surgeons actively involved in the study. Sandeep Mathur is the lead pathologist involved. Sameer Bakhshi, Atul Batra, Ajay Gogia, Akash Kumar, and Kaushal Kalra are medical oncologists who will be directly involved with the patient care, drug prescription, and toxicity management. Akash Jha contributed to the study design and to development of the proposal. Krithika Rangarajan and Ekta Dhamija are the radiologists, while Shamim Ahmed Shamin is nuclear medicine specialist. Kalaivani Mani is the biostatistician involved who has helped in the calculation of the sample size and feasibility of the study. No professional writer has been used for writing the protocol.

Funding {4}

The trial is funded by the Indian Council of Medical Research (ICMR), Government of India. A copy of the original funding document has been attached as an additional file on submission.

Data availability {29}

Only the principal investigator and chief moderator shall be having access to the final trial dataset.

Declarations

Ethics approval and consent to participate {24}

Trial protocol has been approved by the institute ethics committee for postgraduate research at All India Institute of Medical Sciences; Ref. No.: AIIMSA00540/18.01.2024, RT-39/21.02.2024.

Consent for publication {32}

Not applicable.

Competing interests {28}

The authors declare no competing interests.

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