Trials

STUDY PROTOCOL

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Efficacy and safety of platelet-rich plasma as an adjunct therapy to split thickness skin graft in burn patients with granulating raw wounds: a prospective, randomized, double-blind study—study protocol

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Abstract

Background Burn wounds are commonly encountered in clinical settings and the management aims at the prevention of mortality and morbidity due to disability. The platelet-rich plasma (PRP) is blood-derived biomaterial that is enriched with growth factors and cytokines that facilitate wound healing. The PRP has proven its efficacy in various other wounds, but its role in post-burn raw areas and graft take has not been validated. This proposed multicentre randomized controlled trial aims to evaluate the efficacy and safety of platelet-rich plasma as an adjunct therapy to split-thickness skin graft in burn patients with granulating raw wounds.

Method/design This trial is an investigator-initiated, double-blind multicentre, randomized controlled parallel arm trial alongside trial cost-effectiveness analysis. Granulating deep second-degree and third-degree burns affecting 3–20% of total body surface area (TBSA) at 10–14th post-burn day will be included in the study. A total of 550 patients (275 in each group) will be randomized to receive either standard skin graft or allogenic PRP with skin graft treatment. The primary endpoint will be the mean percentage of graft-take on the 14th postoperative day. The result will be analyzed by two independent assessors who are blinded to the study. Secondary endpoints include (a) time taken for complete wound healing; (b) frequency of adverse events; (c) follow-up with scar index at 3 months, 6 months, and 1 year using the Patient and Observer Scar Assessment Scale (POSAS) score; (d) cost-effectiveness analysis of the intervention compared to the comparator; and (e) to estimate in a subset of participants the association between growth factor levels (PDGF BB and TGF ß-1) of activated PRP and clinical response.

Discussion The proposed trial will be expected to verify the efficacy and safety of PRP for split-thickness skin graft (STSG) in deep second-degree or third-degree granulating wounds of burn patients based on the outcome of the study.

Keywords PRP, Post burn raw area, Graft take

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Introduction

Background and rationale {6a}

Globally, burns are one of the major causes of disability, with more than 8 million disability-adjusted life-years (DALYs). In 2019, more than 23,000 fire-related deaths occurred in India, which accounts for 20% of the global mortality burden. Burn survivors can be financially distressed, vocationally challenged, and socially excluded [1].

In burns, the depth of the wound is the most important prognostic factor for the survival of patients [2]. Superficial burns usually heal in 2 weeks. Second-degree deep burns and third-degree burns that do not heal in two to three weeks are conventionally treated by split-thickness skin graft (STSG) [3]. Resurfacing of large skin defects remains challenging in plastic and reconstructive surgery. Now, with proper harvest techniques, skin grafts, especially the STSG, have transitioned into popularity as an adjuvant to promote the resurfacing of refractory wounds, such as diabetic foot ulcers, venous leg ulcers, and burns [4–6]. Generally, skin graft undergoes three steps for healing: anchorage, inosculation, and maturation (7). However, in 15 to 20% of cases, graft loss is due to hematoma, shearing of graft, or infections, leading to adverse outcomes. The failure of graft-take might require reoperation, and thus increase hospital stay, medical expenses, and socioeconomic burden.

Interventions that can reduce hematoma formation, promote adhesion of skin graft, and increase revascularisation can increase the success of skin graft take [7, 8]. Platelet-rich plasma (PRP) is a blood-derived biomaterial that was first introduced in 1984 by Assoian [9], enriched with a 2 to sixfold concentration of platelets [10], which has displayed therapeutic potential in wound healing and tissue regeneration in the inflammation, repair and remodeling phases. There is evidence for the use of PRP in chronic wound healing. The rationale behind the widespread use of platelet-rich plasma in various fields of regenerative medicine is the abundant presence of growth factors and other signal-transmitting molecules which play critical roles in the regeneration and healing of damaged tissue. The growth factors enhance cell proliferation and differentiation and enhance extracellular matrix production. All these properties of PRP help in better graft anchorage and graft take. The healing process is enhanced by the release of supra-physiologic amounts of growth factors to the injury site.

PRP can prevent hematoma, provide anchorage to skin grafts, and prevent infection. So, it has the potential to increase graft take. While there is adequate evidence of the benefits of PRP in wound healing, there is limited evidence of the benefits of PRP in burn wound healing. Allogenic PRP is found to be safe and it can be obtained from a single voluntary blood donor. Also, allogenic PRP involves methods for extraction and preparation which can be easily standardized across various blood centres. Hence, the application of PRP for graft take in granulating raw areas of post-burn patients can have a potential therapeutic effect.

The effectiveness of PRP has been studied for both burn wounds as well as traumatic, infective, and post-burn wounds [11–13]. The use of PRP has also been evaluated in patients with post-excisional defects after vascular malformation excision, post-traumatic defect, post-burn contractures, etc. [14]. However, few studies have assessed the effectiveness of PRP in burn wounds [15]. Most of the other studies were biased during allocation concealment [16], outcome bias [17], and attrition and reporting bias [18]. Additionally, none of the studies were carried out at multiple centers.

This study aims to evaluate the efficacy and safety of PRP as an adjunct to meshed STSG on granulating wounds of burn patients. The study will also evaluate the correlation between clinical outcome and growth factor levels of platelet-derived growth factor (PDGF) and transforming growth factor ß (TGF ß) in the PRP.

Objectives {7}

Primary objective

1. To assess the efficacy of platelet-rich plasma as an adjunct therapy to split thickness skin graft (STSG) in patients with granulating burn wounds involving 3–20% total body surface area with deep second-degree and/ or third-degree burns by evaluating graft take on postoperative day 14 (± 1 day) compared with only STSG.

Secondary objective

1. To compare the time taken for complete wound healing between the two trial groups
2. To compare the proportion of adverse events between the two trial groups
3. To assess burn scar by Patient and Observer Scar Assessment Scale (POSAS) at 3 months, 6 months, and 1 year after intervention
4. To conduct a cost-effectiveness analysis (CEA) to estimate the incremental cost-effectiveness ratio (ICER) of PRP as an adjunct therapy to split thickness skin graft (STSG) (intervention arm) to only STSG (comparator arm) in the treatment of granulating raw areas in post-burn patients.
5. To estimate in a subset of participants the association between growth factor levels (PDGF BB and TGF

beta 1) of activated PRP and clinical response– as measured by graft take and wound healing.

Hypotheses

Null hypothesis

There is no difference in the mean graft take percentage among patients with 3–20% deep second or second-degree between day 10–14 post burns having granulating raw area among patients given PRP as an adjunct therapy to skin grafting vs those who received only skin grafting, as assessed at 14 (+1 day) days after grafting.

Alternate hypothesis

There is an increase in the mean graft take percentage by at least 10% in patients with 3–20% deep second or third degree between day 10–14 post-burn among patients given PRP as an adjunct therapy to skin grafting vs those who received only skin grafting, as assessed at 14 (+1 day) days after grafting.

Trial design {8}

It is the first multicentric randomized trial to evaluate the efficacy of PRP on skin graft burn patients. Previous studies had evaluated the effect of PRP in post-traumatic wounds, post-burn wounds, post infective wounds. Further, PRP was used either in gel form or spray form etc. The method of preparation is also standardized.

To avoid selection bias, a random sequence with unequal block sizes will be generated to allocate participants in a 1:1 ratio to receive either PRP with split-thickness skin grafts or split-thickness skin grafts alone. This study is double-blinded, ensuring that both participants and the outcome assessor are blinded to the interventions to eliminate performance bias. To ensure unbiased interpretation, all results will be analyzed by an independent observer who is not affiliated with any of the participating centers and belongs to a different institution. Additionally, NIE Chennai will conduct a cost-effectiveness analysis to evaluate the financial implications of this trial. Attrition bias will be addressed by NIE Chennai in the event of incomplete data collection.

While many commercial products are currently available to enhance graft take and improve outcomes for burn patients, PRP offers a more affordable and potentially cost-effective alternative.

The study design includes a two-arm, parallel group, 1:1 allocation, randomized active-controlled multicentre clinical trial. The sample size was calculated considering drop-out rates, with an alpha level of 0.05 and a power of 90%, ensuring robust statistical validity. All data from the trial will be securely uploaded to the REDCap portal for future reference and analysis.

Methods: participants, interventions, and outcomes

Study setting {9}

This multi-center study will be conducted at four tertiary care institutes having a specialized burn care unit in which medical and paramedical professional staff are specifically trained in burn care. All institutes also have a blood transfusion unit, with an in-house facility for the preparation of platelet-rich plasma.

The four institutes are:

1. SCB Medical College & Hospital, Cuttack, Odisha, India
2. King George Medical University, Lucknow, Uttar Pradesh, India
3. Government Kilpauk Medical College, Chennai, Tamil Nadu, India
4. Institute of Postgraduate Medical Education and Research (IPGMER), Kolkata, West Bengal, India

The data will be generated at these four hospitals and will be accessible to the lead site, SCB Medical College & Hospital, Cuttack, via an online data collection platform.

Eligibility criteria {10}

Granulating second-degree deep and/or third-degree burns involving 3–20% total body surface area, at 10–14 days post burn patients.

The following patients will be included as per the inclusion criteria:

Inclusion criteria

1. Age 18–50 years
2. Three to 20% total body surface area burns at deep second-degree and/ or second-degree thermal burns at 10–14 days post burns
3. Granulating wound with post-burn raw areas
4. Suitable for STSG between 2 and 3 weeks from the burn event, as close to day 14 as possible.

Exclusion criteria

The following patients will be excluded as per the exclusion criteria:

1. Patients unfit for surgery
    a Sepsis and septic shock
    b Multiple organ dysfunction
2. Patient unfit to receive skin graft
    a ß hemolytic streptococcus infection at the site of application

b Hemoglobin less than 10 gm%
c Serum Albumin less than 2.5 g/dl
d Uncontrolled diabetes (HbA1c > 8%)

3. Patient follow-up not possible—based on investigator discretion

a At 14.th post-operative day (if patient was discharged before day 14)
b At 3 months, 6 months and one year for evaluation of scar

4. Others

a Coagulation disorder
b Pregnancy
c Patients on systemic steroid use > 21 days
d Malignancy
e Immuno-compromised state

Who will take informed consent? {26a}

A researcher from the site-specific team of investigators will obtain full informed written consent before the eligibility and baseline assessment, which will be conducted in person. Detailed information concerning study procedures will be explained to all potential participants in a language they can easily understand, and at the point of consent, they will be encouraged to ask and clarify any additional questions. All personnel taking consent would be trained by the principal investigator. All investigations envisaged would be explained in due course of the consent taking. The participants would have full right to withdraw from the trial at any point in time, without any consequence to their course of treatment which would also be explained while taking consent. Consent will only be obtained from individuals capable of making an informed decision.

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

Biological specimens will be collected as a part of this trial. The study protocol has been approved by the Institutional Ethics Committee of SCB Medical College, Cuttack (Reg No: ECR/84/Inst/OR/2013/RR-20 and IEC Application No.- 1480) and will follow the National Ethical Guidelines for Biomedical and Health Research involving human participants by the Indian Council of Medical Research (ICMR). Separate consent will be taken from donors whose PRP will be used in the study.

Interventions

Explanation for the choice of comparators {6b}

Previous studies have only looked at the effects of STSG independently. Therefore, the proposed research will assess the combined effects of STSG with PRP evaluating the outcome of graft take.

The patients will be randomized into two study groups:

(i) Intervention group: ABO and Rh compatible platelet-rich plasma (5 mL/100 cm.^{2}) topically administered through a 5-mL syringe and 18-gauge cannula + standard of care (Debridement followed by meshed STSG and regular dressing)
(ii) Control group: standard of care (debridement followed by meshed STSG & regular dressing)

Intervention description {11a}

Allogenic PRP will be applied over the wound bed, i.e., post burn raw area with a 18 G needle attached to a 5-mL syringe. PRP will be applied on the wound bed as a thin film just before applying the graft in a dose of 5 mL for 100 cm^2 area. Sample collection for platelet-rich plasma preparation will be done as described below.

Collection of whole blood

The whole blood will be collected in 450 mL/350 mL Triple blood bag (top and top) containing 63/49 mL of CPD anticoagulant with SAGM from healthy voluntary blood donors who give consent for use of their blood for research purposes and after fulfilling the screening criteria as per the guidelines given in Gazette of India, issued by Department of Health and Family Welfare, Notification, New Delhi, 11th March 2020. The blood units will be tested for mandatory transfusion-transmitted infection testing like HIV, HCV, HBV, malaria, and syphilis as per the Drug and Cosmetic Act 1940, and Rules 1945 and Amendments from time to time. The blood units should be non-reacting both in ELISA and NAT testing methods for relevant diseases as mentioned in the guidelines.

Preparation of PRP

The whole blood will be centrifuged using soft spin (relative centrifugal force 1515 RPM for 12 min at 20 ± 2 °C) in a refrigerated centrifuge (CRYOFUGE-16, Thermo Fisher Scientific (preferable)/as available). After the centrifuge, the PRP will be transferred to the platelet bag. The parent bag containing the PRBC will be detached by using a tube sealer. The platelet bag containing the PRP will be centrifuged using heavy Spin (3535 RPM for 8 min at 20 ± 2 °C) in the refrigerated centrifuge. Then the supernatant platelet-poor plasma

(PPP) will be transferred to the plasma bag and it will be detached using a tube sealer. The amount of PRP remaining in the platelet bag will be 50–60 mL approximately. Leukocyte reduction will be done by using a pre-storage platelet leucofilter. The leukocyte reduction filters are designed to remove > 99.9% of white cells by at least 3 log reduction (AABB Standard).

Aliquots

The bag will be aliquoted into equal sterile vials 10 ml each by using a three-way stopcock with an extended tube. The tube of the platelet bag will be attached with an extended tube part of a three-way stopcock by a sterile connecting device. Under the laminar airflow, the stopcock will be opened and PRP will be transferred to the sterile vials. One vial will be used for quality control and the other vials will be placed in a zipper pack and stored at minus 80 °C.

Quality control

For quality control of PRP, the platelet count should be above 4.5×10^{10}/bag, and PRP should be sterile by culture.

Activation of PRP (freeze–thaw cycle)

The leuko-reduced PRP aliquot vials will be stored at minus 80 °C for 24 h in a plasma refrigerator. After 24 h the PRP will be thawed in the plasma thaw bath at 37 °C for 8–12 min. The same cycle will be repeated for another time. After the second thaw cycle, one vial will be stored at − 20 °C for activated growth factor estimation and other vials will be again stored at − 80 °C for the third cycle [19]. The third thaw will be done one hour before the application.

Transportation of PRP for therapeutic application

Then the vials will be transported to the operation theatre site in a sterile cool box for application. The vials will be used within one hour after thawing. The PRP vial which will be applied to the patient must be ABO and Rh compatible to the patient.

Growth factor estimation

The growth factor estimation will be done after the activation of PRP in the stored vials for a subset of patients. Quantitative growth factor estimation will be done collectively after storing the sample at minus 20 °C by ELISA method for the first 200 activated PRP before administration at the lead site only. The concentration of PDGF BB and TGF ß 1 in PRP (the representative growth factors contained in the platelets) which are responsible for epithelialization and wound healing. PDGF BB and TGF ß will be estimated by commercially available ELISA kit according to the manufacturer's instructions. The kits required are for the estimation of Human PDGF BB and Human TGFß1 ELISA kit.

Standard of care

Peri-operative care—investigations and antibiotics

Early grafting, which is considered the standard of care in Western literature, is often not possible in the Indian setting—since patients often present between 2 and 10 days after burns. Often the primary care center where the patient presents manages the wound and stabilizes the patient, before referring the patient to a tertiary care center for surgical management.

Post-burn raw areas of 10–14 days duration that do not heal naturally will be clinically assessed for granulating wounds and signs of marginal healing. Healthy granulations are flat, red, vascular, and free from surface film. Clinically a glazed, gelatinous granulation wound that bleed easily to touch indicates the presence of β hemolytic streptococcus which is the only absolute contraindication to skin grafting. The swab will be taken for culture and sensitivity to rule out infection. Colonization of granulation tissue with organisms other than β hemolytic streptococcus will not contraindicate the application of skin grafting to post-burn raw areas [20]. Antibiotics will be given according to culture and sensitivity reports. Combination of injection piperacillin + tazobactam IV in a dose of 4.5 gm 8 hourly and injection amikacin 500 mg IV twice daily will be given for 2 days followed by oral antibiotics—amoxycillin + clavulanic acid (625 mg) will be prescribed thrice daily for 5 days. All the investigations on fitness for surgery will be done with special reference to clotting parameters—PT INR. All wounds will be prepared as per usual clinical practice, which is appropriate wound dressings to achieve a healthy granulating bed. Wound swabs will be performed to ensure no bacterial growth. After anesthesia fitness, surgery will be planned in elective OT.

Operative care—debridement followed by STSG

All surgeries will be done by the investigator (senior surgeon) and another surgeon (of more than two years post-MCH experience in plastic surgery) equally competent in doing the skin graft.

The first step of operative care is wound debridement. Hemostasis will be maintained by pressure and topical application of adrenaline in 1:200,000 concentration.

Skin graft

Grafting will be performed between day 10 to 14 (as close to day 14 as possible) of post-burn patients. Grafts will be

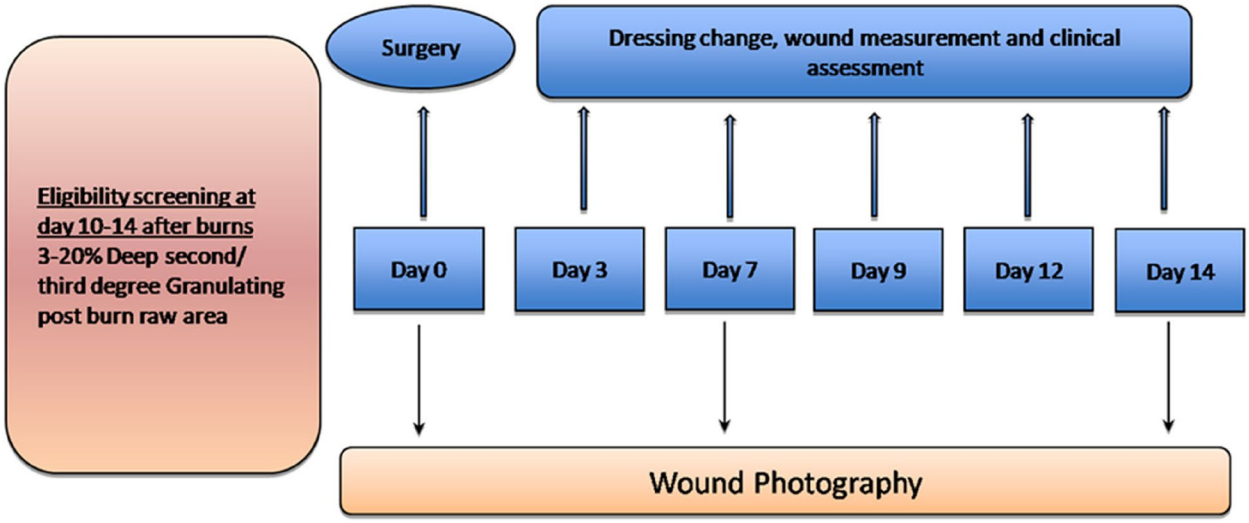

Fig. 1 Timeline for when outcome measures will be taken

harvested from the patient's available donor sites (thigh, arm, etc.) with dermatome. An intermediate split-thickness skin graft will be harvested (0.3 to 0.45 mm). The graft will be meshed in a 1:2 ratio. Then it will be applied to the post-burn raw area. It will be fixed with the skin staplers.

Three-layer dressing will be done. The first layer will be a non-medicated non-adhesive dressing. The second layer will be saline-soaked gauze and cotton dressing. The third layer will be by crepe bandage/Elastoplast compression dressing. This is followed by the immobilization of the part. For the mobile areas like the neck and chest tie-over dressing will be done. Dressing change has to be done by the principal investigator, Co-PI along with the help of a plastic surgery trainee of the hospital. The dressing above the non-adhesive material will be removed gently taking care to avoid shearing of the graft. The graft will be inspected for any discharge, odour, and pain during removal. The first dressing change will be done on the 3rd postoperative day. The next dressing change will be on the 7th, 9th, 12th, and 14th postoperative days. Wound examination and fixation results will be observed on all days of dressing change. Once the operated area dries and the graft becomes adherent, it will be kept open.

Criteria for discontinuing or modifying allocated interventions {11b}

The intervention is given one time, during the surgery. The intervention would not be modified in any circumstances, except if the participant decides to withdraw from the study before giving the intervention.

Strategies to improve adherence to interventions {11c}

To reduce the risk of data loss, participants will receive guidance when they sign the informed consent form and will be expected to attend all scheduled treatment sessions. An evaluator will be assigned to contact and monitor participants weekly through telephone, text messages, and/or email, and will support them throughout the study.

Relevant concomitant care permitted or prohibited during the trial {11d}

All medical care apart from the intervention will be provided to the patient without any modification.

Provisions for post-trial care {30}

Adverse events will be managed by the investigator(s) by providing free medical management as long as required if it is due to a clinical trial or until it is established that the injury is not related to the trial.

Outcomes {12}

The outcome will be assessed as per the evaluation of primary and secondary endpoints.

Primary endpoint: the primary endpoint will be measured as a percentage of graft-take on the 14th day after surgery (± 1 post-operative day). Skin graft-take will be observed on all days of dressing change. Additionally, photographs will be taken on 0, day 7, and day 14 postoperative days (which overlap with dressing change days). Patients may be discharged earlier if the wound heals completely. If the patient is discharged before day 14 postoperative day, because the wound has healed, the

Table 1 Schedule of enrolment, interventions, and assessments

Timepoint	1st Year				2nd Year				3rd Year				Close Out
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	After 3rd Year
Enrolment		—	—	—	—	—	—	—					
Eligibility Screening		—	—	—	—	—	—	—					
Informed Consent		—	—	—	—	—	—	—					
Allocation		—	—	—	—	—	—	—					
Intervention			—	—	—	—	—	—					
Assessment			—	—	—	—	—	—	—	—			
Report Writing & Publication											—	—	

*1st quarter (Q1) in the 1st year will be used for approval of codals, recruitment of manpower, purchase of equipment, etc.

patient will be requested to come to the hospital for a follow-up on day 14, when the wound will be examined, and a photograph will be taken (Fig. 1). Discharge will be based on the discretion of the treating doctor.

Secondary endpoints

1. Time is taken for complete wound healing: defined for this study as skin re-epithelialization without drainage or dressing requirements (> 95% epithelialization). The maximum duration for assessing the secondary endpoint has been determined to be two weeks. Typically, even without the application of PRP, more than 95% epithelialization occurs within two weeks. If complete wound healing and epithelialization do not occur within this period, regrafting (a second surgical procedure) will be done to facilitate early healing. Wound assessment will be done by two independent assessors.
2. Frequency of adverse events: the expected adverse events including graft loss, hematoma, and seroma will be assessed clinically. All adverse events—expected and unexpected will be recorded during the period of hospital admission. Need for re-operation—defined for this study as the patient having to undergo skin grafting again for complete wound healing. The need for re-operation is indicative of graft failure and will be recorded as an adverse event.
3. Growth factors like PDGF BB and TGF ß level will be correlated in a subset of samples with the clinical outcomes. Quantitative Growth factor estimation will be done collectively after storing the sample at − 20 °C by ELISA method for the first 200 activated PRP before administration at the lead site only. SOP for the ELISA will be as described by the manufacturer.
4. Scar assessment will be done by POSAS score at 3, 6, and 12 months postoperatively in an outpatient clinic. It is a reliable and validated subjective scar assessment scale including both the patient scale and observer scale. The POSAS is composed of two numerical scales that evaluate signs and symptoms of healing. It consists of the two following parts: a scale for patients and a scale for observers. Both contain six items punctuated numerically from 1 to 10, which comprise the "total score" of the scale for both the patient and observer.
5. Cost-effectiveness endpoints
   - Unit costs of treating burn patients.
   - Quality of life utility scores of burn patients in India using EuroQol 5D-5L.
   - Incremental cost-effectiveness ratios (ICERs) will be calculated for each of the outcomes viz QALY, percentage of graft uptake.

Participant timeline {13}

Total study period: 36 months.

Each patient will be followed up for 12 months (Table 1).

Sample size {14}

Assuming an expected mean difference in graft take of 10% and a standard deviation of 23.4, an alpha level of 0.05, and a power of 90% [9], the number of participants needed in each group was calculated to be 386. Assuming

15% lost to follow-up, the sample size in each group has been calculated as 275, with a total sample size of 550. The sample size for the cost-effectiveness and out-of-pocket expenditure will be the same.

Recruitment {15}

Strategies will be adopted for achieving adequate participant enrolment to reach the target sample. Patients can be recruited directly from the plastic surgery ward and general surgery ward. Since in our study, grafting will be done after 10–14 days of burn injury, all the patients admitted to the surgery and plastic surgery ward will be counselled by a project technician to get enrolled in the study. The photograph of the previously cured patient can be shown to the participants to increase their confidence in the treatment procedures and to encourage their participation in this study. Numerous Continuing Medical Education (CMEs) are being conducted at registered medical institutes. Many NGOs are also trained to educate people at the ground level regarding the benefits of skin grafting on burn wounds.

Assignment of interventions: allocation

Sequence generation {16a}

A central randomization scheme will be designed by an independent statistician. Randomization will be stratified by site, and at each site block randomization with unequal block sizes will be performed to allocate participants to receive PRP with a split-thickness skin graft or only split-thickness skin graft in a 1:1 ratio.

Concealment mechanism {16b}

The randomization sequence will not be available to the site investigators, or study statistician. The randomization scheme will be fed to an Interactive Voice Response System (IVRS) and will be available to the study physician at the time of individual enrolment.

Implementation {16c}

The allocation sequence will be generated by an independent statistician instructed by ICMR. The participants will be enrolled from the Dept. of Plastic Surgery, General Surgery, and Casualty by the project staff upon verification with inclusion criteria followed by supervision of the PI and Co-PI. The operating surgeon will be assigning the participants to interventions.

Assignment of interventions: blinding

Who will be blinded {17a}

The surgeon performing the graft procedure will not be blinded, however, the participant and outcome assessor will be blinded to the allocation groups. Study statisticians will also be unaware of the trial allocation.

Procedure for unblinding if needed {17b}

Researchers will only be unblinded if knowledge of the treatment arm is deemed essential to the patient's management by their clinical team. Any instances of unblinding will be documented, but we anticipate that they will not affect the follow-up assessments.

Data collection and management

Plans for assessment and collection of outcomes {18a}

1. Guideline finalization and protocol establishment: an expert consultative meeting will be held to finalize and agree on the guidelines to be followed as a reference for PRP preparation and STSG protocols. This includes enumerating all the laboratory and hospital procedures involved in PRP and STSG procedures, including laboratory investigations, operative setups, and equipment requirements.
2. Consultative process for cost identification: a consultative process will be undertaken by the investigating team to identify what costs are already available in the CHSI Cost database. Costs that need to be generated from primary data will be identified.
3. Primary data collection from tertiary public health facilities: for primary data collection, cost data will be collected from the identified study sites for STSG procedure and PRP preparation.

Wounds will be measured using a scaled transparent grid dressing by the treating doctor. The investigator then measures the area within the outline by counting the number of 1 cm squares that the wound occupies and adding to it the partial squares. In case of multiple wounds, they will have to be measured differently and total area will have to be calculated. The wound healing will also be measured: defined for this study as skin re-epithelialization without drainage or dressing requirements (>95% epithelialization). Necessary recordings will be made on the CRF.

Wound photography

2D Photographs of the wounds will be taken with a Digital Single Lens Reflex Camera (DSLR) as described by Sarah et al. (2024) and Robert et al. (2009) [21, 22]. Briefly, the dressing will be removed. The surrounding area will be cleaned with normal saline. The grafting area will be cleaned. A permanent marker will be used to outline the edge of the wound. A disposable ruler will be held flat along the most distal edge of the wound. The camera

resolution will be a minimum of 5 MP. The photographs will be taken in the same room without any window with a light blue background. The camera will be placed on a tripod stand to level with the photographed area, approximately 1.5 m from the patient. To minimize error, the camera lens will be oriented parallel to the plane of the wound. The private parts and eyes of the patient will be made dark to hide the identity of the participant. The consent will be taken for the use of these photographs in the publication and promotional activities.

Serial photographs of the wound must be in the same relative position as previously; hence it is ideal to have all patients take similar positions to the extent possible. The anatomical location of the wound should also be evident. Two independent blinded assessors will analyze pictures using scaled grids to compare the take percentage of skin grafts. The assessors will be trained plastic surgeons with more than 15 years of experience. The mean of all assessments will be used for further analysis. In case of discordance of readings > 50% between the two independent assessors, a third assessor will be invited for adjudication.

Graft take is defined as a graft that is vital, dry, and shows good adherence to the wound bed [9, 10]. Graft-take % for each participant will be calculated using the formula.

$$\text{Percentage (\%) of graft take} = (\text{area of graft take}/\ \text{total area of graft}) \times 100$$

The patient and observer scar assessment scale is shown in Appendix III.

Cost-effectiveness analysis

The study PICOST

The population intervention and comparator will same as the RCT.

Study design: Alongside CEA.

Outcome:

a) Unit cost of treating one burn patient using STSG; specific unit costs for different procedures involved in STSG.
b) Unit cost of treating a burn patient using PRP as an adjunct therapy to STSG; specific unit costs for different procedures involved in PRP as an adjunct therapy to STSG.
c) Incremental cost-utility ratio (ICUR) per quality-adjusted life years (QALY) of PRP as an adjunct therapy to STSG compared to STSG.
d) Incremental cost-effectiveness ratio (ICER) per graft taken in PRP as an adjunct therapy to STSG compared to STSG.

Perspective: the analysis will be conducted from a disaggregated societal perspective, considering not only the direct medical costs incurred by the healthcare system but also the direct non-medical costs borne by patients and their families, as well as out-of-pocket expenditure (OOPE). Additionally, the results will also be reported from a public payers (health system) perspective.

Time horizon: one-year time horizon (RCT duration of follow-up).

Discounting: since the year study time horizon, no discounting of costs and outcomes will be done for estimation of ICER. However, while estimating the unit costs of STSG and PRP-add-on STSG a discount rate of 3% will be used for capital costs.

Data collection methods

Guideline finalization and protocol establishment: an expert consultative meeting will be held to finalize and agree on the guidelines to be followed as a reference for PRP preparation and STSG protocols. This includes enumerating all the laboratory and hospital procedures involved in PRP and STSG procedures, including laboratory investigations, operative setups, and equipment requirements.

Consultative process for cost identification: a consultative process will be undertaken by the investigating team to identify what costs are already available in the CHSI Cost database. Costs that need to be generated from primary data will be identified.

Primary data collection from tertiary public health facilities: For primary data collection, cost data will be collected from the identified study sites for STSG procedure.

PRP preparation

Estimation of costs and health outcomes.

Costing methodology

Health system costing

This analysis will adopt micro-costing with a *bottom-up costing* approach, which involves identifying and measuring the resources used at each stage of the intervention.

The major health system cost components for which data collection will be undertaken will include human resources, building space, drugs and consumables, medical and non-medical equipment, and overhead costs for the PRP and STSG procedures. The sources to obtain this data will include health facility records, HMIS, facility plans, and staff interaction along with secondary sources of available data. Time allocation, discounting, and apportioning will be done as per standard guidelines (Costing Handbook, PGIMER).

Cost components: the following cost components will be included in the analysis:

1. Intervention costs: the costs associated with the preparation and application of PRP, including the preparation of PRP, equipment, and personnel involved in PRP preparation.
2. Surgical costs: the costs related to debridement, STSG, dressing, and subsequent dressing changes, including anesthesia costs, surgeon fees, operating room expenses, and consumables.
3. Hospitalization costs: the costs associated with hospital stays, including bed charges, nursing care, medications, laboratory tests, imaging, and other related services.
4. Outpatient costs: the costs of follow-up visits, consultations, tests, medications, and any additional treatments required during the healing process.
5. Adverse event costs: the costs resulting from adverse events associated with the intervention, such as infection, graft failure, or other complications, including additional treatments, hospitalizations, and follow-up care.

The cost items can be classified into the following services for PRP and STSG procedures:

PRP

1. Diagnostic and laboratory services:
    - Blood collection for PRP preparation
    - Testing for blood compatibility and screening for infectious diseases
    - Laboratory processing to isolate and concentrate PRP.
    - Specialized medical services:
    - PRP preparation procedure
    - Application of PRP to the wound bed
    - Follow-up visits for monitoring and evaluation
    - Medicines:
    - Anticoagulants or other medications used during PRP preparation.
    - Pain medications or anti-inflammatory drugs are prescribed post-treatment.

STSG

1. Diagnostic and laboratory services:
    - Pre-operative assessments, including clinical evaluations and diagnostic tests to determine the need for STSG.
    - Specialized medical services:
    - Surgical procedure for skin graft harvesting and application.
    - Operating room costs, including anesthesia, surgical equipment, and personnel.
    - Medicines:
    - Analgesics and pain medications for postoperative pain management
    - Antibiotics to prevent or treat infections.
    - Dressings and wound care products are used during the healing process.

A pretested validated health system-costing tool will be used for data collection. Trained staff will undertake the proposed data collection.

Out-of-pocket expenditure

In the context of this study, assessing OOPE is important to understand the financial burden placed on patients and their families when undergoing the interventions of PRP as an adjunct therapy to STSG in post-burn patients with granulating raw areas.

The study will identify the specific cost components contributing to OOPE, including expenses related to diagnostic and laboratory services, specialized medical services, and medicines associated with PRP and STSG. These cost components may encompass payments for consultations, diagnostic tests, skin grafting procedures, post-operative visits, wound care materials, medications, and any other out-of-pocket payments made by patients. Additionally, non-medical costs such as transportation, and accommodation, may also be considered. The study sites will assess OOPE using adapted out-of-pocket expenditure tools designed to collect accurate and reliable information on OOPE.

Utility data

Health outcomes will be measured in terms of quality-adjusted life years (QALYs), following the recommendations of the Health Technology Assessment in India (HTAIN). The chosen instrument for assessing health-related quality of life (HRQOL) will be the EuroQol-5D (EQ-5D) questionnaire [23]. We will additionally use a burn-specific quality-of-life measuring tool, Burn-Specific Health Scale (BSHS) as well. Utility data will be collected using the Burn-Specific Health Scale (BSHS) and the EQ-5D Tool. The EQ-5D-5L questionnaire is a EuroQol instrument that assesses HRQOL across five dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) [24]. India-specific value sets will be applied to derive the utility scores [25]. The Burn-Specific Health Scale (BSHS), is a 20-item scale measuring five domains of HRQOL (Physical

functioning, Pain, Emotional well-being, Social interaction, and Body image) [26, 27]. Utility scores will be recorded at baseline, 14 days after the procedure (taking graft/re-graft status into account), and at the 12-month follow-up for participants who have provided consent to complete the questionnaires.

Analytical methods

Willingness to pay the threshold

The willingness to pay threshold (WTP) will be considered for determining cost-effectiveness. We will use the one-time gross domestic product (GDP) per capita for the year 2023, as suggested by the Indian reference case for conducting economic evaluations in health technology assessments [28]. Additionally, as part of a scenario analysis, we will consider the World Health Organization (WHO) guidelines: ICER < 1 times GDP of India will be considered highly cost-effective; 1–3 times GDP of India will be considered cost-effective; and > 3 times GDP of India will be considered not cost-effective [29].

Results reporting

Deterministic results will be reported as quality adjusted life years (QALYs) and per life years (LYs) as the measure of effectiveness. The total costs and total QALYs gained for the intervention and comparator will be calculated for the trial period of 1 year. Incremental cost/QALY will be determined as the difference between the total cost/QALY of the intervention and the comparator. ICER is obtained by taking the ratio of incremental costs over incremental QALY.

ICER = (Costs of intervention − Costs of intervention)/(QALY of intervention − QALY of the comparator).

We will additionally report the Incremental Net Benefit (INB), which is calculated using the formula: INB = K * ΔE − ΔC. Here, K is the willingness to pay threshold, ΔE is the incremental QALY, and ΔC is incremental costs.

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

Telephonically reminders will be given for contacting patients. The POSAS Score can also be evaluated in a video call (with all parameters) if the patient shifts to a distant place or the project technical support can travel to the patient's place.

Data management {19}

Data will be entered in an electronic case record form in the RedCap online portal. Each study site will be provided with unique login credentials. The data will be stored on a server hosted by ICMR. Only authorized personnel will have privileged access to the data. The photographs will have to be pseudonymized using RedCap patient ID so that it is blinded to the assessors.

Confidentiality {27}

The patients' details would be available to the study physician only. The data will be de-identified and all collected data will be preserved in password-protected computers, accessible only to the study team.

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

There is no requirement for any kind of genetic and molecular analysis in this trial.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

For primary outcome

The primary analysis will be an intention-to-treat analysis, that includes all participants that were randomized. Mean graft uptake will be compared between the two groups using a linear regression model, adjusting for relevant covariates and allowing for fixed center effects to adjust for variable effects at each study center. Duration of hospital stay and POSAS score will be calculated as mean with standard deviation and will be compared using t-test or linear regression. Time to healing will be analyzed using survival analysis methods.

For secondary outcomes

a) The cost-effectiveness analysis will involve calculating the ICERs, representing the additional cost incurred to achieve an additional unit of effectiveness.
b) *Sensitivity analysis*: to account for uncertainties and variations in key parameters, sensitivity analysis will be conducted to assess the robustness of the results by varying the input parameters within a plausible range and examining the impact on the cost-effectiveness outcomes. The robustness will be assessed using sensitivity analysis, including one-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA). In one-way sensitivity analysis, upper and lower limits with 25% or 95% Confidence Interval values of the inputs will be used and reported as tornado diagrams. PSA will be performed with Monte Carlo simulation for 5000 times, based on the data distribution. Cost data would be simulated using a Gamma distribution, while prevalence and/or proportions will follow a normal distribution. Results will be presented with a cost-effectiveness plane and CE-acceptability curve. Total and incremental dis-

counted costs, QALYS, and the resulting ICER will be computed for each scenario. The overall analysis and reporting of results will be conducted in compliance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).

c) *Scenario analysis*: scenario analysis will be performed to evaluate the cost-effectiveness of PRP under different assumptions or hypothetical scenarios. This analysis may include variations in resource utilization, pricing, or clinical outcomes to explore the potential impact on the cost-effectiveness results.

d) Implications: the cost-effectiveness analysis evidence of PRP as an adjunct therapy to STSG in post-burn patients with granulating raw areas could offer evidence-based recommendations for the inclusion of PRP in public policy. The findings can inform policymakers about the economic implications and potential benefits of adopting PRP therapy, aiding in decision-making regarding its coverage and reimbursement.

Interim analyses {21b}

There is no interim analysis planned.

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

Currently, there is no planned additional subgroup or adjusted analyses. However, there will be an analysis of the association between Growth factor levels (PDGF BB and TGF B1) of activated PRP and clinical response in a subset of participants at the lead site (SCB Medical College, Cuttack).

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

According to SPIRIT guidance: The effect that any missing data might have on results will be assessed via sensitivity analysis of augmented data sets. Dropouts (essentially, participants who withdraw consent for continued follow-up) will be included in the analysis by modern imputation methods for missing data. After the imputations are completed, all of the data (complete and imputed) will be combined and the analysis will be performed for each imputed-and-completed dataset.

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

The protocol will be available at the Clinical Trials Registry of India (CTRI). The detailed protocol would be shared on a reasonable request after permission from the competent authority of the lead institute.

Oversight and monitoring

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

(i) Steering and Advisory Committee (SAC)—the overall scientific and administrative oversight and supervision of the trial will remain with the Steering Committee. This is the group responsible for scientific and clinical oversight and supervision of the Clinical Trial, including design, conduct, analysis, and interpretation. The steering committee will be constituted by the sponsor, trialists/subject experts, biostatisticians, independent assessors, and various PIs.

(ii) Project Management Committee (PMC) that will include a central core operations team from PIs, and site PIs/co-PIs for day-to-day running and management of the trial, review of trial monitoring reports related to consent, recruitment, and data quality, and recommending follow-up actions as appropriate.

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

The Data & Safety Monitoring Board (DSMB) which the Steering Committee will appoint will be an independent committee that will have expertise in clinical trial conduct and methodology, subject experts (surgical and transfusion medicine), and will include at least one statistician. The DSMB can periodically look at blinded or unblinded data to monitor patient interest and make recommendations regarding the progress of the study. SAE evaluation will also be done by DSMB and hence should include transfusion medicine experts, plastic surgeons, and pharmacologists, all independent and unrelated to the trial.

The frequency of planned meetings will be annual for the steering committee, monthly for PMC, and 6-monthly for DSMB. DSMB will evaluate all SAEs that occur in the trial to conclude on the relatedness of the SAE to the trial. Besides this, members of the committees can call a meeting based on the need. The study will be compliant with the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017. Participant Information Sheet (PIS) will be shared with each participant and informed consent (ICF) will be taken from the participants. Site-specific details will be added in the PIS as per requirements which will be centrally monitored by ICMR. The study will also be reviewed, approved, and monitored by the local ethics committee. Any change or modification in the protocol will be informed to the local ethics committee.

Table 2 How is the present study adding value to the current body of evidence

Study population	The rationale for preparation of the intervention	Standardization of surgical technique	Methodological differences
Burns only—type IIB/III	Standardization of procedure and adherence rates to SOPs Allogenic—activation technique leukoreduction	Standardization of procedure and adherence rates to SOPs Video review of a subset of perioperative care standardized	Randomization Blinding Sample size Long-term follow-up 12 months, with attempts to have > 95% follow-up Cost evaluation

Adverse event reporting and harms {22}

All adverse events will be identified, captured, and reported. The PI from the lead institute, SCB Cuttack is responsible for the ongoing safety evaluation of the study intervention. Safety reports will be submitted to the DSMB and the ethics committee. The reporting will adhere to the timelines provided in Table 5 of the Third Schedule in the New Drugs and Clinical Trial Rules (2019). Adverse events will be managed by the investigators by providing free medical management as long as required, or until it is established that the injury is not related to the clinical trial. In case the injury or death is related to the trial, financial compensation will be given according to CDSCO's rule, over and above any expenses incurred due to the medical management of the participant. Clinical trial liability insurance will be purchased by SCB Cuttack.

Frequency and plans for auditing trial conduct {23}

The frequency of planned meetings will be annual for the steering committee, monthly for the Project Management Committee, and 6-monthly for the Data & Safety Monitoring Board. DSMB will evaluate all SAEs that occur in the trial to conclude on the relatedness of the SAE to the trial. Besides this, members of the committees can call a meeting based on the need.

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

All protocol amendments will be done after approval from the ethics committee of SCB Cuttack followed by the other three participating institutes.

Dissemination plans {31a}

The results of the study would be published, in a peer-reviewed indexed journal.

Discussion

The use of PRP in burn wounds can be validated only by a randomized multicentric blinded study. Still, there are no such reports on randomized multicentric studies on PRP application. Previous studies had used PRP as a gel form for different wounds. The amount of PRP has not been standardized. Most of the studies have utilized autologous PRP. In this study, we have used allogenic PRP. Multicentric studies have been designed to avoid bias. To ensure graft is taken & a better cosmetic graft ratio has been hypothesized to be 1:2. Graft thickness has been standardized & dermatome will be used to control the thickness of the skin graft for skin graft harvest.

It is not possible to draw blood in acute burn patients because of edema of part or involvement of parts. Allogenic platelets can avoid these problems.

The interventional product is allogenic PRP (5 mL/100 cm^2) to be applied on the granulating post-burn raw area as an adjunct to split-thickness skin graft (Tables 2, 3, and 4).

Growth factors were released at higher concentrations from the platelets after activation with a cycle of freezing/thawing compared to the basal values in the autologous PRP without the formation of the gel. The study established that a cycle of freezing/thawing was the only independent factor affecting the growth factors content of the PRP.

Three repeated cycles of freeze-thawing for PRP activation were performed in a fully closed system in a certified hospital blood center. The leucocyte-poor PRP injection technique was utilized in > 70 patients. They are applied in the treatment of patients presenting with chronic mild to moderate hip and knee osteoarthritis [30]. But they have not measured the outcome.

PRP activation: repetitive freeze–thaw

The study by Strandberg et al. [31] demonstrated that platelet lysate produced by the freeze–thaw procedure resulted in approximately four- to tenfold enrichment of transforming growth factor-β1, epidermal growth factor, PLT-derived growth factor (PDGF)-AB/BB, PLT factor-4, and fibroblast growth factor-2. The increase in concentrations plateaued at cycles 3 and 5.

The study by K. Fukuda et al. [20] demonstrated that PRP samples after freezing for 1 month and were subjected to single (*Fr1*), double (*Fr2*), triple (*Fr3*), or

Table 3 Growth factors: levels of some growth factors in blood versus PRP

Growth factor	Physiologic level in the blood	Level in PRP
PDGF	3.3 ± 0.9 ng/ml	17 ± 8 ng/ml
TGF	35 ± 8 ng/ml	120 ± 42 ng/ml
VEGF	155 ± 110 pg/ml	955 ± 1030 pg/ml
EGF	129 ± 61 pg/ml	470 ± 320 pg/ml

Table 4 Comparison of mean growth factor concentrations in the fresh autologous PRP, post-freeze PRP

Growth factor	Fresh autologous PRP (pg/mL)	Post-freeze PRP (pg/mL)	*p*-value*
PDGF-BB	78.95 ± 49.42	218.90 ± 30	0.0001

quadruple *(Fr4)* freeze thaw cycles, with repeated overnight freezing at − 30 °C and thawing at room temperature. Platelets appeared to maintain their morphology, whereas leukocytes were not observed in *Fr1*, *Fr2*, and *Fr3*. The concentrations of PDGF-BB in the *Fr2*, *Fr3*, and *Fr4* supernatants were significantly higher than that in the *Fr1* supernatant, whereas no significant differences in PDGF-BB concentration were noted among the *Fr2*, *Fr3*, and *Fr4* supernatants. It was also reported that the concentrations of PDGF-BB, TGF-β1, EGF, and FGF increased by repetitive freeze-thawing and plateaued at 3 and 5 cycles.

Trial status

The Study protocol was approved and funded by the Indian Council of Medical Research under the Extramural grant program, 2023. The trial has been registered under the Clinical Trial Registry of India (CTRI) of India with registration number CTRI/2014/05/068042. The trial is yet to commence the recruitment of patients. The Ethics committee of all study sites has already approved the study.

Abbreviations

DALY Disability-adjusted life years
STSG Split-thickness skin graft
PRP Platelet-rich plasma
PDGF Platelet-derived growth factor
TGF ß Transforming growth factor-beta
ICER Incremental cost-effectiveness ratio
ELISA Enzyme-linked immunosorbent assay
QOL Quality of life
QALY Quality-adjusted life years
RCT Randomized control trial
ICUR Incremental cost-utility ratio
OOPE Out-of-pocket expenditure
INB Incremental Net Benefit
HRQOL Health-related quality of life
PSA Probabilistic sensitivity analysis
ILGF I Insulin-like growth factor I
OSA One-way sensitivity analysis
TBSA Total body surface area
EGF Epidermal growth factor
VEGF Vascular endothelial growth factor
NICE National Institute for Health and Care Excellence

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08757-2.

Supplementary Material 1. Appendix I Operational definitions used in the study. Appendix II The patient and observer scar assessment scale (POSAS Scale). Appendix III SCB Medical College, Cuttack.

Supplementary Material 2. SPIRIT checklist.

Supplementary Material 3. Table 5.

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Authors' contributions {31b}

Dr. Susmita Behera and Dr. Biswajit Mishra are the principal investigators and conceived the study idea, wrote the manuscript, and led the protocol development. Dr. Jerin Jose Cherian, Dr. Gunjan Kumar, Dr. Aparna Mukherjee, and Dr. Sudipto Roy led the protocol development, writing of the manuscript draft, and reviewing the final draft. All authors read and approved the final manuscript.

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Data availability {29}

The final trial dataset will be available with the Primary Investigator of the lead study site, SCB Cuttack. The dataset will be made available on a reasonable request.

Declarations

Ethics approval and consent to participate {24}

The study protocol has been approved by the Institute Ethics Committee of SCB Cuttack. The Ethics approval letter is available in Appendix V.

Consent for publication {32}

Consent for publication will be asked from all the participants who will be enrolled in the trial. Model Consent form is available in Appendix IV.

Competing interests {28}

The authors declare that they have no competing interests.

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