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Combination of InnoSEAL plus TR band compared to TR Band alone for Radial Artery Outcomes in patients undergoing transradial coronary intervention (InnoSEAL - II): An open label randomized controlled trial (Protocol)

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3 **Combination of InnoSEAL plus TR band compared to TR Band alone for Radial Artery**
4 **Outcomes in patients undergoing transradial coronary intervention (InnoSEAL - II): An open**
5 **label randomized controlled trial (Protocol)**
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Abstract**Introduction**

About 2-30% of cardiac catheterization procedures get complicated by radial artery occlusion (RAO). Ensuring patent hemostasis appears to be an important factor in reducing RAO. Currently employed method is a radial compression device (RCD) such as TransRadial Bands (TRB) that takes hours to achieve hemostasis and causes discomfort to the patients. Hemostatic pads offer an alternative to RCD with reduced time to achieve hemostasis. Our trial aims to determine the non-inferiority of the catecholamine chitosan-based pad (InnoSEAL hemostatic pad) used in conjunction with TRB (InnoSEAL+TRB) when compared with the TR band (TRB) alone in reducing composite adverse access site outcomes.

Methods and analysis

It will be an open label, parallel, randomized controlled trial on 714 adult patients (325 in each arm) undergoing coronary procedure using transradial approach at a cardiac health facility over seven months duration. InnoSEAL patch along with TRB will be used to control bleeding in intervention arm and TRB alone in control arm which is the standard practice. Study primary outcomes include RAO and hematoma; secondary outcomes are compression time, patient discomfort, time to discharge and ease of use of the intervention technique by the health care staff. Chi-square test will be used to compare the categorical outcomes between two arms and student's t-test for continuous outcomes. A p-value of <0.05 will be considered significant.

Ethics and dissemination

Ethical approval for the study has been obtained from Institutional Review Board of Tabba Heart Institute # IORG0007863. Findings will be disseminated through seminars and scientific publications.

Registration

Trial is registered at clinicalTrials.gov # NCT04380883 on 7 May 2020.

Strengths and limitation of this study:

- This is the first powered clinical trial comparing chitosan-based hemostatic pad to pneumatic band. The trials done previously were on lesser number of patients with no power calculation.

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- One of the secondary outcomes of the study is ease of the use of any of the techniques of access site closure by the cathlab staff. This will inform the feasibility of translating the trial results in to practice.
- The lack of blinding of the data collectors is a limitation of the study.

Introduction

Trans-radial procedures are frequently complicated by radial artery occlusion (RAO) with reported incidence of 2-30%(1). RAO may limit future use of this site for catheterization, as an arterial conduit for surgical revascularization or for hemodialysis access. Independent predictors of RAO are the diameter of the sheath and its relationship to the size of the radial artery, amount of heparin used, post procedure compression time and presence of antegrade flow in the artery during hemostasis(2). Ensuring patent hemostatic compression i.e. the control of arterial bleeding while maintaining radial arterial flow appears to be an important factor in reducing RAO(3).

Hemostasis after radial sheath removal has been achieved using multiple methods including manual compression, tourniquets and compression bandages, a variety of pneumatic compression devices and more recently hemostatic pads impregnated with pro-coagulant chemicals. Currently the most frequently employed method for hemostasis following trans-radial procedures is a compression device (RCD)(4).

Hemostatic pads offer an alternative to RCD where overall compression time is inherently low and patent hemostasis can possibly be achieved. Chitosan, one of the materials used in hemostasis pads, is a biodegradable polysaccharide which is converted to a hemostatic agent after contact with blood, and has shown similar efficacy in terms of reducing local bleeding and hematoma formation compared to RCDs with added advantage of shorter time of compression and therefore less patient discomfort(5).

The combined use of trans-radial band (TRB) with a hemostatic device may allow ease of use with reduced hemostasis time(6). Patent hemostasis is also likely to be achieved with the combined use of both devices and possibly improve radial artery patency with added benefit of reduced bleeding complications. So far two trials have been undertaken that compared RCD alone with RCD plus catechol conjugated homeostasis pads (7, 8). Both trials showed reduced time to achieve hemostasis with RCD plus hemostatic pad but both were underpowered with small number of participants. Also, we did not find any trial from lower middle income countries (LMICs) hence we planned a trial with adequate power which will test the applicability of the hemostatic pad with pneumatic band in a LMIC.

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Our trial aims to test the hypothesis that compared to TRB alone, catecholamine chitosan-based pad (InnoSEAL hemostatic pad, InnoTherapy, Inc. S Korea) used in conjunction with TRB (InnoSEAL+TRB) is non-inferior in terms of the composite adverse access site outcomes including RAO and hematoma. Secondary objectives include testing the non-inferiority of InnoSEAL+TRB in terms of ease of use by the cath lab staff compared to TRB; and superiority of InnoSEAL+TRB for shortened total hemostasis time, total observation time for the radial site and time to hospital discharge for daycare patients sub group. Lastly we aim to test superiority of InnoSEAL+TRB for reduced patient discomfort compared to TRB alone.

Methods and analysis

This open label randomized controlled trial will be conducted in cardiac catheterization laboratory (CCL) at Tabba Heart Institute (THI) Karachi, Pakistan. Tabba heart institute is a 160 bedded cardiac tertiary care hospital with 24hrs emergency and facilities for primary PCI and cardiac surgeries. The institution has two fully equipped cardiac catheter labs. There is a fully trained and experienced faculty of more than 15 cardiologists and 06 interventionists. On average more than 1400 PCIs are performed annually. This is one of the major referral centers in the city for primary PCI. THI is also a teaching hospital with approved training programs in adult cardiology and interventional cardiology.

Adult patients of both gender undergoing coronary procedure using transradial approach including diagnostic coronary angiogram (CAG) or PCI and who are hemodynamically stable will be included. Patients in which radial sheath of larger than 6 F will be used; who are on anticoagulants after procedure or on an ongoing anticoagulation therapy will be excluded. Also patients who are diagnosed with ipsilateral arteriovenous fistula, Barbeau's class D or have history of RAO at baseline, or unable to give consent will be excluded.

All consecutive patients coming to CCL for coronary procedures will be screened for eligibility by data collectors. If the participants meet the eligibility criteria of the study, they will be offered to participate in the trial. Before the start of the coronary procedure, patients will be approached for enrollment in the study and informed consent will be taken. If the participant himself/ herself assigns a surrogate, then consent will be signed by the surrogate. In case of urgent need of coronary procedures, consent will be taken post coronary procedure when patient is shifted in the cath lab recovery area. Consent form will be provided in English or Urdu according to patient's preference. One signed copy will be given to the patient for the reference. For an uneducated patient, form will be verbally read and thoroughly

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3 explained by the research coordinator. A thumb impression will be obtained along with the sign from a
4 witness.
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7 Some participants can be excluded after giving consent due to procedure related exclusion criteria like
8 continued intravenous (IV) anticoagulation as per discretion of the primary interventionist. To preserve
9 randomization and to reduce utilization of the resources, allocation of treatment will be performed at
10 the end of procedure.
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15 Randomization will be performed by a core research team member of the hospital who is not part of this
16 study using variable sized blocks of 4 or 6 through computer software and will be kept in password
17 protected computer. Randomization will be revealed to the data collector over phone by the same
18 person who generated the sequence. Blinding of the participant or the data collectors is not possible in
19 this study.
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24 Data collectors will receive half day training for consent taking and data collection. A dry run of the
25 study will be undertaken to identify challenges in the study execution and provide hands on training to
26 the research staff. The plan is to recruit about 10 participants during dry run. The data of these patients
27 will not be used in the final analysis.
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32 Procedure details: All patients receive IV heparin at a dose of at least 70-100 IU/Kg at the start of
33 procedure for diagnostic CAG; dose will be higher for PCI at the discretion of the primary operators.
34 After insertion of radial sheath all patients receive intra-radial verapamil (max 5 mg) and nitroglycerin
35 (max 500micrograms) at a dose titrated to patient's blood pressure. At the end of the radial
36 procedures, both the groups will receive up to 500 micrograms of nitroglycerin into the sheath
37 according to patient's blood pressures.
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42 **Intervention group (InnoSEAL+TRB)**

- 43 1. The sheath is pulled 2-3cm and the area surrounding the puncture site is cleaned and dried.
- 44 2. The InnoSEAL is placed over the sheath at the puncture site.
- 45 3. A transparent adhesive clear dressing is placed over the InnoSEAL.
- 46 4. TR band is applied over the transparent adhesive clear dressing centered over the InnoSEAL.
- 47 5. 12cc air is inflated to apply pressure. **(Figure: 1)**
- 48 6. The sheath is removed. There is a small amount of blood at the sheath tip that is enough to
49 activate the hemostatic pad.
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7. Air is removed from the TR band at 20 minutes intervals, removing 2cc air at 20 minutes, 4cc at 40 minutes and 6cc at 60 minutes from the time of sheath removal. Thus 10cc air remains at 20 minutes, 6cc at 40 minutes and 0cc (total deflation) at 60 minutes. Total compression time is recorded.
 8. TR band is left in place with 0 cc air for further 30 minutes so patient keep his/her arm in resting position. The total duration of TR band application including the arm rest is 90 minutes. Reverse Barbeau's test is repeated just after the removal of TR band.
 9. If there is bleeding at any time, 2 cc air is reintroduced in the TR band.
 10. After the band is removed, clear adhesive dressing and InnoSEAL is left in place.
 11. Radial site is observed for re-bleeding for another 30 minutes after removal of the TR band.
 12. Adhesive dressing and InnoSEAL is removed after 24 hours of the procedure. If patient remains admitted, site is reassessed at 24 hours for RAO and hematoma.
 13. Same day patients will be discharged one hour after the end of the observation period.

Standard group (TRB alone)

(Protocol is identical for both diagnostic angiogram and PCI)

1. The area surrounding the puncture site is cleaned and dried.
2. Sheath is pulled out 2-3 cm.
3. TR band is applied centered over the puncture site and the bladder is inflated with 15cc air to apply pressure.
4. The sheath is now removed.
5. Air is removed gradually leaving at least 10 cc air provided there is no oozing. In case of oozing at any time, 2cc air is reintroduced and final amount of air is recorded. This time is recorded as time of start of hemostasis protocol.
6. At 90 minutes from the time of hemostasis protocol, 2 cc air is removed. From then on at every 20-minute interval, further air is removed starting from with maximum 4 cc from the remaining air at first 20 minutes (110 minutes from the start of protocol), followed by maximum 6 cc at 40 minutes and then if still there is remaining air, maximum 6 cc at each 20 minutes until all the air is removed from the bladder. Total compression time is recorded.
7. If there is bleeding at any time, 2 cc air is reintroduced in the TR band.
8. TR band is left in place at 0cc air for further 30 minutes for safety and Barbeau's test is repeated just after TR band removal.

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9. Radial site is further observed for re-bleeding for another 30 minutes after the removal of the TR band.
10. If patient remains admitted, site is reassessed at 24 hours for RAO and hematoma.
11. Same day patients will be discharged one hour after the end of the observation period.

Patient and public involvement

No patient involved.

Sample Size Calculation

As per our standard practice of only TR Band based hemostasis, the radial occlusion rate is 9.4% and radial hematoma rate is 3.4% (combined event rate of 12.8%). Through a pilot on 40 patients to devise the protocol for InnoSEAL+TRB, we determined a combined rate of 17.7% (RAO: 7.7%, Hematoma: 10%). If there is a true difference in favor of the experimental treatment of 4.89% (17.7% vs. 12.8%), then a total of 648 patients (324 in each group) are required to be 80% sure that the upper limit of a one-sided 97.5% confidence interval (or equivalently a 95% two-sided confidence interval) will exclude a difference in favor of the standard group of more than 3%. If 10% attrition is considered then 33 additional patients are required in each group, thus 357 patients in each group and a total of 714 patients.

Study outcome assessment

Primary outcome

It is a combination of RAO and presence of hematoma of any grade.

1. **Radial artery occlusion:** Radial artery will be defined as occluded if reverse Barbeau's test shows absence of flow on pulse oximetry just after the removal of the TR band in both groups. In patients identified to have RAO, findings will be confirmed using US Duplex using color flow with pulse wave imaging within 24 hours of the radial procedure. US Duplex will be performed during the index hospital stay.
2. **Radial Hematoma:** Radial artery site will be assessed for presence of hematoma at the end of hemostasis protocol. Hematoma will be marked if present, and graded according to categories of I-IV(9). Hematomas grade II-IV will be considered significant.

Patients who develop these complications will be managed as per the standard of care in the hospital. For RAO, usually no intervention is required. Radial hematoma is also a self-limiting complication and

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occasionally may need manual compression and milking and use of sphygmomanometer cuff. After 24hrs of radial hemostasis, no patient follow up is involved in the study.

Secondary outcomes

These include:

- 1. Ease of use:** Ease of use of InnoSEAL will be assessed by a system usability scale (SUS)(10), 5 point Likert scale by the cath lab personnel who routinely perform post procedure hemostasis. Ease of use is reported as percentage acceptability where 100% means highly acceptable and vice versa. Ease of use proforma will be filled by the participating cath lab staffs at the end of the study. Informed consent will be taken from the cath lab staff.
- 2. Total compression time:** Time required from radial sheath removal to the removal of all the air from TR band.
- 3. Total observation time:** Time required from radial sheath removal to the removal of TR band (included time for observation at 0 cc for safety purpose).
- 4. Time to hospital discharge:** (For daycare patients only) Time from removal of radial sheath till patient discharge from hospital
- 5. Patient discomfort:** Standard visual pain scale of 1-10 will be utilized (11). Pain will be assessed after the hemostasis protocol is ended.

Adverse events

Re-bleeding at the end of intervention protocol in either group i.e. bleeding after removal of InnoSEAL+TRB or TRB will be considered as an adverse event. If adverse event occurred it will be recorded and TRB will be applied at the puncture site and inflated with 2 cc air or more till no bleeding is observed. Then 2cc air will be removed at 20 minutes, 4cc at 40 minutes and 6cc at 60 minutes when needed. After 30 minutes of zero air, TRB will be removed and site will be observed for bleeding. Final observation will be made after 30 minutes of removal of TRB. IRB and funders will be informed about the adverse events in the final report.

Statistical Analysis Plan

Data quality will be assured by random checking of 10% of the weekly data by the study investigators and random observation of the participant recruitment and live data collection. Data will be entered in Microsoft Access which will have in-built checks (like value ranges and pop-up for invalid values) to minimize data entry errors. Means and standard deviation will be reported for continuous data based on

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normality assumption along with histograms and compared using Independent Student's t-test. And frequencies with percentages will be reported for the categorical variables. The differences between categorical variables will be examined by the Chi square test and p-value < .05 will be considered significant. Statistical analysis will be performed using the SPSS version 24.0. Chi square test will be utilized to assess primary composite outcome and its components. Independent sample t-test will be used for comparison of time intervals. Kruskal Wallis test will be utilized for significance testing between ordinal secondary outcomes of ease of use and patient discomfort. Intention to treat analysis will be undertaken. If there would be many cross-overs then per protocol analysis will also be conducted and results of both will be compared and discussed.

An interim analysis will be undertaken when 50% of the required sample has been achieved. If there is a skewed distribution of primary outcome or adverse events in any of the arm the trial will be stopped. The analysis of the primary outcome of the study will be undertaken by the core research team member who is not part of the study. The decision to stop the trial will be taken by the PI.

Ethics and dissemination

Ethical approval will be taken from Institutional Review Board of Tabba Heart Institute. Written informed consent will be obtained from all study participants prior to the enrollment in the study.

(Appendix: Consent form).

No personal or clinical information of study participants will be made public. All study information will be stored in lock and key and in password protected software after data entry. The study will be carried out in compliance with Good Clinical Practice guidelines and all the study investigators and key members will be IRB certified to conduct human research. IRB will conduct an independent audit of the trial execution as per their policy.

Study findings will be disseminated to the study hospital staff and intervention arm with favorable results will be implemented as hospital protocol for radial site closure after cath lab procedures. The results will also be published in scientific journals and will be presented in seminar and conferences.

Author contributions:

SA developed the protocol, estimated sample size and data analysis plan, AP initially conceived the idea and provided intellectual input to design the methodology and critically reviewed the protocol. SS is involved in execution of the trial as well as supervision of the study staff.

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Funding statement:

This work was supported by InnoTherapy Inc. S. Korea. Funding agency has no role in designing the study, writing the protocol, study execution, data management or analysis and interpretation of the results.

Sponsor contact number: 201-944-0445

Competing interest statement

Authors declare no competing interests.

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Figure: 1 InnoSEAL patch is applied over the sheath and TRB is tied over it

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3 **Appendix**4
5 **Patient's consent form**6
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| Title of the study: Combination of InnoSEAL plus TR band compared to TR Band alone for Radial Artery Outcomes in patients undergoing transradial coronary intervention (InnoSEAL – II) | |
| ERC Ref No: IORG 000 _____ | Sponsor: InnoTherapy Inc. S. Korea |
| Principal investigator: Dr Asad Z Pathan Co-Investigators: Dr Saba Aijaz, Dr Sana Sheikh | Organization: Tabba Heart Institute, Karachi |
| Patient's name: _____ | MR No: _____ |

PURPOSE OF THE STUDY

This study will be conducted in Tabba Heart Institute in which patients who undergo trans-radial coronary procedures will be randomized within few minutes after the procedure to either Catechol conjugated chitosan based pad plus TRBand or TRBand alone. The main purpose of this study is to compare the effect of InnoSEAL plus TR band or TR band alone on subsequent radial artery outcomes (Acute radial artery blockage and/or significant bleeding) after transradial intervention and to compare the difference in time needed to stop the bleeding from radial artery, time to termination of radial artery monitoring, patient's discharge and patient's discomfort between InnoSEAL plus TR band versus TRBand alone.

PROCEDURES

All adult patients coming to Coronary Catheterization Laboratory, Tabba Heart Institute (THI) for elective and urgent Trans-radial diagnostic catheterization and percutaneous coronary interventions will be invited to participate in the study. Those patients who consent to participate will get assigned to either TR band alone or in InnoSEAL plus TR band arm. TR band is a tight band like device which is routinely used in THI to stop bleeding from the cannula site at your wrist after the radial coronary procedure is completed. This band remains in place for few hours and is removed once radial bleeding is stopped. If you are assigned to InnoSEAL plus TR band arm, then an additional square patch which contains a chemical that helps in blood clotting will be applied to your wrist before the TR band. This patch and band remains in place for few hours and is removed once radial bleeding is stopped. Routine care after the bleeding stops is same for both the treatment arms. Pulse in your arm will be checked multiple times during this time. An ultrasound of our wrist may be performed to further confirm blood flow at the site of cannula.

The treatment you get assigned to will be totally based on chance and is pre-decided by a computer program. Our research coordinator has no control to allocate you to any treatment according to her or your choice.

RISKS OR DISCOMFORT

There are no adverse effects of this study. It will only take your valuable time which can cause inconvenience to you. We apologize for this inconvenience in advance.

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POSSIBLE BENEFITS

The possible benefits might include early removal of the TR band, which may lead to early discharge if you are planned same day discharge by your treating cardiologist. Also since the band and/ or InnoSEAL is applied for a lesser duration, there may be less discomfort in your hand related to hemostasis procedure.

FINANCIAL CONSIDERATIONS

No financial compensation will be provided to any of the study participants.

AVAILABLE MEDICAL TREATMENT FOR ADVERSE EXPERIENCES

Since you are our study participant, we will assist you in directing you to your correct care provider if any unrelated medical issue arises during the course of our study. Additionally, your participation in this study will not affect the care that you will continue to receive in THI.

CONFIDENTIALITY

Your identity will be kept confidential. Special measures will be taken to protect your identity and personal information. You will be given a unique identifier (code). Your data will be kept in lock and key and will only be accessible by the research team. In the electronic system one of the personal data will be entered and you will only be identified by a unique code. The results of the study will only be published for scientific purposes and your name or any identifiable references to you will not be included. The results will not be shared with anyone. Only the combined results will be shared in scientific meeting and journals.

WITHDRAWAL OF CONSENT

You have full authority to participate in the study or refuse to participate in it. You also have right to leave study anytime without any reason. Your decision to participate or refuse to participate will not affect the course of your treatment at THI at this time and even in the future.

AVAILABLE SOURCES OF INFORMATION

If you have any questions regarding this study please call at this number.

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AUTHORIZATION

I have read and understood this consent form, and I volunteer to participate in this research study. I understand that I will receive a copy of this form. I voluntarily choose to participate, but I understand that my consent does not take away any legal rights in the case of negligence or other legal fault of anyone who is involved in this study.

3

Participant's Name: _____

Date: _____

Participant's Signature or thumb impression:

Signature of witness (use for non-literate patient)

Principal Investigator's/Co-PI's Signature:

Date: _____

Name/ Signature of Person Obtaining Consent:

Date: _____



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | ItemNo | Description | Page number |
|-----------------------------------|--------|--|-------------------------|
| Administrative information | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 2 |
| Protocol version | 3 | Date and version identifier | In footers on all pages |
| Funding | 4 | Sources and types of financial, material, and other support | 9 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 9 |
| | 5b | Name and contact information for the trial sponsor | 9 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 9 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | Not applicable |

Introduction

| | | | |
|--------------------------|----|---|-----|
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3 |
| | 6b | Explanation for choice of comparators | 3 |
| Objectives | 7 | Specific objectives or hypotheses | 3-4 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 4 |

Methods: Participants, interventions, and outcomes

| | | | |
|----------------------|-----|--|----------------|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 4 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 4 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 5-7 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | Not applicable |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | Not applicable |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | Not applicable |

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| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 7-8 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 4 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 7 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 4 |

Methods: Assignment of interventions (for controlled trials)

Allocation:

| | | | |
|----------------------------------|-----|--|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 5 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 5 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 5 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 5 |

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4 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a
5 participant's allocated intervention during the trial
6 Not applicable

7 **Methods: Data collection, management, and analysis**

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9 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any
10 related processes to promote data quality (eg, duplicate measurements, training of assessors)
11 and a description of study instruments (eg, questionnaires, laboratory tests) along with their
12 reliability and validity, if known. Reference to where data collection forms can be found, if not in
13 the protocol
14
15
16 18b Plans to promote participant retention and complete follow-up, including list of any outcome data
17 to be collected for participants who discontinue or deviate from intervention protocols
18 Not applicable
19 Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote
20 data quality (eg, double data entry; range checks for data values). Reference to where details of
21 data management procedures can be found, if not in the protocol
22 8
23 Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other
24 details of the statistical analysis plan can be found, if not in the protocol
25 8-9
26 20b Methods for any additional analyses (eg, subgroup and adjusted analyses)
27 Not applicable
28 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised
29 analysis), and any statistical methods to handle missing data (eg, multiple imputation)
30 9
31

32 **Methods: Monitoring**

33
34 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure;
35 statement of whether it is independent from the sponsor and competing interests; and reference
36 to where further details about its charter can be found, if not in the protocol. Alternatively, an
37 explanation of why a DMC is not needed
38 DMC is not needed as it
39 Is a low risk study with no
40 Life-threatening events
41 Anticipated as a result of
42 Intervention.
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| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 9 |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 8 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 9 |
| Ethics and dissemination | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 9 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | Not applicable |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 4 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | Not applicable |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 9 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 10 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | Not applicable |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | Not applicable |

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|----|----------------------------|-----|---|
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| 4 | Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions |
| 5 | | | 9 |
| 6 | | | |
| 7 | | | |
| 8 | | 31b | Authorship eligibility guidelines and any intended use of professional writers |
| 9 | | | ICMJE guidelines will be |
| 10 | | | Followed for authorship |
| 11 | | | Eligibility. No professional |
| 12 | | | Writers will be used. |
| 13 | | | |
| 14 | | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code |
| 15 | | | The data can be provided |
| 16 | | | On reasonable request |
| 17 | Appendices | | |
| 18 | | | |
| 19 | Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
| 20 | | | 12 |
| 21 | | | |
| 22 | Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |
| 23 | | | Not applicable |
| 24 | | | |

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BMJ Open

Combination of InnoSEAL plus TR band compared to TR Band alone for Radial Artery Outcomes in patients undergoing transradial coronary intervention (InnoSEAL - II): An open-label randomized controlled trial (Protocol)

| | |
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3 1 **Combination of InnoSEAL plus TR band compared to TR Band alone for Radial Artery**
4 2 **Outcomes in patients undergoing transradial coronary intervention (InnoSEAL - II): An open**
5 3 **label randomized controlled trial (Protocol)**

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7
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26 15
27 16
28 17 **Word count: 2738**

29
30 18 **Keywords:**

31
32 19 transradial, access site, complication, hemostatic pad, trial

2

30 Abstract**31 Introduction**

32 About 2-30% of cardiac catheterization procedures get complicated by radial artery occlusion (RAO).
33 Ensuring patent hemostasis appears to be an important factor in reducing RAO. Currently employed
34 method is a radial compression device (RCD) such as TransRadial Bands (TRB) that takes hours to achieve
35 hemostasis and causes discomfort to the patients. Hemostatic pads offer an alternative to RCD with
36 reduced time to achieve hemostasis. Our trial aims to determine the non-inferiority of the
37 catecholamine chitosan-based pad (InnoSEAL hemostatic pad) used in conjunction with TRB
38 (InnoSEAL+TRB) when compared with the TR band (TRB) alone in reducing composite adverse access site
39 outcomes.

40 Methods and analysis

41 It will be an open label, parallel, randomized controlled trial on 714 adult patients (325 in each arm)
42 undergoing coronary procedure using transradial approach at a cardiac health facility over seven
43 months duration. InnoSEAL patch along with TRB will be used to control bleeding in intervention arm
44 and TRB alone in control arm which is the standard practice. Study primary outcomes include RAO and
45 hematoma; secondary outcomes are compression time, patient discomfort, time to discharge and ease
46 of use of the intervention technique by the health care staff. Chi-square test will be used to compare the
47 categorical outcomes between two arms and student's t-test for continuous outcomes. A p-value of
48 <0.05 will be considered significant.

49 Ethics and dissemination

50 Ethical approval for the study has been obtained from Institutional Review Board of Tappa Heart
51 Institute # IORG0007863. Findings will be disseminated through seminars and scientific publications.

52 Registration

53 Trial is registered at clinicalTrials.gov # NCT04380883 on 7 May 2020.

54 Strengths and limitation of this study:

- 55 • This is the first powered clinical trial comparing chitosan-based hemostatic pad to pneumatic band.
56 The trials done previously were on lesser number of patients with no power calculation.

3

- One of the secondary outcomes of the study is ease of the use of any of the techniques of access site closure by the cathlab staff. This will inform the feasibility of translating the trial results in to practice.
- The lack of blinding of the data collectors is a limitation of the study.

Introduction

Trans-radial procedures are frequently complicated by radial artery occlusion (RAO) with reported incidence of 2-30%(1). RAO may limit future use of this site for catheterization, as an arterial conduit for surgical revascularization or for hemodialysis access. Independent predictors of RAO are the diameter of the sheath and its relationship to the size of the radial artery, amount of heparin used, post procedure compression time and presence of antegrade flow in the artery during hemostasis(2). Ensuring patent hemostatic compression i.e. the control of arterial bleeding while maintaining radial arterial flow appears to be an important factor in reducing RAO(3).

Hemostasis after radial sheath removal has been achieved using multiple methods including manual compression, tourniquets and compression bandages, a variety of pneumatic compression devices and more recently hemostatic pads impregnated with pro-coagulant chemicals. Currently the most frequently employed method for hemostasis following trans-radial procedures is a compression device (RCD)(4).

Hemostatic pads offer an alternative to RCD where overall compression time is inherently low and patent hemostasis can possibly be achieved. Chitosan, one of the materials used in hemostasis pads, is a biodegradable polysaccharide which is converted to a hemostatic agent after contact with blood, and has shown similar efficacy in terms of reducing local bleeding and hematoma formation compared to RCDs with added advantage of shorter time of compression and therefore less patient discomfort(5).

The combined use of trans-radial band (TRB) with a hemostatic device may allow ease of use with reduced hemostasis time(6). Patent hemostasis is also likely to be achieved with the combined use of both devices and possibly improve radial artery patency with added benefit of reduced bleeding complications. So far two trials have been undertaken that compared RCD alone with RCD plus catechol conjugated homeostasis pads (7, 8). Both trials showed reduced time to achieve hemostasis with RCD plus hemostatic pad but both were underpowered with small number of participants. Also, we did not find any trial from lower middle income countries (LMICs) hence we planned a trial with adequate power which will test the applicability of the hemostatic pad with pneumatic band in a LMIC.

4

Our trial aims to test the hypothesis that compared to TRB alone, catecholamine chitosan-based pad (InnoSEAL hemostatic pad, InnoTherapy, Inc. S Korea) used in conjunction with TRB (InnoSEAL+TRB) is non-inferior in terms of the composite adverse access site outcomes i.e. RAO within 24 hours and hematoma as per Bleeding Academic Research Consortium (BARC) grading (9). Secondary objectives include testing the non-inferiority of InnoSEAL+TRB in terms of ease of use by the cath lab staff compared to TRB; and superiority of InnoSEAL+TRB for shortened total hemostasis time, total observation time for the radial site and time to hospital discharge for daycare patients sub group. Finally, we aim to test superiority of InnoSEAL+TRB for reduced patient discomfort compared to TRB alone.

Methods and analysis

This open label randomized controlled trial will be conducted in cardiac catheterization laboratory (CCL) at Tabba Heart Institute (THI) Karachi, Pakistan. Tabba heart institute is a 160 bedded cardiac tertiary care hospital with 24hrs emergency and facilities for primary PCI and cardiac surgeries. The institution has two fully equipped cardiac catheter labs. There is a fully trained and experienced faculty of more than 15 cardiologists and 06 interventionalists. On average more than 1400 PCIs are performed annually. This is one of the major referral centers in the city for primary PCI. THI is also a teaching hospital with approved training programs in adult cardiology and interventional cardiology.

Adult patients of both gender undergoing coronary procedure using transradial approach including diagnostic coronary angiogram (CAG) or PCI and who are hemodynamically stable will be included. Patients in which radial sheath of larger than 6 F will be used; who are on continuous infusion of anticoagulants (unfractionated Heparin, gpIIb/IIIa inhibitors) after procedure or on an ongoing anticoagulation therapy (Warfarin, Rivaroxaban), or with INR > 3 will be excluded. Also patients who are diagnosed with ipsilateral arteriovenous fistula, Barbeau's class D or have history of RAO at baseline, or unable to give consent will be excluded.

All consecutive patients coming to CCL for coronary procedures will be screened for eligibility by data collectors. If the participants meet the eligibility criteria of the study, they will be offered to participate in the trial. Before the start of the coronary procedure, patients will be approached for enrollment in the study and informed consent will be taken. If the participant assigns a surrogate, then consent will be signed by the surrogate. In case of urgent need of coronary procedures, consent will be taken post coronary procedure when patient is shifted in the cath lab recovery area. Consent form will be provided

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3 117 in English or Urdu according to patient's preference. One signed copy will be given to the patient for the
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5 118 reference. For an uneducated patient, form will be verbally read and thoroughly explained by the
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7 119 research coordinator. A thumb impression will be obtained along with the sign from a witness.

8
9 120 Some participants might be excluded after giving consent due to procedure related exclusion criteria like
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11 121 continued intravenous (IV) anticoagulation as per discretion of the primary interventionist. To preserve
12
13 122 randomization and to reduce utilization of the resources, allocation of treatment will be performed at
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15 123 the end of procedure.

16
17 124 Randomization will be performed by a core research team member of the hospital who is not part of this
18
19 125 study using variable sized blocks of 4 or 6 through computer software and will be kept in password
20
21 126 protected computer. Randomization will be revealed to the data collector over phone by the same
22
23 127 person who generated the sequence. Blinding of the participant or the data collectors is not possible in
24
25 128 this study.

26 129 Data collectors will receive half day training for consent taking and data collection. A dry run of the
27
28 130 study will be undertaken to identify challenges in the study execution and provide hands on training to
29
30 131 the research staff. The plan is to recruit about 10 participants during dry run. The data of these patients
31
32 132 will not be used in the final analysis.

33 133 Procedure details: All patients receive IV heparin at a dose of at least 70-100 IU/Kg at the start of
34
35 134 procedure for diagnostic CAG; dose will be higher for PCI at the discretion of the primary operators.
36
37 135 After insertion of radial sheath all patients receive intra-radial verapamil (max 5 mg) and nitroglycerin
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39 136 (max 500micrograms) at a dose titrated to patient's blood pressure. At the end of the radial
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41 137 procedures, both the groups will receive up to 500 micrograms of nitroglycerin into the sheath
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43 138 according to patient's blood pressures.

44 139 **Intervention group (InnoSEAL+TRB)**

- 46 140 1. The sheath is pulled 2-3cm and the area surrounding the puncture site is cleaned and dried.
- 47
48 141 2. The InnoSEAL is placed over the sheath at the puncture site.
- 49
50 142 3. A transparent adhesive clear dressing is placed over the InnoSEAL.
- 51
52 143 4. TR band is applied over the transparent adhesive clear dressing centered over the InnoSEAL.
- 53
54 144 5. 12cc air is inflated to apply pressure. **(Figure: 1)**
- 55
56 145 6. The sheath is removed. There is a small amount of blood at the sheath tip that is enough to
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58 146 activate the hemostatic pad.

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5 148 7. Air is removed from the TR band at 20 minutes intervals, removing 2cc air at 20 minutes, 4cc at
6 149 40 minutes and 6cc at 60 minutes from the time of sheath removal. Thus 10cc air remains at 20
7 150 minutes, 6cc at 40 minutes and 0cc (total deflation) at 60 minutes. Total compression time is
8 151 recorded.
9
10 152 8. TR band is left in place with 0 cc air for further 30 minutes and patient will keep his/her arm in
11 153 resting position. The total duration of TR band application including the arm rest is 90 minutes.
12 154 Reverse Barbeau's test is repeated just after the removal of TR band.
13 155 9. If there is bleeding at any time, 2 cc air is reintroduced in the TR band.
14 156 10. After the band is removed, clear adhesive dressing and InnoSEAL is left in place.
15 157 11. Radial site is observed for re-bleeding for another 30 minutes after removal of the TR band.
16 158 12. Adhesive dressing and InnoSEAL is removed after 24 hours of the procedure. If patient remains
17 159 admitted, site is reassessed at 24 hours for RAO and hematoma. For patients discharging on the
18 160 same day, final observation for RAO and hematoma will be made at the time of TR band removal
19 161 after leaving it at zero pressure for 30 minutes. Same day patients will be discharged one hour
20 162 after the end of the observation period.

Standard group (TRB alone)

(Protocol is identical for both diagnostic angiogram and PCI)

- 21 163
22 164
23 165 1. The area surrounding the puncture site is cleaned and dried.
24 166 2. Sheath is pulled out 2-3 cm.
25 167 3. TR band is applied centered over the puncture site and the bladder is inflated with 15cc air to
26 168 apply pressure.
27 169 4. The sheath is now removed.
28 170 5. Air is removed gradually leaving at least 10 cc air provided there is no oozing. In case of oozing
29 171 at any time, 2cc air is reintroduced and final amount of air is recorded. This time is recorded as
30 172 time of start of hemostasis protocol.
31 173 6. At 90 minutes from the time of hemostasis protocol, 2 cc air is removed. From then on at every
32 174 20-minute interval, further air is removed starting from with maximum 4 cc from the remaining
33 175 air at first 20 minutes (110 minutes from the start of protocol), followed by maximum 6 cc at 40
34 176 minutes and then if still there is remaining air, maximum 6 cc at each 20 minutes until all the air
35 177 is removed from the bladder. Total compression time is recorded.
36 178 7. If there is bleeding at any time, 2 cc air is reintroduced in the TR band.

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3 179 8. TR band is left in place at 0cc air for further 30 minutes for safety and Barbeau's test is repeated
4
5 180 just after TR band removal.
6
7 181 9. Radial site is further observed for re-bleeding, for another 30 minutes after the removal of the
8
9 182 TR band.
10 183 10. If patient remains admitted, site is reassessed at 24 hours for RAO and hematoma. For patients
11
12 184 discharging on the same day, final observation for RAO and hematoma will be made at the time
13
14 185 of TR band removal after leaving it at zero pressure for 30 minutes.
15 186 11. Same day patients will be discharged one hour after the end of the observation period.

17 187 **Patient and public involvement**

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19
20 188 No patient involved.

21 22 189 **Sample Size Calculation**

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24 190 As per our standard practice of only TR Band based hemostasis, the radial occlusion rate is 9.4% and
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26 191 radial hematoma rate is 3.4% (combined event rate of 12.8%). Through a pilot on 40 patients to devise
27
28 192 the protocol for InnoSEAL+TRB, we determined a combined rate of 17.7% (RAO: 7.7%, Hematoma: 10%).
29
30 193 If there is a true difference in favor of the experimental treatment of 4.89% (17.7% vs. 12.8%), then a
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32 194 total of 648 patients (324 in each group) are required to be 80% sure that the upper limit of a one-sided
33
34 195 97.5% confidence interval (or equivalently a 95% two-sided confidence interval) will exclude a difference
35
36 196 in favor of the standard group of more than 3%. If 10% attrition is considered then 33 additional patients
37
38 197 are required in each group, thus 357 patients in each group and a total of 714 patients.

38 198 **Study outcome assessment**

39 40 199 **Primary outcome**

41
42 200 It is a combination of RAO and presence of hematoma of any grade.

- 43 201 1. **Radial artery occlusion:** Radial artery will be defined as occluded if reverse Barbeau's test shows
44
45 202 absence of flow on pulse oximetry just after the removal of the TR band in both groups. In
46
47 203 patients identified to have RAO, findings will be confirmed using US Duplex using color flow with
48
49 204 pulse wave imaging within 24 hours of the radial procedure. US Duplex will be performed during
50
51 205 the index hospital stay.
52 206 2. **Radial Hematoma:** Radial artery site will be assessed for presence of hematoma at the end of
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54 207 hemostasis protocol. Hematoma will be marked if present, and graded according to categories
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56 208 of I-IV(10). Hematomas grade II-IV will be considered significant.

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209 Patients who develop these complications will be managed as per the standard of care in the hospital.
210 For RAO, usually no intervention is required. Radial hematoma is also a self-limiting complication and
211 occasionally may need manual compression and milking and use of sphygmomanometer cuff. After
212 24hrs of radial hemostasis, no patient follow up is involved in the study.

213 **Secondary outcomes**

214 These include:

- 215 **1. Ease of use:** Ease of use of InnoSEAL will be assessed by a system usability scale (SUS)(11), 5
216 point Likert scale by the cath lab personnel who routinely perform post procedure hemostasis.
217 Ease of use is reported as percentage acceptability where 100% means highly acceptable and
218 vice versa. Ease of use proforma will be filled by the participating cath lab staffs at the end of
219 the study. Informed consent will be taken from the cath lab staff.
- 220 **2. Total compression time:** Time required from radial sheath removal to the removal of all the air
221 from TR band.
- 222 **3. Total observation time:** Time required from radial sheath removal to the removal of TR band
223 (included time for observation at 0 cc for safety purpose).
- 224 **4. Time to hospital discharge:** (For daycare patients only) Time from removal of radial sheath till
225 patient discharge from hospital
- 226 **5. Patient discomfort:** Standard visual pain scale of 1-10 will be utilized (12). Pain will be assessed
227 after the hemostasis protocol is ended.

228 **Adverse events**

229 Re-bleeding at the end of intervention protocol in either group i.e. bleeding after removal of
230 InnoSEAL+TRB or TRB will be considered as an adverse event. If adverse event occurred it will be
231 recorded and TRB will be applied at the puncture site and inflated with 2 cc air or more till no bleeding is
232 observed. Then 2cc air will be removed at 20 minutes, 4cc at 40 minutes and 6cc at 60 minutes when
233 needed. After 30 minutes of zero air, TRB will be removed and site will be observed for bleeding. Final
234 observation will be made after 30 minutes of removal of TRB. IRB and funders will be informed about
235 the adverse events in the final report.

236 **Statistical Analysis Plan**

237 Data quality will be assured by random checking of 10% of the weekly data by the study investigators
238 and random observation of the participant recruitment and live data collection. Data will be entered in

1
2
3 239 Microsoft Access which will have in-built checks (like value ranges and pop-up for invalid values) to
4
5 240 minimize data entry errors. Means and standard deviation will be reported for continuous data based on
6
7 241 normality assumption along with histograms and compared using Independent Student's t-test. And
8
9 242 frequencies with percentages will be reported for the categorical variables. The differences between
10
11 243 categorical variables will be examined by the Chi square test and p-value < .05 will be considered
12
13 244 significant. Statistical analysis will be performed using the SPSS version 24.0. For comparison of baseline
14
15 245 characteristics, Independent Student's t-test and chi-square tests will be used for quantitative and
16
17 246 categorical variables respectively. Chi square test will be utilized to assess primary composite outcome
18
19 247 and its components. Independent sample t-test will be used for comparison of time intervals. Kruskal
20
21 248 Wallis test will be utilized for significance testing between ordinal secondary outcomes of ease of use
22
23 249 and patient discomfort. Intention to treat analysis will be undertaken. If there would be many cross-
24
25 250 overs then per protocol analysis will also be conducted and results of both will be compared and
26
27 251 discussed.

28
29 252 An interim analysis will be undertaken when 50% of the required sample has been achieved. If there is a
30
31 253 skewed distribution of primary outcome or adverse events in any of the arm the trial will be stopped.
32
33 254 The analysis of the primary outcome of the study will be undertaken by the core research team member
34
35 255 who is not part of the study. The decision to stop the trial will be taken by the PI.

36 256 **Ethics and dissemination**

37 257 Ethical approval will be taken from Institutional Review Board of Tabba Heart Institute. Written
38
39 258 informed consent will be obtained from all study participants prior to the enrollment in the study.

40 259 **(Appendix: Consent form).**

41 260 No personal or clinical information of study participants will be made public. All study
42
43 261 information will be stored in lock and key and in password protected software after data entry. The
44
45 262 study will be carried out in compliance with Good Clinical Practice guidelines and all the study
46
47 263 investigators and key members will be IRB certified to conduct human research. IRB will conduct an
48
49 264 independent audit of the trial execution as per their policy.

50 265 Study findings will be disseminated to the study hospital staff and intervention arm with favorable
51
52 266 results will be implemented as hospital protocol for radial site closure after cath lab procedures. The
53
54 267 results will also be published in scientific journals and will be presented in seminar and conferences.

55 268 **Author contributions:**

10

1
2
3 269 SA developed the protocol, estimated sample size and data analysis plan, AP initially conceived the idea
4
5 270 and provided intellectual input to design the methodology and critically reviewed the protocol. SS draft
6
7 271 the protocol for publication, is involved in execution of the trial as well as supervision of the study staff.
8

9 272 **Funding statement:**

10
11 273 This work was supported by InnoTherapy Inc. S. Korea grant # THI-INNOSEAL2-2020. Funding agency has
12
13 274 no role in designing the study, writing the protocol, study execution, data management or analysis and
14
15 275 interpretation of the results.
16

17 276 Sponsor contact number: 201-944-0445
18

19 277 **Competing interest statement**

20
21 278 Authors declare no competing interests.
22

23 279 **Figure: 1 InnoSEAL patch is applied over the sheath and TRB is tied over it**
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Figure: 1 InnoSEAL patch is applied over the sheath and TRB is tied over it



For peer review only

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3 **Appendix**4
5 **Patient's consent form**6
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|---|---|
| Title of the study: Combination of InnoSEAL plus TR band compared to TR Band alone for Radial Artery Outcomes in patients undergoing transradial coronary intervention (InnoSEAL – II) | |
| ERC Ref No: IORG 000 _____ | Sponsor: InnoTherapy Inc. S. Korea |
| Principal investigator: Dr Asad Z Pathan Co-Investigators: Dr Saba Aijaz, Dr Sana Sheikh | Organization: Tabba Heart Institute, Karachi |
| Patient's name: _____ | MR No: _____ |

PURPOSE OF THE STUDY

This study will be conducted in Tabba Heart Institute in which patients who undergo trans-radial coronary procedures will be randomized within few minutes after the procedure to either Catechol conjugated chitosan based pad plus TRBand or TRBand alone. The main purpose of this study is to compare the effect of InnoSEAL plus TR band or TR band alone on subsequent radial artery outcomes (Acute radial artery blockage and/or significant bleeding) after transradial intervention and to compare the difference in time needed to stop the bleeding from radial artery, time to termination of radial artery monitoring, patient's discharge and patient's discomfort between InnoSEAL plus TR band versus TRBand alone.

PROCEDURES

All adult patients coming to Coronary Catheterization Laboratory, Tabba Heart Institute (THI) for elective and urgent Trans-radial diagnostic catheterization and percutaneous coronary interventions will be invited to participate in the study. Those patients who consent to participate will get assigned to either TR band alone or in InnoSEAL plus TR band arm. TR band is a tight band like device which is routinely used in THI to stop bleeding from the cannula site at your wrist after the radial coronary procedure is completed. This band remains in place for few hours and is removed once radial bleeding is stopped. If you are assigned to InnoSEAL plus TR band arm, then an additional square patch which contains a chemical that helps in blood clotting will be applied to your wrist before the TR band. This patch and band remains in place for few hours and is removed once radial bleeding is stopped. Routine care after the bleeding stops is same for both the treatment arms. Pulse in your arm will be checked multiple times during this time. An ultrasound of our wrist may be performed to further confirm blood flow at the site of cannula.

The treatment you get assigned to will be totally based on chance and is pre-decided by a computer program. Our research coordinator has no control to allocate you to any treatment according to her or your choice.

RISKS OR DISCOMFORT

There are no adverse effects of this study. It will only take your valuable time which can cause inconvenience to you. We apologize for this inconvenience in advance.

2

POSSIBLE BENEFITS

The possible benefits might include early removal of the TR band, which may lead to early discharge if you are planned same day discharge by your treating cardiologist. Also since the band and/ or InnoSEAL is applied for a lesser duration, there may be less discomfort in your hand related to hemostasis procedure.

FINANCIAL CONSIDERATIONS

No financial compensation will be provided to any of the study participants.

AVAILABLE MEDICAL TREATMENT FOR ADVERSE EXPERIENCES

Since you are our study participant, we will assist you in directing you to your correct care provider if any unrelated medical issue arises during the course of our study. Additionally, your participation in this study will not affect the care that you will continue to receive in THI.

CONFIDENTIALITY

Your identity will be kept confidential. Special measures will be taken to protect your identity and personal information. You will be given a unique identifier (code). Your data will be kept in lock and key and will only be accessible by the research team. In the electronic system one of the personal data will be entered and you will only be identified by a unique code. The results of the study will only be published for scientific purposes and your name or any identifiable references to you will not be included. The results will not be shared with anyone. Only the combined results will be shared in scientific meeting and journals.

WITHDRAWAL OF CONSENT

You have full authority to participate in the study or refuse to participate in it. You also have right to leave study anytime without any reason. Your decision to participate or refuse to participate will not affect the course of your treatment at THI at this time and even in the future.

AVAILABLE SOURCES OF INFORMATION

If you have any questions regarding this study please call at this number.

Dr. Saba Aijaz, Dr Sana Sheikh

Department of Cardiology. Tabba Heart Institute, Karachi. Pakistan

Phone: 021 36811842-50 (ext: 1372)

E-mail: saba.aijaz@tabbaheart.org

AUTHORIZATION

I have read and understood this consent form, and I volunteer to participate in this research study. I understand that I will receive a copy of this form. I voluntarily choose to participate, but I understand that my consent does not take away any legal rights in the case of negligence or other legal fault of anyone who is involved in this study.

3

Participant's Name: _____

Date: _____

Participant's Signature or thumb impression:

Signature of witness (use for non-literate patient)

Principal Investigator's/Co-PI's Signature:

Date: _____

Name/ Signature of Person Obtaining Consent:

Date: _____



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | ItemNo | Description | Page number |
|-----------------------------------|--------|--|-------------------------|
| Administrative information | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 2 |
| Protocol version | 3 | Date and version identifier | In footers on all pages |
| Funding | 4 | Sources and types of financial, material, and other support | 9 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 9 |
| | 5b | Name and contact information for the trial sponsor | 9 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 9 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | Not applicable |

Introduction

| | | | |
|--------------------------|----|---|-----|
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3 |
| | 6b | Explanation for choice of comparators | 3 |
| Objectives | 7 | Specific objectives or hypotheses | 3-4 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 4 |

Methods: Participants, interventions, and outcomes

| | | | |
|----------------------|-----|--|----------------|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 4 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 4 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 5-7 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | Not applicable |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | Not applicable |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | Not applicable |

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| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 7-8 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 4 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 7 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 4 |

Methods: Assignment of interventions (for controlled trials)

Allocation:

| | | | |
|----------------------------------|-----|--|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 5 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 5 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 5 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 5 |

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4 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a
5 participant's allocated intervention during the trial Not applicable
6

7 **Methods: Data collection, management, and analysis**

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9 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any
10 related processes to promote data quality (eg, duplicate measurements, training of assessors) 5, 7-8
11 and a description of study instruments (eg, questionnaires, laboratory tests) along with their
12 reliability and validity, if known. Reference to where data collection forms can be found, if not in
13 the protocol
14
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16 18b Plans to promote participant retention and complete follow-up, including list of any outcome data Not applicable
17 to be collected for participants who discontinue or deviate from intervention protocols
18
19 Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote
20 data quality (eg, double data entry; range checks for data values). Reference to where details of
21 data management procedures can be found, if not in the protocol 8
22
23 Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other
24 details of the statistical analysis plan can be found, if not in the protocol 8-9
25
26 20b Methods for any additional analyses (eg, subgroup and adjusted analyses) Not applicable
27
28 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised
29 analysis), and any statistical methods to handle missing data (eg, multiple imputation) 9
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32 **Methods: Monitoring**

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34 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure;
35 statement of whether it is independent from the sponsor and competing interests; and reference
36 to where further details about its charter can be found, if not in the protocol. Alternatively, an
37 explanation of why a DMC is not needed DMC is not needed as it
38 Is a low risk study with no
39 Life-threatening events
40 Anticipated as a result of
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| 4 | | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 9 |
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| 7 | Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 8 |
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| 10 | Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 9 |
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| 14 | Ethics and dissemination | | | |
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| 16 | Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 9 |
| 17 | | | | |
| 18 | Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | Not applicable |
| 19 | | | | |
| 20 | | | | |
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| 22 | Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 4 |
| 23 | | | | |
| 24 | | | | |
| 25 | | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | Not applicable |
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| 28 | Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 9 |
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| 32 | Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 10 |
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| 35 | Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | Not applicable |
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| 38 | Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | Not applicable |
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| 4 | Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions |
| 5 | | | 9 |
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| 8 | | 31b | Authorship eligibility guidelines and any intended use of professional writers |
| 9 | | | ICMJE guidelines will be |
| 10 | | | Followed for authorship |
| 11 | | | Eligibility. No professional |
| 12 | | | Writers will be used. |
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| 14 | | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code |
| 15 | | | The data can be provided |
| 16 | | | On reasonable request |
| 17 | Appendices | | |
| 18 | | | |
| 19 | Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
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| 22 | Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |
| 23 | | | Not applicable |
| 24 | | | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

Combination of InnoSEAL plus TR band compared to TR Band alone for Radial Artery Outcomes in patients undergoing transradial coronary intervention (InnoSEAL - II): An open-label randomized controlled trial (Protocol)

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|---------------------------------|--|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2020-042101.R2 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 17-Nov-2020 |
| Complete List of Authors: | Aijaz, Saba; Tabba Heart Institute, Department of Cardiology sheikh, sana; Tabba Heart Institute, Clinical Research Department Pathan, Asad; Tabba Heart Institute, Department of Cardiology |
| Primary Subject Heading: | Cardiovascular medicine |
| Secondary Subject Heading: | Cardiovascular medicine |
| Keywords: | Adult cardiology < CARDIOLOGY, Coronary intervention < CARDIOLOGY, Coronary heart disease < CARDIOLOGY |
| | |

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3 1 **Combination of InnoSEAL plus TR band compared to TR Band alone for Radial Artery**
4 2 **Outcomes in patients undergoing transradial coronary intervention (InnoSEAL - II): An open-**
5 3 **label randomized controlled trial (Protocol)**

6
7
8 4 **Saba Aijaz¹, Sana Sheikh¹, Asad Z. Pathan¹**

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18 10 Karachi, Pakistan

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27 15
28 16
29
30 17 **Word count: 2738**

31
32 18 **Keywords:**

33
34 19 transradial, access site, complication, hemostatic pad, trial

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Abstract**Introduction**

About 2-30% of cardiac catheterization procedures get complicated by radial artery occlusion (RAO). Ensuring patent hemostasis appears to be an important factor in reducing RAO. Currently employed method is a radial compression device (RCD) such as TransRadial Bands (TRB) that takes hours to achieve hemostasis and causes discomfort to the patients. Hemostatic pads offer an alternative to RCD with reduced time to achieve hemostasis. Our trial aims to determine the non-inferiority of the catecholamine chitosan-based pad (InnoSEAL hemostatic pad) used in conjunction with TRB (InnoSEAL+TRB) when compared with the TR band (TRB) alone in reducing composite adverse access site outcomes.

Methods and analysis

It will be an open-label, parallel, randomized controlled trial on 714 adult patients (325 in each arm) undergoing coronary procedure using transradial approach at a cardiac health facility over seven months duration. InnoSEAL patch along with TRB will be used to control bleeding in intervention arm and TRB alone in control arm which is the standard practice. Study primary outcomes include RAO and hematoma; secondary outcomes are compression time, patient discomfort, time to discharge, and ease of use of the intervention technique by the health care staff. Chi-square test will be used to compare the categorical outcomes between two arms and student's t-test for continuous outcomes. A p-value of <0.05 will be considered significant.

Ethics and dissemination

Ethical approval for the study has been obtained from the Institutional Review Board of Tabba Heart Institute # IORG0007863. Findings will be disseminated through seminars and scientific publications.

Registration

Trial is registered at clinicalTrials.gov # NCT04380883 on 7 May 2020.

Strengths and limitation of this study:

- This is the first powered clinical trial comparing chitosan-based hemostatic pad to the pneumatic band. The trials done previously were on a lesser number of patients with no power calculation.

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- 57 • One of the secondary outcomes of the study is the ease of the use of any of the techniques of access
58 site closure by the cath lab staff. This will inform the feasibility of translating the trial results in to
59 practice.
 - 60 • The lack of blinding of the data collectors is a limitation of the study.

61 **Introduction**

62 Trans-radial procedures are frequently complicated by radial artery occlusion (RAO) with a
63 reported incidence of 2-30%(1). RAO may limit future use of this site for catheterization, as an arterial
64 conduit for surgical revascularization or for hemodialysis access. Independent predictors of RAO are the
65 diameter of the sheath and its relationship to the size of the radial artery, amount of heparin used, post-
66 procedure compression time, and presence of anterograde flow in the artery during hemostasis(2).
67 Ensuring patent hemostatic compression i.e. the control of arterial bleeding while maintaining radial
68 arterial flow appears to be an important factor in reducing RAO(3).

69 Hemostasis after radial sheath removal has been achieved using multiple methods including
70 manual compression, tourniquets and compression bandages, a variety of pneumatic compression
71 devices, and more recently hemostatic pads impregnated with pro-coagulant chemicals. Currently, the
72 most frequently employed method for hemostasis following trans-radial procedures is a compression
73 device (RCD)(4).

74 Hemostatic pads offer an alternative to RCD where overall compression time is inherently low
75 and patent hemostasis can possibly be achieved. Chitosan, one of the materials used in hemostasis pads,
76 is a biodegradable polysaccharide which is converted to a hemostatic agent after contact with blood,
77 and has shown similar efficacy in terms of reducing local bleeding and hematoma formation compared
78 to RCDs with the added advantage of the shorter time of compression and therefore less patient
79 discomfort(5).

80 The combined use of trans-radial band (TRB) with a hemostatic device may allow ease of use with
81 reduced hemostasis time(6). Patent hemostasis is also likely to be achieved with the combined use of
82 both devices and possibly improve radial artery patency with the added benefit of reduced bleeding
83 complications. So far two trials have been undertaken that compared RCD alone with RCD plus catechol
84 conjugated homeostasis pads (7, 8). Both trials showed the reduced time to achieve hemostasis with
85 RCD plus hemostatic pad but both were underpowered with a small number of participants. Also, we did

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not find any trial from lower-middle-income-countries (LMICs) hence we planned a trial with adequate power which will test the applicability of the hemostatic pad with the pneumatic band in an LMIC.

Our trial aims to test the hypothesis that compared to TRB alone, catecholamine chitosan-based pad (InnoSEAL hemostatic pad, InnoTherapy, Inc. S Korea) used in conjunction with TRB (InnoSEAL+TRB) is non-inferior in terms of the composite adverse access site outcomes i.e. RAO within 24 hours and hematoma as per Bleeding Academic Research Consortium (BARC) grading (9). Secondary objectives include testing the non-inferiority of InnoSEAL+TRB in terms of ease of use by the cath lab staff compared to TRB; and superiority of InnoSEAL+TRB for shortened total hemostasis time, total observation time for the radial site and time to hospital discharge for daycare patients sub-group. Finally, we aim to test the superiority of InnoSEAL+TRB for reduced patient discomfort compared to TRB alone.

Methods and analysis

This open-label randomized controlled trial will be conducted in the cardiac catheterization laboratory (CCL) at Tabba Heart Institute (THI) Karachi, Pakistan. Tabba heart institute is a 160 bedded cardiac tertiary care hospital with 24hrs emergency and facilities for primary PCI and cardiac surgeries. The institution has two fully equipped cardiac catheter labs. There is a fully trained and experienced faculty of more than 15 cardiologists and 06 interventionists. On average more than 1400 PCIs are performed annually. This is one of the major referral centers in the city for primary PCI. THI is also a teaching hospital with approved training programs in adult cardiology and interventional cardiology.

Adult patients of both gender undergoing coronary procedure using transradial approach including diagnostic coronary angiogram (CAG) or PCI and who are hemodynamically stable will be included. Patients in which radial sheath of larger than 6 F will be used; who are on continuous infusion of anticoagulants (unfractionated Heparin, gpIIb/IIIa inhibitors) after the procedure or on ongoing anticoagulation therapy (Warfarin, Rivaroxaban), or with INR > 3 will be excluded. Also, patients who are diagnosed with ipsilateral arteriovenous fistula, Barbeau's class D, or have a history of RAO at baseline, or unable to give consent will be excluded.

All consecutive patients coming to CCL for coronary procedures will be screened for eligibility by data collectors. If the participants meet the eligibility criteria of the study, they will be offered to participate in the trial. Before the start of the coronary procedure, patients will be approached for enrollment in the study and informed consent will be taken. If the participant assigns a surrogate, then consent will be

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3 116 signed by the surrogate. In case of urgent need of coronary procedures, consent will be taken post
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5 117 coronary procedure when the patient is shifted in the cath lab recovery area. The consent form will be
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7 118 provided in English or Urdu according to the patient's preference. One signed copy will be given to the
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9 119 patient for the reference. For an uneducated patient, the form will be verbally read and thoroughly
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11 120 explained by the research coordinator. A thumb impression will be obtained along with the sign from a
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121 witness.

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14 122 Some participants might be excluded after giving consent due to procedure-related exclusion criteria
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16 123 like continued intravenous (IV) anticoagulation as per the discretion of the primary interventionist. To
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18 124 preserve randomization and to reduce utilization of the resources, the allocation of treatment will be
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20 125 performed at the end of the procedure.

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22 126 Randomization will be performed by a core research team member of the hospital who is not part of this
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24 127 study using variable-sized blocks of 4 or 6 through computer software and will be kept in password-
25
26 128 protected computer. Randomization will be revealed to the data collector over the phone by the same
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28 129 person who generated the sequence. Blinding of the participant or the data collectors is not possible in
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30 130 this study.

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32 131 Data collectors will receive half-day training for consent taking and data collection. A dry run of the
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34 132 study will be undertaken to identify challenges in the study execution and provide hands-on training to
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36 133 the research staff. The plan is to recruit about 10 participants during the dry run. The data of these
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38 134 patients will not be used in the final analysis.

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40 135 Procedure details: All patients receive IV heparin at a dose of at least 70-100 IU/Kg at the start of the
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42 136 procedure for diagnostic CAG; the dose will be higher for PCI at the discretion of the primary operators.
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44 137 After insertion of radial sheath, all patients receive intra-radial verapamil (max 5 mg) and nitroglycerin
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46 138 (max 500micrograms) at a dose titrated to the patient's blood pressure. At the end of the radial
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48 139 procedures, both the groups will receive up to 500 micrograms of nitroglycerin into the sheath
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50 140 according to patient's blood pressures.

51 141 **Intervention group (InnoSEAL+TRB)**

- 52 142 1. The sheath is pulled 2-3cm and the area surrounding the puncture site is cleaned and dried.
- 53 143 2. The InnoSEAL is placed over the sheath at the puncture site.
- 54 144 3. A transparent adhesive clear dressing is placed over the InnoSEAL.
- 55 145 4. TR band is applied over the transparent adhesive clear dressing centered over the InnoSEAL.

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- 146 5. 12cc air is inflated to apply pressure. **(Figure: 1)**
- 147 6. The sheath is removed. There is a small amount of blood at the sheath tip that is enough to
- 148 activate the hemostatic pad.
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- 150 7. Air is removed from the TR band at 20 minutes intervals, removing 2cc air at 20 minutes, 4cc at
- 151 40 minutes, and 6cc at 60 minutes from the time of sheath removal. Thus 10cc air remains at 20
- 152 minutes, 6cc at 40 minutes, and 0cc (total deflation) at 60 minutes. Total compression time is
- 153 recorded.
- 154 8. TR band is left in place with 0 cc air for further 30 minutes and the patient will keep his/her arm
- 155 in resting position. The total duration of TR band application including the armrest is 90 minutes.
- 156 Reverse Barbeau's test is repeated just after the removal of TR band.
- 157 9. If there is bleeding at any time, 2 cc air is reintroduced in the TR band.
- 158 10. After the band is removed, clear adhesive dressing and InnoSEAL is left in place.
- 159 11. Radial site is observed for re-bleeding for another 30 minutes after removal of the TR band.
- 160 12. Adhesive dressing and InnoSEAL is removed after 24 hours of the procedure. If the patient
- 161 remains admitted, the site is reassessed at 24 hours for RAO and hematoma. For patients
- 162 discharging on the same day, final observation for RAO and hematoma will be made at the time
- 163 of TR band removal after leaving it at zero pressure for 30 minutes. Same day patients will be
- 164 discharged one hour after the end of the observation period.
- 165 13. Patients screened positive for RAO will be re-assessed at 6 months.

166 **Standard group (TRB alone)**

167 (Protocol is identical for both diagnostic angiogram and PCI)

- 168 1. The area surrounding the puncture site is cleaned and dried.
- 169 2. The sheath is pulled out 2-3 cm.
- 170 3. TR band is applied centered over the puncture site and the bladder is inflated with 15cc air to
- 171 apply pressure.
- 172 4. The sheath is now removed.
- 173 5. Air is removed gradually leaving at least 10 cc air provided there is no oozing. In case of oozing
- 174 at any time, 2cc air is reintroduced and the final amount of air is recorded. This time is recorded
- 175 as time of start of hemostasis protocol.

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- 176 6. At 90 minutes from the time of hemostasis protocol, 2 cc air is removed. From then on at every
177 20-minute interval, further air is removed starting from with maximum 4 cc from the remaining
178 air at first 20 minutes (110 minutes from the start of the protocol), followed by maximum 6 cc at
179 40 minutes and then if still there is remaining air, maximum 6 cc at every 20 minutes until all the
180 air is removed from the bladder. Total compression time is recorded.
- 181 7. If there is bleeding at any time, 2 cc air is reintroduced in the TR band.
- 182 8. TR band is left in place at 0cc air for further 30 minutes for safety and Barbeau's test is repeated
183 just after TR band removal.
- 184 9. Radial site is further observed for re-bleeding, for another 30 minutes after the removal of the
185 TR band.
- 186 10. If the patient remains admitted, the site is reassessed at 24 hours for RAO and hematoma. For
187 patients discharging on the same day, final observation for RAO and hematoma will be made at
188 the time of TR band removal after leaving it at zero pressure for 30 minutes.
- 189 11. Same day patients will be discharged one hour after the end of the observation period.
- 190 12. Patients screened positive for RAO will be re-assessed at 6 months.

191 **Patient and public involvement**

192 No patient involved.

193 **Sample Size Calculation**

194 As per our standard practice of only TR Band based hemostasis, the radial occlusion rate is 9.4% and
195 radial hematoma rate is 3.4% (combined event rate of 12.8%). Through a pilot on 40 patients to devise
196 the protocol for InnoSEAL+TRB, we determined a combined rate of 17.7% (RAO: 7.7%, Hematoma: 10%).
197 If there is a true difference in favor of the experimental treatment of 4.89% (17.7% vs. 12.8%), then a
198 total of 648 patients (324 in each group) are required to be 80% sure that the upper limit of a one-sided
199 97.5% confidence interval (or equivalently a 95% two-sided confidence interval) will exclude a difference
200 in favor of the standard group of more than 3%. If 10% attrition is considered then 33 additional patients
201 are required in each group, thus 357 patients in each group and a total of 714 patients.

202 **Study outcome assessment**

203 **Primary outcome**

204 It is a combination of RAO and presence of hematoma of any grade.

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3 205 1. **Radial artery occlusion:** Radial artery will be defined as occluded if reverse Barbeau's test shows
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5 206 absence of flow on pulse oximetry just after the removal of the TR band in both groups. In
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7 207 patients identified to have RAO, findings will be confirmed using US Duplex using color flow with
8
9 208 pulse wave imaging within 24 hours of the radial procedure. US Duplex will be performed during
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11 209 the index hospital stay.

12 210 2. **Radial Hematoma:** Radial artery site will be assessed for presence of hematoma at the end of
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14 211 hemostasis protocol. Hematoma will be marked if present, and graded according to categories
15
16 212 of I-IV(10). Hematomas grade II-IV will be considered significant.

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18 213 Patients who develop these complications will be managed as per the standard of care in the hospital.
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20 214 For RAO, usually no intervention is required. Radial hematoma is also a self-limiting complication and
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22 215 occasionally may need manual compression and milking and use of sphygmomanometer cuff. After
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24 216 24hrs of radial hemostasis, no patient follow up is involved in the study.

25 217 **Secondary outcomes**

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27 218 These include:

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29 219 1. **Ease of use:** Ease of use of InnoSEAL will be assessed by a system usability scale (SUS)(11), 5
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31 220 point Likert scale by the cath lab personnel who routinely perform post procedure hemostasis.
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33 221 Ease of use is reported as percentage acceptability where 100% means highly acceptable and
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35 222 vice versa. Ease of use proforma will be filled by the participating cath lab staffs at the end of
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37 223 the study. Informed consent will be taken from the cath lab staff.
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39 224 2. **Total compression time:** Time required from radial sheath removal to the removal of all the air
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41 225 from TR band.
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43 226 3. **Total observation time:** Time required from radial sheath removal to the removal of TR band
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45 227 (included time for observation at 0 cc for safety purpose).
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47 228 4. **Time to hospital discharge:** (For daycare patients only) Time from removal of radial sheath till
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49 229 patient discharge from hospital
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51 230 5. **Patient discomfort:** Standard visual pain scale of 1-10 will be utilized (12). Pain will be assessed
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53 231 after the hemostasis protocol is ended.

54 232 **Adverse events**

55 233 Re-bleeding at the end of intervention protocol in either group i.e. bleeding after removal of
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57 234 InnoSEAL+TRB or TRB will be considered as an adverse event. If adverse event occurred it will be

235 recorded and TRB will be applied at the puncture site and inflated with 2 cc air or more till no bleeding is
236 observed. Then 2cc air will be removed at 20 minutes, 4cc at 40 minutes and 6cc at 60 minutes when
237 needed. After 30 minutes of zero air, TRB will be removed and site will be observed for bleeding. Final
238 observation will be made after 30 minutes of removal of TRB. IRB and funders will be informed about
239 the adverse events in the final report.

240 **Statistical Analysis Plan**

241 Data quality will be assured by random checking of 10% of the weekly data by the study investigators
242 and random observation of the participant recruitment and live data collection. Data will be entered in
243 Microsoft Access which will have in-built checks (like value ranges and pop-up for invalid values) to
244 minimize data entry errors. Means and standard deviation will be reported for continuous data based on
245 normality assumption along with histograms and compared using Independent Student's t-test. And
246 frequencies with percentages will be reported for the categorical variables. The differences between
247 categorical variables will be examined by the Chi square test and p-value < .05 will be considered
248 significant. Statistical analysis will be performed using the SPSS version 24.0. For comparison of baseline
249 characteristics, Independent Student's t-test and chi-square tests will be used for quantitative and
250 categorical variables respectively. Chi square test will be utilized to assess primary composite outcome
251 and its components. Independent sample t-test will be used for comparison of time intervals. Kruskal
252 Wallis test will be utilized for significance testing between ordinal secondary outcomes of ease of use
253 and patient discomfort. Intention to treat analysis will be undertaken. If there would be many cross-
254 overs then per protocol analysis will also be conducted and results of both will be compared and
255 discussed.

256 **Ethics and dissemination**

257 Ethical approval will be taken from Institutional Review Board of Tabba Heart Institute. Written
258 informed consent will be obtained from all study participants prior to the enrollment in the study.

259 **(Appendix: Consent form).**

260 No personal or clinical information of study participants will be made public. All study
261 information will be stored in lock and key and in password protected software after data entry. The
262 study will be carried out in compliance with Good Clinical Practice guidelines and all the study
263 investigators and key members will be IRB certified to conduct human research. IRB will conduct an
264 independent audit of the trial execution as per their policy.

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3 265 Study findings will be disseminated to the study hospital staff and intervention arm with favorable
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5 266 results will be implemented as hospital protocol for radial site closure after cath lab procedures. The
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7 267 results will also be published in scientific journals and will be presented in seminar and conferences.
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9 268 **Author contributions:**

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11 269 SA developed the protocol, estimated sample size and data analysis plan, AP initially conceived the idea
12
13 270 and provided intellectual input to design the methodology and critically reviewed the protocol. SS draft
14
15 271 the protocol for publication, is involved in execution of the trial as well as supervision of the study staff.
16

17 272 **Funding statement:**

18 273 This work was supported by InnoTherapy Inc. S grant # THI-INNOSEAL2-2020. Korea. Funding agency has
19
20 274 no role in designing the study, writing the protocol, study execution, data management or analysis and
21
22 275 interpretation of the results.
23

24 276 Sponsor contact number: 201-944-0445
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27 277 **Competing interest statement**

28 278 Authors declare no competing interests.
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31 279 **Figure: 1 InnoSEAL patch is applied over the sheath and TRB is tied over it**
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Figure: 1 InnoSEAL patch is applied over the sheath and TRB is tied over it



For peer review only

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3 **Appendix**4
5 **Patient's consent form**6
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|---|---|
| Title of the study: Combination of InnoSEAL plus TR band compared to TR Band alone for Radial Artery Outcomes in patients undergoing transradial coronary intervention (InnoSEAL – II) | |
| ERC Ref No: IORG 000 _____ | Sponsor: InnoTherapy Inc. S. Korea |
| Principal investigator: Dr Asad Z Pathan Co-Investigators: Dr Saba Aijaz, Dr Sana Sheikh | Organization: Tabba Heart Institute, Karachi |
| Patient's name: _____ | MR No: _____ |

PURPOSE OF THE STUDY

This study will be conducted in Tabba Heart Institute in which patients who undergo trans-radial coronary procedures will be randomized within few minutes after the procedure to either Catechol conjugated chitosan based pad plus TRBand or TRBand alone. The main purpose of this study is to compare the effect of InnoSEAL plus TR band or TR band alone on subsequent radial artery outcomes (Acute radial artery blockage and/or significant bleeding) after transradial intervention and to compare the difference in time needed to stop the bleeding from radial artery, time to termination of radial artery monitoring, patient's discharge and patient's discomfort between InnoSEAL plus TR band versus TRBand alone.

PROCEDURES

All adult patients coming to Coronary Catheterization Laboratory, Tabba Heart Institute (THI) for elective and urgent Trans-radial diagnostic catheterization and percutaneous coronary interventions will be invited to participate in the study. Those patients who consent to participate will get assigned to either TR band alone or in InnoSEAL plus TR band arm. TR band is a tight band like device which is routinely used in THI to stop bleeding from the cannula site at your wrist after the radial coronary procedure is completed. This band remains in place for few hours and is removed once radial bleeding is stopped. If you are assigned to InnoSEAL plus TR band arm, then an additional square patch which contains a chemical that helps in blood clotting will be applied to your wrist before the TR band. This patch and band remains in place for few hours and is removed once radial bleeding is stopped. Routine care after the bleeding stops is same for both the treatment arms. Pulse in your arm will be checked multiple times during this time. An ultrasound of our wrist may be performed to further confirm blood flow at the site of cannula.

The treatment you get assigned to will be totally based on chance and is pre-decided by a computer program. Our research coordinator has no control to allocate you to any treatment according to her or your choice.

RISKS OR DISCOMFORT

There are no adverse effects of this study. It will only take your valuable time which can cause inconvenience to you. We apologize for this inconvenience in advance.

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POSSIBLE BENEFITS

The possible benefits might include early removal of the TR band, which may lead to early discharge if you are planned same day discharge by your treating cardiologist. Also since the band and/ or InnoSEAL is applied for a lesser duration, there may be less discomfort in your hand related to hemostasis procedure.

FINANCIAL CONSIDERATIONS

No financial compensation will be provided to any of the study participants.

AVAILABLE MEDICAL TREATMENT FOR ADVERSE EXPERIENCES

Since you are our study participant, we will assist you in directing you to your correct care provider if any unrelated medical issue arises during the course of our study. Additionally, your participation in this study will not affect the care that you will continue to receive in THI.

CONFIDENTIALITY

Your identity will be kept confidential. Special measures will be taken to protect your identity and personal information. You will be given a unique identifier (code). Your data will be kept in lock and key and will only be accessible by the research team. In the electronic system one of the personal data will be entered and you will only be identified by a unique code. The results of the study will only be published for scientific purposes and your name or any identifiable references to you will not be included. The results will not be shared with anyone. Only the combined results will be shared in scientific meeting and journals.

WITHDRAWAL OF CONSENT

You have full authority to participate in the study or refuse to participate in it. You also have right to leave study anytime without any reason. Your decision to participate or refuse to participate will not affect the course of your treatment at THI at this time and even in the future.

AVAILABLE SOURCES OF INFORMATION

If you have any questions regarding this study please call at this number.

Dr. Saba Aijaz, Dr Sana Sheikh

Department of Cardiology, Tabba Heart Institute, Karachi, Pakistan

Phone: 021 36811842-50 (ext: 1372)

E-mail: saba.aijaz@tabbaheart.org

AUTHORIZATION

I have read and understood this consent form, and I volunteer to participate in this research study. I understand that I will receive a copy of this form. I voluntarily choose to participate, but I understand that my consent does not take away any legal rights in the case of negligence or other legal fault of anyone who is involved in this study.

3

Participant's Name: _____

Date: _____

Participant's Signature or thumb impression:

Signature of witness (use for non-literate patient)

Principal Investigator's/Co-PI's Signature:

Date: _____

Name/ Signature of Person Obtaining Consent:

Date: _____



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | ItemNo | Description | Page number |
|-----------------------------------|--------|--|-------------------------|
| Administrative information | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 2 |
| Protocol version | 3 | Date and version identifier | In footers on all pages |
| Funding | 4 | Sources and types of financial, material, and other support | 9 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 9 |
| | 5b | Name and contact information for the trial sponsor | 9 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 9 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | Not applicable |

Introduction

| | | | |
|--------------------------|----|---|-----|
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3 |
| | 6b | Explanation for choice of comparators | 3 |
| Objectives | 7 | Specific objectives or hypotheses | 3-4 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 4 |

Methods: Participants, interventions, and outcomes

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|----------------------|-----|--|----------------|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 4 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 4 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 5-7 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | Not applicable |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | Not applicable |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | Not applicable |

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| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 7-8 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 4 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 7 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 4 |

Methods: Assignment of interventions (for controlled trials)

Allocation:

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|----------------------------------|-----|--|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 5 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 5 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 5 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 5 |

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4 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a
5 participant's allocated intervention during the trial
6 Not applicable

7 **Methods: Data collection, management, and analysis**

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9 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any
10 related processes to promote data quality (eg, duplicate measurements, training of assessors) 5, 7-8
11 and a description of study instruments (eg, questionnaires, laboratory tests) along with their
12 reliability and validity, if known. Reference to where data collection forms can be found, if not in
13 the protocol
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15
16 18b Plans to promote participant retention and complete follow-up, including list of any outcome data Not applicable
17 to be collected for participants who discontinue or deviate from intervention protocols
18
19 Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote 8
20 data quality (eg, double data entry; range checks for data values). Reference to where details of
21 data management procedures can be found, if not in the protocol
22
23 Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other 8-9
24 details of the statistical analysis plan can be found, if not in the protocol
25
26 20b Methods for any additional analyses (eg, subgroup and adjusted analyses) Not applicable
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28 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised 9
29 analysis), and any statistical methods to handle missing data (eg, multiple imputation)
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32 **Methods: Monitoring**

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34 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; DMC is not needed as it
35 statement of whether it is independent from the sponsor and competing interests; and reference Is a low risk study with no
36 to where further details about its charter can be found, if not in the protocol. Alternatively, an Life-threatening events
37 explanation of why a DMC is not needed Anticipated as a result of
38 Intervention.
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| 4 | | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 9 |
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| 7 | Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 8 |
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| 10 | Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 9 |
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| 14 | Ethics and dissemination | | | |
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| 16 | Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 9 |
| 17 | | | | |
| 18 | Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | Not applicable |
| 19 | | | | |
| 20 | | | | |
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| 22 | Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 4 |
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| 25 | | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | Not applicable |
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| 28 | Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 9 |
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| 32 | Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 10 |
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| 35 | Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | Not applicable |
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| 38 | Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | Not applicable |
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| 4 | Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions |
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| 8 | | 31b | Authorship eligibility guidelines and any intended use of professional writers |
| 9 | | | ICMJE guidelines will be |
| 10 | | | Followed for authorship |
| 11 | | | Eligibility. No professional |
| 12 | | | Writers will be used. |
| 13 | | | |
| 14 | | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code |
| 15 | | | The data can be provided |
| 16 | | | On reasonable request |
| 17 | Appendices | | |
| 18 | | | |
| 19 | Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
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| 22 | Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |
| 23 | | | Not applicable |
| 24 | | | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.