PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a prospective, controlled study of assertive and timely reperfusion for patients with ST-segment elevation myocardial infarction in Tamil Nadu - The TN-STEMI Programme
AUTHORS	Alexander, Thomas; Nallamothu, Brahmajee; Victor, Suma; Mullasari, Ajit; Veerasekar, Ganesh; Subramaniam, Kala

VERSION 1 - REVIEW

REVIEWER	Morten Schmidt Department of Clinical Epidemiology Aarhus university Hospital Denmark
REVIEW RETURNED	18-Sep-2013

GENERAL COMMENTS	This protocol by Alexander et al. titled “A prospective, controlled study of assertive and timely reperfusion for patients with ST-segment elevation myocardial infarction in Tamil Nadu- The TN-STEMI Programme” describes a study following up the results from the Kovai Erode Pilot STEMI Study. The study aim is considered relevant (to improve use and timeliness of reperfusion therapy in India) considering that India overall do not follow the same trends in declining incidence and mortality that have been observed in most Western countries over the last decades (Nabel, E. G., & Braunwald, E. (2012). A tale of coronary artery disease and myocardial infarction. The New England journal of medicine, 366(1), 54–63. doi:10.1056/NEJMra1112570) However, concerns remain regarding the study design: Objective 1. The second objective (“increase rates of early invasive risk stratification in eligible patients.”) is not entirely clear. Please elaborate on what is meant by risk stratification. 2. Regarding: “We plan to measure our ability to achieve this overall objective through explicit measurement of changes in processes of care”. Please be more specific on what “measurements” that will be estimated. Study population, facilities and enrolment period 3. Please specify the baseline data that will be collected and how detailed each variable will be categorized (e.g., smoking: pack years or only ever vs. never). When analysing the data it must be clear which variables were collected to evaluate the completeness of the data collection and potential residual confounding. 4. Please clarify how the enrolment period (start in 2012) can start before the current protocol registration? 5. Please provide the assumptions for reaching an estimated loss to

	follow up of 20%. TN-STEMI programme: the hub and spoke model 6. Is it correct understood that a STEMI patient arriving to a Class C hospital will be transported to a Class B hospital INDEPENDENT of whether it is outside working hours of the Class B hospital (i.e., no PCI capability). It would then seem that the time-to-needle (transport time-to-hospital B + door-to-needle time) would be unfavourable for the patients compared with just being treated with fibrinolysis at the Class C hospital (eliminating the transport time to class B hospital) and then later transported to a PCI facility if indicated (e.g., rescue PCI). It would seem more appropriate to use the approach described under Class D hospitals if it is outside the PCI working hours of the class B hospital. Please clarify? Treatment Protocols 7. Please specify which dual antiplatelet therapy that is recommended? Primary Outcomes 8. It is unclear how the estimates of association for the primary outcomes are calculated. For example in “Use of reperfusion therapy with either fibrinolytic therapy or primary PCI” what are the comparison categories and reference groups. This description needs to be more detailed for all primary and secondary outcomes. 9. Please specify what is meant by “early invasive risk stratification” and how this is defined. 10. A power calculation should be performed so a sample size is reached that allows for statistical inference for all outcomes selected. It is inappropriate to perform an underpowered study for the outcomes of interest. The argument that the sample size calculation is not performed “since this is a real-world implementation study” does not seem valid. Even in a “real-world scenario” a sufficient sample size is needed to make statistical inference. If the sample size cannot be fulfilled within one year, then the study period should be extended or the objectives should be revised accordingly. Statistical considerations 11. Regarding the control group: For the comparison to be unbiased the control patients must be compared (e.g., matched) to intervention patients from the same distance to a Class A, B, C, D hospital, respectively. Otherwise, patients with different probability of reaching a PCI facility will be compared. Data collection and quality control: 12. Please specify how personnel will be blinded to the aim of the study? References 13. Please make references to original literature and not news media articles like e.g. reference 1.

REVIEWER	Mohammad Abdul Salam The George Institute for Global Health Sydney, Australia
REVIEW RETURNED	30-Sep-2013

GENERAL COMMENTS	I strongly recommend undertaking 'process evaluation' as part of this study (using interviews and/or focus group discussions with the patients and providers involved) to augment the findings from this research. Whatever might be the outcome of this research (positive, negative or indeterminate) it is very important to understand what underpins such findings, and a qualitative process evaluation would help do that. It will also inform real life applicability of such a program and its transferability to other settings.

VERSION 1 – AUTHOR RESPONSE

The methods and analysis section of the abstract doesn't contain either. Please see our instructions for authors for instructions on how to format a protocol abstract.

Response: We apologize for this oversight. We have now formatted the abstract per your instructions and included the information that we believe is relevant for readers.

Reviewer Name: Morten Schmidt

Institution and Country Department of Clinical Epidemiology, Aarhus university Hospital, Denmark

Please state any competing interests or state ‘None declared’: None

This protocol by Alexander et al. titled “A prospective, controlled study of assertive and timely reperfusion for patients with ST-segment elevation myocardial infarction in Tamil Nadu- The TN-STEMI Programme” describes a study following up the results from the Kovai Erode Pilot STEMI Study. The study aim is considered relevant (to improve use and timeliness of reperfusion therapy in India) considering that India overall do not foljlow the same trends in declining incidence and mortality that have been observed in most Western countries over the last decades (Nabel, E. G., & Braunwald, E. (2012). A tale of coronary artery disease and myocardial infarction. The New England journal of medicine, 366(1), 54–63.doi:10.1056/NEJMra1112570)

Response: We appreciate the positive comments by the reviewer.

However, concerns remain regarding the study design:

Objective

1. The second objective (“increase rates of early invasive risk stratification in eligible patients.”) is not entirely clear. Please elaborate on what is meant by risk stratification.

Response: We appreciate this point that has been raised. Early risk stratification refers to early diagnostic cardiac catheterization with coronary angiography to help define high-risk anatomy and to select patients appropriately for risk stratification. This approach is now endorsed by both the European and North American guidelines, but its use in India has been marginal. We specifically defined this approach under the section entitled “Pharmacoinvasive Strategy” where we noted that it referred to transfer and PCI within 3 to 24 hours of fibrinolytic therapy. We have now expanded this

language to also include it in other sections of the text where appropriate.

2. Regarding: “We plan to measure our ability to achieve this overall objective through explicit measurement of changes in processes of care”. Please be more specific on what “measurements” that will be estimated.

Response: Please see the response above. We have now expanded on language in the manuscript where we now note that our measurement of the early invasive risk stratification will be refer to use of coronary angiography within a 3 to 24 hour period of time in patients treated with fibrinolytic therapy.

Study population, facilities and enrolment period

3. Please specify the baseline data that will be collected and how detailed each variable will be categorized (e.g., smoking: pack years or only ever vs. never). When analysing the data it must be clear which variables were collected to evaluate the completeness of the data collection and potential residual confounding.

Response: The baseline data will include clinical and demographic data including patient’s age, name, sex, place he (or she) hails from, historical data of hypertension, diabetes, smokers (current, ex, never), dyslipidemia, previous heart disease, previous interventions, time intervals of onset of chest pain, time reached the hospital, time taken to perform ECG, time of starting of treatment, etc. This will also include assessment of systems of care- how did the patient come to the hospital, total ischemic time, the mode of treatment, transport etc. We submit a copy of our CRF for your perusal.

4. Please clarify how the enrolment period (start in 2012) can start before the current protocol registration?

Response: The trial protocol has been registered with Clinical trial registry of India, No: CTRI/2012/09/003002. The same has been mentioned in the manuscript.

5. Please provide the assumptions for reaching an estimated loss to follow up of 20%.

Response: This estimate is based on our experiences with clinical research in these communities and is conservative. However, we acknowledge that this is difficult to estimate for certain. As a comparison, the loss to follow up from the Polycap Indian study was 16% (Yusuf S et al. Lancet 2009;6736(09)60161:1-5. We have added a phrase to reflect this in the revised manuscript.

TN-STEMI programme: the hub and spoke model

6. Is it correct understood that a STEMI patient arriving to a Class C hospital will be transported to a Class B hospital INDEPENDENT of whether it is outside working hours of the Class B hospital (i.e., no PCI capability). It would then seem that the time-to-needle (transport time-to-hospital B + door-to-needle time) would be unfavourable for the patients compared with just being treated with fibrinolysis at the Class C hospital (eliminating the transport time to class B hospital) and then later transported to a PCI facility if indicated (e.g., rescue PCI). It would seem more appropriate to use the approach described under Class D hospitals if it is outside the PCI working hours of the class B hospital. Please clarify?

Response: We are grateful for this comment and appreciate the opportunity to clarify. Class C hospitals are those without fibrinolysis capability, and we have clarified this better in the manuscript. These are small primary clinics where only ECG facility is available. If the transmitted ECG confirms STEMI these hospitals will then transfer the patient to either class A or class B, depending on the

availability primary PCI. They will not be transported for fibrinolysis. These are hospitals within 30 minutes of travel from class A/B hospitals, so the process of transfer should take less than 60 minutes. In India, there are many Class C type of healthcare where facilities for even thrombolysis are not present unfortunately.

Treatment Protocols

7. Please specify which dual antiplatelet therapy that is recommended?

Response: We recommend Aspirin and one of the theinopyridine group of drugs such as clopidogrel or prasugrel or ticagrelor. We have added this information to the text.

Primary Outcomes

8. It is unclear how the estimates of association for the primary outcomes are calculated. For example in “Use of reperfusion therapy with either fibrinolytic therapy or primary PCI” what are the comparison categories and reference groups. This description needs to be more detailed for all primary and secondary outcomes.

Response: We aim to assess how many patients with STEMI have received any reperfusion treatment at all before and after implementation of STEMI programme. It is not uncommon for a patient with STEMI in India not to receive any reperfusion modality (CREATE registry). The reference group for comparison of the outcomes in this study will be the pre programme implementation group. Thus, we are examining the change from the baseline rates for these outcomes over time.

9. Please specify what is meant by “early invasive risk stratification” and how this is defined.

Response: We have addressed this above.

10. A power calculation should be performed so a sample size is reached that allows for statistical inference for all outcomes selected. It is inappropriate to perform an underpowered study for the outcomes of interest. The argument that the sample size calculation is not performed “since this is a real-world implementation study” does not seem valid. Even in a “real-world scenario” a sufficient sample size is needed to make statistical inference. If the sample size cannot be fulfilled within one year, then the study period should be extended or the objectives should be revised accordingly.

Response: We have included estimates of the sample size as follows and the same text has been added to the manuscript. We now write: “The estimated sample size for the present study that allows for statistical inference for the primary end point uses as reference the Kovai Erode pilot study 1. It is estimated that the study would be adequately powered at 80% with a superiority margin of 10% if 36 patients are enrolled per cluster or 108 patients in 3 clusters. Considering the design of the study (all comers) and the objective of a state-wide program implementation, the enrolment period of 9 months will result in a sample size of 1500 patients. If the sample size cannot be fulfilled during the study time frame, the enrolment period will be extended”.

1. Ref: Alexander T, Mehta S, Mullasari A et al. Systems of care for ST-elevation myocardial infarction in India: is it time? Heart doi:10.1136/heartjnl-2011-301009.

11. Regarding the control group: For the comparison to be unbiased the control patients must be compared (e.g., matched) to intervention patients from the same distance to a Class A, B, C, D hospital, respectively. Otherwise, patients with different probability of reaching a PCI facility will be

compared.

Response: As noted earlier, we aim to assess how many patients with STEMI have received any reperfusion treatment at all before and after implementation of STEMI programme. Thus, our comparisons will include an overall study population that is matched in terms of distance from the different types of facilities over time. In our analysis, we plan to examine rates of change across the different 2-group units of Class A/B and Class C/D hospitals through stratification.

12. Please specify how personnel will be blinded to the aim of the study?

Response: We have employed one person from each study site to collect and manage all the data from that site. The person who collects the data will not be a part of the study and will enter all the data directly in to the eCRF.

References

13. Please make references to original literature and not news media articles like e.g. reference 1.

Responses: We have eliminated references to news media articles. For example, we have replaced reference 1 with the following reference:
1. Kohn D. Getting to the heart of the matter in India. Lancet 2008; 372 (Issue 9638): 523-4.

Reviewer Name Mohammad Abdul Salam

Institution and Country The George Institute for Global Health, Sydney, Australia
Please state any competing interests or state 'None declared': None declared

21-34 needs reference.

Response: Unfortunately we are uncertain of the sentence the reviewer is referring to and would be happy to respond if pointed in the correct direction.

Abstract needs description of the study type and methods.

I think the Ideal study type/design would be jcluster RCT. Needs more explanation about the study type and design, as it is not clear from the current manuscript.

Response: We appreciate the opportunity to clarify. This study uses a pre test/post test Quasi-experimental study design (Ho PM et al. Circulation 2008;118:1675). The 2 reasons for this approach are:

1. The project is about establishing a system of care to quicken the process of patient transfer right from identification of STEMI, triage, and an effective pre hospital care following standard protocols in an Indian environment.
2. The study involves more than one point of care and requires standardisation of different levels of care for a given patient, a before and after design for the given cluster is considered suitable

A cluster RCT design was not chosen primarily because it was not attempting to prove efficacy of a certain treatment or causality assessment. Instead our goal was more focused on implementation of a program that would facilitate quick recognition and shifting of patients for definitive treatment following a standardised pre hospital care in the challenges of India. This approach has become the standard

of care in Western countries but has not been used to a great extent in Southeast Asia.

The manuscript has been changed accordingly- “Study design and objectives
The TN- STEMI programme is a prospective, multi-centre pre test/post test Quasi- experimental study that has been planned as a community-based treatment programme for improving use and timeliness of reperfusion therapy in patients diagnosed with STEMI as confirmed by an ECG. It involves a stepwise approach that facilitates rapid and definitive restoration of coronary blood flow using a combination of pharmacological and mechanical reperfusion therapies based on the presentation of the patient.”

I strongly recommend undertaking 'process evaluation' as part of this study (using interviews and/or focus group discussions with the patients and providers involved) to augment the findings from this research. Whatever might be the outcome of this research (positive, negative or indeterminate) it is very important to understand what underpins such findings, and a qualitative process evaluation would help do that. It will also inform real life applicability of such a program and its transferability to other settings.

Response: We appreciate this suggestion and agree that it would add great value to the outcomes of study in terms of applicability to other settings. Although we may be unable to add this to the present study in a formalized manner, we have begun discussions about how to develop a focus group during our annual STEMI India meetings, which have occurred over the last few years. We are also exploring the possibility of gaining additional funding to consider adding a qualitative process evaluation to our final evaluation of this STEMI programme and any additional programmes that are developed in the future. This type of qualitative evaluations are rare in India but would provide unique and powerful insights into the challenges for developing these STEMI programmes in the context of Southeast Asia.

VERSION 2 – AUTHOR RESPONSE

1. The title needs to make clear that this is a protocol.
Response: We agree with the suggestion and have modified the title. The title of the manuscript now reads as-
“Protocol for a prospective, controlled study of assertive and timely reperfusion for patients with ST-segment elevation myocardial infarction in Tamil Nadu - The TN-STEMI Programme”

2. I couldn't see where in the paper you report what baseline data will be collected, as requested by the reviewer.
Response: We apologize for this oversight. We have now included the same in the manuscript.
“Study population, facilities and enrolment period
Baseline data on management and outcomes of STEMI patients will be collected for 3 months at all the participating hospitals during an enrolment period that started in the fall of 2012. This data includes patient’s details with address and telephone number, demographic details, personal and medical history in detail such as smoking status whether patient is a current smoker or smoker in the past or non smoker, if a smoker, then the details of quantity of consumption and duration will be collected. Clinical examination findings, investigations, diagnosis, treatment modality, medication details, cardiac catheterization details, outcome will be noted. Baseline data will also include assessment of systems of care- how did the patient come to the hospital, total ischemic time, the mode of treatment, transport, time intervals of onset of chest pain, time reached the hospital, time taken to perform ECG, time of starting of treatment etc. The enrolment period will be “rolling” for each of the hospitals and followed by 9 months of post-implementation data collection on STEMI patients after execution of the TN-STEMI programme.”

3. I believe the reviewer's comment about 21-34 referred to lines 21-34, i.e. these sentences: 'For

example, reperfusion therapy with fibrinolysis is received by less than 60% of Indian patients with STEMI and those that undergo it often do so after great delays. Furthermore, few patients go on to early invasive evaluations and less than 10% receive percutaneous coronary intervention (PCI) during their hospitalization despite growing support for this type of pharmacoinvasive approach. Improving access to these critical treatments is a key opportunity to improve STEMI care that has large implication for India as the epidemic of cardiovascular diseases continue.
Response: We appreciate the clarification. We have made the appropriate changes to the manuscript as follows.
“For example, reperfusion therapy with fibrinolysis is received by less than 60% of Indian patients with STEMI and those that undergo it often do so after great delays (3). Furthermore, few patients go on to early invasive evaluations and less than 10% receive percutaneous coronary intervention (PCI) during their hospitalization despite growing support for this type of pharmacoinvasive approach (3).”

4. It may be worth elaborating in the design section why a cluster RCT is not the most appropriate design for the study.
Response: We agree with this comment and added the same to the manuscript.

“The TN- STEMI programme is a prospective, controlled, multi-centre pre test/post test Quasi-experimental study that has been planned as a community-based treatment programme for improving use and timeliness of reperfusion therapy in patients diagnosed with STEMI as confirmed by an ECG. RCT design was not chosen for this study, primarily because it was not attempting to prove efficacy of a certain treatment or causality assessment. Instead our goal was more focused on implementation of a program that would facilitate quick recognition and shifting of patients for definitive treatment following a standardised pre hospital care in the challenges of India. It involves a stepwise approach that facilitates rapid and definitive restoration of coronary blood flow using a combination of pharmacological and mechanical reperfusion therapies based on the presentation of the patient”.