Reviewer's report

Title: Value of signs, symptoms and plasma heart-type fatty acid-binding protein (H-FABP) in evaluating patients presenting with symptoms possibly matching acute coronary syndrome: background and methods of a diagnostic study in primary care

Version: 2
Date: 5 August 2014

Reviewer: Richard Body

Reviewer's report:

This work addresses a scientifically important and topical question. Positive findings could have significant clinical impact. I wish the authors the very best of luck with this good work.

Major compulsory revisions

This is a derivation study, designed to derive a diagnostic algorithm for patients presenting to primary care with suspected acute coronary syndromes. It is important to acknowledge this, as the algorithm will require validation (and subsequent evaluation in practice) before it could be considered for clinical implementation. Without validating the algorithm, there is the potential that the model may be over-fitted to the data and therefore that diagnostic accuracy is over-estimated.

It would be useful to know the covariates that are being considered for inclusion in the model. How many covariates are there? (This will influence sample size). How were they identified? How will they be recorded? Including a copy of the case report form as an appendix would be very helpful.

The sample size calculation should be revisited. The authors don't really provide justification for the proposed levels of precision. As the primary goal is to derive a diagnostic algorithm incorporating point of care H-FABP levels, the sample size calculation ought to be based on this.

Minor essential revisions

The proposed statistical analyses could be described in some more detail. There are published methodological criteria for the derivation of clinical decision rules (e.g. Stiell et al, Ann Emerg Med April 1999;33:437-447; Steyerberg on Clinical Prediction Models, ISBN-13 978-1441926487). This work would benefit from providing some details in accordance with those publications.

There are a few minor grammatical errors, e.g. page 2, Background line 1: "Patients presenting chest complaints". This ought to be changed to, "Patients presenting with chest complaints"

Also Page 2, Background lines 9-10: "Therefore, referring any patient with chest
complaints to secondary care facilities is not applicable" should be re-phrased. The issue is perhaps that this would overwhelm secondary care resources.

It would be useful to have more details about the proposed economic evaluation. How will costs be calculated? Which costs will be included? If ICERs are to be determined, how and when will health state be evaluated?

Discretionary revisions

The lack of blinding to H-FABP results does present some challenges. It is probably naive to think that the judgement of GPs will not be influenced, at least to some extent, by the levels of a cardiac marker that are available immediately. There is no way of time stamping manual entry into a paper case report form to ensure that data were entered prior to the results being available. Therefore, this does still warrant some attention. Perhaps levels of H-FABP could be evaluated after the patients have left? (E.g. by collecting whole blood into sample tubes with venipuncture)

Only patients who have provided full written informed consent will be included. What if patients die? This is an extremely important outcome. Would the ethics committee consider issuing a waiver (or relative assent) for these circumstances, given the scientific importance of this work in emergency settings?

Point of care troponin tests are available. Have the authors considered including this in the protocol?

It is notoriously difficult to adjudicate a diagnosis of 'unstable angina' as there is no acceptable reference standard and clinical features are notoriously unreliable. Evaluating major adverse cardiac events after 30 days may act as a reasonable (and more objective) surrogate.

Page 3. The authors state that the study by Bruins et al "lacked diagnostic strength". Presumably this refers to the statistical "power" of the study rather than "strength".

There are existing alternative prediction models that have already been derived, although they do include additional parameters (e.g. troponin) and they were derived in other settings. (E.g. the MACS rule and the HEART score). It would be a very useful secondary objective to validate existing scores. If those scores can be successfully validated in the primary care setting and with the use of point of care tests, it could reduce the time taken to clinical implementation and therefore benefit patients sooner.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

I also do research in this area. This has included accepting the donation of reagents from research from H-FABPulous (which is also funding this research), Roche, Siemens, Abbott, Abbott Point of Care (pending), Randox and Alere.

I am designated as the inventor of the MACS decision rule, which is currently being patented by The University of Manchester. I have no pecuniary interest in this. I am also designated as the inventor of an algorithm incorporating H-FABP, hs-troponin and ECG findings for early exclusion of acute myocardial infarction. The patent is (as I understand it) still pending and owned by Randox Laboratories. Again, I have no pecuniary interest in this patent or in the organisation that has applied for it.