12-Sep-2016

Dear Dr. Hess


Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Jose Merino
jmerino@bmj.com

https://mc.manuscriptcentral.com/bmj?URL_MASK=e2303ad2a5b04961be12b5cfdcfbcddc

**Report from The BMJ’s manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: José Merino (chair), Richard Riley (statistical consultant), Rubin Minhas, Tiago Villanueva, Amy Price, Wim Weber, Elizabeth Loder.

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

It is good to see an RCT of shared decision making. This fits with BMJ priorities on many levels. We are interested in the paper but would like clarification to several points. Please also address all the comments of the reviewers.

1. Why was knowledge chosen as the primary outcome? We agree with one of the reviewers that it does not seem to be the most clinically meaningful outcome (compared with for example, clinical outcomes or decisional regret)). It is of more interest to know what is done with the knowledge and what changes about outcomes: do patients use more or less testing, and what
happens as a result? For example, the secondary outcome of fraction of patients who underwent the next step in the diagnostic work-up seems relevant. But you may be able to justify your choice (and this is the outcome that must be reported in the paper). How was this assessed (open ended questions, multiple choice, etc.)? How did you select 16% difference as meaningful? Was this done a priori? The difference in knowledge does not seem that large given that one group had an "educational" intervention. The actual increase in number of questions answered correctly is not that impressive: 4.2 vs 3.6. What does that actually mean?

Response: The process of outcome selection in this trial elicited the input of multiple stakeholders, including patients and caregiver representatives, emergency clinicians, cardiologists, a payer representative, and shared decision-making scientists. Each stakeholder emphasized the outcome they considered to be of greatest importance to them and that would likely impact their willingness to implement the intervention should the trial show a positive effect. Patient and caregiver representatives emphasized the deleterious perception and effect of being “left in the dark” regarding their emergency department evaluation, including the rationale for each of the tests being ordered, the results of those tests, and the advantages and disadvantages of each management option, given their ACS risk. As the goal of patient centered outcomes research is to provide patients the information they need to help them make decisions that affect their desired health outcomes, the perspective of the patient was prioritized over the perspectives of the other stakeholders in selecting the primary outcome. Thus, patient knowledge was selected as the primary outcome. Emergency clinicians and cardiologists prioritized clinical outcomes, which were collected and classified as secondary outcomes. Shared decision-making scientists prioritized decisional quality outcomes such as decisional conflict and patient engagement, which were also collected as secondary outcomes.

From this perspective, the increased number of questions answered correctly represents a significant increase in patient’s knowledge, indicating that the intervention improved the outcome of greatest interest to patients. The 16% difference in knowledge (presented as % difference in the statistical analysis section but reported as mean (SD) difference in the pilot trial and results section of this manuscript to more clearly indicate the # of questions answered correctly between arms) was selected a-priori, as it was the % increase in knowledge observed in the pilot trial, and there was no a-priori magnitude of knowledge gain that would be considered important.

Knowledge was assessed by means of a patient survey administered immediately after the ED encounter that contained 9 questions. These questions are included in Supplementary file 2A.

Changes:
1. The following statement was added to the “Primary outcome” section of the methods (lines 277-280), “As the goal of patient centered outcomes research is to provide patients and the public the information they need to help them make decisions that affect their desired health outcomes, the perspective of the patient was prioritized over the perspectives of the other stakeholders in determining the primary outcome.”
2. A reference to Supplementary file 2A, which lists the knowledge questions included in the patient post-visit survey, is included in the description of the primary outcome (line 296).

The trial registration includes two primary outcome measures: Test if Chest Pain Choice safely improves validated patient-centered outcome measures (on day 1) and Test if the intervention significantly increases patient knowledge. The paper reports on the latter. The former is more abstract but the
manuscript must include both primary outcomes and provide an explanation if one is not included in detail.

Response: The primary outcomes listed in clinicaltrials.gov were abstracted by a study team member from the aims of the grant proposal originally submitted for funding, not the outcomes section. The principal investigator delegated this detail, but it is his oversight in missing this error in reviewing the submission to clinicaltrials.gov. There is only 1 primary outcome for the study: patient knowledge. The phrase “Test if Chest Pain Choice safely improves validated patient-centered outcome measures” listed under the primary outcome at clinicaltrials.gov refers to the 5 patient outcome measures listed under the secondary outcomes section (a through e) and is actually redundant; there are no additional patient outcome measures that were collected. This is documented in the published protocol, which was submitted on January 1, 2014 and accepted on April 23, 2014, well in advance of when enrollment was complete for the trial and data were available for analysis in August 2015. Furthermore, the results on the primary and secondary endpoints are consistent in showing the same direction and commensurate magnitude of impact. Thus, in this case, there is no case for hiding or switching outcomes at the last minute as the trial has similar implications across its primary and secondary endpoints.

The trial manuscript under review refers to the published study protocol on line 139 (reference 13). We are open to reporting this oversight differently or more explicitly in the manuscript if the editorial team thinks a different approach is preferable.

3. The REGISTERED secondary outcomes were: 1) Test if the decision aid has an effect on healthcare utilization within 30 days after enrollment; 2) Evaluate if the intervention significantly reduces the rate of hospital admission, rate of cardiac testing, and total healthcare utilization; 3) Test if the decision aid safely improves additional validated patient outcome measures (patient engagement in the decision-making process; decisional conflict: trust in the physician; patient satisfaction with the decision made; safety (major adverse cardiac events within 30 days).) Please make sure that ALL these outcomes are reported (or if you plan to report them elsewhere, mention this fact in the manuscript). Where is satisfaction reported in the paper? MACE is not clearly mentioned in the registry (although it refers to the last secondary outcome; you may need to clarify that MACE was selected a posteriori or not registered adequately, as the case may be). In the response to editors, please provide a reconciliation report of where each outcome is described in the manuscript.

Response: A report of the secondary outcomes follows.

1) Healthcare utilization: We plan to report the impact of the DA on healthcare utilization in a separate manuscript.
2) The effect of the DA on the rates of hospital admission and cardiac testing are reported in Table 3.
3) The effect of the DA on patient engagement (OPTION scale scores), decisional conflict, and trust in the physician are reported in Table 2.
4) Patient satisfaction with the decision made is a question embedded in the decisional conflict scale, “I am satisfied with my choice,” codified on a 5-point Likert scale, ranging from “strongly agree” to “strongly disagree.”
5) Safety: the rate of major adverse cardiac events is reported on the last row of Table 3. MACE is listed as the safety outcome in clinicaltrials.gov, and a more detailed description of the approach to classifying a case as a MACE, which was defined a priori, is described in our protocol paper. The protocol paper is referenced in the manuscript (reference 13).
Changes:
1) The following statement was added to the end of the secondary outcomes section (lines 348): “We plan to report the effect of the DA on healthcare utilization in a separate manuscript.”
2) We created a dichotomous variable, Strongly satisfied versus other; the DA group was substantially but not significantly more often strongly satisfied (49% versus 43%, p-value from a logit model accounting for site=0.06). The following statement was added to the results section (lines 398-400): “The proportion of patients who were “strongly satisfied” with the decision made was not significantly different between arms (CPC, 49% versus UC, 43%, AD 6%, p=0.06).

4. Age and sex were included as stratification factors in the randomization as these were known to be risk factors for CVD. Why did the analysis not adjust for these factors? It was done for site.

Response: The dynamic randomization procedure that adjusted for age and sex resulted in study arms that were balanced on these factors. Table 1 reports the mean (SD) age for each arm [50.6 (14.1) DA versus 50.0 (15.0) UC, p=0.57] and proportion in each arm that were female (58.2% DA versus 60.8% UC, p=0.43). As these two factors were effectively balanced between study arms, we did not adjust for this in the analysis.
Change: None.

5. Please provide additional information about the MIs at the 'index point' in the intervention arm.

Response: Three of the 4 MI’s at the “index point” in the intervention arm had an initial troponin < 99th percentile, no acute ischemic changes on the ECG and a subsequent elevated troponin detected on serial cardiac biomarker testing. (This serial biomarker testing was performed according to pre-existing local protocols at each site and not standardized as part of the trial.) These patients were appropriately diagnosed as having a NSTEMI and admitted to the hospital for further evaluation and management. The 4th MI in the intervention arm occurred in a patient who had negative serial cardiac troponins and no acute ischemic changes on the initial ECG but symptoms that were concerning for ACS. This patient was admitted to the hospital, underwent PCI, and subsequently experienced in-stent thrombosis. This post-PCI in-stent thrombosis, which occurred in the hospital, was accompanied by a troponin elevation and ST-segment elevation on ECG. The patient underwent a second PCI procedure and recovered uneventfully.

Change: The following description was added to the results section (lines 433-442): “Three of the 4 AMI’s in the intervention arm had an initial troponin < 99th percentile, no acute ischemic changes on the initial ECG and a subsequent elevated troponin detected on serial cardiac biomarker testing. These patients were admitted to the hospital for further evaluation and management and diagnosed with non-ST segment elevation MI. The 4th MI in the intervention arm occurred in a patient who had negative serial cardiac troponins and no acute ischemic changes on the ECG but symptoms concerning for ACS. This patient was admitted to the hospital, underwent PCI, and subsequently developed in-stent thrombosis. The in-stent thrombosis event, which occurred in hospital, was accompanied by troponin elevation and ST-segment elevation on ECG. The patient underwent a second PCI procedure and recovered uneventfully.”

6. The screenshots of the app are very helpful. Could you also provide a screenshot of the pretest probability web tool?
Response: yes
Change: A screen shot of the pre-test probability web tool is now included as Figure 2. A short description of the screen shot is included both in the “Delivery of the intervention” section (lines 201-202) and the caption to Figure 2.

7. Will you make the app publicly available? Can we include a link to it on our website alongside the paper?

Response: The pre-test probability web tool and the Chest Pain Choice DA are publically available and can be accessed at the Mayo Clinic Shared Decision Making National Resource Center (http://shareddecisions.mayoclinic.org/decision-aid-information/chest-pain-choice-decision-aid/). There is a video demonstrating use of the decision aid in a simulated encounter at the Shared Decision Making National resource center website and links to pre-test ACS consult and the Chest Pain Choice DA.

Change: We added the following statement to the data sharing section of the manuscript (lines 607-609): “A link to the pre-test probability web tool and the Chest Pain Choice DA can be accessed at the Mayo Clinic Shared Decision Making National Resource Center at http://shareddecisions.mayoclinic.org/decision-aid-information/chest-pain-choice-decision-aid/.”

8. Please provide additional information about the physicians using the SDM tool with patients. How senior were they? How involved were they in the care of each patient? Were they from the ED, from cardiology or from the interventional cardiology team? This information would provide important context, particularly to readers outside the US who may not be familiar with the staffing pattern of emergency rooms in the US. Was the setting representative of emergency rooms in the US or were all these sites academic centers with residents and other staff not available at smaller hospitals? How would the tool be applied in the latter?

Response: The clinicians using the tool with the patients included board certified emergency physicians with varying years of post-residency experience, nurse practitioners, and physician assistants. Five of the six sites were academic emergency departments with residency training programs. Mayo Clinic Jacksonville, which does not have an emergency medicine training program, is staffed by board-certified emergency medicine physicians who provide the majority of their patient care directly without resident involvement, a model similar to the U.S. community setting. Cardiologists were not involved in the trial. The participants in the trial are described in lines 154-155 of the manuscript.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Comments:
Originality –
This study is original as SDM is used as the intervention in an RCT of patients with chest who may be discharged from the ED or admitted to hospital. The study is based on a pilot RCT that was published in 2012.

Importance of work to general readers – The importance of the issue is largely based on this claim: “As a consequence, low risk patients are frequently admitted for observation and cardiac stress testing or coronary computed tomography coronary angiography (CCTA). This results in unnecessary hospital admissions, false positive test results, and unnecessary invasive downstream investigations, at an estimated cost to the healthcare system of over 7 billion US dollars annually.” Reference 5 supports this statement in the United States. This may be an issue elsewhere. References from other countries should be included.

Response: Thank you for this comment.
Change: We have included a reference to the number of annual ED attendances for chest pain in England and Wales published in the BMJ Heart in the introductory paragraph of the manuscript. In addition, the European Society of Cardiology has published that patients classified as low risk for ACS represent the most prevalent group of patients admitted to the hospital with chest pain, and, thus, are the most challenging group to evaluate. This reference was added to the last sentence of the second paragraph of the introduction (line 118, reference 6).

* Scientific reliability

Research Question –
The research question was clearly defined. There is a question about whether it was answered.

Overall design of study –
The primary outcome of the trial is patient knowledge. The main question for both clinicians and patients is: Is it safe to send these patients home? The trial was apparently not powered to detect differences in cardiac outcomes.

Response: We had funding sufficient to recruit a sample size to provide 90% power to detect a 10% minimum clinically important difference in the proportion of patients admitted to the ED observation unit for cardiac testing, the most clinically proximate healthcare utilization decision. This sample size provided 78% power to detect a 5% difference in MACE rate between study arms, using a 1-sided non-inferiority test with an alpha of 0.05. Given the low prevalence of MACE in this patient population, a large-scale implementation trial is needed to definitively test whether there is a significant difference in MACE between study arms.

Participants studied –
Properly described.

Methods –
The trial is well described. I did not see a reporting checklist (e.g. CONSORT) but I might have missed it.

Response: The CONSORT checklist was reviewed and uploaded to the online submission system.

Results –
The research question was answered. But the main question for patients and clinicians was not clearly answered: Is it safe to send these patients home? In this trial, fewer patients in the intervention group were admitted (37 % versus 52 %) but more patients in the intervention group had heart attacks (4 versus 1). So after reading the manuscript I still wonder if this decision aid should be used or not. A larger study might be needed. Perhaps I have misunderstood something about the timing of these 4 heart attacks?

Response: The SDM discussion took place after the results of the initial ECG, laboratory testing, and first cardiac troponin were available and confirmed to be negative. This is the point in the flow of clinical care that the pretest probability estimate was calculated and emergency clinicians selected a management pathway determining subsequent care for chest pain patients. The shared decision was framed with patients such that it was clear that the cardiac stress testing decision presumed subsequent negative troponin testing to definitively rule out an acute myocardial infarction, should additional troponin testing be deemed necessary by the clinician and/or local protocols. Patients were told that the decision for stress testing and/or hospital admission would be reconsidered should their clinical status change or additional troponin testing indicate that a heart attack was occurring. The 4 patients diagnosed with AMI in the intervention arm had an initial ECG without evidence of acute ischemia and an initial troponin < 99th percentile of the reference limit of normal. Three of the 4 had an elevated troponin detected on serial cardiac biomarker testing and the 4th patient was admitted, underwent PCI, and experienced in-stent thrombosis with associated troponin elevation and ST-segment elevation on ECG. All 4 of these patients had an AMI appropriately diagnosed during the index visit.

Change: The description in the “Delivery of the intervention” section of the methods (lines 210-211) was revised to state the following (revised section in green font): Then the treating clinician, after evaluating the patient and the results of the initial ECG and cardiac troponin were available, used the decision aid to educate the patient regarding the results of the initial cardiac troponin and ECG, the potential need for observation and further cardiac testing provided subsequent cardiac troponin testing, if obtained, definitively ruled out AMI, and their personalized 45-day risk for ACS.

Interpretation and conclusions –
The conclusions are fairly positive about the intervention. Is it really true that there were “no adverse events related to the intervention”?

Response: Based on the discussion and response to the previous question, yes.

References –
Up to date. There should be more references about the importance of the issue in other countries.

Response: Agree
Change: References substantiating the importance of the issue in other countries4, 5 were added to the introduction section of the manuscript.

Abstract/summary/key messages/What this paper adds –
See the above issue about the four heart attacks.

Additional Questions:
Reviewer: 2

Comments:
These investigators report the findings of a pragmatic RCT examining the impact of a shared decision-making tool for low-risk chest pain intended for application in the ED setting. The authors have previously published a feasibility study that served as the substrate for this multi-center replication. The primary outcome of patient knowledge has been selected through patient input and assessed through survey, again developed with patient input. Secondary outcomes, likely of more interest from a health services perspective are also reported. In short the trial reports a positive impact across all outcomes and fails to detect a safety issue. Clinicians report a high level of acceptability and the tool appears to be user friendly.
This innovative research project is based on sound methodology and study execution. There are limitations in regards to lack of blinding and missing video recordings but these problems are small in comparison to the overwhelming positives that are provided by this paper.

Response: Thank you for this comment. In the process of conducting the trial, some (40%) clinicians and/or patients were not comfortable with video and audio recording the patient-clinician discussion. Knowing that a methodologically rigorous assessment of patient engagement requires review of video recordings and application of the OPTION scale6 (as opposed to only patient and clinician impressions of
the degree of engagement assessed by survey), we strongly encouraged video recordings throughout the duration of the trial. However, patient engagement was a secondary outcome, and only 221 recordings were needed for sufficient power to test this hypothesis. Thus, according to the intention to treat principle, we opted to enroll patients and clinicians in the study should they be willing to provide consent to participate, regardless of whether consent to audio and/or video recording was obtained. We also agree that, although blinding of the intervention would have been ideal, given the nature of the SDM intervention, blinding of the patient and treating clinician was not possible.

Specifically this research amounts to what can be considered a new era in research i.e. with a patient-centered focus, aligned with the PCORI funding agency that supported this project. From a scientific perspective I think this research fulfills all of the expectations one would place on a pragmatic randomized trial. The study also fulfills its primary mandate which was to show that the intervention will work across a wide range of US emergency settings. Perhaps most enlightening for readers of this work will be a reflection upon the notion of shared decision-making. I would venture, and include myself in the large group of clinicians who currently believe that they engage in shared decision-making. Clearly, after examining the personalized intervention that was developed and tested in this paper I need to reconsider that assessment. In fact, reading the paper actually opens up a whole new way of thinking about SDM and thinking about ways in which it might be applied in other settings.

Response: We agree.
Change: The section below was added to the discussion section as an attempt to highlight this point (lines 511-519).

Implications for practice and policy

The CPC DA frames the decision for the patient, provides standardized terminology, and transparently communicates patient risk and the available management options in a manner that many clinicians may find difficult to reproduce without the DA. Patient-centered decision support interventions such as these are designed to facilitate higher quality conversations with patients than typically occur in contemporary emergency care. Moreover, the results of this trial invite clinicians to consider whether our current perception of the degree to which we engage patients in decision-making as part of our usual practice respects patient autonomy and supports interaction with professional judgment.

The paper is well-written and succinct but it leaves some questions unanswered related to the medicolegal dimensions of the use of a decision-aid as a tool for guiding management. I would venture that medicolegal risk is likely lower with SDM but I didn’t quite gleam this from the paper.

Response: We agree.
Change: The following paragraph was added to the discussion section of the manuscript focusing on practice and policy implications (lines 533-541). “As support for and interest in SDM in the context of emergency care delivery has increased,7, 8 questions have arisen regarding how SDM may affect liability risk.9 Unfortunately, the relationship between SDM and liability risk cannot be assessed as it is clouded by variation in the meaning and implementation of SDM.10 While use of SDM may decrease clinicians’ liability risk by improving the patient-clinician relationship, enhancing communication (which is often at the root of lawsuits brought against clinicians after an adverse outcome11) and decreasing the frequency of invasive procedures,12 SDM may increase liability risk if the care agreed on by the patient and clinician
is sensible but perhaps at odds with what other clinicians would have selected without patient input, as the latter is often used to determine “standard of care.”

In addition, I think it would be fair to state that US practice and guideline recommendations from the AHA which are not noted in the paper argue for a very irrational approach to low risk chest pain assessment. I think the authors might want to note that SDM may not be as impactful in scenarios that are already more evidence-based and coherent in regards to resource consumption.

Response: Thank you for this comment.
Change: We added the following sentence to the Meaning of the Study” section of the discussion (lines 469-471; changes in green font): “Although we observed less extensive evaluation in this trial, use of SDM in other scenarios in which lower utilization occurs than that observed in the US may not have similar results. However, health policy and clinical protocols that encourage transparent communication of risk and patient engagement in care decisions have potential to right-size testing to disease risk in a way that is acceptable to patients, clinicians, and policy makers.

Specific comments.

Intro: The details provided in para 1 are somewhat confusing. The drop in ACS incidence is presumably based on the denominator of patients presenting to the ED with chest pain. This is not clear. The increase in advanced cardiac imaging is also vague and would not likely be true across multiple jurisdictions and are not likely to be ordered from the ED. The high rate of admission for low risk chest pain patients is likely a US-dominant phenomena. I think this merits clarification.

Response: The proportion of ED visits for chest pain has decreased by 10% over the past decade, and the proportion diagnosed with ACS has also decreased. Despite the decreasing incidence of ACS diagnoses, advanced cardiac imaging for chest pain has increased nearly 4-fold. These epidemiologic data are not specific to the clinical setting or ordering physician. In addition, the high rates of admission for low risk chest pain have been documented in countries outside the U.S.

Change: The second sentence of the introduction was revised to state (change in green font), “Over the past decade the proportion of ED visits for chest pain decreased by 10% and the proportion of patients diagnosed with acute coronary syndrome (ACS) in the emergency setting decreased from 26% to 13%. Despite the decreasing incidence of ACS, advanced cardiac imaging for chest pain has increased nearly 4-fold. Also, in response to a comment from reviewer 1, two references were added to the introduction — one in the first paragraph and one in the 2nd paragraph — highlighting the relevance of the challenge of management of low risk chest pain in England and Europe.

Methods: I don’t think CCTA is spelled out but I am presuming coronary CT angiography.

Response: This is correct. The abbreviation “CCTA” is included in the introduction after the term “coronary computed tomography angiography.”

Additional Questions:
Please enter your name: Eddy Lang
Job Title: Emergency Physician / Professor

Institution: University of Calgary

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'> (please see BMJ policy) </a>please declare them here: Research funding unrelated to this project

Reviewer: 3

Comments:
Thank you for the opportunity to review this manuscript by Hess et al. on the value of shared-decision making (SDM) in patients with low-risk chest pain presenting to an ED. In a pragmatic interventional study, the authors enrolled 898 patients and randomized them to “usual care” and to “SDM care”. For the latter, the risk of adverse events was calculated during the ED visit, this risk was communicated to the patient using visual support (“Chest Pain Choice”) and the wishes and decisions of patients were included for the further planning of chest-pain management. The main results of this interventional study were that SDM facilitated by “Chest Pain Choice” increased patient knowledge, increased patient engagement, and decreased decisional conflict not affecting physician trust. The decision aid visualizing risk of adverse events was found to be acceptable to both, patients and physicians. While the need for further observation within the index presentation was significantly reduced by SDM guided communication, secondary outcome demonstrated that this management strategy is safe and trustworthy.

To my knowledge, this is the first randomized multicenter trial examining the value and safety of shared decision making in chest pain patients with low-risk presenting to the ED. Possibly, some of my comments could further improve the reading of this excellent manuscript.
1. The authors enrolled a low-risk group of chest pain patients for further evaluation. I believe that more details of „risk evaluation“ using a web-based tool should be presented. This could be done by supplemental material presented in the online-section of this ms.

Response: Thank you for this comment. A screen shot of the web tool is now included in the manuscript as Figure 2. In addition, we added the following statement to the data sharing section of the manuscript. “The pre-test probability web tool and the Chest Pain Choice DA can be accessed at the Mayo Clinic Shared Decision Making National Resource Center at http://shareddecisions.mayoclinic.org/decision-aid-information/chest-pain-choice-decision-aid/.”

2. I do not completely understand the paragraph on follow-up data (page 17, paragraph above discussion section). Why was it possible to identify 4 patients with AMI during the index visit (3 or 4 of them in the „intervention group“) although those patients should have been discharged after communication. Have those patients been hospitalized? Is there a possible risk that AMI would have been identified in patients discharged for further ambulatory care? I understand that all diagnosis and risk assessment has been done BEFORE enrollment of the study. Please clarify.

Response: Thank you for this request for clarification. We have addressed this issue in responding to reviewer 1. The SDM discussion took place after the results of the initial ECG, laboratory testing, and first cardiac troponin were available and confirmed to be negative. This is the point in the flow of clinical care that the pretest probability estimate was calculated and emergency clinicians selected a management pathway determining subsequent care for chest pain patients. The shared decision was framed with patients such that it was clear that the cardiac stress testing decision presumed subsequent negative troponin testing to definitively rule out an acute myocardial infarction, should additional troponin testing be deemed necessary by the clinician and/or local protocols. Patients were told that the decision for stress testing and/or hospital admission would be reconsidered should their clinical status change or additional troponin testing indicate that a heart attack was occurring. Three of the 4 patients diagnosed with AMI in the intervention arm had an initial ECG without evidence of acute ischemia and an initial troponin < 99th percentile of the reference limit of normal but were diagnosed with AMI on subsequent troponin testing. The 4th patient with AMI was admitted to the hospital on the index visit, underwent PCI, and experienced in-stent thrombosis with associated troponin elevation and STEMI. All 4 of these patients had an AMI diagnosed during the index visit and never left the hospital.

Change:
(1)The following description in the “Delivery of the intervention” section of the methods was revised to state the following (revised section in green font): Then the treating clinician, after evaluating the patient and the results of the initial ECG and cardiac troponin were available, used the DA to educate the patient regarding the results of the initial cardiac troponin and ECG, the potential need for observation and further cardiac testing provided subsequent cardiac troponin testing, if obtained, definitively ruled out AMI, and their personalized 45-day risk for ACS.
(2) A more detailed description of the 4 cases of AMI in the intervention arm was included in the results section (lines 433-442)

3. A study coordinator supported clinicians to obtain risk assessment. I would suggest a new paragraph within the discussion section with a short vision, how „shared decision making“ could be implemented in routine clinical care within the ED.
Response: Thank you for this suggestion.
Change: The following paragraph was added to the “Implication for practice and policy” section of the discussion (lines 521-531). “We recommend using the DA in patients who present with acute chest pain, have no known history of coronary artery disease, the initial ECG and troponin testing are negative, and for whom the clinician is considering further cardiac investigations such as provocative testing or CCTA. The clinician can obtain an estimate of the patient’s 45-day pretest probability for ACS and download the DA corresponding to the appropriate level of risk at http://shareddecisions.mayoclinic.org/decision-aid-information/chest-pain-choice-decision-aid/. Write the patient’s name in the top left corner, and give the DA to the patient for subsequent review. The SDM discussion should also be documented in the medical record. Depending on the local practice setting, the DA can be used by the clinician with a specific patient who meets these criteria or may be implemented in the context of a comprehensive risk stratification protocol for ED patients with potential ACS.”

Additional Questions:
Please enter your name: Michael Christ

Job Title: Director

Institution: Dep of Emergency and Critical Care Medicine, Klinikum Nuernberg

Reimbursement for attending a symposium?: No

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: Received speaking honoraria from Novartis Pharma, Alere, Roche Diagnostics, Univadis, Philips Hand Held Diagnostics. Received Grant from Philips Hand Held Diagnostics, Alere, Roche, Novartis.

Reviewer: 4
Comments:
The paper presents the results of a pragmatic randomized controlled trial of an established shared decision making intervention, Chest Pain Choice, in 6 different emergency departments. The paper is very well written and has several strengths, particularly the multi-site, randomized design and the breadth of outcomes (patient, physician and utilization outcomes). The results provide important new evidence for the field of shared decision making on the use of personalized risk communication in the clinic and the application of decision aids/shared decision making in a highly emotional clinical setting with significant time pressures.
The paper would be strengthened with some attention and clarification in the following areas:

Methods:
1. The primary outcome is knowledge which is appropriate for the intervention, yet there is no information on validity or reliability (or any psychometrics) of the measure used. Please include psychometric information for the primary outcome.

Response: The knowledge questions on the post-visit patient survey were designed to measure how much the patient knows, determined by the number correct. The knowledge questions were a test, not a psychometric instrument. As such, the questions were not constructed to measure a single latent factor and it doesn't make sense to assess the psychometric properties.

Two characteristics of the outcome in this case are relevant: (1) Does it measure what it says it does (face validity)?; and (2) Does it change with the intervention? The second characteristic is supported by the outcome of the trial. The 9 knowledge questions listed in Supplementary file 2A, from a face validity perspective, highlight key points patients need to know to meaningfully engage in the decision-making process as judged by the stakeholders who participated in the design of the trial.

2. Some other measures may be less familiar to readers and having some sense for scoring and interpretation would be helpful (e.g. how is OPTION scale scored and what is clinically meaningful difference? same for Trust in Physician Scale?)

Response: Thank you for this suggestion.
Change: We added the following information to the “Secondary Outcomes” section of the methods (lines 301-322). “The DCS includes 16 items that are scored from 0-4; the items are summed, divided by 16 and then multiplied by 25. The scale is from 0-100, where higher scores are reflective of increased patient uncertainty about the choice. Gattelari and Ward found that for every unit increase in DCS, patients were 19% more likely to blame their doctor for bad outcomes. As such, a 1-unit change in DCS is considered clinically meaningful. The TPS consists of 9 items scored from 1-5; the items are subtracted by 1, summed, divided by 9 and then multiplied by 25. The scale ranges from 0-100, where higher values are reflective of higher levels of patient trust in their physician. To the best of the authors’ knowledge, a clinically meaningful change in TPS score has not been published. The OPTION scale is composed of 12 items with a value of 0-4; they are summed, divided by 48 and then multiplied by 100. This creates a score that ranges from 0-100, where higher scores are reflective of higher levels of patient engagement. Although a clinically meaningful change in OPTION scale score has not been defined, the mean (SD) OPTION score for outpatient clinicians in the original development investigation was 16.9 (7.68). Given that the current trial is conducted in the emergency setting, in which time pressures and patient acuity often impact the clinician-patient interaction, we anticipated OPTION scale scores in the current investigation to be lower than the originally published mean.”
3. The vast majority of shared decision making studies occur in outpatient settings (with recruitment “Mon-Fri 9-5pm). For recruitment in this study, given that many EDs are open 24/7, were patients recruited 24/7 or just during 9-5pm on weekdays? How was research coordinator time/effort allocated across the sites? Were there differences across sites, etc? Perhaps this is included in the protocol paper, but a brief description would be helpful.

Response: The duration of patient recruitment depended on available research personnel staffing at each of the 6 enrolling sites. Funding available through the trial was sufficient to support 1 full time study coordinator at each site. Some sites had existing research infrastructure that they were able to leverage for the trial, and others did not. The Mayo Clinic Rochester, Indiana University, the University of Pennsylvania, Jefferson University, and the University of California Davis had staffing sufficient to recruit patients from at least 7a-11p Monday through Friday, with some sites recruiting during weekends as well. The Mayo Clinic at Jacksonville has characteristics similar to a community practice, and the funding available through this study was the only source available to hire study staff. Recruitment at this site was largely Monday-Friday, 8a-5p, with a shift to include evening hours toward the end of the trial. 5 of the 6 sites had an ED-based observation unit in which protocols to provide care for patients with potential ACS existed as part of routine practice. At Mayo Clinic Jacksonville, there is no separate ED observation unit; rather, patients were assigned an observation “status” after their initial chest pain evaluation. Because of the lack of an ED observation unit, the decision to assign a patient to observation status resulted in an acute care treatment room being occupied for a longer period of time than would be optimal, limiting access of the treatment room for new patients.

Change: The following sentence, which was initially in the “Participants” section of the methods, was moved to the “Study design” section (lines 144-149). “Patients and clinicians were enrolled from the EDs at six United States sites (University of California Davis on the West Coast, Mayo Clinic Rochester and Indiana University in the Midwest, University of Pennsylvania and Thomas Jefferson University on the East coast, and Mayo Clinic Florida in the Southeast).” The following sentence was also added to “Study design” section. “All of the sites, with the exception of Mayo Clinic Florida, had access to an ED observation unit in which protocols to provide care for patients with potential ACS existed as part of routine practice.”

Results:
4. For the patients who decided to follow up with a clinician outside the ED, do the authors have data on how many participants actually had an appointment with a specialists/PCP within recommended time frame? This information seems important, especially as this arm might be difficult to replicate at other sites due to challenges confirming appointments before patients leave the ED.

Response: Thank you for this question. In the UC arm there were 52+100 = 152 patients who opted to follow-up with a cardiologist or PCP, of those 2+2 = 4 did not have a stress test or outpatient visit. In the DA arm there were 101+138 = 249 that opted to follow-up with cardiologist or PCP, of those 0+2 = 2 did not have a stress test or outpatient visit. Thus, 4/152 = 2.6% in the UC arm and 2/249 = 0.8% in the DA arm opted to follow-up as an outpatient and did not follow through on their choice. There was no significant difference between arms (Fisher's exact p= 0.20).

Change: The following sentence was added to the “Management and Outcomes” section of the results (lines 423-426): “There was no significant difference in the proportion of patients who opted to follow-up with a cardiologist or primary care provider and did not have a stress test or outpatient visit within 30 days between arms 2/249 (0.8%) DA versus 4/152 (2.6%) UC, Fisher's exact p= 0.20.”
You report on the time in the visit, yet in the methods do not describe how that result was calculated. Please include details on how the time of each “visit” was assessed and calculated.

Response: The duration of the clinician-patient discussion was determined from time-stamped video/audio recordings.

Change: The following was added to the “Data collection” section of the methods (lines 227-228). “Video/audio recordings were time stamped, and the duration of the clinician-patient discussion was determined from these recordings.”

Table 2 presents data from both arms, but for several of the questions, it is not clear what the usual care arm is rating. For example, clarity of information (what information are they rating?), would they recommend to others (recommend what?) It is difficult to interpret those responses without any sense for what the usual care arm received.

Response: The acceptability of the DA in both the UC and DA arms was assessed by immediate post-visit survey. The questions were asked in such a way that patients in either arm could meaningfully rate aspects of the way they shared information about their chest pain symptoms and options for care on a 7-point Likert scale. For example, one question was, “How would you describe the amount of information about your chest pain symptoms and options for care during this visit?” Additional questions assessing acceptability were similarly phrased and are included in the post-visit survey published with the trial protocol manuscript.  

Change: The following was added to the “Secondary outcomes” section of the methods (lines 324-328). “We assessed the acceptability of the DA by immediate post-visit survey. Patients in both the DA and UC arms were asked to rate the amount, clarity and helpfulness of the information they received and whether they would want to get information in the same way and would recommend the way that they and their provider shared information about their chest pain symptoms and options for care. Responses were recorded using a 7-point Likert scale.”

Discussion:  

The authors say they demonstrated feasibility, however, given that the research coordinator was very involved in setting up and using the Chest Pain Choice decision aid, it would be important for the authors to comment on feasibility of use of the decision aid outside a trial setting. Who would identify eligible patients? Who would enter the clinical data? Do they actually have data that it will be used outside of the trial?

Response: Clinicians in the 6 US sites in the trial used the DA in the routine flow of clinical care, so use of the DA is feasible. How to incorporate use of the DA systematically as part of a practice protocol or clinician practice pattern was not studied in this trial. Reviewer 3 asked a similar question, and the response is included below.

Change: The following paragraph was added to the “Implication for practice and policy” section of the discussion in response to the question posed by reviewer 3 (lines 521-531). “We recommend using the DA in patients who present with acute chest pain, have no known history of coronary artery disease, the initial ECG and troponin testing are negative, and for whom the clinician is considering further cardiac
investigations such as provocative testing or CCTA. The clinician can obtain an estimate of the patient’s 45-day pretest probability for ACS and download the DA corresponding to the appropriate level of risk at http://shareddecisions.mayoclinic.org/decision-aid-information/chest-pain-choice-decision-aid/. Write the patient’s name in the top left corner, and give the DA to the patient for subsequent review. The SDM discussion should also be documented in the medical record. Depending on the local practice setting, the DA can be used by the clinician with a specific patient who meets these criteria or may be implemented in the context of a comprehensive risk stratification protocol for ED patients with potential ACS.”

8. All of the settings were academic centers, would the authors comment on any issues or barriers for adopting the decision aid outside academic EDs?

Response: 5 of the 6 sites were academic practices supported by an emergency medicine residency-training program. Mayo Clinic Jacksonville does not have an emergency medicine residency-training program, and the clinicians frequently provide direct patient care without the involvement of trainees. Two of the primary barriers to implementation that the PI has encountered when presenting the project nationally have been the time required for the clinician to use the DA and potential financial incentives to obtain or not to obtain provocative testing or CCTA. We have addressed the former by reporting the additional 1.3 minutes clinicians spent discussing the DA with patients in the DA arm. The latter is influenced largely by reimbursement policies established by the Center for Medicare and Medicaid Services and other large insurers in the U.S.

Change: The following sentence was added to the “Unanswered questions and future research” section of the discussion (lines 557-560). “Health care policy to encourage, and perhaps incentivize, risk communication and incorporating informed patient preferences in emergency care decisions regarding testing and follow-up may also be needed to align financial incentives with the best interests of the patient.”

Additional Questions:
Please enter your name: Karen Sepucha

Job Title: Director, Health Decision Sciences Center

Institution: Massachusetts General Hospital

Reimbursement for attending a symposium?: Yes

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may
in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) </a>please declare them here: Dr. Sepucha receives salary support as a medical editor for the Informed Medical Decisions Foundation which is now a part of Healthwise, a not-for-profit foundation that develops and distributes patient education and decision support materials.

Reviewer: 5

Recommendation:

Comments:

General Comment
I think that this is a very important paper and ground-breaking piece of research which deserves public dissemination in a high impact journal. To my knowledge this is the first robust research combining accurate probability assessment with patient preference in an emergency setting. The research points the way for other difficult diagnostic decision making scenarios in the emergency department (such as pulmonary embolism and subarachnoid haemorrhage). There will certainly be challenges to implement such an approach into real-life care but this research is an important first step. It might be easy to be distracted by these potential challenges and they should not detract from the key message here, that this approach improved patient knowledge which as described in the methods was the objective that was most valued by the patient.

Introduction

Major points: None

Minor points:

Line 108: Does it really add anything to highlight a 49% relative change when there is an absolute change from 26% to 13%?

Response: Probably not. Removing this percentage actually increases the readability of the introduction.

Change: The phrase, “a 49% relative decrease” was removed.

Line 113: These consequences are not a certainty. Would it be better to highlight that these consequences MAY occur?

Response: Excellent point.

Change: The descriptor “potential” was added to the sentence in the introduction referring to the sequela of missing a diagnosis of ACS.

Line 122: It would be useful to the reader to highlight here that this is about shared decision making.

Response: Agree
Change: The descriptor “shared” was added before the phrase “decisions about testing and follow-up.”

Line 128: Although it is implied by previous mention of the pilot and is obvious in the methods, it would be helpful to the reader to highlight the primary outcome here or expand on what effectiveness is being tested if word count allows.

Response: Agree

Change: The last sentence of the introduction was revised to state (change in green font), “In order to test the effectiveness of CPC to improve patient knowledge and decrease unnecessary resource use in a broader population of patients with greater socioeconomic diversity and in a variety of clinical contexts, we conducted a multicenter pragmatic randomized trial in six geographically diverse ED's across the United States.”

Methods
Major points:
Line 148: This really a point for the discussion-limitations but I mention it here because this is the reference point in the text. The inclusion criteria are very appropriate but this highlights that in other geographical healthcare settings the benchmark for this inclusion (being considered by the treating clinician for observation unit admission for cardiac testing) may be quite different. I don’t think that this would effect the primary outcome of “knowledge” but could impact achieved differences in testing and admission rates. Perhaps this should be mentioned under limitations.

Response: Good point. A major strength of the inclusion criteria is that it is applicable across a variety of settings and can fit within the context of a variety of local practice protocols for patients with potential ACS. A limitation is that selecting patients using this pragmatic approach leaves more work to be done regarding how to implement the DA in the context of a risk-based pathway such as the HEART score. Reviewer 2 highlighted that the impact of SDM on resource use in scenarios that are already more evidence-based may be different, and reviewer 3 asked for more details regarding how the CPC DA might be implemented in practice.

Change:
(1) We added the following sentence to the Meaning of the Study” section of the discussion in response to reviewer 2 (lines 469-471): “Although we observed less extensive evaluation in this trial, use of SDM in other scenarios in which lower utilization occurs than that observed in the US may not have similar results.”

(2) The following paragraph was added to the “Implication for practice and policy” section of the discussion in response to the question posed by reviewer 3 (lines 521-531). “We recommend using the DA in patients who present with acute chest pain, have no known history of coronary artery disease, the initial ECG and troponin testing are negative, and for whom the clinician is considering further cardiac investigations such as provocative testing or CCTA. The clinician can obtain an estimate of the patient’s 45-day pretest probability for ACS and download the DA corresponding to the appropriate level of risk at http://shareddecisions.mayoclinic.org/decision-aid-information/chest-pain-choice-decision-aid/ Write the patient’s name in the top left corner, and give the DA to the patient for subsequent review. The SDM discussion should also be documented in the medical record. Depending on the local practice setting, the DA can be used by the clinician with a specific patient who meets these criteria or may be implemented in the context of a comprehensive risk stratification protocol for ED patients with potential ACS.”
Minor points:
Line 144: I realise that this is an American study but since this is being submitted to a British journal, is
there another descriptor such as ‘central USA’ that could be used rather than ‘midwest’ which even as a
frequent visitor to the USA I find confusing.

Response: Yes
Change: the term “Midwest” was removed and replaced with “central.”

Line 173: Readers may not be familiar with the abbreviation MN for Minnesota

Change: Changed “MN to “Minnesota.”

Line 183: Why was it study coordinator that determined the variables a priori? Could this mean that in
real life that the creation of the shared decision tool would take longer? This relates to line 382 in the
discussion. How much time is taken creating the correct decision tool?

Response: Study coordinators collected the variables for entry into the pre-test probability web tool and
had the clinician sign off on their accuracy for purposes of collecting accurate data for the trial and
standardization across the sites. In practice, < 30 seconds are required to enter the variables for the
decision tool. The reader can verify this by clicking on the following link:
http://pretestconsult.com/v21/acs.
Change: None. This link can be found at the Mayo Clinic National Shared Decision Making Resource
Center website.

Line 209: FedEx is a US tradename – would ‘secure courier’ be better?
Response: yes
Change: This has been changed.

Line 220: I thought that this explanation paragraph was very helpful but was partly repeated under the
outcomes paragraph. Is there scope to put some of this in an appendix? It is a long paragraph.
Response: Agree
Change: The following sentences were removed from the beginning of the “Outcomes” section of the
methods. “Outcomes were selected and prioritized through an iterative process that included input
from the patient and caregiver representative, the ED patient advisory council at Mayo Clinic,
emergency clinicians and cardiologists, the investigative team, and a payer representative (Chief Medical
Officer of Mayo Clinic Health Solutions). Outcome selection and prioritization were undertaken in such
as way that input was sought from patients and key stakeholders potentially influencing the future
adoption of the tool in practice to ensure that their perspectives were taken into consideration.”

Results
Major points:
Line 332: it would be very useful to highlight that these knowledge scores are from a total score of eight
(if that is correct)

Response: Agree
Change: The phrase “out of 8” was added to the following statement in the results section (line 391;
green font below): Patients randomized to CPC had greater knowledge (questions correct out of 8: CPC,
4.2 versus UC, 3.6; mean difference [MD], 0.66; 95% confidence interval [CI], 0.46, 0.86), shown in Table 2.

Table 1 “Pre-test probability of ACS” - was this the percentage calculated by attribute matching?

Response: yes
Change: The following symbol and footnote were added to Table 1. “Calculated from the quantitative pre-test probability web tool.”

Discussion
Major point:
I don’t know if there is room to discuss this here, however, it strikes me that a means of making accurate probability assessment is key to the shared decision making. The tool used here is based on a large dataset of American patients. That is not a flaw but, in order to work safely in other settings (with different patient demographics, prevalence and clinician training) would other datasets specific to those settings be needed? Is this worth discussion?

Response: We agree that a means of making accurate probability assessment is important for risk communication and shared decision-making. However, the pre-test probability web tool was derived from a cohort of over 15,000 patients with potential ACS\textsuperscript{19} and has been prospectively validated in different patient populations in several different practice contexts.\textsuperscript{20-23} As such, the instrument meets prediction rule criteria for level 2 evidence that can be safely used in practice.\textsuperscript{24} Moreover, the racial and ethnic diversity of the U.S. population likely poses greater challenges to successful validation than in many other countries. For these reasons, we think that potential variability in prognostic performance of the web tool between countries or practice settings likely reflects spectrum bias regarding which chest pain patients seek or are referred for emergency care between countries and the associated variability in the prevalence of disease in a given population. We agree that clinician training is important to document for this trial, as elements of the history, physical examination, and ECG interpretation are included as variables in the pre-test probability web tool.

Change: The section “Participants” (line 154) was revised to state (change in green font): “Eligible clinicians included all emergency physicians, nurse practitioners, and physician assistants caring for patients with chest pain.”

Minor points:
Line 412: “There is now evidence to support applying the SDM tool in a greater variety of clinical…” - are there references for this?
Response: Thank you for pointing this out. The sentence was not written as clearly as intended. This sentence was referring to the evidence produced from the trial in this report.
Change: The sentence (lines 492-494) was revised to state, “In addition, there is now evidence to support applying the SDM tool in clinical care contexts in which CCTA is frequently used and in practice settings in which cardiac stress testing is more commonly used.”

In the USA, how will the current dataset be adapted to take into account the predictive values of the next generation of cardiac troponin assays?

Response: We designed the CPC DA in such a way that as more accurate risk scores, such as those that incorporate use of high sensitivity cTn, become available, they can be used in place of the pretest probability web tool used in this trial.
Change: The following sentence was added to the “Limitations and strengths of the study” section of the discussion (lines 484-487): “In addition, more accurate methods to estimate patient risk, such as those incorporating high sensitivity cTn assays, are likely to become available. In the future it may be preferable to generate risk estimates with these methods and select the DA that corresponds with this level of risk.”

Conclusion
The conclusions are sound

Additional Questions:
Please enter your name: MARTIN THAN

Job Title: SPECIALIST EMERGENCY MEDICINE

Institution: CHRISTCHURCH HOSPITAL NEW ZEALAND

Reimbursement for attending a symposium?: Yes

A fee for speaking?: Yes

A fee for organising education?: Yes

Funds for research?: Yes

Funds for a member of staff?: Yes

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy)</a> please declare them here: I HAVE NO COMPETING INTERESTS FOR THIS PAPER

**Information for submitting a revision**

Deadline: Your revised manuscript should be returned within one month.

How to submit your revised article: Log into http://mc.manuscriptcentral.com/bmj and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions."
Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s). As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation ‘Revised Manuscript Marked copy’. Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision. Please include these items in the revised manuscript to comply with BMJ style (see: http://www.bmj.com/about-bmj/resources-authors/article-submission/article-requirements and http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists).

Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

1. What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

2. Name of the ethics committee or IRB, ID# of the approval, and a statement that participants gave informed consent before taking part. If ethics committee approval was not required, please state so clearly and explain the reasons why (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines.)

3. Patient confidentiality forms when appropriate (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality).

4. Competing interests statement (see http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests)

5. Contributorship statement+ guarantor (see http://resources.bmj.com/bmj/authors/article-submission/authorship-contributorship)

6. Transparency statement: (see http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/transparency-policy)

7. Copyright statement/licence for publication (see http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)
8. Data sharing statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research)

9. Funding statement and statement of the independence of researchers from funders (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements).

10. Patient involvement statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research).

11. Please ensure the paper complies with The BMJ’s style, as detailed below:

   a. Title: this should include the study design eg "systematic review and meta-analysis."

   b. Abstract: Please include a structured abstract with key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research). For every clinical trial - and for any other registered study- the last line of the abstract must list the study registration number and the name of the register.

   c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

   d. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

   e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

      i. For a clinical trial: Absolute event rates among experimental and control groups; RRR (relative risk reduction); NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000.)

      ii. For a cohort study: Absolute event rates over time (eg 10 years) among exposed and non-exposed groups; RRR (relative risk reduction.)

      iii. For a case control study: OR (odds ratio) for strength of association between exposure and outcome.

      iv. For a study of a diagnostic test: Sensitivity and specificity; PPV and NPV (positive and negative predictive values.)

      v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used.
For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

f. Discussion: To minimise the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vi) unanswered questions and future research.

g. Footnotes and statements

Online and print publication: All original research in The BMJ is published with open access. Our open access policy is detailed here: [http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse). The full text online version of your article, if accepted after revision, will be the indexed citable version (full details are at [http://resources.bmj.com/bmj/about-bmj/the-bmjs-publishing-model](http://resources.bmj.com/bmj/about-bmj/the-bmjs-publishing-model)). The print and iPad BMJ will carry an abridged version of your article. This abridged version of the article is essentially an evidence abstract called BMJ pico, which we would like you to write using the template downloadable at [http://resources.bmj.com/bmj/authors/bmj-pico](http://resources.bmj.com/bmj/authors/bmj-pico). Publication of research on bmj.com is definitive and is not simply interim "epublication ahead of print", so if you do not wish to abridge your article using BMJ pico, you will be able to opt for online only publication. Please let us know if you would prefer this option. If your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes, and based on the information in your paper’s BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.


