- ***General questions/comments:***
  - Is there a model of the process for developing guidelines? If yes, has that been used for developing the OWL model?
  - Model is very much based on the (diabetes) document model. The guidelines seem to be structured quite differently, so I'm not sure how easily other guidelines are transferable into the model, e.g., rationale doesn't seem to be easily identifiable in CG95.
  - Are there different 'kinds' of guidelines requiring distinct structures? - not with the intention to model them differently, but to guide the modelling process and ensure they're all covered.
  - What is being modelled: the process of developing the guideline, the guideline, or the document version of the guideline?
    - What different views of the guidelines could be modelled?
      - Process of developing a guideline
      - Document structure of guideline
      - Guideline itself (whatever that might be)
      - Interaction / relationship between different guidelines (this could be at various levels, e.g.)
        - Explicit references between guidelines
        - Re-use of recommendations in different guidelines
        - Re-use of evidence in different guidelines
        - Composition of (smaller) (sub-)guidelines to form a whole guideline (chest pain CG95 might be a candidate for that as it contains Acute and Stable Chest Pain)
      - Order (parallel/sequential) in which recommendations are to be followed
  - What is the purpose of the model, what will it be used for?
    - Granularity and level of detail or abstraction most likely depends on the purpose of the model
  - Granularity/level of detail of the model doesn't lend itself to utilising the ontological features, e.g., inference, and seems to make re-use more tricky - if re-use is planned.
  - Perhaps the guidelines could be split into parts that can "sort of" stand alone, then to be combined to form 'complete' guidelines, CG95 seems a candidate for that with stable chest pain and acute chest pain.
    - What's the "unit" of a guideline? Is it a diagnosis?

- ***Questions/comments related to model (diagram of OWL and excel spreadsheet Master Source Content.xlsm):***
  - *General comments:*
    - Would it be possible/an option/is the plan to extract the facts from the text and model those rather than the whole text of sometimes multiple paragraphs (in particular for recommendations and evidence statements)?
    - I wouldn't use IDs that have references to the original guidelines they're coming from, as I would expect that various aspects of different guidelines might be re-usable in other guidelines.
    - I would suggest modelling in such a way and level of detail so that overlap between guidelines can be identified and re-used, and potential inconsistencies spotted.
    - I would suggest using an ontology or at least a terminology/controlled vocabulary (if possible) for the topic and subtopic and subject of evidence statement (e.g., SnomedCT, MESH).
    - There are references to other parts in the guideline mentioned in the actual guidelines (and partly highlighted in red in the spreadsheet for diabetes) - is the plan to model those cross-references explicitly?
    - References to other guidelines or TAs etc., (not in red in spreadsheet): is there a plan to model these cross-references explicitly? The model doesn't seem to contain explicit cross-references as far as I can tell. There might be indirect ways by referring to the same study or reusing a recommendation or evidence statement, but that's not as explicit as the actual reference is in the guideline documents.
    - Potential for re-usability:
      - Could a (sub)topic be part of multiple guidelines?
      - Does it make sense to have recommendations and evidence statements independent of the context of the guideline, i.e., the topic/subtopic, rationale and discussion? This might improve reusability and possibly maintainability, but it might not make sense, as the discussion probably justifies the evidence statements used and resulting recommendations made.
      - Could there be different recommendations based on the same evidence in different guidelines?
      - I would suggest using existing persistent identifiers, e.g., DOIs, for the papers/references to enable keeping track of where, i.e., in which guidelines, particular papers are used as evidence.
    - There doesn't seem to be somewhere in the model to represent the information found in (discussion of) clinical evidence (in CG95 with various tables from the papers; see at the end of this document for an example) or the evidence tables (CG15, but link on page 151 doesn't seem to work, so I'm not sure what exactly is in those tables). Is the plan to include that information in the model? This information is of interest to us and I guess could be to others who want to use the guidelines for example to guide/use in clinical care flow plans (software/tools).
      - What part/information in the discussion of the clinical evidence is important for deciding whether it's suitable to be used as evidence for the guideline, whether it's supporting evidence or not, what it supports or not, and what level of evidence it is? - Could that be modelled?
        - Is really the whole discussion required for the information to be utilised as evidence?
        - What are the essential facts?
        - Is there a pattern in those facts that could be modelled?
    - Should the scope of a guideline, in particular the population groups covered and not covered and the healthcare settings and aspects of clinical management not be represented in the model? This might help identify gaps in the population groups or healthcare settings for which clinical guidelines are lacking.
    - I'd be tempted to break the various aspects of the model down even further (to the actual facts that are represented/contained in a guideline) rather than the parts (single or multiple paragraphs) of the guideline document.
    - PICO seems like a good starting point to model everything related to the evidence, including search strategies, questions etc. (http://www.usc.edu/hsc/ebnet/ebframe/PICO.htm)
    - Once the model is developed, populating it shouldn't be that tricky (will depend on the complexity of the model, but perhaps it could be split up into parts for that purpose - modularised?), as potentially tools like RightField (http://www.rightfield.org.uk/download) or Populous (http://e-lico.eu/populous.html) could be used.
  - *Specific comments to various aspects of the model:*
    - *Guideline, topic, rationale, discussion:*
      - It is a little surprising that *guideline* isn't directly linked to anything, e.g., recommendations, evidence statements, but might be ok.
      - Cardinalities and *SetIDs* are not clear, e.g., does the setId belong to the combination of *topic, subtopic, set rationale, set discussion*?
        - ***set*** *rationale*, ***set*** *discussion* but only one id?
      - Why is consideration in the Diabetes guideline called *set discussion* in the model? Is that were the outcome of a discussion is normally described? It's not the case for the Chest Pain guideline (CG95).
      - Why is there a *hasRationale* for the *rationale* whereas *discussion*, which (as far as I can tell) serves a similar purpose, is linked through *isAbout* to a (sub)topic, why not hasDiscussion to make it consistent? I would suggest to do the same for *evidenceStatements* (hasEvidenceStatement) and *recommendation* (hasRecommendation) for consistency and to make it more explicit than isAbout is at the moment.
    - *Recommendation (see at the end of the document for some examples):*
      - Does *follows* represent the order in which the recommendations appear in the document? Might be worth renaming into documentOrder or something similar to make that more explicit, as I would think that there might be a different order if the recommendations are arranged into some temporal order in which they should be followed/done, which doesn't seem to be included in the model.
      - Granularity of *recommendations* - same issue in Diabetes as in Chest Pain when trying to model the order in which recommendations are to be followed. I'd be tempted to try and model what information is required, what decisions are being made and what actions need to be carried out; i.e., try to figure out what kind of information is generally in a recommendation and model that, the same applies to evidence statements. However, that might result in recommendations that don't have much resemblance with those in the document though. If the plan is to still be able to generate a document version of a guideline from the model, modelling the recommendations and evidence statements very differently might be an issue though.
    - *Evidence statement (see at the end of the document for some examples):*
      - *Evidence statement* doesn't seem to have a subject in the diagram of the OWL model, unless prov:Entity has that, but it has that in the spreadsheet and I think it's useful to have as it's more concrete than the (sub)topic in some cases.
      - Is *Evidence Category Code* (in spreadsheet) = *evidenceLevel* (in OWL diagram)?
      - I think it would be useful to differentiate between health economic evidence and clinical evidence, if that's what *evidenceType* is meant to be used for. It is in the OWL diagram, but doesn't seem to be listed in the spreadsheet though.
      - Does the *evidence level/category* depend on the question, the type of the evidence, i.e., type of study, the context, i.e., (sub) topic with rationale and discussion or more general: what does the evidence level depend on? Where is the justification for the evidence level - it isn't explicitly linked with any of this, but the actual description of an evidence level (e.g., "High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias", or "meta-analysis of randomised controlled trials" seems to suggest that it might depend on the type of study. Is it worth making that explicit somewhere in the model?
      - Towards a finer granularity of the evidence part of the model - What does an evidence statement contain in general?
        - kind of evidence found (if any)
        - whether the evidence is supporting or not
        - what the evidence is (not) supporting (multiple or single things?)
      - Potentially different kinds of negative evidence statements:
        - no evidence was found
        - the evidence does not support …
    - *Link between recommendation(s) and evidence statement(s):*
      - There isn't a direct link between *recommendation* and *evidence statement* in the spreadsheet, even though it is in the OWL model (ng:supportedBy).
        - I'm not sure how easy it is to always have a direct 1:1 or m:n association, but that might indicate that the granularity of one or the other might need reconsidering, e.g., by splitting up the paragraphs of the recommendations or evidence statements.
      - Are all the *recommendations* under a (sub)topic supported by all the *evidence statements* under the same (sub)topic or is there a/multiple evidence statement(s) associated with a/multiple recommendations? (the guideline documents don't seem to help with that, except by reading recommendations and evidence statements in detail and figuring out whether there are associations that are not made explicit - subject of evidence statements don't seem to help (too much) nor is there a link between specific evidence statement and recommendation in the spreadsheet.
    - *Evidence statements and studies:*
      - Multiple studies are referenced in an evidence statement, but sometimes the studies are referenced from different parts of the statement, does that mean in those cases that a study only provides evidence for that part of the evidence statement rather than the whole statement? - If that's the case, there might be a granularity issue.
    - *Search strategy, Study, reference:*
      - Intervention, Outcome and Comparator (in spreadsheet) don't seem to be in OWL model diagram.
      - I'm not sure I would give the search strategy an identifier; it's 'just' a combination of different properties, e.g., strategy type, population, study type, database, and min- and max-year, I don't think the combination of this warrants an identifier.
      - Search strategies seems to be a placeholder for a grab bag of different properties that describe to some extent how the evidence was obtained (Strategy Type, Population, Study Type, Database, Year), but then also what the evidence/references/papers contain and of what kind it is (Population, Study Type, Interventions, Comparisons, Outcomes).
        - Should this be split up and some of the properties renamed to make them unambiguous?
        - Should both kinds of information be available at all times/for all evidence (it isn't at the moment)?
        - Do these properties capture sufficiently the required information?
        - Is this modelled at the appropriate level of detail?
        - Are certain search strategies recommended to be used and others discouraged for guideline development and accumulation of the evidence?
      - Studies (references to papers) are listed multiple times in the spreadsheet with different IDs.
      - Is there medadata available with which the references/papers are already annotated, (e.g., MESH) and could that be reused to a certain extent? Information I have in mind includes information on the topic the paper is about, the study type, etc., i.e., similar to the information captured by the search strategy.
        - What does OMIM do? Do they have some metadata annotation of papers that could be utilised?
      - I would use dublin core to model the references/studies/papers, as that's what it was kinda developed for (for digital libraries that contain metadata of papers/references) and probably not use it elsewhere in the model to avoid confusion. That would result in a finer grained model for the studies/references.
      - Is the plan to keep track of details of when searches were carried out?

- ***Comments related to inconsistencies observed between different guidelines (in particular wrt CG15 and CG95, but most likely will apply to others too)***
  - Different evidence scores/categories in different guidelines (should be consistent, and probably ideally re-use something existing) (e.g., 1++, 1+ etc. in ACS, and Ib, II, IIb etc. and NICE in Type 1 Diabetes) and descriptions don't even seem to make them easily mappable/comparable to each other
    - E.g., evidence categories in CG95:
      - 1++: High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
      - 1+: Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
    - Evidence categories in Diabetes guidelines:
      - Ia: meta-analysis of randomised controlled trials
      - Ib: at least one randomised controlled trial
  - No rating of the recommendations in CG95
  - The level of detail in the evidence statements seem different between guidelines (see examples of evidence statements above), with CG95 appearing to be more detailed and including detailed stats from the papers.
  - No obvious rationale in CG95.
  - Level of detail of information on search strategies differs between the Chest Pain guideline (CG95) and the Diabetes guideline (CG15).
    - Details of which databases were searched and when are mentioned in general for the whole guideline CG95 (Chest Pain) under 2.3 Literature search strategy, but not for each questions separately, as is done in the Diabetes guideline, in contrast, the actual search strings with terms entered are available for Chest Pain, but not for Diabetes (see below for an example of the searches carried out for Question 2 in CG95).

Question 2: What is the utility and cost effectiveness of assessment of cardiovascular risk factors in evaluation of individuals with chest pain of suspected cardiac origin?

CP AND RISK, HISTORY & PHYSICAL EXAM MEDLINE SEARCH STRATEGY

1.	SEARCH:	Risk-Assessment.MJ.
2.	SEARCH:	Medical-History-Taking.MJ.
3.	SEARCH:	Physical-Examination.MJ.
4.	SEARCH:	Risk.W..MJ.
5.	SEARCH:	(pretest ADJ (probability OR likelihood)).TI,AB.
6.	SEARCH:	(history NEAR (take OR takes OR taking)).TI,AB.
7.	SEARCH:	(risk ADJ assess$5).TI,AB.
8.	SEARCH:	((physical OR clinical) ADJ exam$8).TI,AB.
9.	SEARCH:	((medical OR family OR patient OR clinical) ADJ history).TI,AB.
10.	SEARCH:	(probability ADJ disease).TI,AB.
11.	SEARCH:	Framingham.TI,AB.
12.	SEARCH:	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11
13.	SEARCH:	Chest-Pain#.DE.
14.	SEARCH:	angina.TI,AB.
15.	SEARCH:	Angina-Pectoris#.DE.
16.	SEARCH:	(acute ADJ coronary ADJ syndrome$2).TI,AB.
17.	SEARCH:	Myocardial-Infarction#.DE.
18.	SEARCH:	13 OR 14 OR 15 OR 16 OR 17
19.	SEARCH:	12 AND 18

- ***Questions/comments related to Diabetes (in particular wrt CG15):***
  - There are other guidelines listed on the NICE Diabetes site (https://www.nice.org.uk/Guidance/Conditions-and-diseases/Diabetes-and-other-endocrinal--nutritional-and-metabolic-conditions/Diabetes) than there are in the Excel spreadsheet (RDFProvider-master/Source Content/Master Source Content.xlsm) listing all the guidelines used for the initial use case by NICE (small-ish overlap, some additional ones on website, some additional ones in spreadsheet).
  - How were the guidelines etc. selected that are included in this use case?
  - Why are there some included that don't seem to have Diabetes as main subject, e.g., Chronic kidney disease, and why were others that are listed on the diabetes site not included in this use case?
  - How do the different documents relate to each other and how are they represented in the model, if at all
    - http://www.nice.org.uk/guidance/cg15/resources/guidance-type-1-diabetes-pdf
    - http://www.nice.org.uk/guidance/cg15/resources/cg15-type-1-diabetes-in-adults-full-guideline-part-1-2
  - Why was Diabetes chosen? Is the guideline particularly well structured? (At least it seems easier to find the information than in the ACS guideline)

- ***Questions/comments related to Chest Pain (in particular wrt CG95):***
  - ACS guideline structured differently compared to diabetes guideline
    - Evidence statements (numbered) followed by a subsection with the clinical questions followed by clinical evidence which reads more like a discussion - I'm not sure where in the model this is supposed to go - are these further evidence statements or is this additional information that should go elsewhere?
      - Is that the discussion - but it seems to be linked to questions, which it isn't in the model
  - Guideline contains multiple diagnoses: acute chest pain -> acute MI, stable chest pain -> angina
    - I guess it makes sense to have them all together in one guideline, but for the modelling it might make sense to split them up.

- ***Examples to illustrate some of the points made above:***
  - *Recommendations:*
    - Diabetes:
      - CG15R1.6.1.2: Where diabetes is diagnosed, but Type 2 diabetes suspected, the diagnosis of Type 1 diabetes should be considered if:
        - ketonuria is detected, or
        - weight loss is marked, or
        - the person does not have features of the metabolic syndrome or other contributing illness.
      - CG15R1.7.1.3: Each adult with type 1 diabetes should be managed as an individual, rather than as a member of any cultural, economic or health-affected group. Attention should be paid to the recommendations given elsewhere in this guideline with respect to the cultural preferences of individual adults with type 1 diabetes.
      - CG15R1.7.1.4: An individual care plan should be set up and reviewed annually, modified according to changes in wishes, circumstances and medical findings, and the details recorded. The plan should include aspects of:
        - diabetes education including nutritional advice (see section 6.1, 'Education
        - programmes for adults with Type 1 diabetes' and 6.3, 'Dietary management')
        - insulin therapy (see section 7.3, 'Insulin regimens' and 7.4, 'Insulin delivery')
        - self-monitoring (see section 6.2, 'Self-monitoring of blood glucose')
        - arterial risk factor surveillance and management (see chapter 8, 'Arterial risk control')
        - late complications surveillance and management (see sections on late complications)
        - means and frequency of communication with the professional care team
        - follow-up consultations including next annual review.
    - Chest pain:
      - CG95R1.2.1.2 Determine whether the chest pain may be cardiac and therefore whether this guideline is relevant, by considering:
        - the history of the chest pain
        - the presence of cardiovascular risk factors
        - history of ischaemic heart disease and any previous treatment
        - previous investigations for chest pain.
      - CG95R1.2.1.7 Refer people to hospital as an emergency if an ACS is suspected (see recommendation 1.2.1.3) and:
        - they currently have chest pain **or**
        - they are currently pain free, but had chest pain in the last 12 hours, and a resting 12-lead ECG is abnormal or not available.
      - CG95R1.2.2.3 Follow 'Unstable angina and NSTEMI' (NICE clinical guideline 94) for people with a resting 12-lead ECG showing regional ST- segment depression or deep T wave inversion suggestive of a NSTEMI or unstable angina until a firm diagnosis is made. Continue to monitor (see recommendation 1.2.3.4).
  - *Evidence statements:*
    - Diabetes (numbers are references):
      - CG15AdultES14: A number of approaches to medical care without direct patient contact are described in the literature. One RCT of a telecare system for insulin50 provided equivalent control at reduced cost, while another study12 using nurses resulted in improved blood glucose control.
      - CG15AdultES16: Three papers using historical controls or randomised controls address the value of multidisciplinary teams with a specialist interest in diabetes management in the care of inpatients on non-diabetes wards.53–55 Reduced length of inpatient stay is consistently reported. One study suggests improved glucose control.55 One study, also using historical controls, addresses length of stay in a developing country in newly-diagnosed people with diabetes, showing much reduced stays with multidisciplinary team input.
      - CG15AdultES18: Two potentially useful papers consider the type of treatment facility used to deliver care to those with Type 1 diabetes.334,335 One German study334 found that the treatment facility (polyclinics, specialist clinics or general practitioners) makes no difference to diabetes-specific knowledge when this was controlled for age, sex and education. One UK study335 found no difference between hospital- and general practice-based care on a range of outcome measures for metabolic control, satisfaction with treatment or beliefs about diabetic control for a mixed diabetic population. Some differences were observed in the surveillance for complications, with more frequent testing in integrated care. Whilst costly, it is worth noting that fewer patients defaulted from general practice-based care than conventional care. Avoided complications may offset the increased cost of general practice-based care, although this cannot be established on the basis of this study. One UK-based study297 suggested that the provision of a hospital-based diabetes specialist nurse lowered the cost per patient admission without producing a significant difference in readmission, quality of life or patient satisfaction.
      - CG15AdultES21: Research evaluating the effectiveness of support groups for patients and carers, across numerous conditions and groups (not necessarily diabetes), has shown specific benefits including:
        - psychological and emotional benefits 65 including lower pain perception and improved ability to cope with stress 63,66–7
        - reduction of carers' burdens and stresses 68–9
        - improvement in quality of life 70–71
        - improved self-care through health promotion strategies which have been helpful in smoking cessation and management of chronic conditions 72–3
        - improved access to health service provision 74
        - reduced isolation, overcoming depression and loss of self-esteem 64
        - better understanding of conditions, symptoms and healthcare systems through education and information. 67
      - CG15AdultES31: Evaluation, in a large systematic review, 84 of a range of diabetes self-management education (DSME) programmes compared to normal routine levels in populations of people with diabetes found that interventions based in community gathering places were able to reduce blood glycated haemoglobin (GHb) and fasting blood glucose levels. There is some evidence that they can also improve diabetes knowledge and improve physical activity (minutes of walking). Other trials reviewed that were based in the home setting – half of which included children or adolescents – showed a significant decrease in GHb after DSME, and a borderline 6 Education programmes and self-care beneficial effect on weight for people undergoing DSME as compared to conventional care. Specific analysis in patients with Type 1 diabetes found no significant change in diabetes knowledge with such programmes
    - Chest Pain:
      - CG95ES53: The two systematic reviews and twelve cohort studies indicate that troponin I and T have the highest sensitivities and specificities for the diagnosis of acute MI compared to CK-MB, CK and myoglobin. CK-MB had the second highest sensitivities and specificities for diagnosis of acute MI. (Balk, E. M., Ioannidis, J. P., Salem, D. et al, 2001) (Ebell, M. H., Flewelling, D., and Flynn, C. A., 2000), (Guo, Xiaobi, Feng, Jianzhang, and Guo, Hengshan, 2006) (Kost, G. J., Kirk, J. D., and Omand, K., 1998) (Chiu, A., Chan, W. K., Cheng, S. H. et al, 1999) (Falahati, Alireza., Sharkey, Scott W., Christensen, Dane. et al, 1999) (Eggers, Kai Marten, Oldgren, Jonas, Nordenskjöld, Anna et al, 2004) (Fesmire, Francis M., Christenson, Robert H., Fody, Edward P. et al, 2004) (Gust, R., Gust, A., Böttiger, B. W. et al, 1998) (al Harbi, Khalid., Suresh, C. G., Zubaid, Mohammad. et al, 2002) (Vatansever, S., Akkaya, V., Erk, O. et al, 2003) (Planer, David, Leibowitz, David, Paltiel, Ora et al, 2006) (Zarich, Stuart W., Qamar, Asad U., Werdmann, Michael J. et al, 2002) (Zimmerman, J., Fromm, R., Meyer, D. et al, 1999)
      - CG95ES99: The sensitivities and specificities for the diagnosis of CAD with MPS using SPECT are generally higher compared with exercise ECG. From one systematic review the reported sensitivity with MPS with SPECT is 88.1% (95 %CI 86.6% to 89.6%) and the specificity is 73.0% (95%CI 69.1% to 76.9%). (Heijenbrok-Kal, M. H., Fleischmann, K. E., and Hunink, M. G., 2007).. From a second systematic review the stress MPS with SPECT sensitivity is reported as a range from 63% to 93% (median 81%) and the specificity range is 54% to 90% (median 67%). (Mowatt, G., Vale, L., Brazzelli, M. et al, 2004)
      - CG95ES116: For the diagnosis of CAD five systematic reviews (search date 2007 for 2 reviews, and 2006 for 3 reviews) of 64-slice CT coronary angiography reported from meta-analyses higher sensitivities of 97%, 96%, 98%, 99% and 99% and specificities of 88%, 91%, 92%, 93% and 97% respectively compared with the non-invasive tests of stress echocardiography ((sensitivity 79.1% (95%CI 77.6% to 80.5%) and specificity 87.1% (95%CI 85.7% to 88.5%)), stress MPS using SPECT ((sensitivity 88.1% (95%CI 86.6 to 89.6%)) and specificity 73.0% (95%CI 69.1% to 76.9%)), stress MR perfusion imaging ((sensitivity 91% (95%CI 88% to 94%) and specificity 81% (95%CI 77% to 85%)) and stress MR wall motion abnormalities ((sensitivity 83% (95%CI 79% to 88%)) and specificity 86% (95%CI 81% to 91%)). (Abdulla, J., Abildstrom, S. Z., Gotzsche, O. et al, 2007) (Sun, Z., Lin, C., Davidson, R. et al, 2008) (d'Othee Janne, B., Siebert, U., Cury, R. et al, 2008) (Vanhoenacker, Piet K., Heijenbrok-Kal, Majanka H., Van Heste, Ruben. et al, 2007) (Mowatt, G., Cummins, E., Waugh, N. et al, 2008).
  - *(Discussion of) clinical evidence:*
    - Diabetes:
      - not found anything comparable, but link on page 151 of the appendices of CG15 doesn't seem to work.
    - Chest pain:
      - (Section 4.2.1.2 of full guideline): The second systematic review on the accuracy of 10 elements of the clinical history identified 28 prospective and retrospective cohort studies (search date 2006) (Bruyninckx, R., Aertgeerts, B., Bruyninckx, P. et al, 2008). The following individual components were examined; pain in left arm and / or shoulder, pain in right arm and / or shoulder, pain in both arms, pain in neck, pain in back, epigastric pain, oppressive pain, vomiting and / or nausea, sweating, and absence of chest wall tenderness. The 28 studies identified by the systematic review had a combined total of 46,908 patients, with a mean age of 50 to 71 years, and 40% to 71% were male. Of the 28 studies, 16 were of non selected patients (patients presenting to their general practitioners, patients presenting to the emergency department or those selected by paramedics), 11 were of selected patients recruited by coronary care units and cardiologists and 1 was in a chest pain observation unit. Eleven studies were set in the emergency department, 10 studies were set in a coronary care unit, 3 studies were set in the ambulance, 3 in primary care, and 1 was in a chest pain observational unit (Bruyninckx, R., Aertgeerts, B., Bruyninckx, P. et al, 2008). Table 4 and Table 5 detail the results of meta-analyses for the utility of components of the clinical history in the diagnosis of acute MI and ACS, respectively. The results are from studies on unselected patients presenting with chest pain. For acute MI there was homogeneity in the PLR for oppressive pain, and in the negative likelihood ratio (NLR) for chest wall tenderness. For ACS, there was homogeneity in the PLR of left arm pain and the NLR for sweating and tenderness. For all other analyses there was a moderate to high level of heterogeneity, indicating that these results must be carefully interpreted. It is probable that the heterogeneity was due to different settings, inclusion criteria and reference standards. The absence of chest wall tenderness was highly sensitive for acute MI and ACS (92% and 94% respectively), although it was not specific (36% and 33%, respectively). Oppressive chest pain with a pooled sensitivity of 60% and specificity of 58% had almost no influence predicting the likelihood of an acute MI. Other symptoms had even less influence on predicting the likelihood of an acute MI indicating that they could not be used to exclude an acute MI or ACS. Presentation with presence of chest wall tenderness (pain on palpitation) was found to be the only symptom that may rule out the probability of an acute MI or ACS, as indicated by NLRs of 0.23 and 0.17, respectively). However, as found with (Swap, Clifford J. and Nagurney, John T., 2005), overall the results of the meta-analyses suggest that in isolation components of the clinical history and signs and symptoms are not helpful in the diagnosis of acute MI and ACS. Differences in PLRs and NLRs for the individual components between the two systematic reviews may have resulted from different selection criteria for study inclusion. For example, one systematic review excluded studies with less than 80 patients, and included studies that recruited patients with acute MI and / or ACS (Swap, Clifford J. and Nagurney, John T., 2005). The second systematic review differentiated the data from those studies in selected patients (recruited by cardiologists or in the coronary care unit) and unselected patients (selected by general practitioners, paramedic or emergency department staff). No information was given on the minimum number of patients required for inclusion, and studies that were only in patients with acute MI were excluded (Bruyninckx, R., Aertgeerts, B., Bruyninckx, P. et al, 2008).