The diagnosis of Chronic Pancreatitis

1. Background
The diagnosis of chronic pancreatitis (CP) is challenging. Chronic pancreatitis is a disease process consisting of: fibrosis of the pancreas (potentially leading to a combination of exocrine and endocrine insufficiency); usually accompanied by severe pain; and increased cancer risk. The problem with such a definition, however, is that patients can also be symptom free. Further complicating the diagnosis of chronic pancreatitis is the fact that it can develop in a range of patients including a history of alcohol excess or patients with a family history of the disease, but can also develop in otherwise well patients with no apparent explanation (idiopathic).

Due to the variety of phenotypes, the diagnosis of this disease is difficult. The nearest thing to a gold standard of diagnosis is histology, however this is not appropriate to obtain in the vast majority of cases (unless there is also a differential diagnosis of neoplasia suspected) and would only normal be obtained in the most extreme phenotypes.

Several different modalities are used to help diagnose CP including imaging and pancreatic function tests.

In summary there is no consensus about how to diagnose chronic pancreatitis. This review sets out to evaluate all the different modalities available to diagnose CP and how they compare to one another.

2. Objectives of the Review
To summarise the best evidence on the most appropriate methods of diagnosing chronic pancreatitis in humans.

Secondary Objectives:
The following question will also be considered:
Does the diagnostic criteria differ across different aetiologies?
Criteria for inclusion and exclusion of studies in the review
Studies included in the review must contain the following elements:

Inclusion Criteria

Modality: The review is of the diagnosis of chronic pancreatitis (CP) in patients with a suspicion of the disease rather than the differentiation of mass forming CP from cancer. Examples of modalities may include the following (note that this list is not necessarily exhaustive).

1) Clinical history
2) Biomarkers
3) Abdominal X-ray
4) US
5) CT
6) MR/MRCP
7) EUS
8) ERCP
9) Pancreatic function tests (PFT)
10) FNA/Core biopsy/histology

Time and place: Studies produced at any time will be included in the search. Only English language studies will be included.

Study Participants: all adult (18 years or over) patients with suspected chronic pancreatitis of any aetiology.

Outcomes: included studies must contain some measurement of how the modality has impacted on the diagnosis of CP, whether it be in isolation or a comparison of different modalities. Examples of outcomes may include the following (note that this list is not necessarily exhaustive).

1) measured impact on the elucidation of aetiology
2) measured impact on diagnosis of chronic pancreatitis
3) relative improvement in diagnostic accuracy compared with another modality
4) relative improvement in diagnostic accuracy compared with another scoring system within a modality
5) inter-observer agreement of modality

Study Design.

1) Randomised control trials
2) Case control studies
3) Cohort studies
4) Retrospective or prospective studies

Note: data may be quantitative or qualitative

Only original articles – abstracts and reviews may be used to direct to further work but will not be used as part of the analysis

Exclusion Criteria

1) studies that do not attempt to measure diagnostic value of a test
2) general discussion papers not presenting data on diagnosis
3) studies in which the aim is not to diagnose chronic pancreatitis
4) studies relating to disease processes in animals

**Search Strategy**

Academic research and guidelines will be all targeted. Electronic searches will involve the electronic databases and search terms listed below. The initial selection criteria will be broad to ensure that as many studies as possible are assessed as to their relevance to the review. Any articles that are obviously unsuitable can be excluded in the early stages or the search (for example, on the basis of abstracts and titles presented in electronic catalogues), whilst the decision to exclude or include other articles will only be made once the article has been ordered and read. The number of articles included and excluded at the various stages will be noted. At the same time, we will be conducting follow-up searches on citations found in other studies.

**Electronic Search Strategy**

The following electronic databases will be searched from start date of 1st Jan 1980 to 31st December 2012: MEDLINE (PubMed), Web of Science, and Cochrane Central Register of Controlled Trials & Database of Systematic Reviews (CENTRAL).

**Search Terms for Electronic Databases.**

The following terms (with wildcards when necessary) will be used when devising search strategies for electronic databases. The exact search terms and their results will be recorded as the search strategy is refined. The basic search terms used will be:

- chronic pancreatitis[Title] AND ((imaging OR etiolog* OR aetiolog* OR clinical OR history OR abdominal x-ray OR tube OR tubeless OR CCK OR CT OR topography OR tomography OR ultrasound* OR US OR USS OR endoskop* OR EUS OR ercp OR magnetic OR MR OR MRI OR mrcp OR function OR PFT OR faecal elast* OR fecal elast* OR secretin OR Ca199 OR CA-199 OR Ca19.9 OR biomarker* OR guideline*) AND (diagnose* OR diagnostic* OR diagnosis*)) – filter English AND Human

modified as necessary according to database. Searches will be restricted to only human studies. Publications between 01/01/1980 and 31/12/2012 will be included. Abstracts can be used to direct the researchers to further work produced by the authors, but will not be included themselves in the analysis.

A ‘search diary’ will be maintained detailing the names of the databases searched, the keywords used and the search results. Titles and abstracts of studies to be considered for retrieval will be recorded on Endnote, along with details of where the reference has been found. Inclusion/exclusion decisions will be recorded on that database. Retrieved studies will be filed according to inclusion/exclusion decisions.

**Selection Procedure:** See Figure 1. Studies will be selected for retrieval after abstracts and titles identified in electronic searches have been appraised by the information scientist and lead reviewer for relevance (note that abstracts and titles that clearly have nothing to do with chronic pancreatitis will be excluded by the researchers). All references provided by expert contacts will also be retrieved. All retrieved studies will be examined by the lead reviewer who will exclude any that make no reference to diagnosis of chronic pancreatitis or no reference to impact of modalities. Studies that do make a reference to one or more modalities in the diagnosis of CP will be assessed for relevance independently by two reviewers.
Figure 1: Flow diagram of study selection procedure

Data Management: At least two reviewers will insert abstract data for each article onto a proforma and independently summarise what they consider to be the most important results from each study. These summaries will be compared by the two reviewers and any differences of opinion will be resolved by discussion and consultation with the original manuscript. Any further calculations on study data considered necessary will be conducted by the lead reviewer and checked by a second reviewer. The following data will be recorded on the proforma:

- First author of report
- Year of publication of report
- Study design (prospective or retrospective; cross-sectional studies or randomised clinical trials)
- Total number of patients
- Mean age of the participants
- Aetiology of pancreatitis
- Criteria for diagnosis of CP
- Index test being assessed
- Reference standard to assess test against
- True positive, false positive, true negative, and false negative data

4. Compilation of data
When the different aspects of the paper are brought together this should be done with the AGREE II tool in mind to ensure that the recommendations drawn from the contributing studies are forming appropriate opinions that would be suitable for the use in future guidelines.

The studies are expected to be of an extremely heterogenerous nature we will initially employ a narrative synthesis method. However, if a subset of data appears to be amenable to a more formal meta-analysis technique, this will be explored. In such an eventuality the conclusions of our narrative synthesis would be compared with the conclusions of such a meta-analyses to see if there any inconsistencies and potential biases.

For the narrative synthesis, the studies will be grouped by intervention type. The methodologies and results of studies belonging to both the same intervention and outcome category will then be compared to see if there is any association between methodological features and results. The results will then be discussed with appropriate emphasis given to the studies that are more methodologically robust. The results will also be tabulated in a way that demonstrates the methodological robustness of each study. The narrative will be written by the lead reviewer and then checked independently by two other reviewers who will then feed back with comments. Any disagreements will be decided by the whole team.