NCCHTA

09 July 2008

Draft protocol for the rapid review of screening for fragile X syndrome

A. This protocol is provisional and subject to change

B. Details of the review team

Lead reviewer and corresponding author:

Sleightholme, Vicky, Ms[1]	Systematic Reviewer
Other members:	
Song, Fujian, Dr[1]	Senior Research Fellow
Stirling Bryan, Dr[2]	Senior Lecturer in Health Economics
Barton, Pelham, Dr [2]	Lecturer in Mathematical Modelling
Fry-Smith, Anne, Ms[3]	Information Specialist

Addresses:

1 West Midlands Development and Evaluation Service
Department of Public Health and Epidemiology
University of Birmingham
Edgbaston
Birmingham
B15 2TT
Tel: 0121 414 3030
Fax: 0121 414 7878
E-mail: H.V.Sleightholme@bham.ac.uk; F.Song@bham.ac.uk

2 Health Services Management Centre
University of Birmingham
Park House
40 Edgbaston Park Road
Birmingham
B15 2RT
Tel: 0121 414 3170
Fax: 0121 414 7051
E-mail: P.M.Barton@bham.ac.uk

3 Aggressive Research and Intelligence Facility
Department of Public Health and Epidemiology
University of Birmingham
Edgbaston
Birmingham
B15 2TT
Tel: 0121 414 6769
Fax: 0121 414
E-mail: A.S.Fry-Smith@bham.ac.uk

C Full title of the research question

What are the clinical effectiveness and cost effectiveness of different strategies for screening for fragile X syndrome? What are the practicalities and patient acceptability of the different strategies for screening in a UK setting?

D Clarification of the research question and scope

Fragile X syndrome
Fragile X syndrome is an inherited disorder that causes learning difficulties and developmental delay, and is the second most common cause of learning disability after Down's syndrome[1,2]. The disorder affects an estimated one in 4000 males and one in 8000 females, and has a tendency to be more severe in males, who may not be able to live independently as a result of the symptoms[1,2]. There is no cure for fragile X syndrome and management of affected individuals is through specific educational and psychosocial interventions, and treatment of any clinical symptoms[1,2].

The disorder displays an unusual inheritance pattern, and the severity of the disorder can increase over generations within a family. This observation was explained following the discovery of the causative gene, *FMR1* in 1991[3]. This gene contains a variable trinucleotide repeat, cytosine-guanine-guanine (CGG), which can become unstable over successive generations[1,2]. The number of CGG repeats within a gene will determine whether the individual has a premutation ('PM', approximately 55-200 repeats), or a full mutation ('FM', 200 repeats and over) [1,2]. The premutation can become unstable on female transmission, and the risk of expanding to a full mutation will depend upon the number of repeats in the maternal allele (and other unknown factors?). A full mutation leads to the development of fragile X syndrome in all male offspring and about 50% of female offspring[1,2].

The complex genetics of this disorder, and the uncertainty regarding the risk of expansion of CGG repeats of differing sizes, may lead to difficulties in communicating inheritance and risk information in counselling situations[1,2].

Screening strategies
Routine screening for fragile X syndrome is not currently available in the United Kingdom; however, limited neonatal screening and screening of relatives of affected individuals ('cascade screening') is carried out in many UK genetics centres[1,2].

The purpose of screening is to identify women at high risk of transmitting the fragile X mutation to any offspring, and/or to diagnose affected individuals at an early stage in order that they may achieve the maximum benefit from management interventions[1,2].

Options for population and targeted screening for fragile X have been the focus of two previously published HTA reviews[1,2] (Appendix: comparison of major features of the two HTA reports). However, these reached contrasting conclusions and recommendations for further research. Of the possible models for screening for fragile X syndrome, the different approaches recommended by the two HTA reviews were pre-natal screening of all apparently low risk women, and cascade testing of high-risk women following systematic case finding.

Current molecular diagnostic methods utilise DNA amplification technology (polymerase chain reaction, PCR), with the addition of Southern blotting in about one third of women to detect CGG repeats in the *FMR1* gene[1,2].

The costs of screening are psychosocial, especially in terms of anxiety, as well as financial, and the feasibility and acceptability of any screening strategies need to be addressed in view of this[1,2].

Previous estimates of the financial cost of screening for fragile X syndrome have varied, and have often been based upon the unrealistic assumption of 100% uptake[1,2].

The annual cost to the NHS of managing a moderately affected adult was estimated to be approximately £20,000 (1995 data)[2]. Thus a reduction in the number of births of children with fragile X syndrome will reduce the costs required for managing such patients. Other benefits of screening for fragile X syndrome may include the reduction of anxiety in women with normal testing results, a possible improvement in the management of patients with fragile X syndrome, and improved quality of life for parents and other family members.

The UK National Screening Committee does not currently support a national screening programme for fragile X syndrome, but the committee wished to review this position following the publication of the two HTA reports on screening for fragile X syndrome. However, further research is required to consolidate the existing evidence, and to provide effectiveness and economic information on pre-natal screening and systematic case finding to inform the possible development of fragile X syndrome screening strategies.

Thus, the principal objectives of the proposed review are as follows:

1. To compare the effectiveness of different screening strategies (e.g, pre-natal screening, systematic case finding, and preconceptual screening).
2. To estimate the costs associated with different strategies for screening fragile X syndrome.
3. To summarise available evidence about the feasibility and acceptability of different strategies.
4. To answer the above questions (i) by providing an overview and update of the existing reviews, and (ii) by establishing a model for estimating effectiveness and costs of different strategies.

Other existing evidence

A scoping search carried out for this review has identified one protocol[4] in The Cochrane Library, which is expected to be published later this year. A review by Agence d'Evaluation des Technologies d'Intervention en Sante[5] (AETMIS) has also been identified (this is written in French but the English version will become available soon).

E Report methods

General
This review will follow the principles described in the West Midlands Development and Evaluation Service handbook[6] and in CRD's Guidance for those carrying out or commissioning reviews[7].

According to the protocol for the Cochrane review on screening for fragile X syndrome[4], randomised studies will be included. Clearly, RCTs can provide the most valid evidence about effectiveness of different screening strategies. However, we feel that there may be a lack of evidence from RCTs. Therefore, we may have to mainly rely on data from observational or laboratory studies. A preliminary assessment of the two HTA reports suggests that modelling approach is useful to synthesise data from various sources in order to answer the specified questions.

In general, we first plan to conduct a thorough assessment of published reviews, to bring together and **update** the findings of two previous HTA funded reviews (and other relevant reviews) on screening for fragile X syndrome. Then, efforts will be focused on the development of a model that can be used to synthesise data from various sources, to estimate cost-effectiveness of different strategies, and to conduct sensitivity analyses according to different assumptions.

Search strategy
Relevant papers will be identified using:
(i) Electronic databases: MEDLINE, EMBASE and Science Citation Index.
(ii) Citation lists of included papers.
(iii) Clinical experts, who will be contacted to identify unpublished data.
(iv) Abstracts of relevant conference and symposia proceedings will be searched.
(v) Handsearching of appropriate journals. Those journals publish relevant papers most frequently will be regarded as appropriate.

The search strategy will be broad and the MeSH subject headings and keywords used will cover all aspects of fragile X syndrome, different terms for fragile X syndrome (such as Martin-Bell syndrome), screening and surveillance. Costs and quality of life data will also be sought using appropriate MeSH headings and keywords.

The two previously published HTA reviews included searches up to 1996[1] and August 1995[2] (for the psychological data; the dates for the remainder of the review were unclear). The searches for this review will be carried out from 1991 and up to 28 September 2001, as this will identify papers appropriate for the modelling since the identification of the causative gene in 1991, and will also allow an update of the two previous HTA literature searches.

Experts in the field will be contacted to identify any grey literature, unpublished or ongoing studies. (Do we need to contact industry for identifying unpublished studies they sponsored?)

Inclusion and exclusion criteria
Relevant studies of all designs will be considered for inclusion in the review. A study will be considered relevant if it is about:

- performance of diagnostic tests for fragile X syndrome, including DNA amplification technology and Southern blotting.
- prevalence of fragile X syndrome
- frequency of PMs and FMs
- risk of expansion from PM to FM, and associated factors
- outcomes of screening for fragile X syndrome
- costs of screening for fragile X syndrome
- costs of managing patients with fragile X syndrome
- quality of life of patients of fragile X syndrome and their carers.
- feasibility and acceptability of screening for fragile X syndrome
- modelling of screening for fragile X syndrome

There will be no language restrictions.

Data extraction strategy
Two reviewers will independently extract data using a structured, piloted data extraction form. Any discrepancies will be resolved by discussion. Translations of non-English language papers will be obtained where appropriate.

Data extraction forms will be designed according to type of studies, and data required. For example, data may be extracted under the following headings:
- Baseline comparability characteristics of the study and control populations
- Details of the screening intervention(s)
- Outcome measures and methods of assessing the outcomes
- Results of the study, including the extraction of raw data where possible, in addition to summary measures.

Quality assessment strategy
The validity of included study designs will be assessed by two independent reviewers and will assess aspects of the studies' design. The validity will be assessed in terms of any biases in the design, and the generalisabilty of the study population to the target population.

Methods of analysis and synthesis
The characteristics, quality and results of identified studies will be presented in the form of summary tables and a qualitative summary. Where the information is available, and the studies are sufficiently homogeneous, data will be quantitatively pooled to obtain summary estimates of effect.

Modelling for cost-effectiveness and impact of different screening strategies

Firstly, we plan to conduct a thorough assessment of published reviews. From this assessment of existing reviews (and new studies that have not been included in the previous reviews) we will be able to obtain a good summary of available evidence, the structure and assumptions used in the existing models[8,9,10].

Efforts will then be focused on the development of a model that can be used to synthesise data from various sources, to estimate cost-effectiveness of different strategies, and to conduct sensitivity analyses according to different assumptions. The model is likely to be a state-transition (Markov-type) model, showing how the numbers of people in various states changes over time. We intend to implement it using Microsoft Excel. We expect that the model can be used to estimate multiple outcomes from different screening strategies, and to estimate short-term and long-term (e.g., >10 years) consequences of different screening strategies.

F. Project Management

a. Timetable/milestones

The project timetable and milestone dates have been agreed amongst the review team, and where relevant with the NCCHTA, and are as follows:

Draft protocol submission	**31 August 2001**
Finalised protocol submission	**21 September 2001**
Final searches complete	28 September 2001
Assessment of existing reviews complete	31 October 2001
Summary of existing reviews and new evidence complete	16 November 2001
Progress report submission	**7 December 2001**
Modelling complete	25 January 2002
Draft report ready for peer review	22 February 2002
Draft final report submission	**22 March 2002**

b. Competing interests

Members of the review team declare no competing interests.

c. External reviewers

The protocol and draft report will be subject to external peer review by at least two experts. These reviewers will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. Where the review contains data that is regarded as 'academic or commercial in confidence' we will require peer reviewers to sign a copy of a Confidentiality Acknowledgement and Undertaking. We will return peer reviewers' signed copies to NCCHTA. Comments from external reviewers and our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval. We are contacting following experts, asking them to be advisors to this rapid review:

- Dr Angela Barnicoat
  Consultant Clinical Geneticist, Institute of Child Health, London.
- Professor Howard Cuckle
  Professor of Reproductive Epidemiology, the University of Leeds
- Dr Jenny Morton
  Consultant Clinical Geneticist, Birmingham Women's Hospital.

G. References

1. Murray J, Cuckle C, Taylor G, Hewison J. Screening for fragile X syndrome. *Health Technol Assess* 1997;**1**(4)

2. Pembrey M, Barnicoat A, Carmichael B, Bobrow M, Turner G. An assessment of screening strategies for fragile X syndrome in the UK. *Health Technol Assess* 2001;**5**(7)

3. Verhherk A, Pieretti M, Sutcliffe J, Fu Y, Kuhl D, Pizzuti A, *et al*. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell* 1991;**65**:905-14.

4. Kornman L, Chambers H. Pre-conception and antenatal screening for the fragile site on the X-chromosome (Protocol for a Cochrane review). In: The Cochrane Library, Issue 3 2001. Oxford: Update Software.

5. Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante. Fragile X syndrome: the place of molecular diagnosis and screening within an integrated service approach (details to be confirmed). CCOHTA newsletter. 2001.

6. Burls A, Cummins C, Fry-Smith A, Gold L, Hyde C, Jordan R, *et al*. West Midlands Development and Evaluation Service (DES) Handbook. Version 2.2. 8. Birmingham: University of Birmingham; 2000

7. NHS Centre for Reviews and Dissemination. Undertaking Systematic Reviews of Research on Effectiveness. CRD's Guidance for those Carrying Out or Commissioning Reviews. CRD Report 4. The University of York: NHS Centre for Reviews and Dissemination; 2001

8. Morton N, Macpherson J. Population genetics of the fragile-X syndrome: multiallelic model for the FMR1 locus. *Proc Natl Acad Sci USA* 1992;**89**:4215-7.

9. Sved J, Laird C. Population genetic consequences of the fragile X syndrome, based on the X-inactivation imprinting model. *Am J Hum Genet* 1990;**46**:443-51.

10. Winter R. Population genetics implications of the premutation hypothesis for the generation of the fragile X mentality. *Hum Genet* 1987;**75**:269-71.