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The incorporation of data on pre-analytical and analytical factors in model-based Health Technology Assessments (HTAs) of medical tests: a systematic review protocol

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ABSTRACT

Background: Medical tests are becoming increasingly important in modern health care. As the number of tests coming to the global market continues to rise, Health Technology Assessments (HTAs) will play an increasingly important role in directing test adoption decisions. Assessment of health-economic outcomes within HTAs – most often informed via decision model-based evaluations – have not routinely addressed the impact of pre-analytical and analytical factors on test performance, which can have a significant effect on test outcomes. This systematic review will investigate methods utilised in HTA model-based economic evaluations, to identify if and how data on the impact of pre-analytical and analytical factors on test performance is being assessed.

Methods: The Cochrane HTA database and key HTA authority websites will be searched to identify published papers and reports relating to HTAs of in-vitro tests including a model-based economic evaluation. Title and abstract screening will be conducted by a primary reviewer and 10% independently screened by a second reviewer. Full text screening and data extraction will be conducted by the primary reviewer, with 10% of data extraction independently conducted by a second reviewer. For all included studies, basic characteristics of the study, disease area and test technology assessed will be extracted. For studies identified as including an assessment of pre-analytical and analytical factors, additional data on the type of factors assessed, methods utilised, impact on the cost-effectiveness results and study quality will be recorded.

Discussion: Understanding the methods used in this area will enable identification of key gaps in current methodology and potential avenues for future research. The findings of this work will be disseminated via a peer-reviewed journal publication and at national and international conferences.

Background

Medical tests are becoming increasingly important in modern health care. As well as informing initial diagnoses, tests can help to determine disease severity, identify patient risks and monitor ongoing outcomes. In the wake of the personalised medicine revolution, rising numbers of tests are expected to come to market in the future. As a result, comprehensive and accurate evaluations of the impact of tests on both patient outcomes and healthcare resources will be required in order to inform appropriate test adoption and reimbursement decisions.

The established tool for providing necessary evidence on clinical utility and cost-effectiveness to inform health policy decisions is the Health Technology Assessment (HTA). Whilst HTAs of pharmacological interventions span as far back as the 1970's, evaluations of tests began immerging much later in the 1990's and have only been produced in significant numbers since the turn of the century. Over the past decade, the majority of international HTA authorities have expanded their scope to include the evaluation of diagnostic technologies. In particular, the central healthcare commissioning regulator in England – the National Institute for Health and Care Excellence (NICE) – recently became one of the only authorities to-date to establish specific streams for diagnostic and medical device assessments, and to highlight the need for robust evidence on cost-effectiveness as well as clinical utility in their guidance [1, 2].

Various methodological issues arise within evaluations of tests which are not addressed via traditional HTA methods. In addition to issues concerning literature review methodology, statistical techniques and reporting standards, methods for the health-economic evaluation of tests also require tailoring. Key issues of ongoing development include how to appropriately evaluate cost-effectiveness when there is no gold standard reference test [3-5]; when tests are

used repeatedly (i.e. for monitoring purposes), in sequence or in combination [6, 7]; and when there is uncertainty around the optimal test cut-off level to assign [8, 9].

In addition to these issues, an area of unexplored territory concerns the inclusion of evidence on the impact of pre-analytical and analytical factors on test performance. *Pre-analytical factors* are factors affecting tests which occur up to the point that the test sample is analysed: these include patient biological variation (e.g. age, sex, weight), environmental factors (e.g. temperature and time of day), and technical factors (e.g. method of sample collection and storage) (see Table 1). *Analytical factors* are factors that occur during sample analysis, such as how the sample is prepared and measured and the laboratory environment. All of these factors can have a significant impact on the accuracy of test results, by affecting the concentration of substances within a test sample; depending on the mode of action, this can result in biased and/or imprecise test results [10-14].

Although reviews of economic evaluations of tests have previously been conducted [15-17], none have considered the specific issue of including evidence of pre-analytical and analytical factors. In this review, we will systematically investigate if and how data on the impact of pre-analytical and analytical factors on test performance has been included in HTA model-based economic evaluations of in-vitro tests, and whether the inclusion of this data had a reported impact on the cost-effectiveness results. Understanding the current methods utilised in HTAs will help to identify where methods are lacking and highlight potential avenues of methodological development.

Table 1. Examples of pre-analytical and analytical factors which may affect test performance

Pre-analytical and analytical factors
Patient biological variation (e.g. age, sex, comorbidities)
Patient state (e.g. prior exercise, food/drink intake and medication)
Method of sample collection
Sample collection site
Collection tube
Specimen type (whole blood, plasma or serum)
Method of sample transport
Method of sample storage
Storage temperature
Length of storage
Sample freeze/thaw technique
Sample preparation technique
Sample processing technique
Assay platform
Measurement technique
Laboratory environment (e.g. temperature, humidity)

The aim of this review is to answer the following questions:

(1) Within the context of HTAs, is evidence of the impact of pre-analytical and analytical factors on test performance being included in decision model-based economic evaluations of in-vitro tests?

(2) For those studies that include an assessment of pre-analytical and analytical factors on test performance, what factors were assessed, what methods were utilised and did the inclusion of this data have an impact on the model results?

This systematic review protocol has been reported according to the PRISMA-P reporting guidelines [18, 19].

Methods: Eligibility criteria

Studies will be required to meet all of the eligibility criteria outlined in Table 2 in order to be included in the review. All published HTAs including a model-based economic evaluation and evaluating an in-vitro test across any disease area, population or setting and published since 1999 will be considered. No restrictions will be placed on language in the database search; however, only studies with full texts available in English will be included in the final set of studies.

Table 2. Eligibility criteria

Characteristic	Eligibility criteria
Population:	Any human population
Intervention:	In-vitro test(s) (including diagnostic, screening, prognostic, monitoring and staging tests)
Comparators:	Any
Outcomes:	Any
Setting:	Any
Study design:	Health technology assessment (HTA) including a *de novo* model-based economic evaluation
Publication date:	1999 to present
Language:	Full text available in English
Publication status:	Full report monograph or peer reviewed publication available

In addition to the above inclusion criteria, studies identified as falling into the following categories of interest will be recorded:

i) Methodological studies (i.e. not HTAs) but relevant to the topic of evaluation of pre-analytical and analytical factors within technology assessments.

ii) Publication status 'in process' (e.g. protocol/ abstract publications only) but where the study is expected to meet the inclusion criteria once complete.

iii) Full texts not available in English but where the English title/abstract indicates that the study is highly likely to meet all other inclusion criteria.

Methods: Information sources and search strategies

The review will include the following information sources:

- Cochrane electronic HTA database
- Publications listed on websites of prominent HTA authorities
- Citation tracking of included studies

A draft search strategy for the Cochrane HTA database, informed by the Centre for Reviews and Dissemination guidance [20] is provided in Appendix 1. The strategy will include two core elements: (i) test identifiers, consisting of key MeSH and free text terms intended to identify evaluations of tests; and (ii) an economic evaluation filter, consisting of an adapted version of the AUHE economic evaluation filter which aims to isolate studies including an economic evaluation [21]. Within the Cochrane database, the HTA filter will be selected in order to focus the search on HTAs.

Reports produced by prominent HTA authorities will also be reviewed to identify relevant studies that may not have been published or may not be included in the Cochrane HTA database. In particular, the online records of NICE in England, the Molecular Pathology Evaluation Panel (MPEP) in Scotland, the Agency for Drugs and Technologies in Health (CADTH) in Canada and the Pharmaceutical Benefit Scheme (PBS) in Australia will be searched. For all included studies, citation tracking will be conducted to identify any additional relevant studies from the study references.

Methods: Data management and selection

Records will be stored in and managed using Endnote V 7.2 (Thompson Reuters). Following de-duplication, studies will be selected via a two-stage process. First, records will be screened according to title and abstracts to identify any potentially relevant studies. Second, those

records identified for potential inclusion will be screened according to full texts in order to determine final inclusion. At each stage all records will be screened by one primary reviewer according to the defined eligibility criteria (Table 2). In addition, 10% of records will be independently screened at title and abstract by a second reviewer. In cases where the inclusion status for any record is disputed or unclear, inclusion will be determined by discussion with a third reviewer.

In addition to the listed eligibility criteria, included studies will be categorized according to whether or not they include any discussion or analysis of pre-analytical or analytical factors.

Methods: Data extraction

A data extraction form will be developed and piloted, based on the items listed in Table 3. For studies not including any evaluation of pre-analytical or analytical factors, basic data extraction of key study and intervention characteristics will be conducted. For all other studies, further data extraction will be conducted to obtain information on the types of pre-analytical and analytical factors assessed, the specific methods utilised and the reported impact on the cost-effectiveness results. In addition, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist will be used to assess the overall quality of the economic evaluations [22]. If necessary, additional data or confirmation of data will be sought from study investigators. All data extraction will be conducted by one reviewer with 10% independently checked by a second reviewer.

Table 3. Summary of data extraction elements

Basic data extraction (used for all studies)
First Author
Publication date
Country
HTA authority/ Funding source
Test Intervention(s) assessed
Test Technology type (diagnosis, screening, prognostic, monitoring, staging)
Companion diagnostic (Yes/No)
Disease/illness area
Comprehensive data extraction (used only for studies including an assessment of pre-analytical/ analytical factors)
Specific pre-analytical factors addressed
Specific analytical factors addressed
Factors assessed via narrative discussion only (Yes/No)
Factors assessed via quantitative analysis (Yes/No)
Details of quantitative analysis (if applicable)
Results of analysis
CHEERs quality checklist items

Methods: Analysis and reporting

For all studies, a summary will be provided of the numbers and types of technologies assessed, over what years, in what countries and disease areas, and the proportion of studies identified as including an assessment of pre-analytical or analytical factors.

For studies identified as including an analysis of pre-analytical or analytical factors, the type of factors assessed will be summarized and a narrative synthesis will be conducted to outline the utilized methods and any reported impact this had on the cost-effectiveness results. No quantitative synthesis (i.e. meta-analysis) of extracted data will be conducted.

The systematic review will be reported in line with the PRISMA reporting guidelines [23].

Discussion

Variation in pre-analytical and analytical factors can have a significant impact on test results. This has long been recognised by clinical and laboratory scientists, however historically this data has not been systematically collected, has been poorly reported, or has not been well understood amongst researchers conducting downstream technology evaluations. Thanks to the recent introduction of new laboratory accreditation standards requiring systematic evaluation of the impact of such factors on test results [24-26], there is an increasing amount of data available in this area which could enable more comprehensive technology evaluations. In light of the rising demand for HTAs of tests, there is now an opportunity to ensure that appropriate methods are identified and developed in this area, to ensure that accurate assessments are available to inform appropriate test adoption decisions.

The systematic review outlined in this protocol will help to characterise the current state of HTA economic evaluations of in-vitro tests, focusing on methods used to incorporate data on pre-analytical and analytical factors affecting test performance in decision model-based assessments. Understanding the methods used in this area will enable identification of any key gaps in current methodology, and potential avenues for future methodology development.

Dissemination

Dissemination of the review findings to HTA authorities, health economists and other relevant methodologists will be important in order to highlight current gaps in applied methodology. The findings of this work will be disseminated via a peer-reviewed journal publication and at national and international conferences.

Appendix 1 - Cochrane database draft search strategy

Date Run: 30/01/2017 17:46:44
Description:

ID	Search	[Hits]
#1	MeSH descriptor: [Diagnosis] explode all trees	[293872]
#2	MeSH descriptor: [Reagent Kits, Diagnostic] explode all trees	[346]
#3	MeSH descriptor: [Investigative Techniques] explode all trees	[432008]
#4	MeSH descriptor: [Precision Medicine] explode all trees	[227]
#5	MeSH descriptor: [Biomarkers] explode all trees	[18358]
#6	#1 or #2 or #3 or #4 or #5	[481793]
#7	"in vitro*" or test* or assay* or microarray* or "micro array*" or urinalys?s or ELISA* or diagnos* or biomarker* or marker* or signature* or investigat* or indentif* (Word variations have been searched)	[426216]
#8	monitor* or screen* or prognos* or predict* or diagnos* or stratif* or detect* (Word variations have been searched)	[278898]
#9	(analytic* near/2 valid*) or sensitiv* or specific* or (positiv* near/2 predict*) or (negativ* near/2 predict*) or "true positive*" or "true negative*" or "false positive*" or "false negative*" or ((pre-test* or pretest*) near/2 probability) or ("post test*" near/2 probability) or "likelihood ratio*" (Word variations have been searched)	[128988]
#10	#7 or #8 or #9	[529440]
#11	#6 or #10	[702243]
#12	MeSH descriptor: [Economics] this term only	[63]
#13	MeSH descriptor: [Economics, Nursing] this term only	[19]
#14	MeSH descriptor: [Economics, Pharmaceutical] this term only	[244]
#15	MeSH descriptor: [Economics, Hospital] explode all trees	[1757]
#16	MeSH descriptor: [Economics, Medical] explode all trees	[105]
#17	MeSH descriptor: [Economics, Dental] explode all trees	[10]
#18	MeSH descriptor: [Costs and Cost Analysis] explode all trees	[24985]
#19	MeSH descriptor: [Fees and Charges] explode all trees	[505]
#20	MeSH descriptor: [Budgets] explode all trees	[71]
#21	MeSH descriptor: [Value of Life] explode all trees	[146]
#22	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees	[4154]
#23	MeSH descriptor: [Quality of Life] explode all trees	[18736]
#24	MeSH descriptor: [Models, Economic] explode all trees	[2008]
#25	MeSH descriptor: [Markov Chains] explode all trees	[2154]
#26	cost* or pharmacoeconomic* or pharmaco-economic* or economic* or price* or pricing* or budget* or eq5d* or eq-5d* or euroquol* or euroqol* or euroqual* or euro-quol* or euro-qol* or euro-qual* or finance* or financial* or fee or fees or "economic model*" or markov* or "quality adjusted life" or qaly* or qald* or qale* or qtime* or "disability adjusted life" or daly* or SF6D or "sf 6d" or "short form 6d" or shortform6d or "health* year* equivalent*" or hye or hyes or "health utilit*" or hui or hui1 or hui2 or hui3 or disutil* or "standard gamble*" or "time trade off" or time tradeoff or tto or (value near/2 money) or (value near/2 monetary) or hql or hqol or "h qol" or hrqol or "hr qol" or pqol or qls (Word variations have been searched)	[90923]
#27	Cost* near/2 (effective* or utilit* or benefit* or minimi* or evaluat* or analy* or study or studies or consequenc* or compar* or efficienc*) (Word variations have been searched)	[41776]
#28	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27	[103988]
#29	#11 and #28	[87293]
#30	#29 in Technology Assessments	[2036]
#31	#30 Publication Year from 1999 to 2017	[1908]

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