Improved methods and actionable tools for enhancing HTA

D11.1 WP 11

A systematic review of decrementally cost-effective health technologies and case studies

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Executive Summary

Background: HTA guidance has been mostly driven by situations where innovative and usually more expensive technologies are compared to the prevailing standards of care. Cheaper and less effective interventions have usually received scarce attention, although for several reasons strategies with minimal individual benefit losses might produce collective health gains.

Objectives and methods: This systematic review of health economic evaluations aims to identify interventions in the south-west quadrant of the cost-effectiveness plane to procure a list of candidate decrementally cost-effective (d-CE) technologies. It provides the primary evidence necessary to support the development of a toolbox for local HTA projects for implementation of d-CE strategies. European Health Authorities' decisions for a subset of these candidate technologies were reviewed. The obstacles and the potential drivers of implementation from the different stakeholders' perspectives were documented.

Findings: After filtering 3,689 studies found through a systematic review, 94 d-CE health technologies (HT) were identified. Nearly a third were services (n=29) and nearly a third were drugs (n=27). Only one non-pharmaceutical intervention (NPI) was identified and it seems that economic data for NPIs is rare. Seven HTs were selected from the list of d-CE technologies in order to focus on the decisions made by HTA agencies and medical associations. Among these, two were selected in order to perform budget impact analyses that explore the potential opportunity cost that could be generated by implementation of d-CE interventions. For example, the budget savings over a three-year period following an increase in prescription of conventional DMARDs for Rheumatoid Arthritis would be €51 million from the perspective of the French Social Health Insurance for an average loss of 0.017 QALYs.

Action: The next steps for WP11 are to carry out a systematic inquiry using a multinational Discrete Choice Experiment (DCE) to ascertain different stakeholders' perspectives and propose a d-CE threshold. Using the technologies identified in this report (D11.1), the pros and cons of each type of priority-setting situation will be reviewed in the light of HTA recommendations and in sociological, ethical or legal literature. The full results will be synthesised into a toolbox and will include guidance for implementation including public and patient involvement (PPI).

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Glossary

ACBT	Active cycle of breathing techniques
AD	Antidepressants
AIFA	Italian Medicines Agency
ART	Antiretroviral therapy
bDMARD	biological Disease-Modifying Anti-Rheumatic Drug
BIA	Budget Impact Analysis
BMI	Body Mass Index
CBA	Cost benefit analysis
CCG	Clinical Commissioning Group
CEA	Cost effectiveness analysis
CNAMTS	National Health Insurance Fund for Employees
COPD	Chronic Obstructive Pulmonary Disease
csDMARD	conventional synthetic Disease-Modifying Anti-Rheumatic Drug
CT	Cognitive Therapy
CUA	Cost utility analysis
DAS28	Disease Activity Score for rheumatoid arthritis
d-CE	Decrementally Cost-Effective
DCE	Discrete Choice Experiment
DCER	Decremental Cost-Effective Ratio
DRG	Diagnostic related Groups (GHM in French)
EACS	European AIDS Clinical Society
EE	Economic Evaluation
EGFR-TKI	Epidermal growth factor receptor tyrosine kinase inhibitor
EU	European Union
EUnetHTA	European network for health technology assessment
GBD	Global Burden of Disease
H2020	Horizon 2020
HIV	Human Immunodeficiency Virus
HT	Health Technololgy
HTA	Health Technology Assessment
ICER	Incremental Cost-Effective Ratio
ICUR	Incremental Cost-Utility ratio
ITT	Intention to treat

MBCT	Mindfulness-Based Cognitive Therapy
MCP	Manual Chest Physiotherapy
Medic'AM	Monthly and annual data on French Social Health Insurance drug reimbursements
MEDLINE	Medical Literature Analysis and Retrieval System Online (health sciences bibliographic database)
nAMD	Neovascular age-related macular degeneration
NIHR	National Institute for Health Research
NNR	Number Needed to Read
NPI	Non-pharmaceutical interventions
NSCLC	non-small-cell lung cancer
OA	Osetoarthritis
OKS	Oxford Knee Score
PCS	Physical Component Summary
PI	Protease inhibitors
PMSI	Programmation de médicalisations des systèmes d'informations (French National Hospital Accounting Database)
PP	Per protocol
PPP	Purchasing Power Parities
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
QALY	Quality-adjusted life year
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial
RTD	Research and Technological Development
TKR	Total Knee Replacement
TT	Triple Therapy
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organisation
WP11	Work package 11 of the H2020 Impact HTA project
WTA	Willingness to Accept
WTP	Willingness to Pay

I Background and objectives

Since the 1970s Health Technology Assessments (HTAs) have been increasingly used to evaluate the benefits and costs of Health Technologies (HTs). Against a background of increasing demands on limited resources, HTAs have a growing impact on health policy.

The typical situations met in HTA consist of incremental innovations that are characterised by cost and quality enhancements. These belong to the north-east quadrant of the cost-effectiveness plane. An undesirable consequence of this use of cost-effectiveness is the failure to implement HTs that would increase overall health gain by being less effective in the condition concerned, but generate more benefits elsewhere. (1)

As part of the European Union (EU) Horizon 2020 (H2020) project "IMPACT HTA" that aims to improve the effectiveness and efficiency of HT procurement by implementing cross-country collaboration in a range of activities, including Health Technology Assessment (HTA), we have carried out a systematic review of the health economic literature to identify decrementally cost-effective (d-CE) HTs that are associated with a cost and quality reduction profile. These are under-implemented yet they are potentially cost-saving or cost-effective because they allow redistribution of resources. This work comes under the aegis of WP11 of the IMPACT HTA project.

Many interventions exist with a strong rationale for being cost-effective, while at risk of unsuccessful development or implementation, because the case could not be made for their clinical and social value. For example, in 2009, published results of d-CE interventions represented only 0.4% of the articles in a literature review of 887 publications. On a per-patient basis, these innovations yielded savings from $122 to almost $12,000, but losses of 0.001 to 0.021 quality-adjusted life years (QALYs) (2). This is in contrast to the increasing popularity of non-inferiority studies and equivalence studies where the non-inferiority margin or the margin of equivalence represents an acceptable loss of effectiveness on the primary outcome. Regarding decremental cost-effectiveness decisions, the reticence in accepting that a small QALY loss in one area may generate gains in another is not currently accommodated in routine reimbursement decisions and should be addressed and overcome at the policy level. This review focuses on these priority-setting issues where evaluation results are often most difficult to implement.

This report outlines the methods and results of the systematic review with the main objective of identifying evidence on d-CE technologies that have been investigated and published, and to investigate non-inferior or equivalence studies for which economic evidence appears to be unpublished. This systematic review should identify services that are of low added value to individual patients and to the healthcare systems and could be replaced by non-inferior, slightly decremental or complementary options. This systematic review is exempted from ethics approval because the work is carried out on published documents.

II Methods

The review was not restricted to any specific pathology or type of HT.

This systematic review protocol has been registered in PROSPERO (Registration number: CRD42018095504) and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines (3).

At the time of conducting this study, no standard methods existed for the preparation of economic systematic reviews. (4) The Cochrane group oeuvre is considered the gold standard for methodology of systematic reviews and some of their guidelines include information on incorporating economic evidence into a systematic review. However, there was not a comprehensive methodology guideline available at the time of starting this work. After a review of the methods available, we opted for the five-step approach published in the “Expert Review of Pharmacoeconomics & Outcomes Research” journal as a guide for the preparation of our systematic review of economic evaluations (5–7).

Information sources

Systematic electronic searches were conducted using the PubMed bibliographic database (https://www.ncbi.nlm.nih.gov/pubmed) and the Clinical Trials registry (https://clinicaltrials.gov/). Other databases were investigated with non-systematic searches such as Tufts, EuroCT, EbscoHost, CRD York, ISRCTN and EMBASE as well as grey literature, published in English between 1st January 2005 and 14th February 2019. Manual searches were carried out using a snowballing technique and investigating citations found in pertinent articles. We looked for published economic results as well as protocols. Published protocols that include an economic analysis were investigated to link the

protocol to the results, should they have been diffused, or to enable further investigation into potential reasons for not communicating the economic results.

Inclusion criteria

The search was conducted according to the following inclusion criteria:

1. The intervention is being applied to human subjects.

2. Studies to be selected will include full economic evaluations thus comparing at least two HTs: model or trial-based (or mixed), cost-minimization, cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA) or cost-consequence analysis.

3. The interventions will be evaluated in a country defined as an upper-middle-income or high-income economy by the World Bank's 2018 country classification income level.

4. The interventions will be traditional HTs according to the WHO definition - Health technology: "the application of organized knowledge and skills in the form of medicines, medical devices, vaccines, procedures and systems developed to solve a health problem and improve quality of life". (http://www.who.int/health-technology-assessment/about/healthtechnology/en/) and we include NPIs such as physical activity, diet, psycho-social support or patient education.

5. Studies should demonstrate d-CE interventions.

6. Studies should be written in English.

Definition of d-CE

The fifth inclusion criteria, that studies should demonstrate d-CE interventions, would normally require definition of a threshold related to willingness to pay (WTP). Given that our study covers multiple countries that have different criteria for evaluating cost-effectiveness, we did not use a threshold to determine inclusion or exclusion of a study. When the ICER and the ICUR were calculated and a cost-effectiveness plane used to show the uncertainty around cost-effectiveness outcomes, often represented as a scatter plot on the plane corresponding to different iterations of an economic model in a probabilistic sensitivity analysis, we were able to quickly identify that the cloud of points fell mostly in the south-west quadrant. Where this information was not available in

the article, we checked the confidence intervals of the disaggregated data (cost and outcome) to estimate that a cloud would almost certainly be at least 50% in the south-west quadrant.

Whilst this study focuses on technologies with a very strong economic rationale for implementation balanced by a weak medical rational, due to the non-inferior medical benefit, a HT that was found to be non-inferior does not necessarily translate to a d-CE HT as shown in Figure 1. The four examples of results below the dotted line in this figure are for technologies where it can be concluded that they are non-inferior to the comparator which is in general usual care. In the event that the EE demonstrates large potential cost savings, two of these four (the two closest to the x axis) would not result in a DCER since these technologies are actually superior to usual care. The results above the horizontal dotted line have not been shown to be non-inferior, yet there is a possibility that an ICER for two of the examples shown could be of interest given that the point value is within the non-inferiority margin and the confidence intervals are right skewed from the margin value (as shown by Δ). Whilst from a clinical point of view, the classic rules of inference based on using the p-value to demonstrate significance of (in this case) non-inferiority are still applied, these are arbitrary rules and not relevant to the decisions which are informed by health economic evaluations. (8)

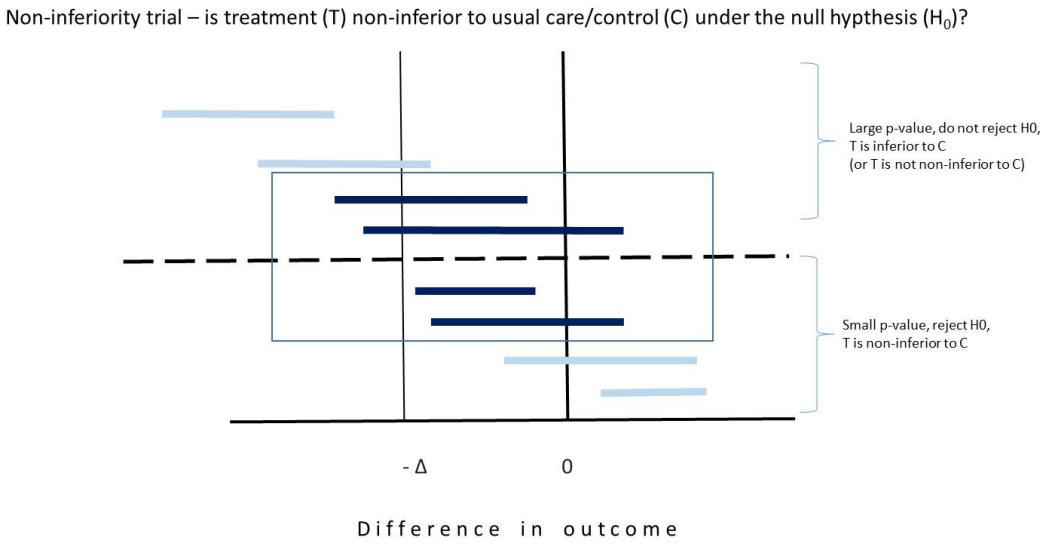

Figure 1 Non-inferiority and decremental cost-effectiveness

However, with respect to decremental cost-effectiveness decisions, there can be difficulty in accepting that a small QALY loss in one area may generate gains in another and this need to be addressed and overcome at the policy level and currently cannot easily be accommodated in routine reimbursement decisions.

Exclusion criteria

Publications reporting on methodological issues, discussion articles, partial economic evaluations, HT being compared to a generic component, comment letters and editorials were excluded. Furthermore, we excluded duplicates found in more than one database. The reasons for exclusion for each study were reported on a PRISMA flowchart. Studies comparing generic drugs to the commercial variety were excluded from the study since HTA agencies or other decision makers do not need convincing that these equivalent, but much cheaper identical molecules, should be prescribed and many campaigns exist to convince the general public of their equivalence. On the other hand, biosimilar products, that are not identical with regard with the original branded drug and that must have their own clinical data and pharmacovigilance, are included in this review.

Search strategy

The search string consisted of two domains: the first domain included terms related to clinical outcomes and the second domain included terms related to economic evaluation.

The first step was to develop multiple terms for each of the two domains eg. “non-inferior” (clinical domain) and “cost” (economic domain). The search strategy included the Boolean terms OR and AND. Database specific filters were used to limit the search to “humans” and for start and end dates of publication or trial completion. After consultation with subject experts, we used controlled terms such as Medical Subject Heading (MeSH) terms (for example, in PubMed). We also used free text terms and truncations (*) in order to conduct the literature search and to maximise results from the searches. Full search strategies are provided in Appendix 1. These search strategies were shared with all IMPACT HTA partners prior to the RTD meeting in Warsaw (January 2019) for peer review and verification of our approach.

Study selection

The review followed a two-stage method. The results of the search strategy in PubMed and ClincialTrials.gov were exported to and managed in Excel files. Study selection was based on the inclusion and exclusion criteria and was carried out in double.

Two reviewers (XC and RS) independently screened titles and abstracts using the inclusion criteria. Following completion of the PubMed review, full text access to EMBASE became available and Rayyan QCRI (http://rayyan.qcri.org) was used to manage the bibliography database hits from EMBASE and by checking for doubles with the PubMed results and facilitating screening d-CE HTs from titles and abstracts by different reviewers (9). This software was selected following searches on the Systematic Review Toolbox. This toolbox is a community-driven, searchable, web-based catalogue of tools that support the systematic review process across multiple domains and is also used by the York Health Consortium (http://www.systematicreviewtools.com/).

Secondly, the full-text version was screened in double by the two reviewers and a final decision made with respect to the inclusion/exclusion criteria.

Any disagreement or conflicting views between the reviewers over the eligibility of specific studies was resolved by discussion or the final judgment of a third reviewer (MD). Both stages of the selection process were piloted and if necessary modified.

The precision and the number needed to read (NNR = 1 / precision) was measured for the PubMed search filter. NNR is an index of how many papers have to be screened to find one of relevance. (10)

ClinicalTrials.gov screening strategy

The search of the ClinicalTrials.gov entailed identifying studies that had non-inferior or equivalence designs and included a planned economic evaluation (EE). Following the initial screening on the title and description, the next stage of the screening methodology involved reviewing the registry entry and ascertaining via internet searches if any economic results had been published for these trials (Figure 2). If any EEs were found, they were then screened with the articles found through the PubMed search to decide whether they should be included or excluded. For trial entries that did not have a published EE, we investigated whether or not a clinical article had been published and if so, reviewed this to see if the results were non-inferior or equivalent in which case the investigators

were contacted. In the event that no clinical paper and no EE could be found, the investigators were contacted with a view to finding out both the clinical and economic results if possible, as well as reasons why the results had not been diffused.

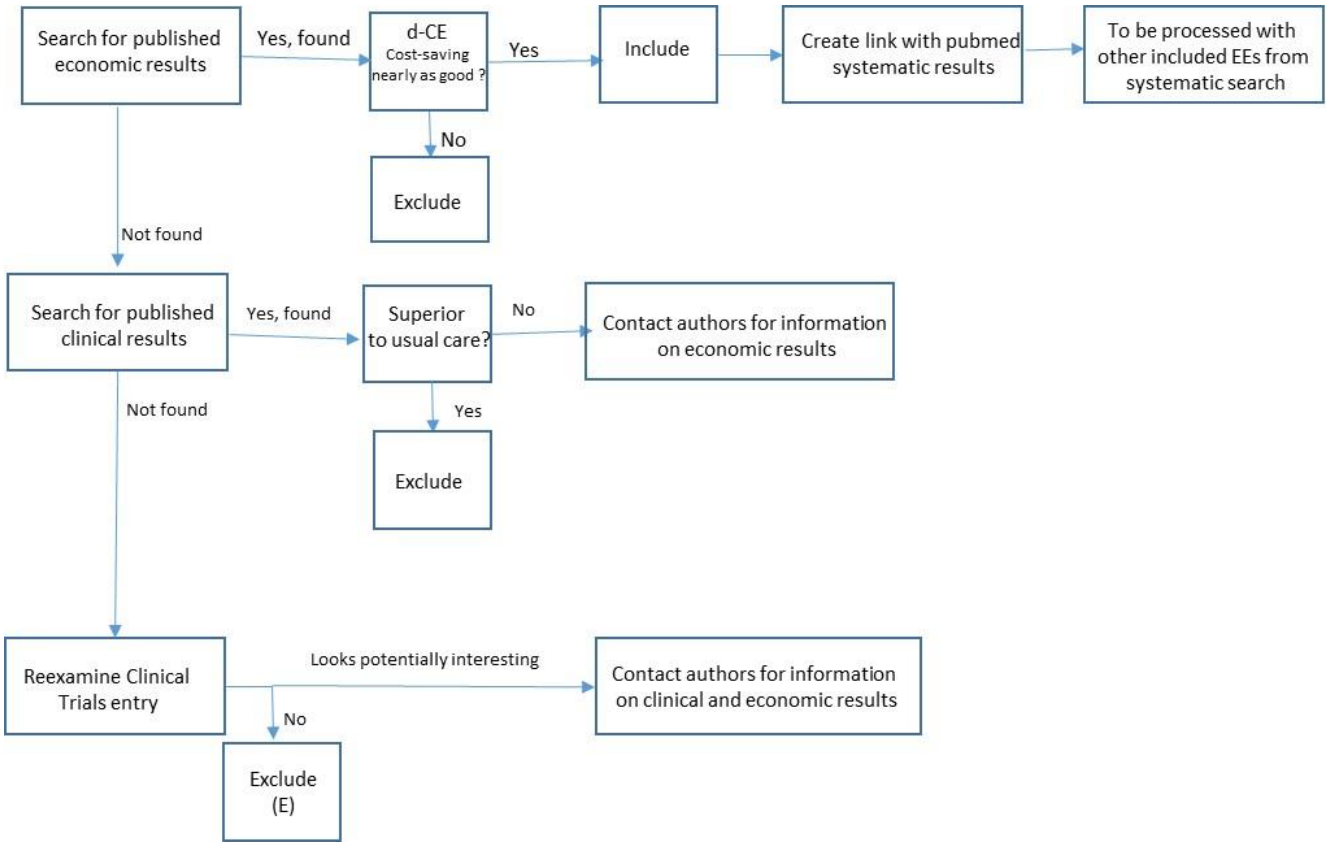

Figure 2 Screening methodology of studies found in ClinicalTrials.org

Data analysis and synthesis

Publication information, study characteristics and findings from the included studies, related to the research question, were gathered in a database form using Excel.

The data extraction list from Wijnen et al (2016) was used as a basis. Other items were included that are directly related to non-inferiority or equivalence trials such as study analysis approach of intention to treat versus per protocol. (11) The data extraction list template can be found in Appendix 2.

In some articles, the decremental cost-effectiveness ratio (DCER) was not given in the text. For these, we calculated the DCER ourselves where possible by dividing the differential cost and the differential effect (QALY, LY, etc) both found in the text.

Given that the different locations, year of study and country-specific elements such as different currencies, the costs were converted into a common currency and price year using the CCEMG – EPPI-Centre Cost Converter as recommended in the 5-step methodology, which enable us to convert the DCER of each article and to adjust it into 2018 euros (€).(12).

Quality assessment, bias and transferability of included studies

There are a number of checklists available to evaluate the quality, bias and transferability of economic evaluations. We reviewed five checklists for quality assessment and three for transferability.

Quality assessment

For quality assessment, we examined the Drummond Checklist (13), Philips checklist (14), CHEERS checklist (15) and the CHEC list (16) and created a final list of quality items to be assessed. Some additional questions were added to address the specific objective of our systematic review into d-CE HTs such as selecting the correct analytic approach of intention to treat (ITT) and/or per protocol (PP). In addition, since a number of choices have to be made at every stage of the process of an economic evaluation, such as perspective, discount rate, costs to include, and these might lead to uncertainty, each trial-based economic evaluation study should include a sensitivity analysis to address this (17). The final list that was used for the screening of the full text articles had 23 questions. In order to calculate a quality score, a value of 1, 0.5, 0 or not applicable (NA) was given to each question. A score of 1 indicated that the reviewer considered that the article fully satisfied the question. A score of 0 indicated that the paper did not satisfy the criteria at all. The score of 0.5 was awarded when it seems that some attempt had been made to address the question, but that it was not completely adequate. NA applied in cases where it was not appropriate to answer the question. For example, if the time horizon was one year or less then discounting would not be carried out and NA was coded. The overall score of the paper was the sum of the scores for each question divided by the number of applicable questions and were calculated as percentages. We

scored papers into 4 quality categories: low (<50%), medium (50-60%), high (60 – 80%) and very high (>80%). A sample of the quality assessments were checked for accuracy by the third reviewer (MD).

Bias

The Cochrane Handbook defines bias as ". . . a systematic error, or deviation from the truth, in results or inferences." (18). Several biases that can be unintentional can occur when performing economic evaluations (EE) and it is important for researchers to minimize these biases, as they can significantly affect economic outcomes. The Bias in Economic Evaluation checklist (ECOBIAS) (19), a 22-item checklist that covers specific biases for model-based economic evaluations (EEs) and trial-based studies EEs, was used to assess the overall risk of bias for the selected studies that had scored very highly in the quality assessment as described above.

Transferability

In the case of economic evaluations, there are many reasons why the cost-effectiveness of HTs might vary from place to place (20). A number of aspects must be customised to country-specific circumstances to attain external validity since the cost-effectiveness criteria may vary according to their resources for health services. Obvious differences will include the unit prices of HTs that are different across jurisdictions, different discounting rates, country specific QALY values as well as the existence or not of an explicit WTP threshold.

Decision makers must acknowledge the importance these and other factors that might affect the transferability of data from one geographic area to another as well as the alternative approaches available for transferring the data, and have in mind that transferring clinical efficacy data is not as challenging as transferring EEs (21).

In addition, there is not full agreement on the gradient or "skewness" of the "WTP threshold" versus the "willingness to accept (WTA) threshold" which could lead to different jurisdictions assigning decrementally cost-effectiveness to a different set of standards. Other issues such as disease prevalence, healthcare budgets and healthcare organisation will affect the transferability of the results of a cost-effectiveness analysis from one country to another.

We used three studies to guide the analysis of transferability for the final list of HT candidates over the European region (20,22,23). However, since this study does not investigate a particular condition or pathology and there are a variety of settings (potentially 28 EU countries) and types of HTs to be

considered, the transferability issue may be beyond the scope of this systematic review. The list of candidate technologies (high-quality d-CE HTs as defined previously in the Quality Assessment section) will be used for discussion with different stakeholders in different settings in the second task of WP11 and thus whilst the data extraction, quality scoring and bias analysis will provide guidance, in the context of this European study and systematic review, transferability analysis of each HT to all 28 EU countries will be limited. What we have tried to assess is the transparency of the EE, that is, ascertaining that the data required to adapt the results to a different setting are reported in the article. Thus, we hope to be able to identify certain key factors, for example, if a simple adaptation such as substituting local prices would be sufficient, or whether further data and modelling would be required.

The three components of quality, bias and transferability had a certain amount of overlap in the questions and we collated the questions and eliminated redundancy from the different sources to create a reduced list that can be found in Appendix 3.

Selection of case studies

From the articles identified through the systematic search, a small sample of HTs was selected for analysis in order to best illustrate implementation issues that may reflect stakeholders willingness to accept a decremental efficacy given prospects of cost reductions or, alternatively, of gains in other attributes of HT such as a better tolerance, another method of administration or a greater certainty about long-term effects. This will be a draft list of case studies and our finding will contribute to the workshop described by milestone 42 (MS42) for IMPACT HTA WP11.

From the list of d-CE technologies, we focused on the decisions made by HTA agencies and medical associations for sample interventions for pathologies that cause significant burden of disease in European countries (such as cancer, mental disorders and cardiovascular diseases) or interventions that were shown to be highly d-CE. We carried out a literature review and looked at reports published by EMA, NICE, HAS and guidelines from European medical associations. The aims are to describe the level of recommendation by health authorities of the selected interventions and identify the level of implementation by examining whether or not studies contributed to change clinical practice in the country examined or identify under-implemented technologies. It is intended that the results of the analysis into these case studies will nourish the discussions that will take place

in the workshop with stakeholders and the multinational Discrete Choice Experiment (DCE) that are planned as next steps of WP11.

In addition, we will focus on two under-implemented d-CE HTs in order to perform a budget impact analysis to evaluate at a national level. That is, we seek to answer the following question: if a d-CE HT were gradually implemented over a three to five year period for the eligible population (people with the pathology and with access to healthcare system), how much money could be saved from a societal and/or a payer point of view and at what clinical loss to the study population, or benefit to the overall population? Given the reticence by decision makers and doctors to implement HTs that reduce rather than increase the quality profile, we hope that the value of these case studies would be to show that the annual change in mortality or morbidity would be very slight with respect to the financial savings that would be gained. In the context of a fixed national health budget, these potential financial savings could be translated into QALY gains in other pathologies or populations leading to an overall societal public health gain within this fixed budget.

III Results

Results – published articles

In total, 3,689 studies were found from PubMed, EMBASE, ClinicalTrials.gov and manual searches. The latter included the results retrieved by using the snowballing technique among the rest of databases such as Tufts, EuroCT, EbscoHost, CRD York, ISRCTN. After filtering studies according to the inclusion criteria, we found 94 d-CE HTs as shown in the PRISMA flowchart (Figure 3).

After title and abstract screening of the remaining 3,180 records, 2,795 were excluded. Of these exclusions, 287 were publications that were not d-CE, 47 were not upper-middle-income or high-income economies according to the World Bank's 2018 country classification income level, 13 concerned generic drugs and 2,448 were clinical trial entries that were not relevant. 385 records were assessed for eligibility.

The second screening assessed a total of 269 entries on full text. These entries were economic evaluation (EE) articles, study protocols and abstracts. After this second screening, 72 EE articles were included that were found through the systematic search of PubMed. With respect to the PubMed systematic review, the number needed to screen was 26, meaning that 26 articles had to be

screened in order to identify one of relevance. Thus the precision of the PubMed systematic search was 3.9%.

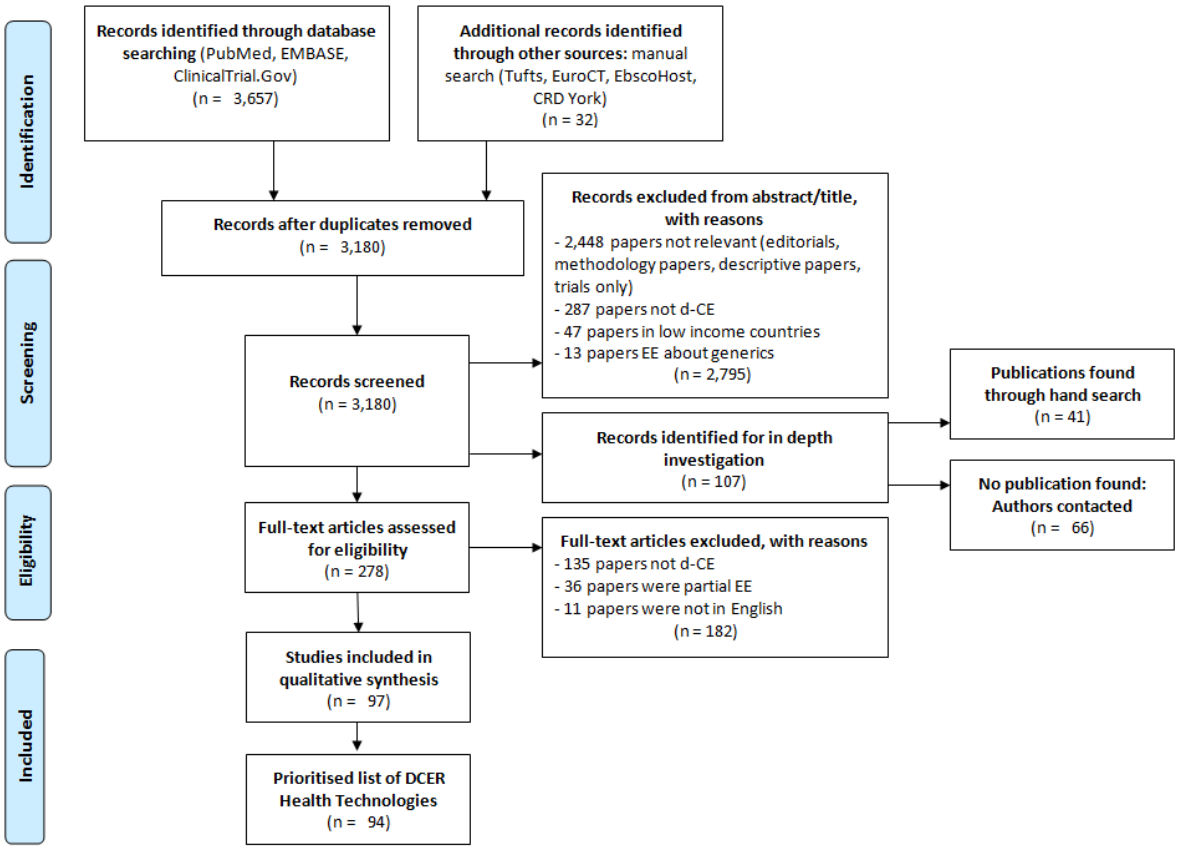

Figure 3 PRISMA Flow Diagram of Study Search and Selection Process

After removing the duplicate studies that had already been found through the PubMed search, EMBASE search identified 44 records and after the second screening, 32 conference abstracts were found. After screening 39 ClinicalTrials.org records and carrying out internet searches to identify linked articles, 20 trials records of potential interest for further investigation were found. Hand searching led to 16 EE article inclusions. Overall, inclusion criteria were fulfilled by 97 economic evaluation articles covering 94 d-CE HTs (Appendix 4). With respect to studies that had been identified as of potential interest (non-inferiority or equivalence registry entries or protocols with economic evaluations planned) 20 trial records and 15 published protocols were identified for which published EEs could not be found.

The scope of the articles varied considerably and not all of the 97 published EEs, representing 94 HTs, reported ICERs or ICURs. Of these 94 HTs, 22 had calculated ICURs and 5 had calculated ICERS. For 37 studies, where QALYs were not calculated, the information was left in disaggregated form. For the remaining HTs, it was possible to calculate the ICUR from the disaggregated data in the article for an additional 30 studies and these calculated ICURs that by necessity do not have a confidence interval are marked with an asterisk in the results table that can be found in Appendix 4. Of the 97 articles, 13 were published HTA reports.

All of the 97 papers were assessed for quality using the checklist (see Appendix 3). In total, 84.6% of the studies evaluated had good or excellent quality scores and only 15.4% had low quality scores. The articles that scored very high or high on quality (n=71) were then evaluated for bias and transferability. Full data extraction was carried out for these high to very quality studies. The quality, bias, transferability detailed checklists for each of these quality articles as well as the data extraction will be made available in the public domain at the end of the H2020 IMPACT HTA study and can be requested from the authors in the meantime.

Nearly a third of the 94 HTs were services (n=29) and nearly a third were drugs (n=27). Only one NPI was found. The papers were almost equally split between new/alternative technologies and strategies that were using the same technology, but were comparing reduction or tapering drug doses, or using a different method of administration of the same molecule, with usual care. The articles came from 76 different journals. The open access NIH medical journal Health Technology Assessment was the only journal to have more than 2 articles in the final results with 10 hits. Sixty-four of the journals were specific to a pathology or medical theme (84%).

Key characteristics of the HTs can be found in table 1. The studies were analysed for the type of pathologies implicated in these d-CE HT results and found that there was a large variety of disease with cancer, cardiovascular disease, respiratory diseases and rheumatoid arthritis being the most frequent. Over half of the studies were publicly funded and were primarily carried out in the USA (n=29) and the UK (n=20) which would seem to reflect the importance and quantity of EE studies in general carried out in those countries. Over half of the EEs were conducted alongside randomised control trials (n=55).

Health Technology Type	n	%
Services	29	31%
Drug	27	29%
Surgery	13	14%
Devices	8	9%
Diagnostic tests	7	7%
Screening	6	6%
Vaccine	2	2%
Watchful waiting	1	1%
Non-pharmaceutical interventions	1	1%
Study design		
RCT	55	59%
Models	29	31%
Non randomised trial	7	7%
Mixed (trial & model)	3	3%
Country		
USA	29	31%
UK	20	21%
The Netherlands	12	13%
Canada	9	10%
France	6	6%
Spain	5	5%
Australia	4	4%
China	2	2%
Others	7	7%
Pathology		
Cancer, pre-cancer	25	27%
Cardiovascular	12	13%
Respiratory diseases	9	10%
Rheumatoid arthritis	6	6%
Diverse (<4 mentions per pathology)	42	45%
Study Funding		
Public	57	61%
Private	18	19%
Mixed	4	4%
Unknown	15	16%

Table 1 Characteristics of the health technology studies

Whilst the cost-effectiveness results of the studies cannot be directly compared due to methodological differences such as the different economic perspectives, different discount rates and different health systems, Figure 4 and table 2 show the ICURs for a sample of the articles found by selecting 16 papers that scored highly in terms of quality for which ICURs were available (either reported in the text or calculated from the disaggregated data) and converted to 2018 euros using the CCEMG – EPPI-Centre Cost Converter to allow better comparison.

One British high-quality paper was not included in this subgroup despite an extremely high ICUR comparing continuous Ranibizumab to off-label use of continuous Bevacizumab for neovascular age-related macular degeneration (nAMD) in the UK (24). The study demonstrated that Bevacizumab would achieve substantial cost savings over Ranibizumab with negligible differences in quality of life, but there was great uncertainty around this finding. This paper will be discussed further in the case studies.

There is a great variety of perspectives in the subgroup of 16 studies. For example, only six of the economic analyses were carried out from the societal perspective and this typically meant an estimation of productivity costs in terms of absenteeism from work and cost of caregiving. The costs estimated rarely included out of pocket payments or private health insurance payments that are very important in some countries despite universal coverage and social health insurance. In this subsample of 16 papers the time horizons also varied considerably – from six months follow up to lifetime extrapolations in the case of modelling studies.

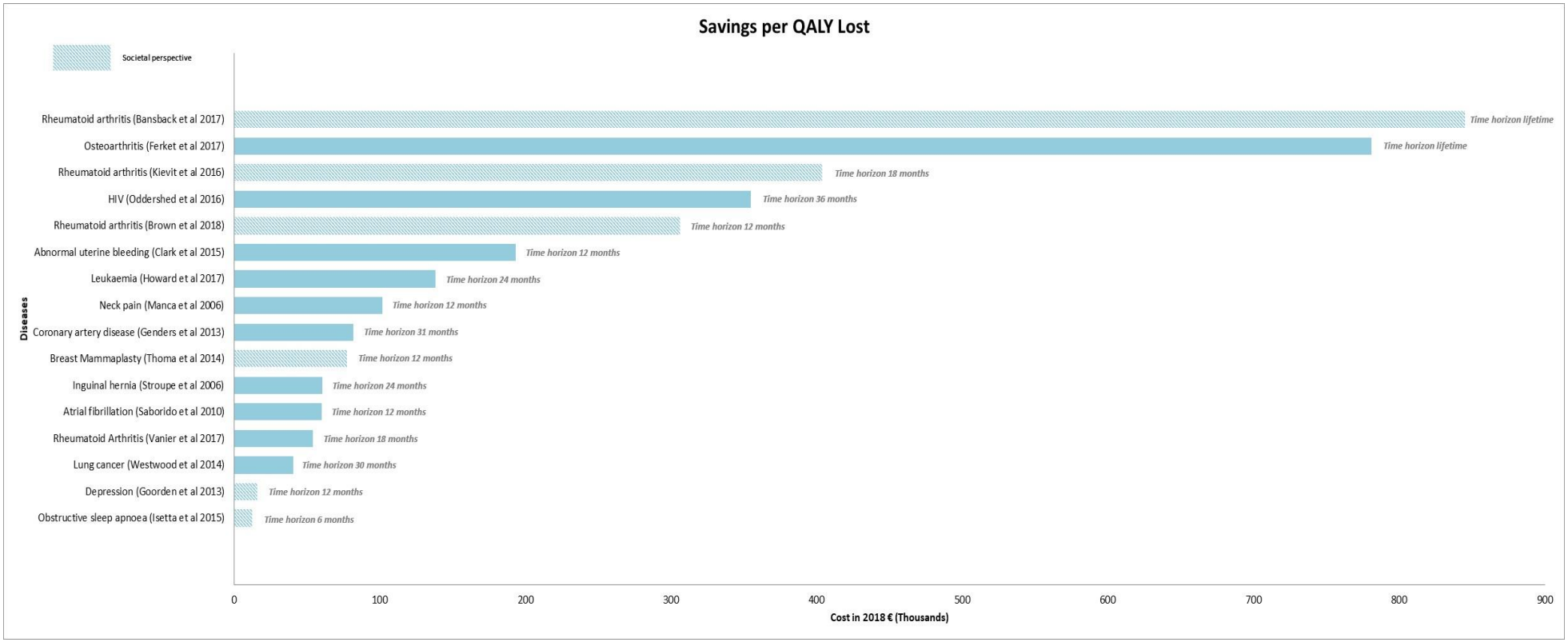

Figure 4 Comparison of ICUR for a sample of 16 top scoring papers in the systematic review

PMID	Author	Year	Country	Disease/Condition	Intervention	Comparator	Effects	DCER (€, 2018)
28554192	Bansback et al	2017	US	Rheumatoid arthritis	Triple Therapy	Etanercept	-0.017 QALYs	€ 845 050 saved per QALY Lost
28351833	Ferket et al	2017	US	Osteoarthritis	TKR <35 SF PCS	TKR to all	-0.008 QALYs	€ 750 936 saved per QALY Lost
26764260	Kievit et al	2016	Netherl.	Rheumatoid arthritis	Dose optimisation	Usual care	-0.02 QALYs	€ 403 977 saved per QALY lost
26966125	Oddershed et al	2016	UK	HIV	PI monotherapy	ART	-0.0227 QALYs	€ 355 018 saved per QALY Lost
29900829	Brown et al	2018	UK	Rheumatoid arthritis	Etanercept/Adalimumab	Abatacept	-0.02 QALYs	€ 306 177 saved per QALY Lost
26240949	Clark et al	2015	UK	Abnormal uterine bleeding	Outpatient	Inpatient	-0.006 QALYs	€ 193 310 saved per QALY Lost
28628003	Howard et al	2017	UK	Leukaemia	FCM-miniR	FCR	-0.059 QALYs	€ 138 180 saved per QALY Lost
16673682	Manca et al	2006	UK	Neck pain	Brief physiotherapy	Usual physiotherapy	-0.001 QALYs	€ 101 830 saved per QALY Lost
22520158	Genders et al	2013	Netherl.	Coronary artery disease	Coronary CT angiography	Standard of care	-0.003 QALYs	€ 81 942 saved per QALY Lost
25255113	Thoma et al	2014	Canada	Breast Mammaplasty	Vertical Scar Reduction	T–Shaped Reduction	-0.01 QALYs	€ 77 739 saved per QALY Lost
17000388	Stroupe et al	2006	US	Inguinal hernia	Watchful waiting	Surgical repair	-0.031 QALYs	€ 60 731 saved per QALY Lost
20569652	Saborido et al	2010	UK	Atrial fibrillation	Pill in Pocket	Continuous therapy	-0.02 QALYs	€60 127 saved per QALY Lost
28407999	Vanier et al	2017	France	Rheumatoid Arthritis	Spacing arm	Maintenance arm	-0.158 QALYs	€ 54 023 saved per QALY Lost
24827857	Westwood et al	2014	UK	Lung cancer	EGFR PCR Kit mutation test	Exon 19–21 test	-0.286 QALYs	€ 40 440 saved per QALY Lost
24085535	Goorden et al	2013	Netherl.	Depression	Collaborative care	Usual care	-0.05 QALYs	€15 798 saved per QALY Lost
26310452	Isetta et al	2015	Spain	Obstructive sleep apnoea	Telemedicine	Usual monitoring	-0.0012 QALYs	€ 12 653 saved per QALY Lost

Table 2 Sample of 16 top scoring papers in the systematic review

Results - unpublished studies

We carried out a systematic search of trials as well as protocols characterized as equivalence or non-inferiority studies and for which an economic analysis was planned. A total of 107 studies were identified as potentially interesting and a more in depth internet investigation was carried out to ascertain if results could be found. Among these conference abstracts, posters, published protocols and ClinicalTrials.gov registry entries, 66 studies were identified for which we could not identify an economic published paper.

In EMBASE four posters and 27 abstracts were retrieved, in ClinicalTrials.gov 20 registry entries were found and in PubMed 15 published protocols were found. For further details, see Appendix 5.

For the studies that had planned to be completed by the end 2017, the first author was contacted to ask if the study article had been published and if so, to request the full manuscript. In case of non-response, the same first author and/or other collaborating authors were contacted a month after the first contact e-mail in order to remind them of the request. A total of 48 authors were contacted and to date we have received 20 replies. For those studies that were not completed by 2017 (n=18) , a further follow-up will take place during the period of the IMPACT HTA project in order to ascertain if the results are d-CE and potentially, find out the reasons for not diffusing the results.

More information can be found in Appendices 5, 6, 7 and 8.

Case-studies

Seven HTs were selected from the list of d-CE technologies (appendix 4) in order to focus on the decisions made by HTA agencies and medical associations for pathologies that cause significant burden of disease in European countries or interventions that were shown to be highly d-CE.

The results for these seven examples are reported in Table 3 and recommendations are updated to the most recent publication available. For these seven d-CE HTs that appear to be economically attractive for conducting cases-studies, the aim is to examine the level of implementation across countries, ascertain if they have become current practice or standard of care and explore the causes of under-implementation. In addition to this review of implementation, we are conducting budget impact analyses for two of the studies that demonstrated the highest potential financial gain based on the ICURs estimated in the articles.

Intervention and Indication	PMID	HTA agencies / Medical association	Decision
1. Triple csDMARDs Therapy *Rheumatoid arthritis*	28554192	EULAR (16) NICE (17) SFR (18)	Recommended in specific cases
2. Rationing access to Knee Total Replacement *Knee Osteoarthritis*	28351833	NICE (19) HAS (20)	NA
3. Bevacizumab *Neovascular age-related macular degeneration*	25079928	EMA (21) NICE (22)	Not recommended
4. Protease Inhibitor monotherapy (Ritonavir boosted) *HIV*	26986803	EACS (23) EMA (24)	Not recommended (recommended only in combination)
5. Manual Chest Physiotherapy *COPD*	20487638	ERS (25)	Recommended in specific cases
6. Erlotinib *Lung Cancer*	21967156	ESMO (26) NICE (27)	Recommended as an option treatment
7. Long-term antidepressants discontinuation (tapering programme) *Depressive and anxiety disorders*	25121977	NICE (28)	Recommended

Table 3 HTA agencies and Medical association guidelines recommendations

Triple csDMARDs Therapy in Rheumatoid Arthritis

Triple Therapy (TT) is a combination therapy with three conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), composed of Methotrexate, Sulfasalazine and Hydroxychloroquine, for patients with Rheumatoid Arthritis (RA).

An American multicentre and double-blind RCT published in 2013 (25) showed that TT is non-inferior to Etanercept–Methotrexate therapy for patients with active RA who have failed csDMARD mono-therapy and found to be highly d-CE in a recent CEA (26), with an average reduction in QALY of -0.017 and cost savings of $977,805 per QALY lost, mainly attributable to the lower drug costs.

TT has been included in most recent international guidelines for treating patients with RA and it can be adopted in case of failure of a therapy with Methotrexate. Both the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) (27,28) recommend considering TT in patients with established RA and good prognostic factors when remission or low disease activity is not achieved with DMARD mono-therapy. The ACR also *conditionally recommends*

TT in patients with early RA to those who demand faster short-term benefit and are willing to accept potential added risk.

For this case-study we have focused on the level of implementation of TT in France and the UK. In France, a large HAS report indicated that the percentage of French patients treated with a combination of three csDMARDs was less than 1% (29). Conversely, a diverse trend has been reported in England. A National Clinical Audit for RA indicated that at least 46% of English patients received a combination of csDMARDs at some point (30).

Several reasons can explain why TT is under-implemented in France. From a clinical point of view, the main issues are related with tolerability and noncompliance to treatment. It has been demonstrated that TT is associated with higher gastrointestinal adverse events (31) and these findings have been confirmed in a recent systematic review in which has been also discussed that biologic agents are preferred because their high efficiency is likely to decrease long-term costs (reduced hospitalization and surgical joint procedures) and indirect costs (absenteeism from work) (32).

Reimbursement policies might also affect TT implementation, since among European countries there are different eligibility criteria for biological disease-modifying anti-rheumatic drugs (bDMARDs) reimbursement in RA (Figure 5). In France eligibility criteria for bDMARD reimbursement do not require minimal disease duration nor that a certain number of csDMARDs fail prior to prescribing a biologic therapy. In other European countries (including the UK), a reimbursement requires a minimum score of DAS28 >3.2, disease duration of more than 6 months and failure of at least one or more csDMARDs (33). This has resulted in low rates of use of biologic agents in some European countries: approximately 8% of patients in Germany receive bDMARDs, 10% in the UK, and 13% in France (34). In the UK, NICE recommends biologics for patients with rheumatoid arthritis only if the disease activity is severe and has not responded to treatment with a combination of csDMARDs. In France, biologics are already recommended after a failure with a csDMARD monotherapy.

Finally, the launch of biosimilars bDMARDs can further affect the use of TT in France. For example, the sales of biosimilar Etanercept (Benepali®) have increased by 172% in the last year according to French Medic'AM data 2018 (35). However, biosimilars are still relatively expensive compared with csDMARDs and thus TT remains substantially the least costly option in people failing csDMARD monotherapy.

Figure 5 Access to bDMARDs in Europe. Source: Kaló et al, 2017

A Budget Impact Analysis (BIA) using a dynamic model was developed in Microsoft Excel to estimate the impact of a hypothetical increased usage of TT therapy, prior to biotherapy, on direct healthcare costs for adults with moderate to severe disease activity after a failure of csDMARD monotherapy (Methotrexate) over three years from French National Health Insurance perspective. An estimate of the annual eligible population (N =2,500) was based on French epidemiological data and a literature review; model inputs (probabilities of withdrawal treatments) were calculated from the RACAT trial (25) and the related cost-effectiveness article (26) . Methotrexate and other direct medical costs were not included since they were similar across treatments and therefore, non-contributory to differential costs. Total costs (€, 2018) were calculated based upon six-monthly assessments of treatment response; 50%, 65% and 80% of the annual eligible patients were assumed to be treated with TT in the first, second, and third years. The cumulative budget savings over a three-year period following an increase in prescription of TT was €51 million, which corresponds to a reduction of approximately 41% on the overall pharmacy expenditure for RA for this eligible population (Figure 6). However, this analysis was limited, since the model did not consider significant factors that could influence negatively the budget impact, such as non-compliance and dose de-escalation rates.

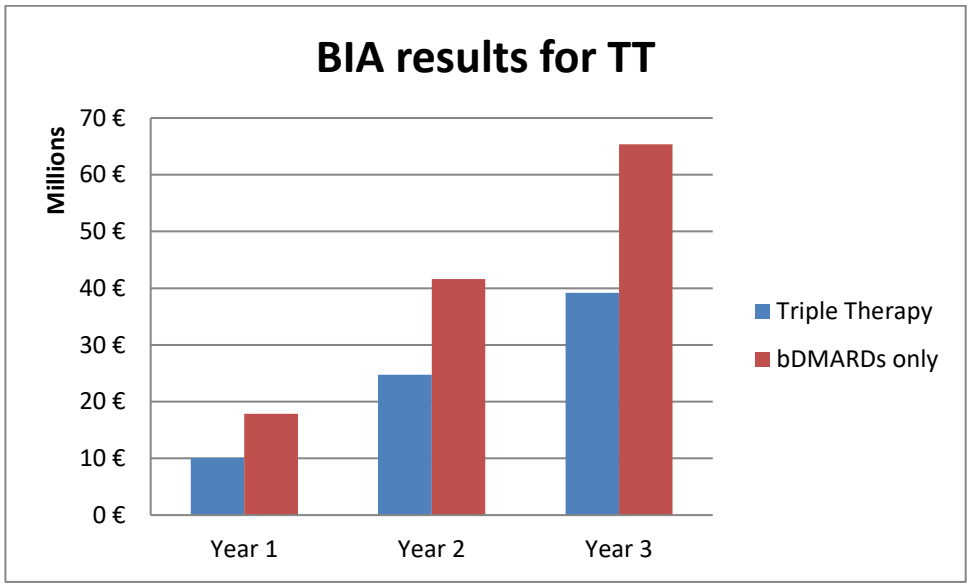

Figure 6 BIA results for Triple Therapy in Rheumatoid Arthritis

Rationing access to Total Knee Replacement in Knee Osteoarthritis

Total Knee Replacement (TKR) is a surgical procedure indicated to replace a diseased knee with an artificial prosthesis. The main reason for surgery is knee osteoarthritis (OA), a degenerative joint disease causing pain, swelling and limiting joint function. Rationing access to TKR is an approach aimed at restricting the eligibility criteria to surgery according to a functional scale. The objective of rationing is to avoid surgery for patients who would obtain little or no benefit from TKR and reduce economic pressure for healthcare systems.

International guidelines recommend a combination of non-pharmacological and pharmacological treatments in case of knee OA and a surgical procedure is indicated only in end-stage arthritis (37). Indication criteria for surgery are based on different clinical and radiologic examinations (38). A large number of functional and quality of life assessments are also available for measuring the degree of knee OA with varying characteristics and levels of validation and these items are widely used in clinical studies. However, their validity is sometimes disputed (39) and none of these scales are used to establish a threshold value involved in the decision to perform a TKR. This is also the case of the SF-12 physical component summary (PCS), suggested in Ferket et al (40), to be used as a scale to identify when TKR would become an economically more appropriate approach for the US healthcare system. The threshold suggested in this study (surgery only for patients with a score of >35 SF-12 PCS) would generate cost savings of $871,750 per QALY lost compared with current practice.

Many health authorities have not specified clear cut-points to define eligibility criteria for surgery. In some countries with universal healthcare systems such as the UK, Canada and Finland, the demand for joint replacement is managed by waiting lists (41). In the UK access to TKR is often rationed based on patient characteristics (such as age and functional assessments) given that it is a non-urgent procedure with a high impact on the healthcare budget. In particular, the Oxford Knee Score (OKS) is used in some British regions to define threshold values above which patients are not eligible for surgery (42). This is based on the rationale that patients with lower preoperative functional status benefit more from surgery, but the evidence to support this approach is limited as some studies argue that OKS is not predictive of post-operative outcomes and it should not be used in prioritising access to surgery (43).

Further economic evaluations have assessed the approach of rationing the provision of TKR by exploring the impact of applying different score thresholds or time lapse before surgery. Whilst the results of one study indicated that an early TKR strategy was not recommended since it yields minimal utilities gains over a late TKR strategy (44), other studies demonstrate that the score thresholds proposed by some practices are inappropriate and would limit cost-effective treatment for thousands of patients with severe arthritis (45).

Surgical innovations have reduced the operating risk, leading to the lowering of threshold values for indicating TKR (46) and therefore facilitating an increase of the number of surgeries carried out. The rate of TKR has nearly doubled in OECD countries over the last 20 years (47) as shown in Figure 7. Austria, Germany, Switzerland and Belgium have the highest rate of TKR in Europe, having rates of 240, 215, 206 and 202 TKRs per 100 000 habitants respectively in 2015. Data from Austria showed that the increase of TKR is disproportional to the growth of the Austrian population (46) and this finding is similar to many other European countries.

Some studies have discussed the appropriateness of TKR (48,49) and a systematic review indicated that about 20% of patients are unsatisfied about post-operative outcomes in terms of improvement in knee function and pain relief (50). However, there does not appear to be a consensus concerning how access to surgery could be rationed, waiting lists are unpopular measures and functional scales are not comprehensive tools to determinate how to prioritise patients. We looked at different clinical guidelines and very few reports have identified indication criteria for surgery using threshold

values. In many practices in the UK, TKR is commissioned when OKS is ≤23 (0 to 48 scoring system), the patient is fit for surgery with a BMI ≤35 and a non-smoker (51).

In France no threshold is used and the evaluation of a rationing approach of TKR in a BIA using data from a national hospital database (PMSI; programmation de médicalisations des systèmes d'informations) was performed. The costs were based on the French Insurance tariff system based on DRGs (GHM; Groupe Homogene Malades).

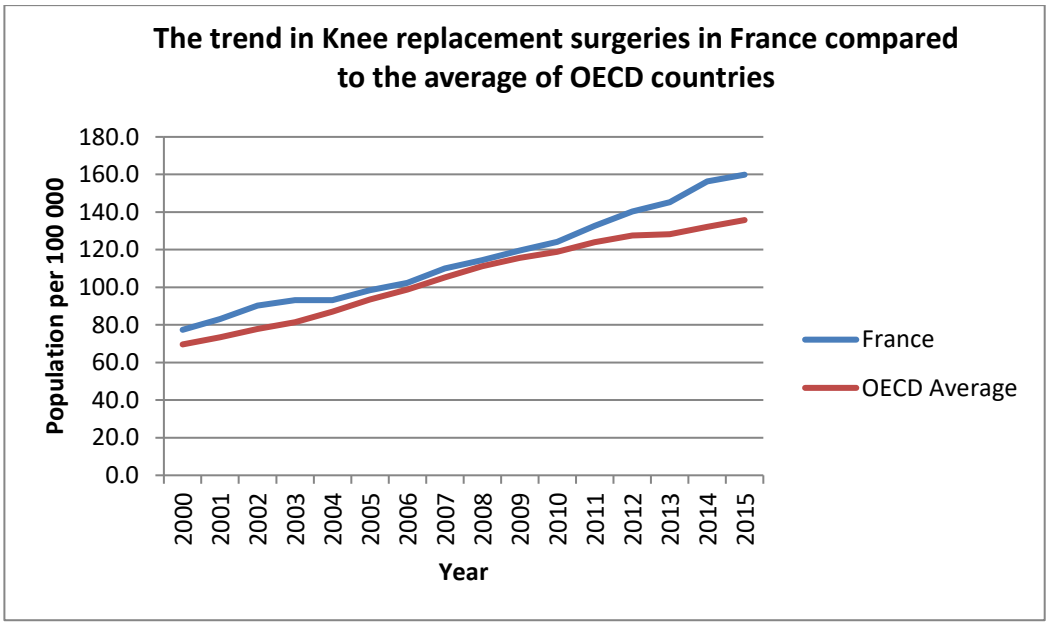

Figure 7 Trend of TKR in France. Source: OECD.stat

From the PMSI data we have established the 2018 expenditure for patients suffering from OA who have undergone TKR surgery (n=96,467) in France. The total cost to the French National Insurance system was € 696 million and average cost per patient for the intervention was €6,554. Using data from 2011 to 2018 an average 5-year follow-up cost for revision surgery of TKR has been established as just under € 500. The PMSI data does not carry detailed characteristics of the patients due to strict data protection laws in France and only age and gender are recorded as well as the level of severity as indicated by the DRG which takes into consideration length of stay and co-morbidities of the patient. No data is available about pre-surgery assessments (BMI, functional scales, etc.).

Our hypothesis is that France is accelerating the use of TKR at a higher rate than the average observed in other high income countries and we have endeavoured to identify subgroups of patients

that would be potential candidates for a rationing strategy according to OECD data and age and severity level. A one-year BIA was executed identifying three different hypothetical subgroups of patients who were considered for a rationing strategy based on the PMSI 2018 data. Scenario 1) older patients (>80) with high severity levels reflected in the DRG codes (N = 1,153); Scenario 2) 8% of patients randomly selected based on lowering the rate of TKR to match the OECD average; Scenario 3) 18% patients randomly selected based on lowering the rate of TKR to match Italy. The alternative intervention to surgery was a combination of non-pharmacological and pharmacological treatments.

The direct medical costs of the non-pharmacological and pharmacological treatments proposed instead of TKR included rehabilitation costs after surgery are calculated from CNAMTS (National Health Insurance Fund for Employees) tariffs; the cost of the alternative intervention was calculated from the Medic'AM 2018 database and CNAMTS tariffs according to the international guidelines for the non-surgical management of knee OA. The cost of the alternative pharmacological and non-pharmacological treatment varied from €500,000 to €8 million according to the different scenarios considered, leading to total costs between €578 million and €688 million for the surgical treatment of knee OA. Based on the three scenarios, between €7 million and €117 million could be saved if a percentage of the total population were assigned to the alternative pharmacological and non-pharmacological treatment (Table 4).

	Cost of TKR (€)	Cost of Alternative (€)	Total Cost (€)	Difference in Cost
Reference	**696 061 111**	**0**	**696 061 111**	
Scenario 1	687 741 598	532 686	688 274 284	-7 786 827
Scenario 2	640 378 820	3 564 328	643 943 148	-52 117 963
Scenario 3	570 770 111	8 022 196	578 792 307	-117 268 804

Table 4 Budget Impact Analysis TKR rationing

Bevacizumab to treat neovascular age-related macular degeneration

Bevacizumab is an anti-VEGF (vascular endothelial growth factor) monoclonal antibody approved for the treatment of many cancer therapies. Anti-VEGF drugs are also the standard of care for neovascular

age-related macular degeneration (nAMD) (52): the anti-VEGF Ranibizumab is the licensed drug and the mainstay therapy in nAMD.

Bevacizumab has found to be non-inferior to Ranibizumab for the off-label treatment of nAMD in a large multicentre RCT (53) and highly d-CE, with savings of £ 3,805,500 per QALY lost (24). Despite further evidence suggesting the non-inferiority and economic advantages of Bevacizumab, this therapy has not been approved by FDA and EMA for the treatment of nAMD (54,55).

Bevacizumab is an inexpensive drug (estimated cost in the EU: €50-100 per injection) and it is often used off-label in the EU (56), several studies indicate that it is administrated for the treatment of nAMD in Spain, Belgium, Italy, France and to a lesser extent in the UK (54–57). European health authorities are usually divided when the issue of use off-label drugs is raised. NICE discourages UK physicians to implement Bevacizumab in clinical practice and other countries such as Germany, Switzerland, Belgium, and France also do not recommend its use, since their national health authorities declare that off-label use should be avoided when a registered alternative is available (61).

Bevacizumab is manufactured by Roche (Avastin®), who possess the ownership rights, which means only Roche can request a registration by health authorities. The use of Bevacizumab has led to legal disputes in the UK and in Italy. In 2017 Novartis and Bayer brought legal proceedings against the Clinical Commissioning Group (CCG) of the UK NHS because they decided to propose Bevacizumab, alongside Ranibizumab and Aflibercept for the treatment of nAMD. Recently, this application was dismissed for judicial review on all grounds and found to be in favour of the CCG's policy (62), since the British High Court of Justice stated that this policy was lawful and UK NHS has the right to treat nAMD with Bevacizumab according to CCG's decision. In 2014, the Italian Medicines Agency (AIFA) placed Bevacizumab on the list of drugs to be reimbursed for nAMD. Novartis considered that AIFA favoured the use of Bevacizumab and filed a lawsuit again, in this case against AIFA. The European Court of Justice closed the proceedings determining that Bevacizumab can be reimbursed by the Italian NHS (60).

By contrast, in the US, medical society surveys and claims data analyses have shown that Bevacizumab is preferred by most ophthalmologists (63). The American Academy of Ophthalmology has supported the use of Bevacizumab to treat nAMD in its preferred practice guidelines, despite being an off-label treatment.

The patent of many monoclonal antibodies is about to expire (64) including Ranibizumab (patent already expired in the EU), biosimilars are now under regulatory review by health authorities and Ranibizumab biosimilar is currently being tested in two phase III RCTs (NCT03150589 and NCT02611778). Biosimilars will lead to less costly licensed alternatives in the next few years, however it is unlikely that they would be cheaper than Avastin®.

Protease Inhibitor monotherapy (single ritonavir boosted) in HIV

Protease inhibitors (PI) are antiviral drugs used to treat infection diseases such as HIV and Hepatitis C. PIs are used in combination with other antiviral drugs with different mechanisms of action, forming part of the antiretroviral therapy (ART) which represents the standard of care in HIV.

In 2015, PI monotherapy has been found to be non-inferior to ART in a multicentre open-label RCT in the UK (PIVOT trial) in patients who achieved viral load suppression once this was established with ART and d-CE with cost savings of £282,641 per QALY lost (65). PI monotherapy was a considerably cheaper approach due to the lower use of other antiviral drugs. An Italian study reported that its implementation would lead to economic savings of €12-24 million, namely between 4.80% and 9.72% of the 2010 total budget expenditure for HIV management in the Lombardy Region of Italy (66).

The current European AIDS Clinical Society (EACS) treatment guidelines do not recommend PI as maintenance strategy, although it might represent an option for patients with intolerance to some classes of antiviral drugs or for treatment simplification for patients with documented frequent interruption of ART (67). British and American guidelines also recommend continuing standard combination ART in patients with virological load suppression (68).

Thus it would seem that the findings of the PIVOT trial have not changed international clinical practice guidelines, in the UK it has been reported that physicians have a significant number of patients on PI monotherapy (68), and in Italy, the Italian HTA agency has approved PI monotherapy as a therapeutic option (66).

However, it seems unlikely that there will be an increase of PI monotherapy use in the next years. Many first-line antiviral drugs will be off-patent in the coming years and so ART consisting of generic drugs could eventually become cheaper than PI monotherapy. Furthermore, there are more options recently available for first-line therapy since the introduction of new classes of antiviral drugs such as Integrase Inhibitors (Raltegravir price in France: ~€0.12 per pill), which are cheaper than PIs (Ritonavir price in France: ~€1.16 per pill). Therefore, in agreement with *Paton et al* (68), the economic drivers to implement this therapy might disappear in the near future.

Manual Chest Physiotherapy in COPD

Manual Chest Physiotherapy (MCP) is a strategy intended to improve lung volume and facilitate the removal of airway secretions in Chronic Obstructive Pulmonary Disease (COPD). It involves external manipulation of the thorax using percussion and vibration techniques with the purpose to displace bronchial secretions for improving lung function.

In 2010, MCP was tested in a multicentre RCT in the UK. It was observed that MCP performed together with active cycle of breathing techniques (ACBT) were clinically equivalent to ACBT only (69). A further economic evaluation assessed that MCP was a less costly strategy (cost savings of £ 205,395 per QALY lost) due to substantially reduced hospital admission costs over the period of the study (70).

European clinical guidelines do not recommend MCP to be offered to all patients, since it has little effect on secretion clearance, lung function, cough, dyspnoea, quality of life, and length of hospital stay (71). American guidelines expressed no recommendation to support MCP as an airway clearance technique for COPD patients (72). A recent Cochrane review concluded that the effects of MCP are unreliable across trials and that MCP may be considered in specific patients with acute exacerbation COPD, however the benefits are limited (73).

The impact of MCP is difficult to ascertain due to the poor evidence available in literature regarding the level of implementation of this intervention. In the UK, a national survey has been reported that MCP was widely used for airway clearance; 77% of physiotherapists used this technique for the management of their patients (74). Conversely, in the US, a study described that MCP was delivered in 37.5% of cases (75) and lower utilization rates were also found in Australia (76).Whilst it is hard to estimate the future trends of MCP use in clinical settings, it was confirmed that airway clearance

techniques are regularly used for treating acute exacerbation of COPD (77) and these reduce overall hospital length of stay (73). However, positive pressure devices, forced expiration and active cycle of breathing techniques are preferred strategies (77).

Erlotinib in Lung Cancer

Erlotinib is an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) used to treat non-small-cell lung cancer (NSCLC) after a failure of at least one chemotherapy regimen as a second- or third-line treatment. It is approved by EMA and FDA as well as for several other types of cancer.

In 2011, a NICE Technology Appraisal showed that Erlotinib was d-CE versus Pemetrexed for maintenance treatment in NSCLC patients, with cost savings of £ 84,011 per QALY lost (78). However at that time, the NICE appraisal committee concluded that UK patients would not routinely receive Erlotinib because it would not have been a cost-effective use of NHS resources for patients with stable NSCLC after first-line chemotherapy. The manufacturer requested to provide a second appraisal and submitted three new economic analyses that compared Erlotinib with best supportive care in all patients with stable disease and a further economic analysis comparing Erlotinib with Pemetrexed. Nonetheless, the NICE appraisal committee did not consider that robust evidence had been provided and therefore did not accept that Erlotinib met the criteria for end-of-life treatments (79). In 2012 NICE approved Erlotinib as an option treatment of people with NSCLC after testing positive for the EGFR mutation (80). In fact, nowadays, Erlotinib is prescribed preferentially for treatment of selected NSCLC patients with EGFR mutation (81,82) and the European Society for Medical Oncology (ESMO), in the latest clinical guidelines available, recommends Erlotinib as a maintenance treatment for NSCLC patients with an EGFR mutation (83).

It is difficult to assess the level of implementation of Erlotinib in recent years due to the lack of real-world studies regarding Erlotinib and, in general, on the use of EGFR TKIs (84). A European survey reported that Erlotinib is often implemented for the treatment of brain metastases in NSCLC patients (40-44% of cases) (85).

The introduction of second and third generation EGFR-TKIs might affect the use of Erlotinib in lung cancer, although the optimal sequence for administration of EGFR TKIs remains to be determined (86). Recent evidence suggests that the third generation EGFR-TKI Osimertinib is likely to become the new standard of care in EGFR mutant NSCLC patients (87).

Long-term antidepressants discontinuation (tapering program)

Antidepressants (AD) are used for the treatment of major depressive disorder and anxiety disorders. Between 2000 and 2014 the use of AD doubled in OECD countries (88) and an inappropriate AD use (defined as either use of AD therapy in absence of a proper indication or continuation of the therapy despite poor therapeutic efficacy) has been vastly described in the literature (86–88). Furthermore, 10–15% of long-term AD users continue the treatment after remission without trying discontinuation (92).

A tapering program aimed at the discontinuation of long-term use of AD (>9 months), according to a dose reduction scheme, has been found to be a d-CE approach in the PANDA trial in patients who were long-term AD users (93) and the lower costs were mainly imputable to the reduced productivity losses, with cost savings of € 70,180 per QALY lost.

Current guidelines recommend discontinuation of long-term AD use (94,95) and strict programs are designed to prevent relapse of depressive/anxiety disorders. Besides tapering schemes, recommendations also endorse incorporating psychological support, since cognitive behavioural therapy (CBT) and mindfulness-based cognitive therapy (MBCT) can play an important role to avoid relapse/recurrence.

Data from a recent systematic review showed that discontinuation rates through tapering programs were low (96) and higher cessation rates were found in studies where the intervention was the combination of CBT plus tapering programs. However, this review included studies on any patients regardless of the duration of use. Few studies have focused their attention on discontinuation of long-term AD use in patients in remission via tapering programs and we did not find further valuable evidence to compare the level of implementation of this specific intervention in other settings. Looking at consumption data (88), it seems a gap exists between recent guidelines recommendations and what actually happens in clinical practice. Eveleigh et al (97) remark that simply recommending tapering schemes has not been an effective measure and that more actions would be required such as education programs for GPs, restrictive prescriptions and psychological therapies, to support long-term AD users discontinuation.

IV Discussion

This systematic review of the health economic literature from 2005 to 2019 has identified 94 HTs that fit our definition of d-CE. For over half of these HTs (n=50) the DCER was expressed in cost savings per QALY lost and was converted into 2018 euros. ICURs ranged from €9 saved per QALY lost to €4,857,724 saved per QALY lost. Given the international nature of this review, no WTA threshold was used to define d-CE. Current convention in cost-effectiveness analysis is that the cost-effectiveness threshold is the gradient of a straight line through the origin on the cost-effectiveness plane. However, it is under debate whether or not the WTP value would be the same as the WTA value. The societal point of view indicates that WTA is usually higher than WTP, potentially with double the cost difference for one QALY lost than the WTP for one QALY gained (98). In the Netherlands, the WTA is considered to be € 80,000 saved per QALY lost, although this value has not been officially stated (99). If we had applied this threshold value in our review, we would have excluded more than 30% of the papers. However, since there are no consensual thresholds currently used by any country, we decided not to apply such a threshold to our results to inform decision-makers about all possible d-CE HTs found in recent years.

A previous systematic review on d-CE HTs (2), conducted over the time period 2002-2007, identified just eight d-CE interventions. Besides the growth of EEs published in the recent years and the conservative approach of the above-mentioned study (2) since it included only d-CE interventions being at least $ 100,000 cost saving for each QALY lost, there could be other reasons for the higher number of studies found in our review. For example, 44 out of 55 RCT-based EEs were based on non-inferiority or equivalence clinical trials. Non-inferiority clinical trials are being performed with a greater frequency nowadays and a three-fold increase from 2007 to 2010 was found (100). Moreover, the time period covered by our review included the austerity measures on healthcare spending caused by the global financial crisis (36), which has been a key driver to decision making based on maximizing collective health benefits while controlling costs. Fighting over treatment is another key topic in healthcare and nearly half of the 94 d-CE HTs we found were dose reduction/de-escalation interventions.

Despite the increased number of d-CE papers found, it is possible that many studies are still not published due to the results being unable to demonstrate health gains. The publication bias may well be the main limitation of this study, given this reluctance to publish negative results. We

endeavoured to identify studies that were non-inferior or equivalence trials though ClinicalTrials.gov, published protocols and conference proceedings and have contacted authors when an economic evaluation or a cost-analysis was planned, but not published. We had a very low response rate to our correspondence with the leaders of these studies and we are not yet able in a position to ascertain the reasons for the lack of published results. We will continue to follow up with the investigators to see if this low responsiveness is simply reticence encountered in sharing non-published results by researchers or an unwillingness or lack of interest in publishing negative results or in fact, if these non-inferior or equivalent HTs were in fact more expensive and thus dominated.

We only identified one NPI in our review (101) which is coherent in comparison with a systematic review of complementary therapies and integrative care published in 2012 that found a total of 338 economic evaluations, of which 204 were published between 2001 and 2010.(102) Of the 56 comparisons made in the higher-quality studies, 16 (29%) show a health improvement with cost savings for the NPI versus usual care. We requested from the author the full list of EEs found between 2001 and 2010. After screening the data file supplied, we were unable to identify any d-CE results.

Another EU project CAMBRELLA (A pan-European research network for Complementary and Alternative Medicine) reported on HTA NPI provision in the EU in 2013 (103). They found that NPI has a considerable economic and social impact accounting for up to 1% of service, sales and percentage of gross domestic product (GDP) in the EU and that 90% of these services are purchased privately. Due to a lack very limited or absent public funding for research, dependable data is scarce in relation to outcome, health maintenance and the social and economic impact of NPI.

In terms of the data sources used, all of the articles that were included were referenced in PubMed even if it was not the PubMed search string that identified them. The added value of the EMBASE search was to identify posters and abstracts from conference proceedings. Overall a total of 26 papers had to be screened in order to identify one d-CE HT (precision 3.9%) and this compares favourably with the previous systematic review where 2,128 papers were screened to identify eight HTs leading to a precision of 0.4%.

The case-studies demonstrated some of the current practical barriers of implementation for the selected d-CE HTs, yet such obstacles are not applicable for all d-CE HTs found in this review. In some cases, d-CE HTs have had a better level of implementation. The sample of good quality studies

reporting QALYs (Figure 4) covers HTs that are currently widely used in clinical practice such as outpatient treatment of abnormal uterine bleeding, vertical scar reduction in breast mammoplasty and coronary computed tomography for the diagnosis of coronary artery disease with stable chest pain.

The aim of the BIA was to quantify the potential financial savings of two of the most d-CE HTs in a national setting. One of the principal questions posed by these analyses is how the resources could be displaced following the increased use of Triple csDMARDs therapy or rationing TKR.

According to research on the marginal cost of generating health outcomes in the UK NHS (104), it is has been reported that supporting a d-CE HT might represent a cost-effective use of resources. For example, in the case of PI monotherapy in HIV (average reduction in QALY of -0.0227), if 45,000 patients were switched from ART to PI monotherapy, it has been estimated that the cost savings could be used to generate 22,354 QALYs elsewhere, including 1,486 lives prolonged and 6,735 life-years gained (105).

Other rationale includes the possibility that a new intervention, associated with higher costs and better outcomes, could produce lower health benefit nationwide if there are insufficient resources released to fund the new intervention (106).

We are conscious that cost saving is rarely the primary reason for choosing a particular treatment strategy. In case of HIV, for example, the WHO rejects the provision of cheaper and less effective treatments in any situation, to avoid the establishment of a double standard of care (107). It can be argued that it should be mandatory for health professionals to provide the best available option to their patients, but from a broader societal perspective, decision makers would claim that it is more important to achieve equity in the supply of medical innovations. Since 2010, in OECD countries, the expenditure on health has remained relatively flat within a global context of budget constraint, so it would seem that policy recommendations of implementing slightly less effective medical interventions, but at significantly lower cost, might represent a more effective use of resources to provide additional health gains to the population.

A recent article that reviewed methodological projects/frameworks, case studies, dissemination initiatives on disinvestment released by HTA agencies and organizations located in Europe (108) found that disinvestment is a relatively new concept in HTA and that there is currently an absence of a “disinvestment framework” at an International level.

Our ambition is that the remaining tasks of WP11 will address this issue. Through the planned workshops and the multinational Discrete Choice Experiment (DCE), we will identify gaps in the expectations and attitudes from the different stakeholder perspectives and make progress towards identifying the DCER threshold. The final step will synthetize the results into a toolbox readily usable and adaptable to local HTA projects. The results of this systematic review and identification of case-studies will feed into this process.

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APPENDIX 1 Full search strategies used for all databases

A) PubMed search string

(((((("Cost-Benefit Analysis"[MeSH] OR "*economic*" OR "Cost Control"[MeSH] OR "Costs and Cost Analysis"[MeSH] OR"*Cost*" OR "*saving*" OR "*save*" OR "*QALY*" OR "*resource utilisation*" OR "*resource utilization*" OR "*economic*" OR "*expenditure*" OR "*fees*" OR "*charges*" OR "*budget*" OR "*fiscal*" OR "*financ*" OR "*fund*" OR "*price*" OR "*pricing*") AND ("*Non inferior*" OR "*Noninferior*" OR "*non-inferior*" OR "*Decremental*" OR "*De escalation trial*" OR "*De-escalation trial*" OR "*disinvest*" OR "*equivalence*" OR "*less effective*"))))) AND ("2005/05/01"[Date - Publication] : "2019/02/14"[Date - Publication])

B) ClinicalTrials.gov search string

(Cost-Benefit Analysis OR economic impact OR economic analysis OR cost effective OR cost effectiveness OR Costs and Cost Analysis) AND (Non inferior OR non-inferior OR noninferior OR De escalation trial OR disinvest)

C) TUFTS search string

Decremental cost-effective

D) EuroCT search string

(Cost-Effective* OR cost effective* OR cost-benefit analysis OR economic* OR Costs and Cost Analysis) AND (non-inferior OR noninferior OR non inferior OR disinvest OR decremental)

E) EbscoHost search string

("Cost-Benefit Analysis"[MeSH] OR "economic impact" OR "economic analysis" OR "Cost Control"[MeSH] OR "Costs and Cost Analysis"[MeSH]) AND ("Resource Allocation"[MeSH] OR "Non inferior*" OR "Noninferior*" OR "non-inferior*" OR "Decremental* cost effective*" OR "Decremental* cost-effective*" OR "De escalation trial*" OR "De-escalation trial*" OR "disinvest")

F) CRD York search string

Cost-Benefit Analysis AND non inferior* trial

G) ISRCTN search string

(Non inferior OR non inferiority) AND (cost effective OR cost effectiveness)

H) EMBASE search string

('cost effectiveness analysis'/exp OR 'cost effectiveness analysis' OR 'cost benefit analysis'/exp OR 'cost benefit analysis' OR 'cost utility analysis'/exp OR 'cost utility analysis' OR 'cost minimization analysis'/exp OR 'cost minimization analysis' OR 'health economics'/exp OR 'health economics' OR 'economic evaluation'/exp OR 'economic evaluation' OR 'incremental cost effectiveness ratio'/exp OR 'incremental cost effectiveness ratio') AND ('decremental' OR 'equivalence trial'/exp OR 'equivalence trial' OR 'non-inferiority trial'/exp OR 'non-inferiority trial' OR 'disinvest' OR 'less effective') AND [2005-2019]/py AND [english]/lim AND [humans]/lim

APPENDIX 2 Data extraction list template

Reference codes
NCT number
Published protocol DOI or PMID
Published clinical article DOI or PMID
Published economic article DOI or PMID
Published HTA report DOI or PMID
Any other reference
General clinical study information if single study EE
Trial design
Clinical phase
Planned sample size
Actual sample size
Equivalence or non-inferiority margin
ITT and PP
Treatment or follow-up duration
Planned trial period
Primary objective/outcome
Principal clinical result
Authors' conclusions

General economic study characteristics
First author and year of publication
Pathology
Sources of funding
Competing interests
Publication type
Sample size for economic evaluation
Setting
Patient characteristics/population
Type of intervention
Intervention aim
Control treatment
Eligibility criteria
Study perspective
Type of EEs
Analytic approach
Methods and outcomes of economic evaluations
Time frame of the analysis (time horizon)
Discount rate
Discount rate for costs
Discount rate for effects
Inflation rate
Reference year
If model based
Type and category of costs
Data source of resource use
Methods for identifying resource use
Assumptions of the measurement of resources
Costs (in reported currency or in converted currency)
Methods used to calculate unit costs
Data source of effects
Methods of measurement of effects, valuation and thresholds
Incremental cost-effectiveness ratios
Analyses of uncertainty (e.g. sensitivity analyses)
Outcome(s) of analyses of sensitivity analyses
Authors conclusions
HTA
Recommendation of HTA

APPENDIX 3 Quality, transferability & bias checklist template

PMID : _____	
Author : _____	
Quality assessment	
	1. Is the study population well described?
	2. Are competing alternatives clearly described?
	3. Is a well-defined research question posed in answerable form?
	4. Is the economic study design appropriate in order to include relevant costs and consequences?
	5. Is the chosen time horizon appropriate in order to include relevant costs and consequences?
	6. Is the actual perspective chosen appropriate?
	7. Are all important and relevant costs for each alternative identified, measured and valued appropriately?
	8. Are all important and relevant outcomes for each alternative identified, measured and valued appropriately?
	9. Is an incremental analysis of costs and outcomes of alternatives performed?
	10. Are all future costs and outcomes discounted appropriately?
	11. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity?
	12. Do the conclusions follow from the data reported?
	13. Does the article indicate that there is no potential conflict of interest of study researcher(s)?
	14. Are ethical and distributional issues discussed appropriately?
Transferability	
	15. Does the article provide sufficient detail about the study sample(s)?
	16. Are quantitative and/or descriptive analysis conducted to explore variability from place to place?
	17. Does the study discuss generalisability of their results?
Bias	
	18. Inefficient comparator bias. Was the best alternative chosen as comparator? Was current practice chosen as a comparator?
	19. Sponsor bias. Have sponsorships been disclosed? Is the study protocol freely accessible?
	20. Reporting and dissemination bias. Has the study/trial been listed in a trial register? Have all results been reported according to the study protocol?
	21. Bias related to structure. Is the model structure in line with coherent theory? Do treatment pathways reflect the nature of disease?
	22. Bias related to consistency. Has internal consistency in terms of mathematical logic been evaluated?

APPENDIX 4 Systematic review results

PMID	Author	Year	Country	Disease/Condition	Intervention	Comparator	Effects	Savings	DCER (€, 2018)
18342952	Bosmans et al	2008	Netherl.	Depression	No antidepressants	Usual care	-0.81 QALYs	€ 751	€ 1 121 saved per QALY Lost
22520158	Genders et al	2013	Netherl.	Coronary artery disease	Coronary CT angiography	SOC-strategy	-0.003 QALYs	€ 231	€ 81 942 saved per QALY Lost
23435861	Perrier et al	2013	France	Lymphoma and Myeloma	Pegfilgrastim	Filgrastim	+0.24 day of side effect	€ 3 676	€ 16 506 saved per day of side effects
17000388	Stroupe et al	2006	US	Inguinal hernia	Watchful waiting	Surgical repair	-0.031 QALYs	$ 1 831	€ 60 731 saved per QALY Lost
25880024	Wu et al	2015	US	Asthma	Pharmacogenomics testing	Clinical detection	Equivalent	$ 1 735	€ 200 saved per QALY Lost
16673682	Manca et al	2006	UK	Neck pain	Brief physiotherapy	Usual physiotherapy	-0.001 QALYs	£ 68	€ 101 830 saved per QALY Lost
26323045	Picot et al	2015	UK	Breast cancer	INTRABEAM	WB-EBRT	-0.167 QALYs	£ 177	€ 1355 saved per QALY Lost
28628003	Howard et al	2017	UK	Leukaemia	FCM-miniR	FCR	-0.059 QALYs	£ 6 619	€ 138 180 saved per QALY Lost
25255113	Thoma et al	2014	Canada	Breast Mammaplasty	Vertical Scar Reduction	T–Shaped Reduction	-0.01 QALYs	$ 1 104	€ 77 739 saved per QALY Lost
26258496	Neittaanmäki et al	2016	Finland	Actinic keratoses	DL-PDT	LED-PDT	-0.257 QALYs	€ 38	€ 140 saved per QALY Lost
20487638	Cross et al	2010	UK	COPD	Manual chest physiotherapy	Usual care	-0.002 QALY s	£ 410	€ 263 070 saved per QALY Lost
29900829	Brown et al	2018	UK	Rheumatoid arthritis	Etanercept/Adalimumab	Abatacept	-0.02 QALYs	£ 3 768	€ 306 177 saved per QALY Lost
26240949	Clark et al	2015	UK	Abnormal uterine	Outpatient	Inpatient	-0.006 QALYs	£ 923	€ 193 310 saved per QALY Lost

				bleeding					
26966125	Oddershed et al	2016	UK	HIV	PI monotherapy	ART	-0.0227 QALYs	£ 6 417	€ 355 018 saved per QALY Lost
26364905	Cunningham et al	2015	UK	Bronchiolitis	Modified care	Standard care	-0.78 cough resolution	£ 290	€ 1 567 saved per unresolved cough
24827857	Westwood et al	2014	UK	Lung cancer	EGFR PCR Kit mutation test	Exon 19–21 test	-0.286 QALYs	£ 9 194	€ 40 440 saved per QALY Lost
18505669	George et al	2008	UK	Minor surgery procedures	Primary care	Hospital-based	-0.0135 no problems following operation	£ 770	€ 75 373 saved per problem following operation
20569652	Saborido et al	2010	UK	Atrial fibrillation	Pill in Pocket	Continuous therapy	-0.02 QALYs	£ 876	€60 127 saved per QALY Lost
26310452	Isetta et al	2015	Spain	Obstructive sleep apnoea	Telemedicine	Usual monitoring	-0.0012 QALYs	€ 11	€ 12 653 saved per QALY Lost
24085535	Goorden et al	2013	Netherl.	Depression	Collaborative care	Care as usual	-0.05 QALYs	€ 709	€15 798 saved per QALY Lost
24990117	Darlington et al	2014	France	Coronary artery disease	Computed tomography coronary angiography	Conventional invasive coronary angiography	Le s diagnostic accuracy	€ 1 198	€ 6 739 saved per QALY lost
26764260	Kievit et al	2016	Netherl.	Rheumatoid arthritis	Dose optimisation	Usual care	-0.02 QALYs	€ 12 280	€ 403 977 saved per QALY lost
28407999	Vanier et al	2017	France	Rheumatoid Arthritis	Spacing arm	Maintenance arm	-0.158 QALYs	€ 8 440	€ 54 023 saved per QALY Lost
28351833	Ferket et al	2017	US	Osteoarthritis	TKR <35 SF PCS	TKR to all	-0.008 QALYs	$ 6 974	€ 750 936 saved per QALY Lost
27571718	Steinhaus et al	2016	US	Atrial fibrillation	ICM-guided therapy	Standard care	0 QALYs	$ 805	
28554192	Bansback et al	2017	US	Rheumatoid arthritis	Triple Therapy	Etanercept	-0.017 QALYs	$ 15 954	€ 845 050 saved per QALY Lost
25947558	Burnett et al	2015	Canada	Paediatric ophthalmological	Examination under	Examination under	–0.678 successful	$ 729	€ 15 521 saved per unsuccessful

				procedures	sedation (EUS)	anaesthesia (EUA)	procedures		procedure
28659349	Barendese et al	2017	Netherl.	Rectal cancer	Endoscopic mucosal resection (EMR)	Transanal endoscopic microsurgery (TEM)	0.00 QALYs	€ 3 003	
25079928	Dakin et al	2014	UK	nAMD	Continuous Bevacizumab	Continuous Ranibizumab	-0.004 QALYs	£ 15 222	€ 4 857 724 saved per QALY Lost
21967156	Dickson et al	2011	UK	Lung Cancer	Erlotinib	Pemetrexed	-0.1007 QALYs	£ 8 460	€ 105 576 saved per QALY Lost
25355620	Wong et al	2015	China	Transitional care	Home visit	Control (calls)	-0.002 QALY s	$ 1 398	
18290913	Anderson et al	2008	Australia	Cervix Carcinoma	Three-yearly screening	Two-yearly screening	102 LY Lost	$ 12 M	€ 111 487 saved per LY Lost
25121977	Eveleigh et al	2014	Netherl.	Depression and anxiety disorders	Discontinuation antidepressants	Usual care	-0.02 QALY s	1631	€ 74 203 saved per QALY lost
26664666	Thavorn et al	2015	Canada	Liver Fibrosis and Steatosis	Transient elastography	Liver Biopsy	-21 CDS (correctly diagnosed steatosis)	$ 22	
23838763	Latimer et al	2013	UK	Hospital Falls	New Flooring	Standard Flooring	-0.006 QALYs	£ 843	€ 188 804 saved per QALY Lost
25766689	Sánchez et al	2015	Spain	Obstructive sleep apnoea	Primary care	Sleep Unit group	-0.03 QALYs	€ 212	€ 7 195 saved per QALY Lost
24053310	Boyers et al	2013	UK	Urinary incontinence	SIMS	SMUS	-0.003 QALYs	£ 142	€ 618 06 saved per QALY Lost
20871718	Wagmiller et al	2006	US	Prostate cancer	Individualized schedule	Fixed-schedule	-0.005 QALYs	$ 3 463	€ 735 521 saved per QALY Lost
21291510	Lier et al	2011	Canada	Stress Urinary Incontinence	Trans-obturator tape	Tension-free vaginal tape	0.00 QALYs	$ 1 242	
21594605	Boormans et al	2011	Netherl.	Detection of aneuploidies chromosomes	MLPA	Karyotyping	Non-inferior	€ 240	

25714906	Miller et al	2015	US	Abnormal Uterine Bleeding	Global Endometrial Ablation	Hysterectomy	-0.167 QALYs	$ 5 665	€ 84 164 saved per QALY Lost
28301778	Kang et al	2017	US	Gastrointestinal Endoscopy	Risk stratified Testing	Non-Risk stratified	-0.1814 QALYs	$ 1 870	€ 9 024 saved per QALY Lost
29036249	Udkoff et al	2017	US	Psoriasis	Ixekizumab every 4 weeks	Biweekly Etanercept	-0.006 QALYs	$ 21 375	€ 2 960 209 saved per QALY Lost
26975999	O'Day et al	2016	US	Heart Failure	I-mIBG imaging	Current practice	-0.001 QALYs	$ 5 500	€ 4 521 045 saved per QALY lost
22694315	Liew et al	2012	Belgium	Diabetes	Simvastatin	Atorvastatin	-0.03 QALYs	€ 131	€ 4 976 saved per QALY Lost
16961547	Cram et al	2006	US	Cardiac Arrest	Automated external defibrillators	Implantable cardioverter defibrillators	-0.85 QALYs	$ 109 435	€ 4 135 saved per QALY Lost
27513296	Houten et al	2016	Netherl.	Intermittent claudication	Endovascular revascularization (ER)	Supervised exercise therapy (SET)	-0.07 QALYs	€ 6 412	€ 10,18 saved per QALY Lost
29023215	Shapiro et al	2017	US	Breast Cancer	ZA every 3 months	Monthly ZA	-0.01 QALYs	$ 3 623	€ 303 998 saved per QALY Lost
17344670	Borget et al	2006	France	Colorectal cancer	Raltitrexed	HD-LV5FU2	-1.4 median EFS	€ 5 283	€4 705 saved per QALY Lost
28463759	Salehi et al	2017	Sweden	Endometrial cancer	Laparoscopic surgery	Laparotomy	Non-inferior	€ 2 298	€ 142 saved per QALY Lost
28993857	Fargier et al	2018	France	Follicular lymphoma	Subcutaneous Rituximab	Intravenous Rituximab	-0.1 QALYs	€ 109	€ 1 105 saved per QALY Lost
29151700	Rodríguez et al	2017	Spain	Hepatitis B	Tenofovir	Lamivudine + Adefovir	Non-inferior	€ 868	
22998716	Rickard et al	2012	Australia	Peripheral intravenous catheters	Clinically indicated	Routine replacement	Equivalent	$ 7	
23821695	Stoecker et al	2013	US	Pneumococcal diseases (vaccination)	2+1 pneumococcal vaccine	3+1 pneumococcal vaccine	-0.011 QALYs	$ 421 M	€ 267 474 saved per QALY Lost

16613886	Fiddelers et al	2006	Netherl.	Infertility	elective Single Embryo Transfer (eSET)	Double Embryo Transfer (DET)	-18.8% effectiveness	3590	€ 230 saved per QALY Lost
18383356	Wailoo et al	2008	US	Rheumatoid arthritis	Anakinra	Infliximab	-0.2 QALYs	$ 43 421	€ 216 862 saved per QALY Lost
26000677	Beall et al	2015	US	Vertebral compression fractures	Kiva System	BK	Non-inferior	$ 350 055	€ 95 698 saved per QALY Lost
21926570	Schwebel et al	2012	France	Catheter-related Infection	7-day dressing changes	3-day dressing change	Non-inferior	$ 133	€ 183 saved per QALY Lost
16832415	Torrance et al	2006	UK	Screening Breast cancer	Genetic nurse counsellor	Clinical geneticist	Equivalence	£ 11	
23408579	Donnelly et al	2013	US	Obesity	Phone	Face-to-face (FTF)	Equivalent	$ 22	
23516679	Steadman et al	2013	Canada	Liver disease diagnosis	Transient elastography	Liver biopsy	-0.05 min	$ 362	
25769495	Scott et al	2015	UK	Rheumatoid arthritis	csDMARDs	bDMARDs	-0.08 QALYs	£ 5 545	€ 90 331 saved per QALY Lost
28636405	Corral et al	2017	Spain	Obstructive sleep apnoea	HRP	PSG	-0.004 QALYs	€ 292	€ 89 066saved per QALY Lost
17220691	Jakiche et al	2007	US	HAV – HBV	Selective vaccination	Universal vaccination	-113.16 immune patient	$ 17 468	€ 158 saved per QALY lost
26993268	Manchanda et al	2016	UK	Screening breast cancer	DVD-C (audio-visual tool)	Face-to-face counselling	Non-inferior	£ 9 520	€ 4 135saved per QALY Lost
27008836	Huang et al	2016	US	Chronic Idiopathic Constipation	Linaclotide	Lubiprostone	0 QALYs	$ 69	
22776761	Belkora et al	2012	US	Breast cancer	Tele-Consultation	In-Person Consultation	Decisional Self Efficacy: -0.15	$ 30	

16172305	Christenson et al	2005	US	Skin Punch Biopsy	Second-Intention	Primary Closure	+1.8 VAS score	$ 145 332	
26509205	Freene et al	2013	Australia	Physical inactivity	Home-based	Group program	-19% physical activity	$ 37	
27318001	Obdeijn et al	2016	Netherl.	Screening Breast cancer	Modified protocol BRCA1	Current protocol BRCA1	-690 LY	€ 54 580	€ 79 saved per LY lost
17495705	Slavik et al	2007	Canada	Venous Thromboembolism Prophylaxis	Dalteparin	Enoxaparin	+8.1% risk increase	$ 12 485	€ 1 114 saved per QALY Lost
18589314	Volkers et al	2008	Netherl.	Uterine fibroids	Uterine artery embolization	Hysterectomy	-0.016 QALYs	€ 6 937	€ 458 994 saved per QALY Lost
27241876	Müller et al	2016	Norway	Nonacute Headaches	Telemedicine	Traditional consultation	Non-inferior	€ 234	
16176518	Sophonsritsuk et al	2005	Thailand	Infertility	Minimal stimulation	Conventional protocol	No significant differences	$ 4763	
26295268	Shoup et al	2015	US	Influenza vaccination for asthma and COPD	Interactive	Postcard Only	No significant difference	$ 0.05	
20965458	Rinfret et al	2010	Canada	Percutaneous Coronary Intervention	Same-Day Home Discharge	Overnight Stay	Non-inferior	$ 1 127	
21712704	Dorafshar et al	2012	US	Wound Therapy	GSUC	VAC	-0.4% Change in Wound Surface Area	$ 4.37	€ 9 saved per QALY Lost
24449235	Schwartz et al	2014	US	Hereditary Breast and Ovarian Cancer	Telephone Counseling	In-Person Counseling	Non-inferior	$ 114	
24837977	Pallero et al	2014	Spain	Restrictive pulmonary disease	Ambulatory adaptation	Hospital adaptation	Non-inferior	€ 1 192	

27113948	Fillingham et al	2016	US	Blood loss after total knee arthroplasty	Oral TXA	IV TXA	No significant difference	$67 M per year
17357336	Cibor et al	2006	Poland	Non-erosive reflux disease	Intermittent treatment	On-demand treatment	+0.5 VAS score	PLN 41.3
21457390	Xia et al	2011	US	Wound infections in MMS	Sterile gloves	Non-sterile gloves	No significant difference	$ 23 440
28807660	Carris et al	2017	US	Diabetes	Metformin	Metformin + vitamin B12	Equivalence	$ 329
26154249	Devine et al	2015	Canada	Training cardiac life support	DSRL	IRL	No difference	$ 400
16395988	Lechleitner et al	2005	Austria	Diabetes	Insulin glargine (IG) + OADs	Conventional insulin therapy	Equivalent	€ 0.08
21079465	Bausone-Gazda et al	2010	US	Peripheral Intravenous	BD Nexiva Closed IV Catheter	Braun Introcan Safety Catheter	Non-inferior	$1.91
25732570	Foster et al	2015	US	Pregnancies control	OTC OCPs	OCPs	See text	
27648792	Schinsky et al	2016	US	Knee Arthroplasty	Ice/gel pack cryotherapy	Cold water cryotherapy	Non-inferior	$ 9 734
17145220	Chihrin et al	2006	Canada	Bradycardia/ arrhythmia (Monitoring)	Active-Fixation, Permanent Device	Traditional Transvenous	Not Available	$ 585
Abstract	Simon et al	2017	China	Colorectal surgery	Electroacupuncture	Fast-track perioperative program	Non-inferior	$ 381
29420536	Kooiman et al	2018	Netherl.	Chronic kidney disease	Sodium bicarbonate	Saline hydration	Increase in serum creatinine +3.1%	$ 403

30420616	Robles-Zurita et al	2018	UK	Colorectal cancer	3M adjuvant Oxaliplatin + FOLFOX	6M adjuvant Oxaliplatin + FOLFOX	-0.12 QALYs	£ 6 841	€ 67 833 saved per QALY lost
30528811	Hwang et al	2018	Australia	Heart Failure	Home-based Telerehabilitation	Centre-based Rehabilitation	0 QALYs	$ 1 590	
29609205	Kigozi et al	2018	UK	Osteoarthritis	Screening for anxiety and depression	Usual care	-0.029 QALYs	£ 122	€5 193 saved per QALY lost
26011792	Diwakar et al	2016	UK	Abnormal uterine bleeding	Outpatient	Inpatient	-0.0015 QALYs	£ 668	€ 522 853 saved per QALY lost
20093902	Boormans et al	2010	Netherl.	Detection of aneuploidies chromosomes	MLPA	Karyotyping	Non-inferior	$ 433	
26986803	Paton et al	2016	UK	HIV	Protease Inhibitor Monotherapy	Ongoing Triple Therapy	-0.0227 QALYs	£ 6 424	€ 322 597 saved per QALY lost

APPENDIX 5 Unpublished studies found in our systematic review

Source	Authors	Disease(s)	Innovative technology/ies	Usual care	Country	Year	Contact status	Author's response	Full text - Inclusion or Exclusion	Notes
EMBASE	Khanna et al	Rheumatoid arthritis	Subcutaneous abatacept	Adalimumab	USA	2013	Waiting for response			
EMBASE	Suenaga et al	Liver fibrosis	Sofosbuvir-ledipasvir and ombitasvir-paritaprevir-ritonavir	Daclatasvir-asunaprevir	Japan	2017	Waiting for response			
EMBASE	Codreanu et al	Active Rheumatoid Arthritis Axial Spondyloarthritis and Psoriatic Arthritis	Certolizumab Pegol	Other subcutaneous anti-tumour necrosis factors	Romania	2014	Waiting for response			
EMBASE	Peral et al	Rheumatoid arthritis	Tofacitinib	Alternative treatment sequences excluding tofacitinib	Spain	2018	Replied	Article being drafted for further publication		
EMBASE	DeAngelo et al	Anticoagulation disorder	International normalized ratio (INR) reversal	3-PCC and 4-factor PCC (4-PCC)	USA	2018	Waiting for response			
EMBASE	Romero Prada et al	Ankylosing spondilytis	Secukinumab	Tnf-a inhibitors	Colombia	2017	Replied	Article being drafted for further publication		
EMBASE	Borget et al	Functional Menorrhagia	1st generation surgery curettage hysterectomy	2nd generation surgery	France	2017	Replied	Article being drafted for further publication		
EMBASE	Saramago et al	Fetal rhesus D status	High-throughput non-invasive prenatal testing	Prophylactic anti-D immunoglobulin treatment	UK	2017	Replied	Article sent	E	Too many interventions being compared. Hard to extract data
EMBASE	Pattisapu et al	Pediatric Grave's disease	Early total thyroidectomy	Standard treatment	USA	2017	Replied	Article being drafted for further		

								publication		
Source	**Authors**	**Disease(s)**	**Innovative technology/ies**	**Usual care**	**Country**	**Year**	**Contact status**	**Author's response**	**Full text - Inclusion or Exclusion**	**Notes**
EMBASE	Parker et al	Degenerative lumbar spine pathology	Variability in outcomes	Variability in costs	USA	2017	Waiting for response			
EMBASE	Ballreich et al	Diabetic Retinopathy	Automated Retinal Image Analysis	Standard screening	Australia	2016	Waiting for response			
EMBASE	Isaranuwatchai et al	Mental health care	Mental Health Engagement Network	Usual care	Canada	2016	Waiting for response			
EMBASE	Relakis et al	Axial spondyloarthritis	Certolizumab pegol	Conventional care	Greece	2015	Waiting for response			
EMBASE	Smith et al	Muscle-Invasive Bladder Cancer	Cystectomy	Chemo-Radiation	USA	2014	Waiting for response			
EMBASE	Giannopoulou et al	Obstructive Sleep Apnea	Mandibular advancement device	Continuous Positive Airway Pressure	The Netherlands	2013	Waiting for response			
EMBASE	Avxentyeva et al	Endometriosis	Dienogest	Gonadotrophin-releasing hormone analogues (GnRHa) or dydrogesterone	Russia	2013	Waiting for response			
EMBASE	Santos et al	Schizophrenia	Aripiprazole	Olanzapine	Brazil	2017	Replied	No further publication planned	E	This work was conducted only as part of a decision making process
EMBASE	Thalange et al	Type 1 diabetes	Insulin degludec	Insulin detemir	UK	2017	Waiting for response			
EMBASE	Huang et al	Respiratory troubles	Nasal Continuous Positive Airway Pressure	Nasal High Flow Therapy	Australia	2018	Replied	Article sent	E	New intervention is more effective
EMBASE	Rocconi et al	Colorectal cancer	Bethesda criteria Sequence all Immunohistochemistry	No screening	USA	2014	Waiting for response			
EMBASE	Luque et al	NA	Secondary prevention with statins	No statin use	Brazil	2015	Waiting for response			

Source	Authors	Disease(s)	Innovative technology/ies	Usual care	Country	Year	Contact status	Author's response	Full text - Inclusion or Exclusion	Notes
EMBASE	Ribeiro et al	Obesity	Immediate surgery	Surgery	Brazil	2016	Replied	Article sent	E	Both outcomes are not decrementally cost-effective
EMBASE	Becker et al	Postpartum venous thromboembolism	Mechanical prophylaxis RCOG risk-based protocol	Local risk-based protocol	USA	2018	Waiting for response			
EMBASE	Tyree et al	Painful diabetic neuropathy	Second-line treatment Third-line treatment	First-line treatment	USA	2018	Replied	Article sent	E	All interventions are more expensive and more effective than usual care
EMBASE	Wymer et al	Peyronie's Disease	Surgery	Collagenase Clostridium Histolyticum	USA	2018	Replied	Article being drafted for further publication		
EMBASE	Veillard et al	Multiple sclerosis	Oral treatment	IV strategy	France	2017	Replied	Article being drafted for further publication		
EMBASE	Mlcoch et al	Metastatic Renal-Cell Carcinoma	Sorafenib	Everolimus	Czech Republic	2017	Replied	No further publication planned	E	Author thinks that there are too many "simplifying" assumptions which would prevent publication
EMBASE	Krysanov et al	Type 2 diabetes	Twice-Daily Exenatide with Insulin Glargine	Once-Daily Liraglutide with Insuline Detemir	Russia	2015	Replied	No further publication planned	E	Poster only. Did not specify why they won't publish
EMBASE	Kievit et al	Rheumatoid Arthritis	Dose optimisation	Normal dose	The Netherlands	2015	Waiting for response			
EMBASE	Charokopou et al	Type 2 Diabetes	Saxagliptin	Glp-1 Analogues	UK	2014	Waiting for response			
EMBASE	Buresi et al	Dyspepsia	Novel strategy	Current strategy	Canada	2014	Replied	Article being drafted for further publication		

Source	Authors	Disease(s)	Innovative technology/ies	Usual care	Country	Year	Contact status	Author's response	Full text - Inclusion or Exclusion	Notes
Clinical Trials	Sibbing et al	Acute Coronary Syndromes	Antiplatelet therapy	Prasugrel	Germany	2018	Waiting for response			
Clinical Trials	Cooper et al	Severe Traumatic Brain Injury	Hypothermia	Standard management	Australia	2018	Waiting for response			
Clinical Trials	Wijkstra et al	Chronic hypercapnic respiratory failure	Home based setting	Hospital based setting	The Netherlands	2018	Replied	Article being drafted for further publication		
Clinical Trials	Holland et al	Chronic obstructive pulmonary disease	Home-based rehabilitation	Centre-based rehabilitation	Australia	2013	Replied	Article undergoing revisions for further publication		
Clinical Trials	Myles et al	Abdominal Surgery	Fluid restriction	Liberal restriction	Australia	2018	Waiting for response			
Clinical Trials	McIntyre et al	HIV	ART given by an HIV-trained doctor	ART given by an HIV-trained primary health care nurse	South Africa	2011	Waiting for response			
Clinical Trials	van Gelder et al	Permanent Atrial Fibrillation	Lenient rate control	Strict rate control	The Netherlands	2010	Waiting for response			
Clinical Trials	Boutelle et al	Childhood obesity	Parent-only treatment	Parent + child treatment	USA	2015	Replied	Article being drafted for further publication		
Clinical Trials	Jackson et al	Hypertension	titrated disease management	Control arm	USA	2018	Waiting for response			
Clinical Trials	Naylor et al	Osteoarthritis	Hospital Inpatient	Home Rehabilitation	Australia	2016	Replied	No further publication planned	E	Due to a lack of health economist, author cannot publish yet
Clinical Trials	Magaziner et al	Hip fracture	PUSH and Nutrition	PULSE and Nutrition	USA	2017	Waiting for response			
Clinical Trials	Kingston et al	Depresion and anxiety	e-screening	Usual screening	Canada	2016	Waiting for response			
Clinical Trials	Turk et al	Ischemic Cerebrovascular Accident	ADAPT approach	Traditional stent retriever	USA	2018	Waiting for response			

Source	Authors	Disease(s)	Innovative technology/ies	Usual care	Country	Year	Contact status	Author's response	Full text - Inclusion or Exclusion	Notes
Clinical Trials	Ng et al	Postoperative Ileus	Electroacupuncture	Fast-track Perioperative Program	China	2014	Waiting for response			
Clinical Trials	Morton et al	Hernia	Use of collagen mesh (Strattice®)	Standard technique	UK	2018	*NA*	*NA*		
Clinical Trials	Rijnders et al	HIV	Direct switch population	Delayed-switch population	The Netherlands	2017	*NA*	*NA*		
Clinical Trials	Haguenoer et al	Cancer	Targeted Communication	Standard communication	France	2015	*NA*	*NA*		
Clinical Trials	Andersen et al	Homelessness Respite care	Two week respite program	usual care	Denmark	2018	*NA*	*NA*		
Clinical Trials	Della Valle et al	Osteoarthritis	Home-based physical therapy	Formal outpatient physical therapy	USA	2018	*NA*	*NA*		
Clinical Trials	McClurg et al	Bowel Dysfunction	Abdominal massage and optimised bowel care	Optimised bowel care only	UK	2017	*NA*	*NA*		
PubMed	van der Graaf et al	Non-obstructive meniscal tears	Early surgery	Conservative treatment	The Netherlands	2016	Replied	Article undergoing revisions for further publication		
PubMed	Desmettre et al	Pneumothorax	Simple aspiration	Standard drainage	France	2011	*NA*	*NA*		
PubMed	Gross et al	Mental health care	Chicago Parent Program	Parent-Child Interaction Therapy	USA	2014	*NA*	*NA*		
PubMed	Romijn et al	Severe anxiety disorder	Blended cognitive behavioural therapy	Face-to-face cognitive behavioural therapy	The Netherlands	2015	*NA*	*NA*		
PubMed	Abbott et al	Acute otitis	Watchful waiting	Antibiotic treatment	Australia	2013	*NA*	*NA*		
PubMed	Broekema et al	Cervical radiculopathy	Posterior foraminotomy	Anterior discectomy with fusion	The Netherlands	2017	*NA*	*NA*		
PubMed	Worthington et al	Benign prostatic obstruction	Thulium laser transurethral vaporesection	Transurethral resection	UK	2017	Waiting for response			
PubMed	Crowley et al	Diabetes	Medication and weight management	Medication management	USA	2017	*NA*	*NA*		
PubMed	Atalay et al	Psoriasis	Dose of biologics	Usual care	The Netherlands	2017	*NA*	*NA*		

Source	Authors	Disease(s)	Innovative technology/ies	Usual care	Country	Year	Contact status	Author's response	Full text - Inclusion or Exclusion	Notes
PubMed	Manley et al	Respiratory troubles	Nasal high flow	Nasal continuous positive airway pressure	Australia	2017	Replied	Article being drafted for further publication		
PubMed	Boland et al	Cellulitis	flucloxacillin	flucloxacillin/phenoxymethylpenicillin	Ireland	2017	*NA*	*NA*		
PubMed	den Broeder et al	Rheumatoid arthritis	Ultra-low-dose RTX	Standard low dose	The Netherlands	2017	*NA*	*NA*		
PubMed	Dorward et al	HIV	POC HIV VL monitoring	Laboratory VL monitoring	South Africa	2017	*NA*	*NA*		
PubMed	Cornelis et al	Acute psychiatric crisis	Intensive Home Treatment	Care-as-usual	The Netherlands	2018	*NA*	*NA*		

APPENDIX 6 ClinicalTrials.org studies with no published paper

For Clinical Trials, out of the 20 studies retrieved, authors were contacted for fourteen studies. To date, we have got three responses: one author mentioned that their paper has already been submitted to a journal and that it is undergoing revisions; one author said that they were planning to submit the paper soon; and one author said they are planning to publish a full manuscript, but they do not have the support of a health economist to help for the analysis.

For the remaining 6 studies, it transpired that one was recently completed without published articles, one was an on-going study meaning that there were not published articles, and results were found through thorough internet searches for the other four studies and they did not meet our inclusion criteria. The details of these six studies are found below and can be found in appendix 5.

i) **NCT02238964: Reinforcement of Closure of Stoma Site.** This study has been recently completed on 18/05/2018. Given its early date of study completion, there were no study results posted on ClinicalTrials.gov. According to the register, cost benefit analysis and quality of life analysis will be performed in 2020.

ii) **NCT02401828: The Dolutegravir Antiretroviral Mono-Therapy for HIV Trial.** Among its secondary outcomes, a cost-effectiveness study was initially planned where cost per QALY during DTG monotherapy was going to be compared with the costs of therapy with the patient's own cART regimen used before study inclusion. To date, not only the recruitment status is unknown, but the non-inferiority trial performed concluded that Dolutegravir should not be used as maintenance monotherapy due to a virological failure that led to dolutegravir resistance.

iii) **NCT02367001: Randomized Trial Evaluating the Effectiveness of the General Practitioner Involvement in Cancer Screening Invitations.** A cost-effectiveness of different strategies for each cancer screening (breast, colorectal and cervical) as measured by the cost-effectiveness ratio (total costs in Euros divided by total screened people) was planned according to the information displayed on ClinicalTrials.gov. The participants of this study are no longer being examined or treated and the study was ended normally. We could not find a clinical trial nor an economic evaluation indexed to this register. However, after manual search, we found its randomized controlled trial which seemed to be a superiority trial.

iv) **NCT02649595: Bridge Copenhagen - Respite Care for Homeless People.** The primary and secondary outcome measures of this study record included health economic costs and it was planned to carry out a cost-utility analysis which could be presented as an incremental cost-effectiveness ratio. Although the recruitment status has been completed and the last update was observed on 30/05/2018, there were no publications provided linked to this register. However, after further extensive manual searching, we found its qualitative study which showed that the intervention was not d-CE.

v) **NCT02883998: Formal vs. Home-Based Physical Therapy After Unicompartmental Knee Arthroplasty**. The non-inferiority clinical trial indexed to this register, concluded that in-home telerehabilitation is non-inferior and supports its use as an effective alternative to face-to-face service delivery after hospital discharge of patients following a total knee arthroplasty. As a part of a secondary outcome measure, a cost comparison was planned in order to assess both interventions 3 weeks, 3 months, and 1 year after surgery. The cost analysis performed concluded that in-home telerehabilitation iis more effective than usual care and thus not DCE.

vi) **NCT03166007: Abdominal Massage for Bowel Dysfunction**. One of the aims of the AMBER trial was to determine the cost-effectiveness of abdominal massage as part of the adjunct to bowel care in people with Multiple Sclerosis who have problems with their bowel. This should have included the measure of costs of the treatments and any costs to the patient and their family. According to the results, the intervention was more costly than the control group and thus dominated by the control group.

APPENDIX 7 PROTOCOLS with no published paper

For PubMed, we have found 15 published protocols. Two protocols were excluded for the following reasons: one protocol was written in French that had not been identified earlier in the screening and one protocol showed within results reported in ClinicalTrials.gov that it was not d-CE. Ten protocols will not be investigated until 2020 since they are too recent: five protocols were recently completed and five protocols are on-going. Three protocols were investigated since we could not find any article and so the authors of each protocol were contacted. All three authors replied, two of them mentioned that their economic evaluation will be published anytime soon (between end of 2019 and beginning of 2020) and one mentioned that his team was hoping to submit for publication the cost-effectiveness analysis around June 2019. The twelve PubMed protocol papers that were excluded or are on hold are described here -

i) **21482337: Comparison of simple aspiration versus standard drainage in the treatment of large primary spontaneous pneumothorax**. The Protocol main paper was written in French, so it was excluded.

ii) **24581245: Study protocol for a comparative effectiveness trial of two parent training programs in a fee-for-service mental health clinic: can we improve mental health services to low-income families? Protocol only with no articles published**. This study is registered in ClinicalTrials.gov (NCT01517867), where we observed the results of their secondary outcome. The Intervention Chicago Parent Program Arm was indeed cheaper, but less effective than the gold standard of Parent-Child Interaction Therapy. However, the study seems to be underpowered: the original sample size of 262 patients was based on a power calculation that was mentioned, but not described in the protocol. Only 161 patients were recruited according to the NCT results and of these, 33 patients actually completed the trial.

iii) **26651478: Cost-effectiveness of blended vs. face-to-face cognitive behavioural therapy for severe anxiety disorders: study protocol of a randomized controlled trial. Protocol only with no articles published**. An incremental cost-effectiveness ratio was planned to obtain the costs per quality-adjusted life years (QALYs) measured by the EQ-5D (5-level version), but the study is not yet completed.

iv) **26941013: A multi-centre open-label randomised non-inferiority trial comparing watchful waiting to antibiotic treatment for acute otitis media without perforation in low-risk urban Aboriginal and Torres Strait Islander children (the WATCH trial): study protocol for a randomised controlled trial**. Protocol on-going with no articles published. An assessment of the cost-effectiveness of watchful waiting compared to immediate antibiotic prescription was planned. No results were published yet since the date of the last participant enrolment is planned for June 2020.

v) **28057652: Study protocol for a randomised controlled multicentre study: the Foraminotomy ACDF Cost-Effectiveness Trial (FACET) in patients with cervical radiculopathy**. Protocol on-going with no articles published. According to the protocol, the objective was to compare clinical outcomes, complication rates and cost-effectiveness of a posterior foraminotomy to an anterior discectomy with fusion. However, no results were found yet since the date of the last participant enrolment is planned for December 2019.

vi) **28445783: Jump starting shared medical appointments for diabetes with weight management: Rationale and design of a randomized controlled trial. Protocol only with no articles published.** Among its secondary outcomes, it was planned to capture costs associated with the Weight Management/Shared Medical Appointment and Shared Medical Appointment interventions for cost-effectiveness or cost-minimization analysis, including intervention-related costs and health care costs. No results were published yet since the protocol was recently completed in on July 2018.

vii) **28482858: Tight controlled dose reduction of biologics in psoriasis patients with low disease activity: a randomized pragmatic non-inferiority trial**. Protocol only with no articles published. Protocol included a non-inferiority study with cost-effectiveness analysis. For cost-effectiveness analyses, questionnaire iMTA PCQ (productivity cost questionnaire) will be administered in each group at every study visit except baseline. No results were published yet since the protocol was recently completed in on July 2018.

viii) **28760210: A randomized trial of a 1-hour troponin T protocol in suspected acute coronary syndromes: Design of the Rapid Assessment of Possible ACS In the emergency Department with high sensitivity Troponin T (RAPID-TnT) study.** Protocol is on-going. It includes performing a non-inferiority trial which will evaluate the effectiveness, safety and cost-effectiveness of a management strategy. The date of last participant enrolment was anticipated to occur on March 2019. Data collection has not taken place yet.

ix) **28836993: The Penicillin for the Emergency Department Outpatient treatment of CELLulitis (PEDOCELL) trial: update to the study protocol and detailed statistical analysis plan (SAP).** Protocol is on-going. It is planned to perform a cost-effectiveness analysis which will consist of a within-trial evaluation of the cost QALY for oral flucloxacillin compared with oral flucloxacillin and phenoxymethyl penicillin. The estimated study completion date is set for December 2019.

x) **28854956: Ultra-low dose of rituximab in rheumatoid arthritis: study protocol for a randomised controlled trial.** Protocol only with no articles published. Even if the protocol shows that there might be a d-CE intervention, no results were published yet since the protocol was recently completed on December 2018.

xi) **28963304: Protocol for a randomised controlled implementation trial of point-of-care viral load testing and task shifting: the Simplifying HIV TREAtment and Monitoring (STREAM) study.** Protocol only with no articles published. It aims to demonstrate whether POC VL testing combined with task shifting to enrolled nurses is non-inferior and cost-effective compared with laboratory-based VL monitoring and standard HIV care. No results were published yet since the protocol's actual study completion date was on October 2018, which means it was recently completed.

xii) **29486741: Intensive home treatment for patients in acute psychiatric crisis situations: a multicentre randomized controlled trial.** Protocol only with no articles published. It is planned to carry out an economic evaluation alongside a randomized controlled trial in order to assess the cost-effectiveness and cost-utility of Intensive Home Treatment compared to care-as-usual. No results were published yet since the protocol was recently completed on May 2018.

APPENDIX 8 Embase conference abstract status

For EMBASE, full manuscripts for all 31 studies were requested by contacting their first authors.

To date, 14 replies from authors have been received whose studies were found in EMBASE.

Five of them sent us by e-mail either the full article text (n=4) or a poster (n=1). Three of these papers were excluded because they were not decrementally cost-effective, one paper had too many interventions with varying results and no clear DCER could be extracted. The study results in poster form were evaluated and we concluded it was not d-CE.

Seven other authors replied and mentioned that they were thinking of publishing the full text article in the coming months. Among the reasons for their delay on publication, we were informed of the following: one author specified that their delay was due to a last minute demission of some team members in charge of drafting the article; two authors mentioned that the initial objective was set as to be a short abstract for an annual meeting presentation and afterwards they came up with the idea of drafting a full text article; one author mentioned that the article is being revised by a journal; and three authors mentioned their respective articles are being currently drafted. Due to reticence encountered in sharing their non-published results with us, we plan to re-contact these authors in 2020.

Two authors mentioned they had no plans of further publication and argued the following: one said that the work done was only conducted as part of a decision-making process and the other one said that his team thinks there may be too many simplifying assumptions which would avoid the paper's acceptance for further publication.