



Incorporating future unrelated medical costs in cost-effectiveness analysis in China

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ABSTRACT

The occurrence of future unrelated medical costs is a direct consequence of life-prolonging interventions, but most pharmacoeconomic guidelines recommend the exclusion of these costs. The Chinese guidelines were updated in 2020, taking an exclusion approach for the future unrelated medical cost. We notice the research surrounding this issue continues in other countries and leads to an inclusion recommendation in some guidelines. Meanwhile, this issue has not been discussed in China, reflecting an urgent need for extensive research on its impact. We reviewed the theoretical and practical studies surrounding the inclusion of future unrelated medical costs, summarised the landscape of guidelines in other jurisdictions. We found that the inclusion would increase the internal and external consistency of economic evaluation and the comparability of results between different jurisdictions. However, more research is needed surrounding this issue. We proposed a future research agenda to inform the update of Chinese guidelines. We recommend research on individual-level healthcare reimbursement data and end-of-life costs from hospital administrative data to generate the age-specific, sex-specific and condition-specific costs. We also recommend establishing a formal process to evaluate the ethical and economic impact of including future unrelated medical costs and adjust the threshold accordingly in the guidelines.

BACKGROUND

Through cost-effectiveness analysis (CEA), healthcare researchers incorporate health benefits (eg, life-years gained) and costs to evaluate and compare different healthcare programmes and thereby make recommendations to decision-makers on the allocation of health resources.¹ The National Institute for Health and Care Excellence (NICE) in the UK published national pharmacoeconomic guidelines to the CEA practice, and so did some other countries (eg, Canada, Australia). China published the first version of pharmacoeconomic guidelines in 2011 and updated it in 2020 to guide the CEAs in China.² In

Summary box

What is already known?

► Including future unrelated medical costs in cost-effectiveness analysis is in debate and some health technology assessment (HTA) guidelines recommend an inclusion approach.

What are the new findings?

► We reviewed the studies supporting the exclusion or inclusion approach and the HTA guidelines in 43 jurisdictions about their recommendations towards future unrelated medical costs. The inclusion of future unrelated medical costs in cost-effectiveness analysis would increase the internal and external consistency and the comparability of analysis results between different jurisdictions.

What do the new findings imply?

► We proposed a research agenda that what types of fundamental research would inform the Chinese guidelines on estimating future unrelated medical costs.

the updated version, a societal perspective is recommended, especially when the expenditure is publicly funded. The guidelines make it clear that, under the societal perspective, all direct, indirect and intangible costs should be included. Direct costs refer to costs related to the intervention under economic evaluation, whereas indirect costs refer to productivity loss in the guidelines. Intangible costs refer to the physical and psychological discomfort (eg, pain, anxiety, tension) caused by the intervention of interest, being captured by the quality-adjusted life-years (QALYs). The guidelines do not recommend a unified incremental cost-effectiveness ratio (ICER) threshold for economic evaluation. Instead, a range is recommended that lies between one and three times the per capita gross domestic product. Researchers may select a threshold within the range according to the context where the evaluation is conducted.

Although CEA is increasingly used to assess whether healthcare interventions produce value for money, many methodological challenges exist in China that require attention.^{3,4} One such issue is whether to include future medical costs in CEA and, if so, to what extent they should be included.⁵ Future medical costs are incurred by future medical consumption during the life-years gained that would not have been consumed without a life-extending intervention. They are typically divided into future ‘related’ and ‘unrelated’ medical costs. The former refers to costs associated with treatments in the extended life that are directly related to the disease being treated by the life-extending intervention. For example, a heart transplant surgery extends a patient’s life, who should thereafter routinely visit a cardiologist to ensure the heart works normally. The costs associated with the visits are future related medical costs. The latter—future unrelated medical costs—refers to all the costs associated with diseases in the extended life that are *not* related to the disease and the life-extending intervention of interest. Therefore, future unrelated medical costs are the consequences of the life-extending intervention from a societal perspective. In the above-mentioned example, if the patient experiences cancer during the extended life, the costs associated with the cancer treatment belong to future unrelated medical costs.

Future-related medical costs are typically included in current CEA practice. Nevertheless, it is still in a debate whether to include future unrelated medical costs in CEA.^{6,7} This issue has not been discussed among Chinese health economists, because the latest guidelines do not include future unrelated medical costs in the cost inventory.² In contrast, this line of research continues in other countries and leads to the recommendation of including such costs.⁸ Since the Chinese guidelines prioritise the societal perspective, the issue of future unrelated medical costs deserves an extensive discussion. Therefore, we reviewed the theoretical debate surrounding the inclusion of future unrelated medical costs and the recommendations by official pharmacoeconomic guidelines in other jurisdictions and proposed an agenda for future research on this issue in China.

We conducted a scoping review of studies discussing the inclusion of future unrelated medical costs in CEA. The search was conducted in EMBASE and MEDLINE. We used two categories of keywords: (1) terms regarding future unrelated medical cost, including ‘future cost’, ‘future medical cost’, ‘unrelated cost’, ‘unrelated medical cost’ and ‘survivor cost’ and (2) terms regarding economic evaluation, including ‘cost-effectiveness analysis’, ‘cost–utility analysis’, ‘cost–benefit analysis’, ‘health technology assessment’ and ‘economic evaluation’. We conducted the search in May 2021. The inclusion criteria were: (1) peer-reviewed articles discussing the inclusion of future unrelated medical costs in CEA and (2) CEA studies if the analysis was an example to assess the impact of including future costs. In addition, to provide a landscape of official recommendations on the inclusion of

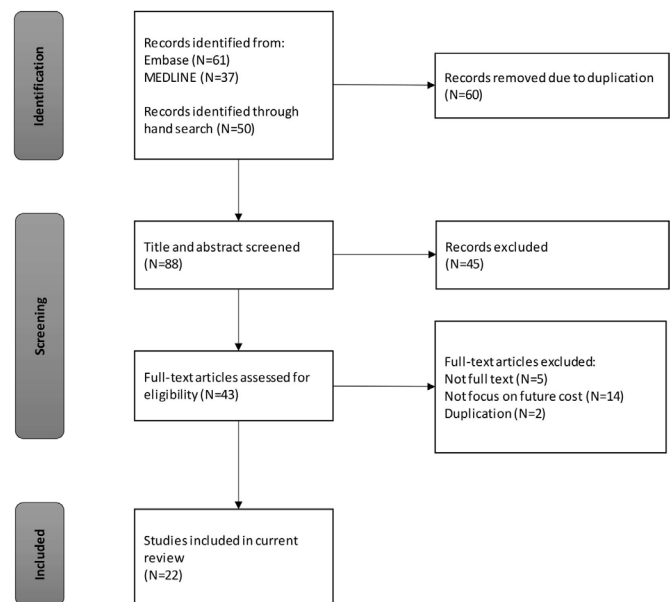


Figure 1 Flow chart for the search of eligible studies (attached as a separate PDF).

future unrelated medical costs, we referred to the Professional Society for Health Economics and Outcomes Research website to search for the pharmacoeconomic guidelines of different jurisdictions.

Two authors (SJ and YW) independently screened the search results to examine their eligibility for inclusion. The references of included studies were also examined to prevent the missing of relevant studies. For the included articles, we extracted their bibliographic and methodological information, opinions and conclusions. For official guidelines, we extracted the bibliographic information (ie, country, year, organisation, title) and their recommendations on whether to include future unrelated medical costs. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans to research. We finally included 22 articles (figure 1). Their main conclusions are presented in table 1 and bibliographic information in online supplemental table S1. Through the review of these articles, we summarised their opinions and associated evidence as below.

ARGUMENTS SUPPORTING EXCLUSION

First, a widely spread argument is that the new treatments should be evaluated independently.¹ It argues that when economic evaluation is being made, there is no commitment to deliver future unrelated care; as such, future unrelated medical care is not a necessary consequence of the life-prolonging intervention and should be excluded. The independence also implies that the future unrelated care could be evaluated separately, apart from the intervention of interest.

Second, some researchers admitted that the incurrance of future unrelated medical costs was a consequence of life-prolonging intervention, but the exclusion

Table 1 An overview of studies discussing the inclusion of future unrelated medical costs in cost-effectiveness analysis

Author	Area	Year	Article type	Recommendation	Key points on unrelated medical costs
Meltzer ¹⁸	USA	1997	Economic model	Inclusion	<ul style="list-style-type: none"> ▶ Cost-effectiveness criteria are strictly consistent with a model of lifetime utility maximisation only if they account for effects on future related and unrelated medical expenditures. ▶ The magnitude of unrelated medical expenditures, consumption, and earnings may be large enough to alter the cost-effectiveness.
Garber and Phelps ⁹	USA	1997	Economic model	Exclusion	<ul style="list-style-type: none"> ▶ The inclusion or exclusion of future unrelated medical costs will not affect the ranking of cost effectiveness ratios, so that they can be neglected. ▶ The inclusion of future unrelated medical costs will only add a constant figure to all cost-effectiveness ratios.
Meltzer and Johannesson ⁴¹	USA	1999	Review	Inclusion	<ul style="list-style-type: none"> ▶ The US Panel made inconsistent recommendations by not including the future unrelated costs, which would seriously distort comparisons of healthcare programmes. ▶ The inconsistency could be corrected by including the future unrelated costs, either medical or non-medical.
van Baal <i>et al</i> ²⁰	NL	2007	Economic model and case study	Inclusion	<ul style="list-style-type: none"> ▶ For primary prevention only a cost utility ratio that includes both the costs and effects of unrelated medical care meets the criterion of internal consistency and is related to a meaningful decision problem.
Rappange <i>et al</i> ⁶	NL	2008	Review	Inclusion	<ul style="list-style-type: none"> ▶ Only inclusion of all costs and effects of unrelated medical care in life-years gained can be considered both internally and externally consistent. ▶ Including or excluding unrelated future medical costs may have important distributional consequences, especially for interventions that substantially increase length of life. ▶ It is becoming increasingly possible to accurately estimate unrelated medical costs in life-years gained.
Garber and Phelps ¹⁰	USA	2008	Editorial	Exclusion	<ul style="list-style-type: none"> ▶ If the future costs were truly unrelated, it did not matter whether such costs were included or excluded, as long as the cost effectiveness threshold was properly adjusted.
Lee ¹¹	USA	2008	Economic model	Exclusion	<ul style="list-style-type: none"> ▶ The controversy for unrelated future costs in the literature is due to differences in modelling budget constraints. ▶ Analyses that use a Conditional budget constraint imply that unrelated future costs need not be considered. ▶ Analyses that use an Annuity budget constraint imply that future savings by a wide range of unrelated future costs need to be considered. ▶ The paper goes on to argue that Conditional budget constraints are preferable. ▶ Health maximisation and utility maximisation require accounting for the present value related future costs and ignoring unrelated future costs. ▶ It is difficult to disentangle 'related' costs from 'unrelated' costs.
Meltzer ¹²	USA	2008	Correspondence	Inclusion	<ul style="list-style-type: none"> ▶ Economic models of intertemporal resource allocation to maximise utility under uncertainty imply that all future costs net of earnings should be included in cost-effectiveness analysis.
Feenstra <i>et al</i> ⁴²	NL	2008	Correspondence	Inclusion	<ul style="list-style-type: none"> ▶ Lee's paper did not resolve any controversy on the inclusion of future unrelated medical costs. ▶ The practical problems in estimating are not unique nor sufficient reasons to ignore them and progress has been made for estimation.
van Baal <i>et al</i> ⁴³	NL	2013	Commentary	Inclusion	<ul style="list-style-type: none"> ▶ Excluding future costs complicates comparisons of economic evaluations across disease areas and patient groups. ▶ Pharmacoeconomic guidelines should be changed to include future unrelated medical costs.
Grima <i>et al</i> ¹⁶	CA	2013	Correspondence	Exclusion	<ul style="list-style-type: none"> ▶ Dialysis costs should be considered unrelated to a life-extending therapy. ▶ Exclusion future unrelated costs is entirely consistent with current pharmacoeconomic guidelines and clinical practice, providing cost-effectiveness ratios that are comparable to other products.
Gros <i>et al</i> ⁴⁴	ES	2015	Review	Inclusion	<ul style="list-style-type: none"> ▶ All relevant costs for the perspective selected should probably be included in economic evaluations including related or unrelated, direct or indirect future costs.
Morton <i>et al</i> ³¹	UK	2016	Editorial	Inclusion	<ul style="list-style-type: none"> ▶ There is no rationale for excluding unrelated future costs, while at the same time including unrelated future benefits in an economic evaluation. ▶ Including the costs of future healthcare decisions may make a material difference to results. ▶ Including 'related' but excluding 'unrelated' future costs requires analysts to make judgements about whether particular costs are related or unrelated.

Continued

Table 1 Continued

Author	Area	Year	Article type	Recommendation	Key points on unrelated medical costs
van Baal <i>et al</i> ¹⁵	NL	2016	Economic model and case study	Inclusion	<ul style="list-style-type: none"> ▶ Practical relevance of including the costs of future unrelated medical care is illustrated using the example of transcatheter aortic valve implantation. ▶ The optimal decisions within a healthcare perspective require future unrelated medical costs to be included. ▶ Consistency requires that the benefits of unrelated medical care should also be excluded if costs thereof are excluded. ▶ Excluding the costs and benefits in some circumstances may erroneously result in labelling a cost-effective intervention as cost-ineffective.
van Baal <i>et al</i> ¹⁷	NL	2017	Head-to-head debate	Mixed	<ul style="list-style-type: none"> ▶ Inclusion: van Baal <i>et al</i> thought more health would result from including all future care costs in decisions to approve interventions. ▶ Exclusion: Sarah Davis worried that always including unrelated costs might lead to unfair distribution of care, including among people with incurable illness.
van Lier <i>et al</i> ⁷	NL	2018	Review and survey	Inclusion	<ul style="list-style-type: none"> ▶ A consensus was not reached on the inclusion of healthcare costs unrelated to the intervention (round 1, 53% agreement; round 2, 50% agreement). ▶ Panellists in favour of inclusion argued that unrelated future healthcare costs should theoretically be included if an intervention prolongs life and if important differences in future costs between interventions are expected. ▶ Others argued against inclusion on the basis that the calculations are difficult as many assumptions are made. ▶ The steering committee recommended the inclusion of related and unrelated future healthcare costs if the intervention is expected to result in an extension of life, because it represent a true use of resources.
McCabe ⁴⁵	CA	2019	Commentary	Exclusion	<ul style="list-style-type: none"> ▶ Economic evaluation is rarely to identify and quantify the impact of ill health but informs decisions about whether a specific technology should be funded from fixed budget. Therefore, consideration of the scope of costs and benefits for inclusion has a normative component that derives from the policy objectives. ▶ The expansion of the scope of costs and benefits beyond direct costs and health accruing to the treated individuals may lead to unintended effects on the distribution.
Tew <i>et al</i> ⁴⁶	AU	2019	Empirical	Inclusion	<ul style="list-style-type: none"> ▶ There is value in the inclusion of future medical costs in economic evaluation to support decision-makers' considerations relating to future healthcare budgets. ▶ This study demonstrated the practicability of including future medical costs in an economic evaluation in cancer patients. ▶ There is considerable heterogeneity in the ICERs across different cancer types and the types of future costs included do not impact all cancers consistently.
de Vries <i>et al</i> ⁵	NL	2019	Review	Inclusion	<ul style="list-style-type: none"> ▶ To allow optimal decisions, both from a healthcare and societal perspective, including the additional related and unrelated medical costs in economic evaluations is required. ▶ Knowledge on how to estimate future (unrelated) medical costs has improved, also allowing inclusion in practice. ▶ Inclusion of these costs would presumably benefit most from lowering the practical difficulties and the burden on the analyst of including these costs in a cost-effectiveness analysis, as well as guidelines prescribing or at least encouraging inclusion rather than prescribing exclusion.
van Baal <i>et al</i> ⁴⁷	NL	2019	Review	Inclusion	<ul style="list-style-type: none"> ▶ Including the costs of unrelated medical care makes sense as these costs also contribute to the health gains which are implicitly included in practice. ▶ Future unrelated costs are real and will affect the budget left for other care. ▶ Ignoring future unrelated medical costs results in an underestimate of QALY losses of unidentified patients in the future. ▶ For some patient groups, including future unrelated medical costs may imply a huge increase in the ICER for life-prolonging technologies and thereby trigger difficult ethical debates.
Kellerborg <i>et al</i> ¹⁴	NL	2020	Guideline	Inclusion	<ul style="list-style-type: none"> ▶ The practical difficulties around the estimation of future costs can be overcome. ▶ The case studies demonstrate that including future costs, even just unrelated medical costs, can have a substantial effect on the ICER, which could affect decision-makers' choices.
Perry-Duxbury <i>et al</i> ¹⁹	NL	2020	Empirical study	Inclusion	<ul style="list-style-type: none"> ▶ The results show that including future unrelated medical costs is feasible and standardisable. ▶ Empirical examples show that this inclusion leads to an increase in the ICER of between 7% and 13%.

AU, Australia; CA, Canada; ES, Spain; ICER, incremental cost-effectiveness ratio; NL, the Netherlands; QALYs, quality-adjusted life-years.

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of these costs would not affect the ranking of the cost-effectiveness ratios of alternative interventions.^{9–11} For example, Garber and Phelps argued that, based on their theoretical model, including the future costs would only add a constant figure to all the ratios and excluding these costs would simplify the calculation.⁹ Their conclusion was based on the assumption that patient's consumption plus medical expenditures were equal to earnings in each period.¹²

Third, some researchers emphasised the difficulties in estimating the future unrelated medical costs as an argument not to include these costs.^{7 13} Indeed, taking a bottom-up approach and predicting the risk of unrelated diseases in the future seems very difficult, if not impossible.¹⁴ Another concern is the difficulties when disentangling the 'related' and 'unrelated' costs.¹⁵ In practice, it is impossible to identify a 'clear-cut' between the two categories because we rarely know the covariance between future diseases. The two difficulties may place an extreme analytic burden on researchers.

Fourth, the ethical concern is another reason supporting the exclusion.^{1 16 17} Some researchers were concerned that the inclusion might cause the removal of some interventions previously funded by public insurance and the patients' lives would be threatened.¹⁷ A frequently mentioned example is dialysis.¹⁷ When assessing a life-extending intervention in patients receiving dialysis, if the costs of dialysis as the future unrelated medical care are included, the value of life-years gained by the intervention may not outweigh the cost of dialysis. In that case, the intervention will not be funded even if it is provided at zero cost.

ARGUMENTS SUPPORTING INCLUSION

All arguments supporting exclusion have received rebuttals. In contrast to the first argument supporting the exclusion, some researchers argued that future unrelated medical care would usually be funded and cause real opportunity costs in the future.¹⁵ Because the healthcare authority functions intertemporally and future medical costs are part of opportunity cost considered by the authority. Therefore, it makes no sense to exclude future unrelated costs just because they are independent of the intervention being evaluated.

Second, unlike Garber and Phelps's model, Meltzer developed a generalised model, proving that lifetime utility maximisation would only be achieved by accounting for future related and unrelated medical costs.¹⁸ He appraised the models by Garber and Phelps and by Lee and criticised that the assumptions of their models were based on unrealistic assumptions that were difficult to justify.¹² In his model, Meltzer relaxed the assumptions and assumed that future medical costs vary under different conditions. Meltzer demonstrated that the inclusion of future unrelated medical costs could be large enough to alter the rank of cost-effectiveness ratios of different interventions. Therefore, to ensure that the

health resources are distributed unbiasedly, including future unrelated medical costs is necessary.

Third, the concerns regarding the practical difficulties have been refuted.¹⁹ Although the difficulties exist, the estimation of ageing effect on healthcare expenditure shed light on how we could predict the future unrelated medical costs.¹⁷ Instead of predicting future risk of unrelated diseases, we could apply a top-down approach and use the healthcare expenditure per capita by age and sex to estimate the average future medical costs.¹⁴ In the Netherlands, this approach has been applied by a group of health economists to develop a future cost estimation tool, known as Practical Application to Include Future Disease Costs (PAID).¹⁴ They linked the age-specific and sex-specific per-capita medical costs to the survival curves and then add these costs to the cost inventory of the intervention in research to approximate the total future medical costs. This approach has made the estimation feasible and straightforward. Moreover, the inclusion of future unrelated medical costs would reduce the analytic burden. In contrast to the exclusion approach, which requires researchers to disentangle 'related' and 'unrelated' costs, the inclusion approach makes it unnecessary to disentangle the two types but consider them all, which is a relief to CEA analysts.

Fourth, the ethical concerns have been refuted.^{5 17} Since the future unrelated medical costs are real opportunity costs, indicating that people in the future may use the money for health gains, the inclusion has ethical implications. If we ignore these costs, are we willing to sacrifice the health gains of patients in the future? As van Baal *et al* said, 'Pretending that future unrelated medical costs do not exist is equivalent to deeming the lives of some future patients worthless, which is neither fair nor ethically acceptable.'¹⁷ The ignorance of these costs is always inappropriate in dealing with ethical questions, threatening the credibility of CEAs. If we care about the ethical issues, we should address them through a formal process to assess the ethical impact of the inclusion and evaluate whether the budget has been optimally allocated.

In addition to the rebuttals, researchers provided other arguments supporting the inclusion, one of which is about the internal consistency of CEA.^{5 20 21} In the current practice, the improved quality of life and prolonged life-years are projected in the analysis. Implicitly, the health benefits require the use of unrelated medical care in the future. It is internally inconsistent to include the future benefits derived from unrelated medical care but exclude the associated costs. To ensure internal consistency, Nyman developed rules and required that all costs producing projected health benefits be included.²²

Another argument is that excluding future unrelated medical costs would underestimate the opportunity cost of life-prolonging interventions.¹⁵ This argument is connected to the rebuttal to the ethical concerns. Under a fixed intertemporal healthcare budget, life-prolonging interventions will consume some budgets in the future. The consumption will lead to a decrease in the per-capita

healthcare budget in the future. In this sense, the life-prolonging interventions cause opportunity costs for others in the future. Thus, intervention with very high opportunity costs may simply mean it is unattractive and should not be invested.

External consistency is another argument.^{6 20} Some researchers argued that the CEAs should be most informative for decision-makers. Thus, excluding future unrelated medical costs would decrease the external validity of CEA, as it reduces the amount of useful information for decision making.

A LANDSCAPE OF CURRENT GUIDELINES IN OTHER JURISDICTIONS

A total of 43 guidelines from 41 jurisdictions are summarised in [table 2](#) with references presented in online supplemental table S2. Of the 43 guidelines, most (60%) do not specify the inclusion or exclusion of future unrelated medical costs in CEA. Three guidelines (7%) from the USA and the Netherlands recommend an inclusion approach. The second panel guidelines from the USA indicate that both the healthcare sector perspective and societal perspective need to include the future related and unrelated medical costs. The Institute for Clinical and Economic Review (ICER) guidelines from the US also recommend the inclusion approach and presenting a separate scenario analysis by excluding future unrelated medical costs when an intervention that increases QALYs is found to be cost-ineffective. The Netherlands guidelines indicate that if the intervention could increase the life expectancy, both related and unrelated future medical costs should be considered. This is the first national guideline that make the inclusion approach mandatory. It is worth noting that the Swedish guidelines experienced a back-and-forth process on the inclusion of future unrelated medical costs.²³ In 2013, the guidelines prescribed an inclusion approach. In 2015, the guidelines were changed by excluding future unrelated medical costs.

Contrarily, 11 guidelines (26%) explicitly recommend an exclusion approach, while most of them do not provide justifications. The NICE guidelines currently exclude future unrelated medical costs from the analysis.²⁴ However, it is reviewing the inclusion in its guidance.²⁵ Three guidelines (7%) from Hungary, Belgium and Germany recommend excluding the future unrelated medical costs in the base case and considering them in the separate analysis if they were deemed essential for some interventions.

A RESEARCH AGENDA TO INFORM CHINESE GUIDELINES

By summarising the arguments supporting the exclusion and inclusion of future unrelated medical costs, we found a growing consensus that the inclusion has a solid theoretical basis. While practical difficulties exist, researchers have made progress in addressing these issues. However, we found that most pharmacoeconomic guidelines do

not yet respond to the methodological progress on this issue, whereas only a few guidelines recognise the importance of this issue and recommend inclusion. Since Chinese pharmacoeconomic guidelines prescribe a societal perspective, this issue is worthy of more attention than other methodological and ethical challenges that persist in China.^{4 26} We acknowledge that recent CEAs have made efforts in defining a clear cost inventory for the Chinese population;^{27–29} however, we deem that more research is needed to reduce methodological difficulties concerning future unrelated medical costs.

First, due to the establishment of province-level electronic reimbursement systems in recent years, most Chinese provinces have accumulated individual-level reimbursement records. Though the variables are limited (eg, age, sex, health condition and reimbursed payment), these data may play as a starting point in estimating the future unrelated medical costs, as what has been done in PAID.²¹ For example, researchers may use the data to establish regression models to predict the age-specific, sex-specific and condition-specific costs paid by the reimbursement system. Since there is no provincial administrative data in most Chinese provinces, the numbers derived from the regression models may provide a justifiable estimate of future unrelated medical costs for patient lives. The regression results could also be used to calculate condition-specific *total* costs because the condition-specific reimbursement rate is transparent.

Second, the end-of-life costs are unclear in China. Since the healthcare expenditure is usually concentrated in the last stage of life,^{21 30} it is essential to figure out how much has been spent at the end-of-life stage by disease-related groups (DRGs). A possible approach is to work with provincial top-tier hospitals and use the hospital administrative data to establish regression models for end-of-life cost estimation by DRGs. As a result, given that the intervention of interest belongs to one DRG, the end-of-life costs of other DRGs contribute largely to the future unrelated medical costs.

Third, the literature discussing future unrelated medical costs implicitly assumes that the standard of care for the unrelated future diseases and associated expenditure remains the same in the projected life-years gained.³¹ This is an unrealistic assumption because healthcare technologies advance over time, and the standard of care and associated costs would change accordingly. However, it would be extremely difficult to predict how we may deal with health conditions in the future and how the technology progress may alter the costs. As a starting point, we may assume that healthcare technology develops constantly in the future and the associated costs decrease at a corresponding rate. With this assumption, we could establish functions to predict the future unrelated medical costs, based on the amount derived from the provincial reimbursement data.

Fourth, the Chinese Health Technology Assessment (HTA) agencies and health economists should establish a formal process to evaluate the ethical and economic

Table 2 Recommendations on future unrelated medical costs by official guidelines for economic evaluation in different jurisdictions

Country/area	Guidelines	Year	Inclusion or exclusion	Recommendations (if available)
Africa				
South Africa	Guidelines for Pharmacoeconomic Evaluations of Medicines and Scheduled Substances	2013	Not specified	▶ In general, indirect costs should not be included in the submission.
Egypt	Recommendations for Reporting Pharmacoeconomic Evaluations in Egypt	2013	Not specified	▶ Direct medical costs should be included. ▶ Other direct non-medical and indirect costs paid by patients, including lost productivity costs, might be included only in the sensitivity analysis.
Latin America				
Brazil	Methodological Guidelines: Economic Evaluation of Health Technologies	2014	Not specified	▶ The included cost components should be described in detail and separated by type of cost (medical-hospital rights, non-medical-hospital, indirect and intangible direct cost).
Colombia	Manual Para la Elaboración de Evaluaciones Económicas en Salud	2014	Not specified	▶ Direct costs for the healthcare system should be considered. ▶ Indirect costs and direct non-medical costs should be excluded, such as productivity and other costs assumed by patients on the base case.
Cuba	Methodological Guidelines for Health Economic Evaluation	2003	Not specified	▶ All relevant cost data should be clearly identified and explained in detail.
Mexico	Economic Assessment Study Guideline for Updating the National Formulary in Mexico	2015	Not specified	▶ The suggested perspective only included the direct costs.
MERCOSUR (Argentina, Brazil, Paraguay, Uruguay)	Guideline for Economic Evaluation of Health Technologies	2015	Not specified	▶ The costs such as direct healthcare costs, indirect costs, patient and family costs and productivity loss should be appropriate for the chosen perspective.
North America				
USA	ICER's Base case for Economic Evaluations: Principles and Rationale	2020	Inclusion	▶ In cases where an intervention that increases QALYs is not found to be cost effective, even with a zero-dollar price, a separate scenario analysis excluding unrelated (non-drug) healthcare costs will be presented.
USA	Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses Second Panel on Cost-Effectiveness in Health and Medicine	2016	Inclusion	▶ The new recommendations suggest the inclusion of future costs (ie, that cost effectiveness analyses account for related or unrelated healthcare costs that occur during the additional life-years produced by an intervention).
USA	AMCP Format for Formulary Submissions Guidance on Submission of Pre-approval and Post-approval Clinical and Economic Information and Evidence	2019	Not specified	▶ The model should be disease-based and depict the costs of the product and other medical resources consumed within each clinical pathway, including the economic impact of adverse events.
Canada	Guidelines for the Economic Evaluation of Health Technologies: Canada fourth Edition	2017	Not specified	▶ The evaluation should include all relevant resources and costs based on the perspective of funded healthcare payer.
Asia				
China (Mainland)	China Guidelines for Pharmacoeconomic Evaluations	2020	Exclusion	▶ The costs unrelated to the target disease or the intervention can be excluded.
Japan	Guideline for Preparing Cost-Effectiveness Evaluation to the Central Social Insurance Medical Council	2019	Exclusion	▶ Healthcare costs of each health state include only related costs that are directly affected by the selected technology and do not include unrelated costs.
Malaysia	Pharmacoeconomic guidelines for Malaysia second edition	2019	Not specified	▶ All direct costs relevant to the services borne by the payer.
Taiwan of China	Guidelines of Methodological Standards for Pharmacoeconomic Evaluations (V.1.1, draft)	2008	Exclusion	▶ For the extended life-year cost, the costs those are not related to target disease should be excluded.

Continued

Table 2 Continued

Country/area	Guidelines	Year	Inclusion or exclusion	Recommendations (if available)
South Korea	Korean Guidelines for Pharmacoeconomic Evaluation (Second and Updated Version)	2013	Exclusion	<ul style="list-style-type: none"> ▶ All costs not including productivity costs, unrelated future medical cost should be considered.
Israel	Guidelines for the Submission of a Request to Include a Pharmaceutical Product in the National List of Health Services	2010	Not specified	<ul style="list-style-type: none"> ▶ The costs are direct and indirect medical costs. ▶ If use of the new technology requires or spares spending on other medical technologies, these costs should be included in the calculation.
Thailand	Guidelines for health technology assessment in Thailand (second edition)	2014	Not specified	<ul style="list-style-type: none"> ▶ The choice whether to include or exclude future unrelated costs will depend on the payer requirement and perspective.
Europe				
Austria	Guidelines on Health Economic Evaluation Consensus paper	2006	Not specified	<ul style="list-style-type: none"> ▶ Fundamentally, all costs relevant to the chosen perspective must be determined and included in the analysis.
Denmark	The Danish Approach to Standards for Economic Evaluation Methodologies	1997	Not specified	<ul style="list-style-type: none"> ▶ All relevant costs should be considered including direct, indirect and intangible costs ▶ Indirect and intangible costs should be reported separately and valued on if they are considered relevant.
Hungary	Professional Healthcare Guideline on the Methodology of Health Technology Assessment	2017	Exclusion in base case. Inclusion in supplementary analysis	<ul style="list-style-type: none"> ▶ Costs generated due to diseases not related to the given health service, costs emerging in the life lengthened by the therapy but not due to the disease examined in the analysis, or other indirect costs cannot be presented, or, in justified cases, can be presented in additional analyses.
Italy	Guidance to applicants for the submission of pharmacoeconomic analysis within the Pricing and Reimbursement Dossier	2020	Not specified	<ul style="list-style-type: none"> ▶ In the base case, it is required to include the direct healthcare costs in line with the NHS perspective. ▶ Indirect costs and non-health care costs could be considered in a supplementary analysis from the societal perspective.
Russian Federation	Guidelines for Conducting a Comparative Clinical and Economic Evaluation of Drugs	2016	Not specified	<ul style="list-style-type: none"> ▶ Direct medical costs are mandatory. ▶ Accounting for other types of costs remains at the discretion of researchers and different types of costs are indicated separately.
Spain	Spanish Recommendations on Economic Evaluation of Health Technologies	2010	Not specified	The societal perspective is recommended considering all the related costs.
Croatia	The Croatian Guideline for Health Technology Assessment Process and Reporting	2011	Not specified	<ul style="list-style-type: none"> ▶ Where measurable and relevant, indirect costs and costs falling outside of Croatian Institute for Health Insurance should be reported separately.
Baltic (Latvia, Lithuania, Estonia)	Baltic Guideline for Economic Evaluation of Pharmaceuticals (Pharmacoeconomic Analysis)	2002	Not specified	<ul style="list-style-type: none"> ▶ The suggested perspective includes only direct healthcare costs. ▶ If relevant, include all costs outside healthcare system, presented separately.
Belgium	Belgian Guidelines for Economic Evaluations and Budget Impact Analyses: Second Edition	2015	Exclusion in base case; Inclusion in supplementary analysis	<ul style="list-style-type: none"> ▶ Costs borne outside the healthcare sector should not be included in the Base case analysis; ▶ If productivity losses, non-health care costs and/or unrelated healthcare costs are deemed important for a specific treatment, they may be presented in a separate analysis.
France	Choices In Methods for Economic Evaluation	2012	Exclusion	<ul style="list-style-type: none"> ▶ Future costs independent of the interventions being studied are not considered
Germany	Working Paper Cost Estimation	2009	Exclusion in base case; Inclusion in supplementary analysis	<p>Summing up the controversial discussion on future costs, the following recommendations apply:</p> <ul style="list-style-type: none"> ▶ Only future related costs should be considered in the base case. ▶ In sensitivity analyses, total healthcare costs (related and unrelated healthcare costs) in life-years gained should also be calculated if possible.

Continued

Table 2 Continued

Country/area	Guidelines	Year	Inclusion or exclusion	Recommendations (if available)
Ireland	Guidelines for the Economic Evaluation of Health Technologies in Ireland	2019	Not specified	▶ Only direct costs relevant to the public-funded health and social care system should be included in the base case.
Netherlands	Guideline for Economic Evaluations in Healthcare	2016	Inclusion	▶ If an intervention increases the life expectancy, 'related' costs and 'non-related' costs should both be considered in an economic evaluation of a life-lengthening intervention.
Norway	Guidelines for the Submission of Documentation for Single Technology Assessment Of Pharmaceuticals	2018	Exclusion	▶ The health service costs related to future unrelated illness will not be taken into consideration.
Portugal	Guidelines For Economic Drug Evaluation Studies	1998	Not specified	▶ When the analysis adopts the perspective of society, the costs included will be the direct costs of providing healthcare, the costs of social services and other sectors related to healthcare and the costs borne by patients and their families.
Slovak	Guidelines for Economic Evaluation of Healthcare Interventions	2011	Exclusion	▶ Direct healthcare costs should be included. These encompass costs directly related to the treatment of the disease as well as direct healthcare costs related to the disease in life-years gained.
Slovenia	Rules on the Classification of Medicine on the List	2013	Not specified	▶ The analysis should include direct health costs (total direct costs of drug and total direct costs of other healthcare procedures connected to changes in drug therapy) for all future years.
Sweden	Assessment of Methods in Healthcare and Social Services	2018	Not specified	<ul style="list-style-type: none"> ▶ Which direct costs to include depends on the type of method that is being evaluated. ▶ In certain cases, costs for sectors of society other than those delivering the services can be the most important for the analysis. ▶ The most important indirect cost is the reduced productivity due to incapacity to work because of disease or social problem.
Czech Republic	Cost-effectiveness Guidelines	2017	Exclusion	▶ All relevant direct costs covered from health insurance company perspective (medical and non-medical) to the disease should be identified.
England & Wales	Guide to the Methods of Technology Appraisal 2013	2013	Exclusion	<ul style="list-style-type: none"> ▶ Costs related to the condition of interest and incurred in additional years of life gained as a result of treatment should be included in the reference-case analysis. ▶ Costs considered to be unrelated to the condition or technology of interest should be excluded.
Finland	Preparing a Health Economic Evaluation to Be Attached to the Application for Reimbursement Status and Wholesale Price for A Medicinal Product	2019	Not specified	▶ The calculation of costs must include, irrespective of the payer, all direct healthcare and comparable social welfare costs related to the therapies that are being compared.
Poland	Health Technology Assessment Guidelines V.3.0	2016	Not specified	▶ The suggested perspective only includes the consideration of direct medical costs.
Scotland	Guidance to Submitting Companies for Completion of New Product Assessment Form	2020	Exclusion	<ul style="list-style-type: none"> ▶ Costs should relate to resources that are under the control of the NHS. ▶ When sensitivity analyses include non-NHS/social work costs, explicit methods of valuation are required.
Oceania				
New Zealand	Prescription for Pharmacoeconomic Analysis: Methods for Cost-Utility Analysis V.2.2	2015	Exclusion	▶ Indirect future healthcare costs including costs associated with patients living longer and hence consuming healthcare resources unrelated to their initial diagnosis or treatment should not be included.
Australia	Guidelines for Preparing a Submission to the Pharmaceutical Benefits Advisory Committee	2016	Not specified	▶ Healthcare resource costs should be considered including those incurred by the patient, and the public or private healthcare provider

AMCP, Academy of Managed Care Pharmacy; ICER, Institute for Clinical and Economic Review; NHS, National Health Service; QALYs, quality-adjusted life-years.

impact of including future unrelated medical costs in CEAs. If the HTA agency determines to include future unrelated medical costs, the ICERs may be significantly impacted, as indicated by previous research.^{15 16 20 32–35} In this case, the ICER threshold recommended the current guidelines would be inappropriate and HTA agencies need to establish an explicit and systematic mechanism to adjust the ICER thresholds.

In addition to the research on future unrelated medical costs, it would be valuable to investigate how patient preference could be engaged^{36 37} and whether to consider future non-medical costs,^{18 38} as required by the societal perspective. Future non-medical costs refer to the consumption during the life-years gained if the patient receives a life-extending intervention. There is no consensus on this issue. Nyman argued that future non-medical costs should be excluded because the benefits of future non-medical consumption are not systematically included in the health outcomes.²² Other health economists disagree and persist that only inclusion of these costs could achieve utility maximisation.^{18 39 40} Chinese health economists should pay attention to it to participate in the discussion on this topic.

CONCLUSIONS

The issue of future unrelated medical costs has been unresolved for over a decade. Recent progress in research leads to an increasing voice supporting the inclusion of these costs in CEA and prescription by some official pharmacoeconomic guidelines that an inclusion approach is recommended. Explicitly, the inclusion would increase the internal and external consistency of CEA and the comparability of results between different jurisdictions. Chinese HTA agencies and health economists should pay attention to this issue, and more research is warranted to inform the update of Chinese guidelines.

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