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COMMENTARY

Pharmacoeconomic Guidelines Should Prescribe Inclusion of Indirect Medical Costs! A Response to Grima et al.

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1 Introduction

Recently, Grima and colleagues [1] made a case for excluding unrelated medical costs in life-years gained from economic evaluations of life-prolonging interventions. They provide an insightful overview of several economic evaluations in patients with chronic kidney disease (CKD) on dialysis and convincingly show that inclusion or exclusion of dialysis costs has an enormous impact on the cost effectiveness of any intervention in this patient group (and that there is considerable practice variation in this respect). This results in life-prolonging interventions such as statin treatment, which are highly cost effective in some target groups, becoming cost ineffective (if judged against conventional thresholds), in CKD patients when including the costs of dialysis in life-years gained. Grima and colleagues [1] argue that the inclusion of dialysis costs in life-years gained in CKD patients thus places an "unreasonable … barrier" to demonstrating cost effectiveness in this patient group. Hence, they advocate exclusion of these costs from economic evaluations of therapies for CKD patients on dialyses. They indicate that this solution would be methodologically correct in light of current pharmacoeconomic guidelines, which commonly advocate the exclusion of so-called unrelated medical costs [2].[1]

In this response, we demonstrate the rather absurd consequences of the line of reasoning by Grima et al. [1] (indeed supported by many guidelines) and how these are in sharp contrast with the underlying goals of economic evaluations. The solution for the problems signalled by Grima and colleagues should be found in changing guidelines on the point of inclusion of indirect medical costs and a sound appraisal phase in which ethical dilemmas are addressed explicitly.

2 Economic Evaluation and Guidelines

Economic evaluations support the goal of maximizing outcomes with available resources, by means of selecting, among the many possible health technologies, only those that offer value for money. The latter is commonly expressed in terms of an incremental cost-effectiveness ratio (ICER). The ICER is the ratio of the additional costs divided by the additional health gains of a (new) health technology relative to some relevant comparator (e.g. usual care). Health gains are commonly expressed in terms of QALYs, which allow comparisons across disease areas and interventions. Thus, ICERs can form an important source of information for decision makers in allocating scarce healthcare funds, which emphasizes the need for a sound methodology in producing ICERs.

The aim of pharmacoeconomic guidelines is to ensure that economic evaluations are performed in a sound way,

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[1] In the literature, the terms 'future unrelated medical costs'/'unrelated medical costs'/'indirect medical costs' are used interchangeably. We will also do this throughout the paper.

aligning with the goals and constraints in particular jurisdictions. It is well known that jurisdictions can differ in the way they formulate the underlying policy aim and constraints, especially relating to perspective. Most notably, while in some jurisdictions (e.g. UK) the emphasis is on maximizing health from a given budget, other jurisdictions (e.g. The Netherlands) attempt to maximize broader welfare through the allocation of scarce resources in healthcare. This reflects differences in perception of the decision context and appropriate decision rules informed by economic evaluation [3]. Differences in perspective may lead to differences in the costs included, but this should be justified in light of the specified decision context. For instance, if healthcare policy makers are solely concerned with maximizing health from a given healthcare budget, ignoring productivity costs can be justified *within* that decision context. If guidelines prescribe inclusion or exclusion of costs that do not align with the (implicitly) adopted decision rules, this obviously is problematic. It leads to the absurd situation that guidance frustrates rather than facilitates decisions in line with policy goals. At present, this seems to be the case for many national guidelines, which commonly prescribe ignoring unrelated medical costs in life-years gained in economic evaluations of life-prolonging interventions. Both from a healthcare perspective and from a societal perspective, inclusion of unrelated medical costs is important to align with underlying goals and comply with appropriate decision rules. Both when maximizing health from a given budget or when spending resources in a such a way to maximize welfare, indirect medical costs in life-years gained represent true opportunity costs.

3 The Case of CKD

Grima et al. [1] appear to deny the real opportunity costs of prolonging life in CKD patients on several occasions. They, for instance, attempt to describe situations in which therapies "… extend the lives of patients with … CKD on dialysis but do not impact the need for or the intensity of dialysis". Obviously, however, extending the lives of CKD patients on dialysis without increasing the need for dialysis is impossible. Life extension in these patients inevitably increases the need for dialysis, with associated opportunity costs. The associated resources could have been allocated to other patient groups, also with real medical needs, and may have yielded more health gains there [4].

Note that we do not deny that legitimate reasons may exist, e.g. equity reasons, to still favour treatment of this group, nor do we deny the ethical dilemmas these opportunity costs raise. We do stress that such dilemmas cannot be defined away by ignoring real costs. Rather they should be dealt with explicitly in fully informed decision rules and decision processes. Extending life in CKD patients, with associated high costs in life-years gained since the costs of dialysis are high yet unavoidable, illustrates this important issue well. These points were also highlighted by Manns et al. [5], who illustrated the impact of including future costs in the context of end-stage renal disease care.

Grima et al. [1] note that:

> regardless of the clinical benefits of a life-extending intervention for dialysis patients, and due to the high cost of dialysis, the inclusion of dialysis costs in the analysis essentially eliminates the possibility of obtaining a favourable cost-effectiveness ratio. This raises the significant risk that dialysis patients may be denied access to interventions that are cost effective in other populations due solely to the high background cost of dialysis itself.

This is an extremely dangerous remark, as such reasoning comes close to setting the goal of economic evaluations to obtaining a favourable ICER. In general, a simple way of obtaining a more favourable ICER indeed is to cut down on the cost categories included in an economic evaluation. Ignoring all costs would be the optimal strategy then. Clearly, this strategy endangers the credibility and usefulness of economic evaluations. Should we also ignore reduced effectiveness of interventions in specific groups since it hampers achieving good cost effectiveness? Such strategies lead to absurdity and start from a perceived 'right answer' (this should be funded) rather than from the right question (do the effects justify the costs in particular patients?).

4 Guidelines and Unrelated Medical Costs in Life-Years Gained

Grima and colleagues [1] rightly indicate that guidelines for economic evaluations in many jurisdictions prescribe exclusion of unrelated medical costs in life-years gained, even though this guidance often is in clear contrast with the general principles on which guidelines are based. For instance, in England and Wales, the National Institute for Health and Clinical Excellence (NICE) guidelines [6] specify in guideline 5.5.6: "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 that are considered to be unrelated to the condition or technology of interest should be excluded". Note that such an exclusion is in clear conflict with NICE guideline 5.5.1, which specifies that *all* relevant costs for the UK NHS should be included: "For the reference case, costs should relate to resources that are under

the control of the NHS and PSS [*personal social services*] when differential effects on costs between the technologies under comparison are possible." [6] In The Netherlands, where guidelines start by stating that a societal perspective needs to be adopted, implying that *all* relevant societal costs and effects need to be included, a similar and again unjustified exception is made for indirect medical costs [7]. Such guidance appears to reflect the fact that the literature on these costs has long appeared to lack a clear theoretical consensus.[2]

5 Theoretical Background

The topic of how to treat unrelated medical costs in economic evaluations has been the cause of quite some debate in the literature. Weinstein and Fineberg [9] already wrote: "Often ignored are the costs of medical care received during extended years of life. Credit given to control of blood pressure for reducing costs associated with treatment of strokes and myocardial infarctions must be balanced against the costs for other diseases incurred during the added years of life". Besides practical arguments (it may be difficult to accurately estimate unrelated costs in life-years gained), ethical arguments (it is unfair to include these costs), the theoretical debate regarding future costs may have reinforced the practical consensus to exclude unrelated medical costs. However, close inspection of the theoretical literature shows that a convincing case to exclude future unrelated medical costs has never been made. The first attempt to show that the inclusion of unrelated medical costs in life-years gained would be unnecessary or undesirable was done by Garber and Phelps [10] who concluded: "Surprisingly, the inclusion of unrelated future costs is without consequence so long as the practice is consistent". In order to reach this conclusion, Garber and Phelps implicitly (and presumably unintentionally) assumed that people consume all of their production each year. This assumption is in conflict with empirical studies on household behaviour as well as economic theory on life-cycle consumption [11]. Using a model that relaxed this key assumption made by Garber and Phelps [10], Meltzer [4] demonstrated that the exclusion of unrelated medical costs is inconsistent with economic welfare theory. Although there has been much discussion since [12], much of the discussion centred on non-medical costs [13–17] and arguments to exclude future medical costs [18] have been refuted [19, 20].[3] While practical difficulties in estimating these costs may have added to the reluctance for their inclusion, methods have been developed to facilitate the inclusion of future unrelated medical costs [21]. Moreover, practical difficulties in estimating unrelated medical costs can never justify ignoring these costs and thus using a zero estimate [22]. The overview by Grima et al. [1] in that sense usefully stresses the non-negligible size of future unrelated medical costs (relative to effects) in some cases.

6 Unrelated Medical Costs in Practice

Current guidelines do not only guide researchers to perform economic evaluations that do not relevantly inform the policy decision and lack theoretical support; they also lead to incomparability of the results of economic evaluations. The latter holds because researchers have much discretion to decide whether or not costs are "considered to be unrelated", as can be derived from NICE's guideline 5.5.6 quoted in Sect. 4, and this distinction is not straightforward. Unrelated costs can be viewed as those costs that relate to other diseases than the one treated and are purely the result of living longer due to successful treatment. They thus relate to costs of 'competing diseases' in gained life time. For instance, successful cardiovascular disease treatment indirectly increases costs for treating dementia in life-years gained through increasing life expectancy. The practical difficulty in separating related and unrelated medical costs may be seen reflected in the real-life economic evaluations shown by Grima et al. [1].

The solution of Grima et al. [1], to ignore these costs, will result in basically arbitrary lines between related and unrelated costs, which will not aid in consistent decision making. In practice, a technology appraisal of successful cancer treatment will then ignore possible costs of heart disease in life-years gained, while an appraisal of heart disease treatment in the same group of people will exclude costs of cancer in life-years gained. It is obvious that this complicates comparisons of economic evaluations across disease areas and patient groups, and fails to relevantly

[2] It should be noted that Grima et al. [1] wrongly indicate that Brouwer et al. [8] advocate exclusion of indirect medical costs and that Brouwer et al. would "suggest the inclusion of medical costs that are a direct result of the intervention and suggest that costs can be omitted if they occur similarly in the control and treatment groups". That is what Brouwer et al. [8] argue for unrelated costs in *normal life-years*. For unrelated costs in life-years gained, after describing the debates in the literature, they indicate: "Indeed, one might conclude it to be best to leave up the decision to include or exclude these costs to the analyst. He or she can determine whether or not these costs may be substantial and whether or not data on these costs for the specific population of the study is available" [8]. They do not recommend exclusion of these costs, therefore.

[3] Here, in accordance with Grima et al. [1], we focus on medical costs in life-years gained, and it suffices to state that inclusion of non-medical costs in life-years gained is equally important when a societal perspective is adopted.

inform the decision policy makers are faced with [23]. In a general sense, the term 'unrelated' is difficult to use when it comes to costs in life-years *gained*. It is best to ignore the distinction between related and unrelated costs in the context of life-prolonging interventions and count all changes in medical costs as representing real opportunity costs within the healthcare sector. The logical conclusion of the problem signalled by Grima et al. [1], consistent with the aim and theory of economic evaluation, therefore would be to include all relevant costs.

7 Difficult Choices

The results of complete economic evaluations may indeed lead to uncomfortable conclusions and tough choices. This is inevitable in a resource-constrained environment. Such choices may well reflect the ethical concerns regarding life-prolonging interventions in frail or sick patient groups. Such issues should, however, be dealt with openly and explicitly. Those carrying out economic evaluations cannot justify systematically ignoring real medical costs. If higher medical costs are incurred in certain patient groups, the relevant question simply is whether we are willing to sacrifice more resources to yield health gains in that particular group. An economic evaluation does not preclude the decision maker from making that decision; it 'simply' informs the decision maker on the consequences of such a choice. A complete assessment of the costs and benefits of a particular technology, in line with the defined goal and decision context, is required to meet that goal.

8 The Logical Conclusion: Change Pharmacoeconomic Guidelines!

Hence, Grima et al. [1] are right to assert that current guidelines result in undesirable variation in practice and lead to results of economic evaluation that do not inform the decision maker in a relevant or complete way. However, the conclusions they draw from the current state of affairs (ignore future unrelated medical costs as a rule) is a wrong one, as they encourage the field to produce uninformative ICERs ignoring real medical opportunity costs. This also is not a general solution to the incomparability problem, since it only reduces variation *within* one disease area, but, in doing so, simultaneously reduces comparability *between* disease groups. Such broad comparability of results has always been an important reason for economic evaluations in the healthcare sector.

Grima et al.'s suggestion [1] moreover appears to be fuelled by the idea that labelling something as cost ineffective in a specific group that is considered cost effective in another group is problematic. Their reasoning ultimately entails labelling any life-saving technology that is cost effective in some patient group without any high background costs (such as dialysis) also as cost effective in all other patient groups with high background costs. It is not difficult to see that this will result in resource allocations that are in clear conflict with the goals of maximizing health or welfare from a given budget.

Hence, only one logical conclusion can be drawn from the insightful overview of Grima et al. [1]: pharmacoeconomic guidelines need to be changed. We therefore reiterate the plea to change pharmacoeconomic guidelines such that they recommend inclusion of all costs relevant from the perspective taken, whether they are 'related' or 'unrelated', 'direct' or 'indirect'. This ensures results that align with the underlying goals of economic evaluations and increases comparability between studies also across diseases. Moreover, this will improve the credibility of economic evaluations as results will be less biased and more meaningful. Such a change in guidelines will stimulate development and refinement of methods to estimate unrelated medical costs.

The results of such evaluations subsequently need to be appraised in a process that allows articulation of the ethical and equity concerns, which are inherent in healthcare decisions and prominent in cases like CKD. Ignoring costs is an absurd solution for these real dilemmas. Rather than following guidelines guiding to absurd conclusions, our efforts should be directed at changing these guidelines!

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