Author's response to reviews

Title: Clearing up the hazy road from bench to bedside. A framework for integrating the fourth hurdle into translational medicine

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Author's response to reviews: see over
Dear Sir or Madam,

Thank you very much for your positive feedback on our submitted manuscript. Enclosed please find the revised document.

Attached to this letter I also send my response to the reviewer comments. In general, I am grateful for the comments because they were very constructive and helpful. If the reviewers agree I would therefore like to mention both of them in the acknowledgement section of this paper.

I would be very happy if this revised manuscript was considered for publication in BMC Health Services Research. Please do not hesitate to contact me in case of any further questions.

Sincerely yours,

Wolf Rogowski
Clearing up the hazy road from bench to bedside. A framework for integrating the fourth hurdle into translational medicine

Response to reviewer comments

Reviewer's report
Reviewer: Jonas Schreyögg

General comments:
The framework is good, but the article would benefit from expanding it slightly:
1. EMEA and FDA have different practices for licensing. Although in a narrow sense licensing does not belong to the fourth hurdle licensing is also affecting the fourth indirectly and should be mentioned. While the FDA requires proving effectiveness to be licensed EMEA only requires to prove safety. Therefore the FDA filters certain technologies/drugs that has to be done in the second stage in Europe. Although FDA and EMEA are included in figure 2 this should be mentioned explicitly in the text.

=> This issue was addressed in more detail the discussion section; additionally, it was made clear in the methods section that an assessment of the complex institutions of market approval was beyond the scope of the article.

2. Comprehensiveness should be one additional criterion in the framework (therefore also in table 1). While NICE only deals with very few technologies/drugs of major interest, other institutes such as IQWIG have to review a much higher number of technologies/drugs. Thus the likelihood of being reviewed from a manufacturer’s point of view differs largely between the countries.

=> On the one hand, this issue already is addressed in the step “Trigger”: indeed it is important for a company to know which body is likely to make the reimbursement decision – whether or not a formal review of the published evidence or a formal cost-effectiveness analysis is likely depends on whether or not the technology’s characteristics trigger such process. In the case of NICE, clear prioritization criteria for decisions exist and, as mentioned in the text, the vast majority of technologies do not undergo a formal NICE appraisal.

On the other hand, thinking about this comment led to a revision of the framework to account for the potentially different roles of different participating groups and institutions in the decision making procedure. As a part of this participation, information not only on the decision but also on process steps may be provided. The previous version of this study only
assessed the decision maker – who for Germany is the Federal Joint Committee of Doctors and Insurance Funds (G-BA). And it simplified the publication to one single step. The framework was modified accordingly, introducing “Participation” and “Publication” as two potential and complementary activities throughout the decision procedure.

Additionally, it was addressed more clearly that frequently, assessments are commissioned out to assessment groups or institutions like IQWiG. Assessment was therefore made an extra step in the value chain graph. The text was modified accordingly.

3. Reimbursement mechanisms/levels of reimbursement are a major part of the fourth hurdle. Reimbursement mechanisms can be explicitly designed to accelerate the adoption of certain technologies e.g. additional reimbursement components for DRG payments such as in Germany or even an additional DRG for a specific technology such as for DES in certain regions of Italy. The employed reimbursement mechanism for a specific technology can be interpreted as a decision to block or accelerate the adoption of technologies. Thus, I would recommend expanding the section on reimbursement and expanding the respective row of the table.

=> The section “Reimbursement” was expanded accordingly

Discretionary Revisions
Specific comments:
Page 5, para 2:
- Why England and Wales and not only England or the whole UK. I would stick to England, because the other UK states differ slightly regarding regulatory matters.

=> Was modified accordingly

- The USA is funding more the 50% by public sources such as Medicare, Medicaid and the VHA. I would not consider the US to be fully private. It is rather a mixed system. For Germany rather social health insurance-based instead of insurance-based.

=> Was modified accordingly

Page 6:
- The last two sentences are not entirely clear: probably negotiated instead of fixed. Please define what is meant by service provision in this context.
Page 7, para 3:
- “Health care payments in England and Germany are dominated by one central payer….” I would rather say dominated by one decision body, since there are many different payers such as sickness funds. In addition it might be worth mentioning the PHI in Germany.

=> “One central payer” was modified to “the sickness funds within the health insurance system”

Page 7, last sentence:
- Probably: “only 50% of HE were covered before 2006.”

Page 8, first sentence:
- This has recently changed with the introduction of Medicare Part D.

=> the section on medigap policies was deleted

Page 8, last sentence:
- Perhaps better: “…any novel procedure is covered implicitly within the DRG framework”. But there can be additional reimbursement components in nearly every country.

=> sentence was modified; additional reimbursement components are mentioned in the reimbursement section

Page 9, para 1:
- As far as I know the final decision is taken by the NHS Business Services Authority (NHSBSA) on behalf of the Department of Health (DH). You better check on this.

=> I searched on the internet and went through the NICE guidance for technology appraisal and the appraisal process without identifying helpful information (nevertheless, this lead to a slight modification of the characterisation of the appraisal groups and an update of the reference because a new version of the appraisal guidelines was released very recently). I then contacted a person working at NICE who told me that appraisals do not need to be signed by the DH. As NICE guidance is nevertheless different from a legally binding decision about the inclusion of a service into a positive list, I modified the term “make decision” to “provide guidance”.

- Might be worth mentioning: Interdisciplinary committees in the US do often consist of researchers and other independent experts.
The section on criteria is excellent!

I was unsure to what extent the comments on the methods section by the second reviewer should be addressed. Given this positive comment and the comments on the considerable length of the paper, the additions to this section were kept short.

Page 13:
- The case study on ACI is ok, but not essential. The article is also good without it. You may consider deleting it since the article is already quite long.

Case study was deleted; the role of ACI was reduced to an illustrative example for novel in-patient procedures only

Page 16:
- The section: how to pave the way from bench to bedside, is not really necessary, because at this stage of the article everything has been said and it seems redundant to a certain extent. You may consider deleting it.

Large parts of this section were deleted

Page 17, para below the bullets points:
- It might be worth mentioning the concept of “HTA in early stages”. There are several companies in the US which offer this service to biotech, pharma etc. companies. HTA in early stages tries to simulate effects of a technology mainly in terms of cost-effectiveness with minimal information and considers information of similar products that have already been launched on the market.

The section was extended accordingly

Figure 1:
- The last arrow “use in healthcare” may be followed by re-evaluation which maybe linked to a revised reimbursement decision (which is often the case e.g. in France). This is mainly due to the discrepancy between efficacy and effectiveness that you also mentioned in the text.

Thank you very much for that hint – I realized that data from the use in healthcare may be used not only for re-evaluation of the coverage decision but also at other stages and modified the figure accordingly
Table 1:
- It might be worth adding a row for reviewing institutes/HTA agencies  
  => row “assessment” was added and modified accordingly
- Row for reimbursement: why do DRGs not appear in the column on the US?/  
  the UK also has a DRG-like reimbursement system called HRG-system  
  => row “reimbursement” was modified accordingly
- the row on service provision remains slightly unclear to me. What do you exactly mean?  
  => given the variety of options for health care payers to exert influence on service provision, the table now lists those which were relevant in the case of ACI as an example. The paragraph before Table 1 gives a brief explanation on that.

I am happy to answer any further questions if any of my comments should be unclear.

Reviewer's report
Reviewer: Mike Drummond
Reviewer’s report:  
This paper discusses the additional challenges posed by the ‘fourth hurdle’ to the manufacturers of health technologies, especially devices and procedures. It develops a ‘process-oriented framework’ that interested parties can use to monitor the changes in fourth hurdle policies. The main audience for the paper appears to be those working within research and development departments within the companies, since there are implications for the studies (of product effectiveness) that they conduct. For this group there is a major need for a general overview paper such as this. Therefore, it should have high priority for publication. I thought that the paper was fairly comprehensive and was fair and accurate in its discussion of the issues. The only major topic that the authors might consider saying more about is the growing field of ‘coverage with evidence development’, or conditional reimbursement. This seems to be being offered as the main way of getting round the evidence gap that the authors highlight.(See Tunis and
=> a paragraph on the option of coverage conditional on data retrieval to enhance the evidence based was included into the section “Management of service provision” as a special case of payers’ additional rules for service provision. The issue of CED also was addressed in Fig. 1 (arrows representing information flow from use in health care to coverage decision)

Although the paper is probably worth publishing as is, I think that several improvements could be made.

1. Although I understand that it makes sense to concentrate on 3 jurisdictions, the authors say that they searched 44 websites of HTA entities. My guess is that in many jurisdictions the situation regarding the fourth hurdle is unclear. However, it would be good if some kind of summary from all 44 institutions could be produced.

=> this was clarified in the methods section: the high number of websites relates to the websites of payers in the US; the results are summarized in the columns for Medicare LCDs and BCBS companies in Table 1.

2. On page 9, more details could be given on the criteria used to select technologies for evaluation. There is a review by Noorani et al in Int J Tech Assess Healthcare 2007;23:310-5

=> thank you very much for the hint to this paper which I was not aware of yet! It was briefly addressed in the “trigger” section.

3. For this audience, more could be said about the criteria being used for evidence. I’m not sure that this audience appreciates the need for comparisons of the technology with relevant alternatives (not discussed), or the difference between a cost-effectiveness and cost-utility study. Perhaps something could be added in the ‘Background’ section, where the fourth hurdle is discussed. Also, for this audience, it is important to stress why the ‘standard’ evidence on efficacy is inadequate for reimbursement discussions, namely: lack of relevant comparisons, lack of meaningful endpoints and too short a follow-up.

=> section “assessment” was modified; all issues mentioned here were addressed. However, as the other reviewer was very positive about the section on criteria for coverage, the modifications were kept as small as possible.

4. Whereas the use of a case study is welcome, I didn’t think that it was
discussed in enough detail to be really meaningful. For example, although there was efficacy data, exactly why was it deemed insufficient? What outcomes are relevant in this field? What is the current standard of care and what potential advantages does the new technology offer? Is it particularly useful for certain patient subgroups? etc.

=> given both reviewers are critical towards the case study, it was deleted (see comment above)