Reviewer's report

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

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Reviewer: Jonas Schreyögg

Reviewer's report:

The authors present a well written article on the existence of fourth hurdles in three very large markets. The general topic of the presented article is very innovative and interesting for an international readership. The merit of this article can be seen in the detailed description and conceptualization of the process from bench to bedside. I am not aware of any similar article. The covered literature is very comprehensive and appropriate. I recommend to accept the article after certain minor revisions.

Minor Essential Revisions

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.

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.

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.
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.

- 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.

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.

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.

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.

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.

- Might be worth mentioning: Interdisciplinary committees in the US do often consist of researchers and other independent experts.

The section on criteria is excellent!

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.

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.

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.

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.

Table 1:

- It might be worth adding a row for reviewing institutes/HTA agencies
- 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
- the row on service provision remains slightly unclear to me. What do you exactly mean?

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

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.