The role of dissemination bias in pharmaceutical coverage decisions: an analysis of practices in European countries

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The OPEN (**O**vercome Failure to **P**ublish N**e**gative Fi**n**dings) Project

- 7th Framework Programme of the European Union
- Current practice by various key groups involved in knowledge generation and translation regarding dissemination bias
- Recommendations for change
- Work Package 10: regulatory institutions responsible for determining value of pharmaceuticals for statutory coverage

Research aim of Work Package 10

- Map pricing and reimbursement processes in all countries included in the project (EU/EFTA), focusing on participating institutions and their standards

- Identify existing approaches towards dissemination bias and determine level of awareness/ operationalization, exemplary practices and possible steps for the future

What is dissemination bias?

- Occurs when the likelihood of clinical research results reaching their intended audience depends on the extent to which they support the research hypothesis
- Publication bias: only studies with positive, significant results are published
- Selective (outcome) reporting bias: outcomes with favorable, significant results from a given study are more likely to get published

Why is it relevant?

- Impacts patient safety and quality of care (underestimates lack of effect and harm, overestimates positive effects)
- May result in resource allocation inefficiencies (e.g. Tamiflu)
- Study participants assume experimental risks and potentially expose themselves to harm without benefit (here: advancement of societal good)

Mixed methods approach

1. Document analysis (systematic searches)
   i. Regulatory documents from institutions responsible for determining value for coverage decisions (websites)
   ii. Publications (Pubmed, Embase, Cochrane Library)

2. Survey among included institutions
   i. Contact persons through author networks and online resources
   ii. Surveymonkey and email invitations
   iii. Up to 5 periodic reminders

Overview of available information

Document analysis

- 105 potentially relevant regulatory documents identified, 42 selected
- 52 potentially relevant publications (after ti/ab screening), 10 selected

Survey

- 35% response rate, 13 valid responses (despite repeated reminders)

=> information of variable extent available for 26/36 countries

General approach to evidence

- Principles of evidence-based medicine, more or less systematic approaches

- Specifications for manufacturer submissions:
  - full list of relevant studies including those used for marketing authorization in several countries (notable exceptions: at least one study in LU, “the most important” studies in CH)
  - variable additional requirements (protocols and reports in DE, UK-Sc; unpublished studies in AT, DE, FR, PT; ongoing studies in DE, FR)

Searching for published information

- At least two databases
- Language and timeline restrictions
- Both evidence syntheses (e.g. HTA) and primary studies

Methods for dealing with incomplete evidence

- Explicit requirement to search for partially reported data before analysis (6 countries)
  - funnel plots (DE, FR, IE, PT)
  - regression methods (DE, IE)
- Consistency check within and across documents
  - clinical study reports (DE, FR, SI)
  - manufacturer submissions (UK)
  - publications (8 countries)
  - retrieval of full study material (MT, for selective outcome reporting)
- Explicit consideration of how including unpublished evidence would influence conclusions/recommendatios (DE, PL)

Transparency and confidentiality

- Variable practices regarding data labelled "in confidence"
- Conflict of Interest declarations standard but practices vary
- Committees bound by secrecy
- Publication of appraisal documentation variable, connected to legal context of freedom of information
- Different types of information made available to different stakeholder groups

Conclusions

- Concerns about dissemination bias rarely consistently embedded in institutional practices, even in well-established systems
- Considerable lack of transparency on approaches towards evidence procurement
- Partial or missing results for some countries
- Encouraging: never only single-source, consultation of registries
- Room for institutional collaboration, declaration of full disclosure from manufacturers, proactive publication of trial data (EMA)

Thank you

for your time and attention!

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