WHO Collaborating Centre for Pharmaceutical Policy and Regulation

Downstream effects of acceptance of uncertainties at approval of medicines

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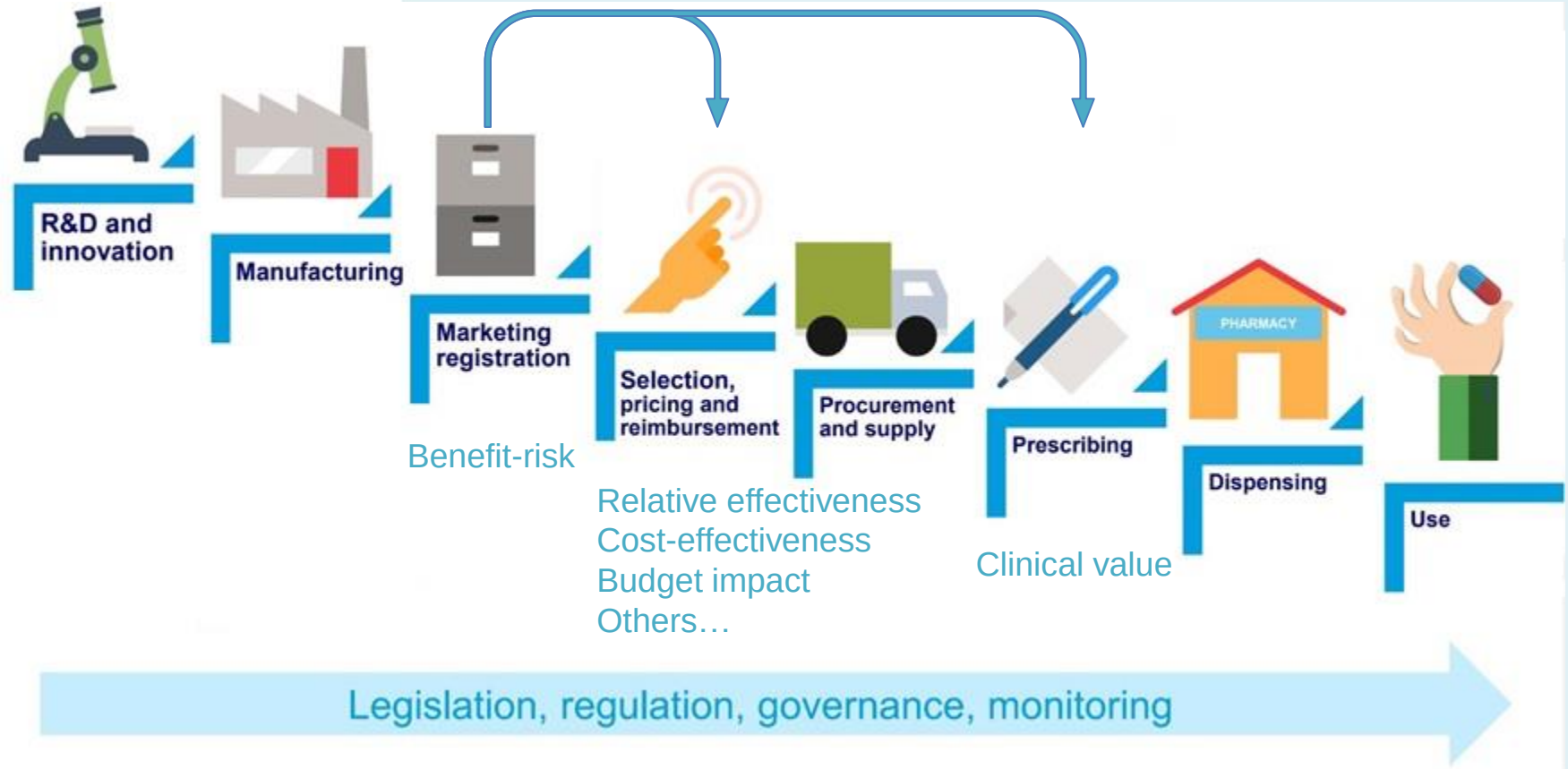
Disclosure

Funding souces for these projects

- Dutch Medicines Evaluation Board (CBG-MEB)

No relationships to disclose

Stakeholders in the drug life-cycle



Adapted from WHO

Consequences?

Examples from studies on regulatory acceptance of uncertainties at approval of medicines

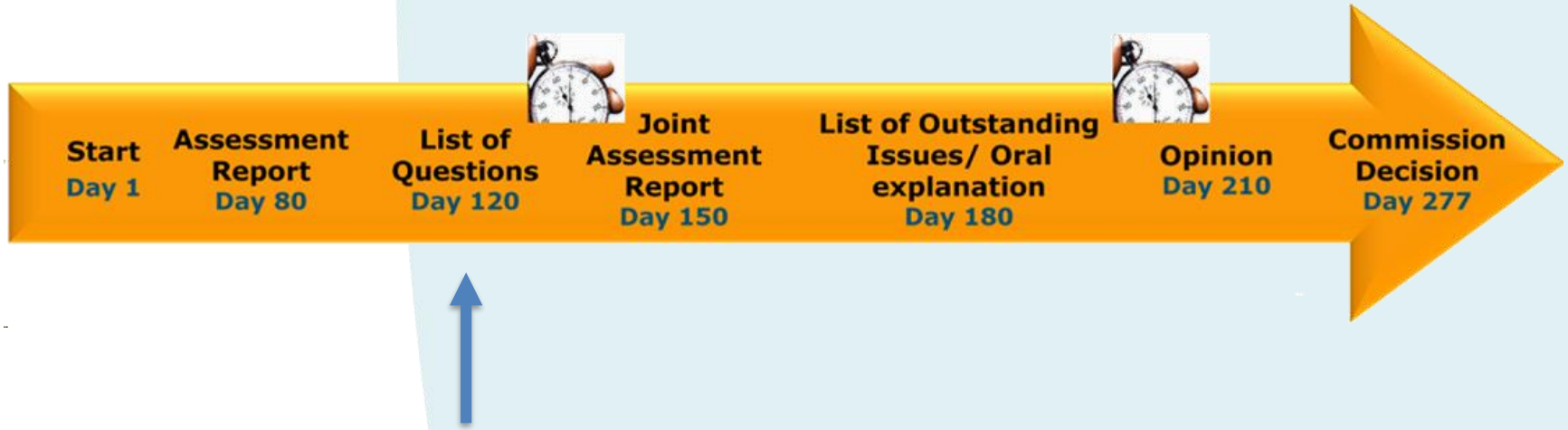
Specific focus:

1. Standard approval: uncertainties w.r.t. pivotal trial data
2. Conditional vs. standard approval
3. Conditional approval: solving uncertainties through post-approval data

→ Effects on decision-making by 'downstream' stakeholders?

Lessons for new monitoring and measurement technologies?

Uncertainty 1: pivotal clinical trials

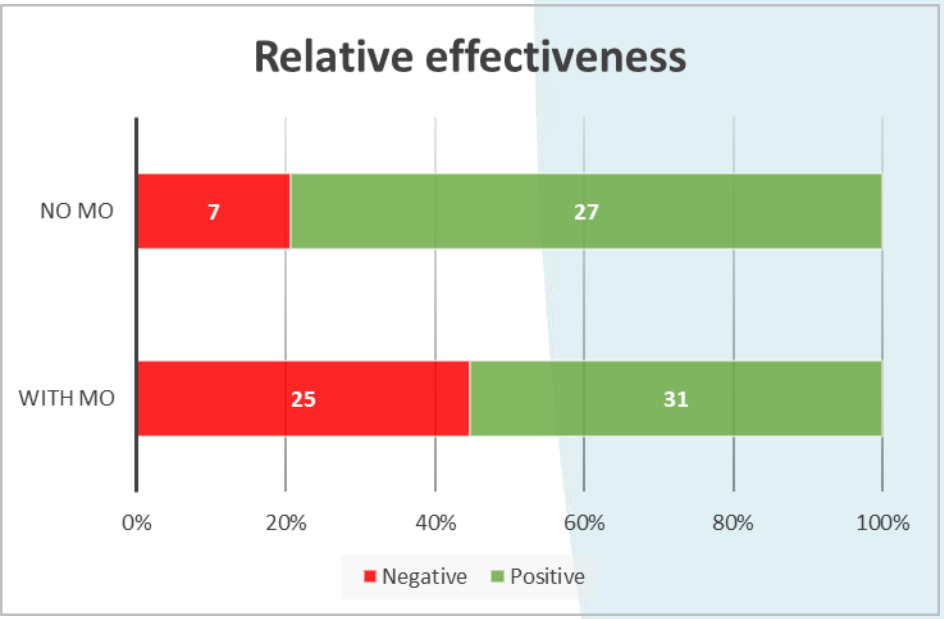


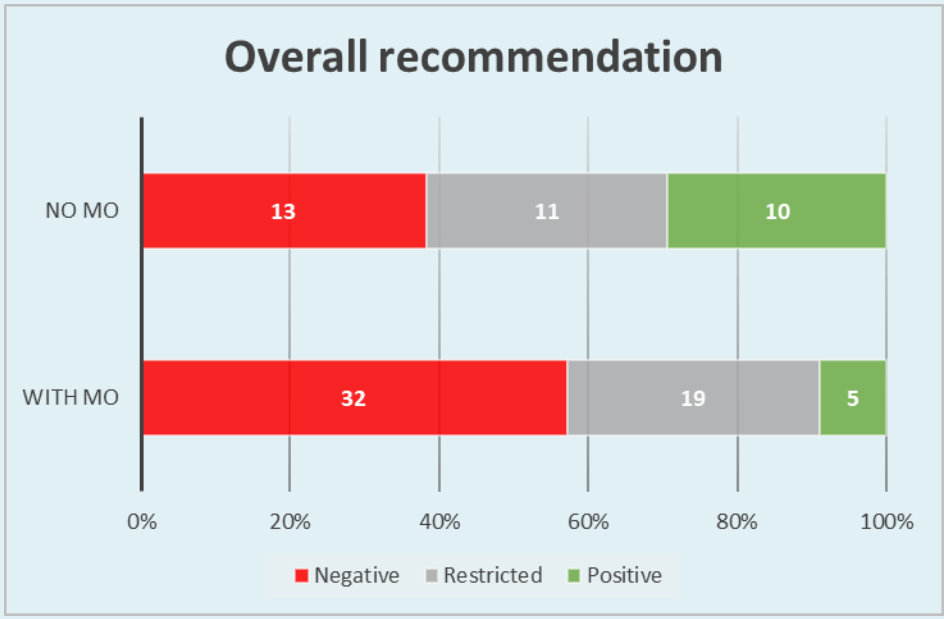
Assumption: higher level of uncertainty accepted for medicines for which EMA raised 'major objections' at day 120

Does this affect HTA decision-making?

MEB / EMA

Pivotal clinical trial data & HTA





NB: 3 HTAs; England (NICE) = work in progress

RR: 2.2 (95% CI 1.1–4.5)

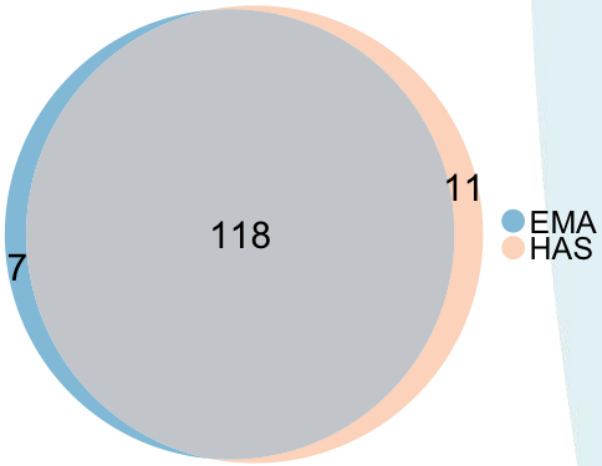
RR: 1.5 (95% CI 0.9–2.4)

But: based on same data?

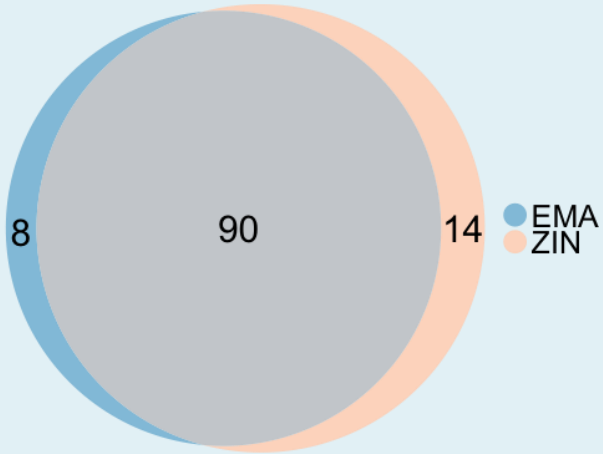
Bloem & Vreman *et al. Ongoing work*

Clinical data underlying decisions

HAS: 33/35 medicines



ZIN: 27/35 medicines



NICE: 14/35 medicines

work in progress

Bloem & Vreman *et al. Ongoing work*

Uncertainty 2: conditional approval

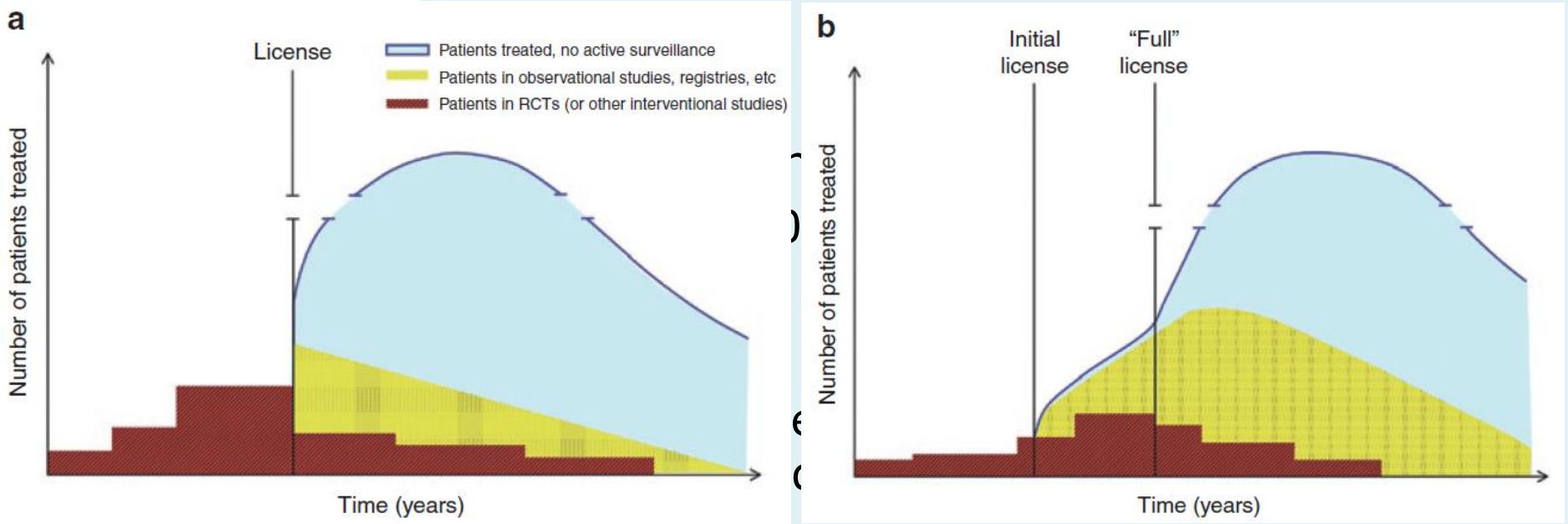
Promising medicines for:

- Seriously debilitating or life-threatening diseases
- Orphan diseases (≤5 in 10,000 patients)
- Emergency situations

No current treatment / major therapeutic advantage over existing treatments ("unmet medical need")

Eichler *et al.* Clin Pharmacol Ther 2012

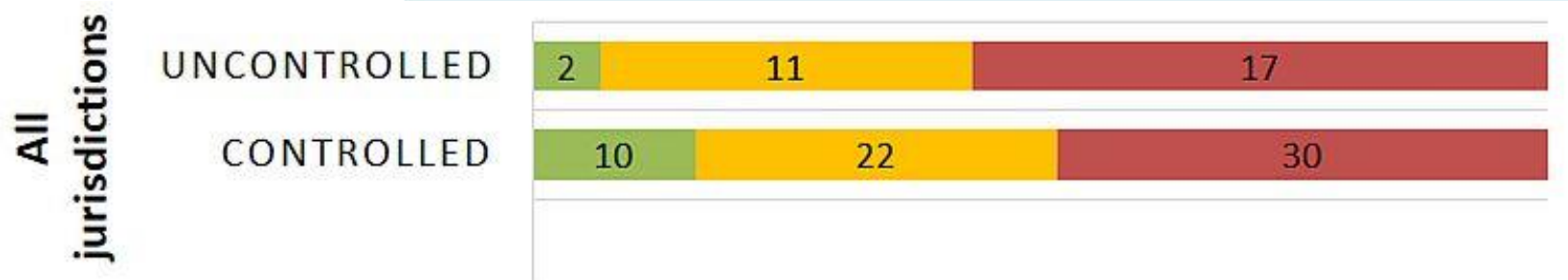
Uncertainty 2: conditional approval



- Yearly renewal (instead of 5-yearly)
- Post-approval data / studies: specific obligations

Eichler *et al.* Clin Pharmacol Ther 2012

Conditional approval & HTA: uncontrolled vs. controlled studies



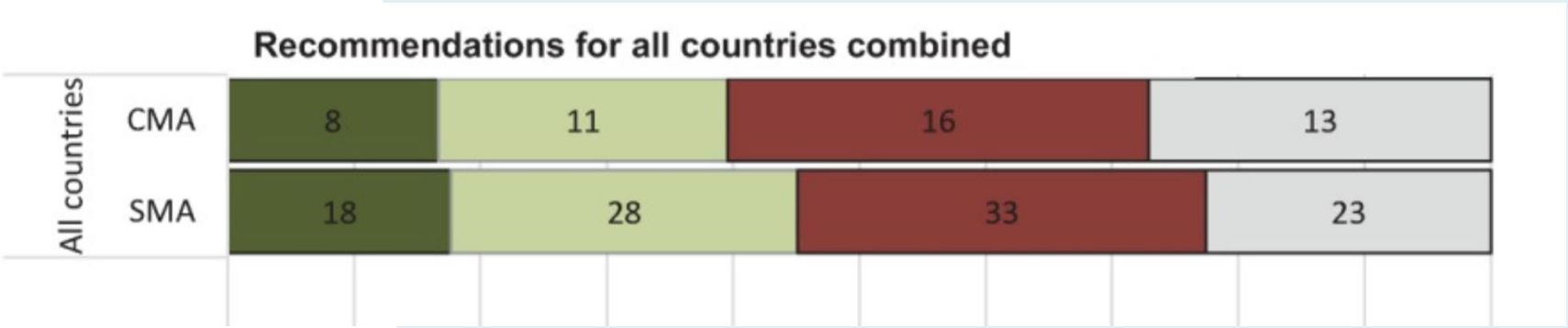
RR: 1.2 (95% CI 0.8–1.8)

But: low proportion unrestricted positive recommendations for conditionally approved medicines overall (13%)!

- Orphan status?
- Lack of comparator treatments?

Vreman *et al.* Clin Pharmacol Ther 2019

Conditional approval & HTA: what about oncology medicines?



Conditional vs. standard approval: no difference

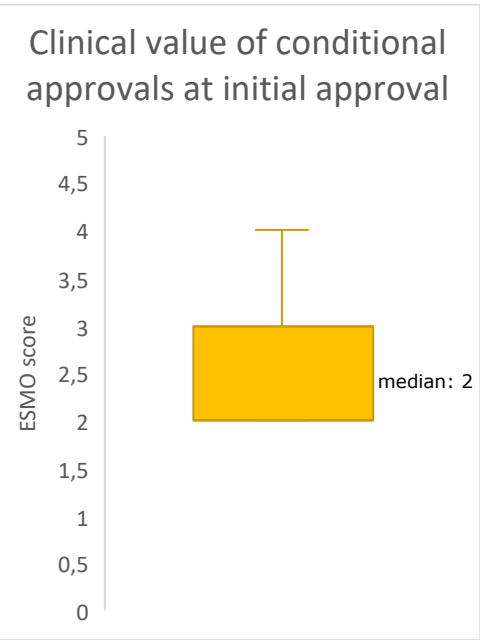
But: substantially higher proportion unrestricted positive recommendations for conditional oncology medicines only:

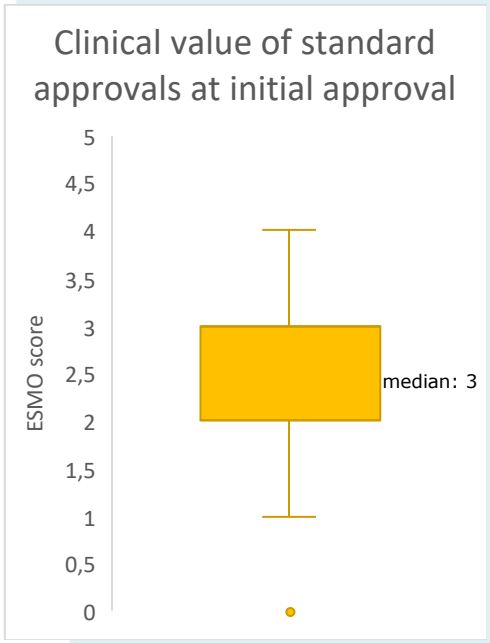
- 23% (8/35) vs. 13% for conditional approvals overall

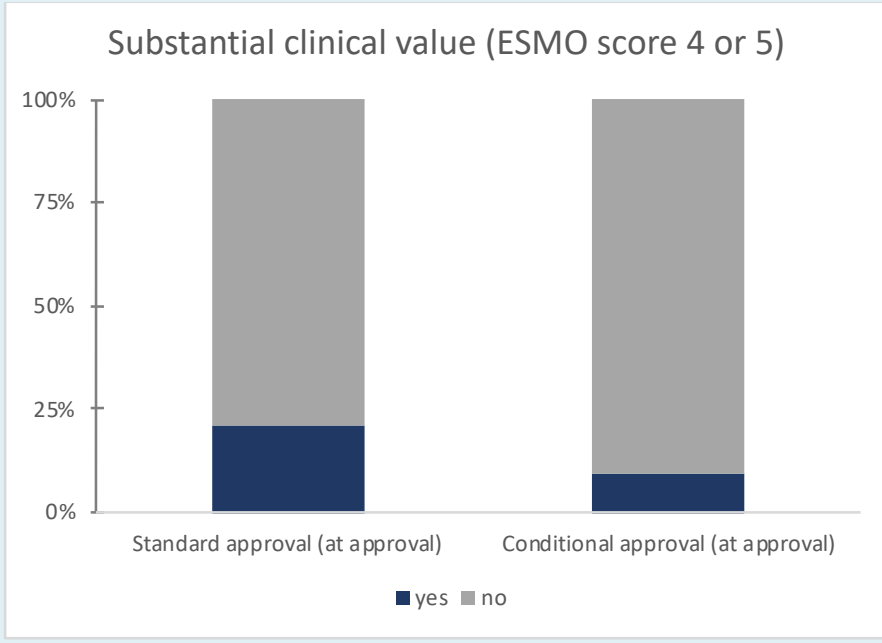
→ More agreement on 'unmet medical need'?

Lipska *et al.* Clin Pharmacol Ther 2015

Conditional approval & clinical value of oncology medicines







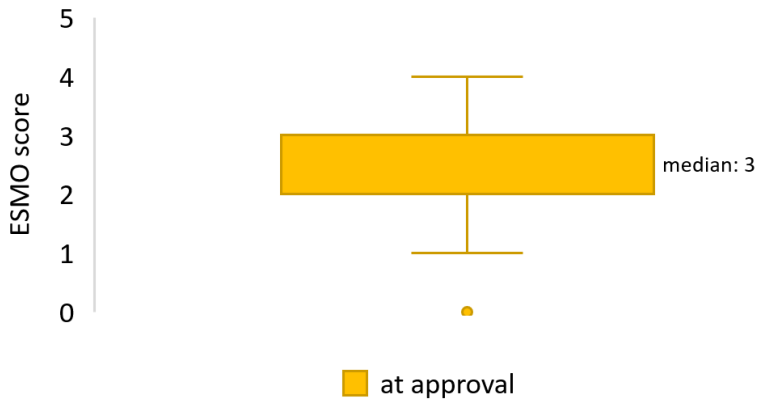
Less often substantial clinical value…

But what about post-approval data: specific obligations (SOBs)?

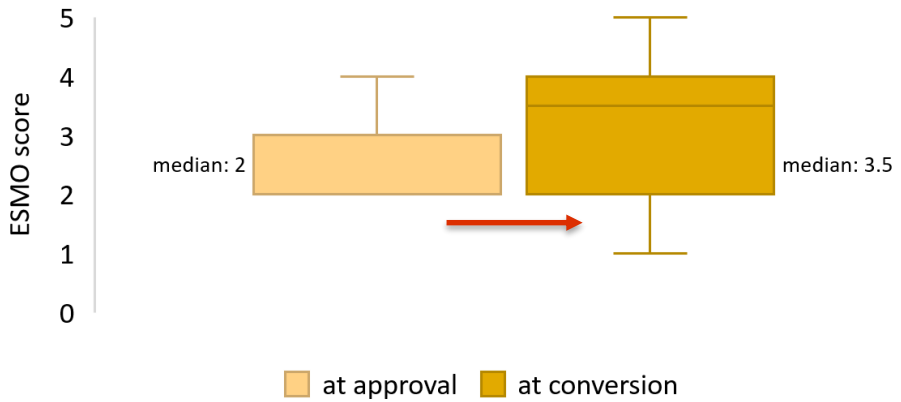
Bloem & Bot *et al. Ongoing work*

Conditional approval: impact of post-approval data on clinical value

Clinical value of standard approvals at initial approval

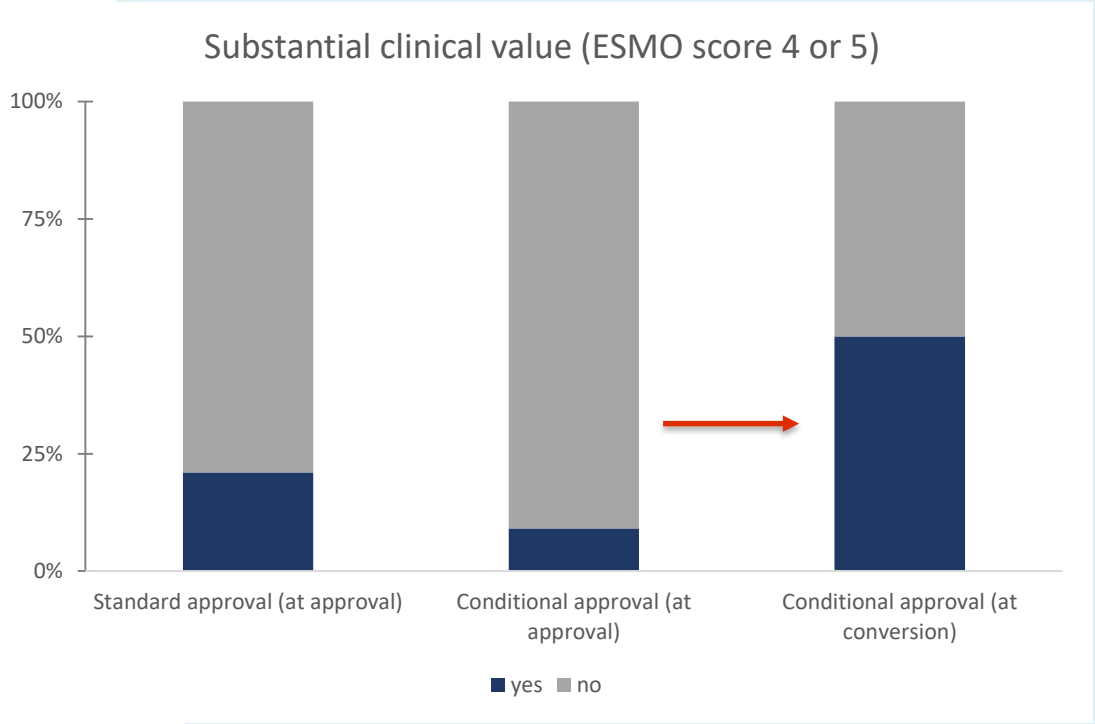


Clinical value of conditional approvals at initial approval & at conversion to standard approval



Bloem & Bot *et al. Ongoing work*

Conditional approval: impact of post-approval data on clinical value



Single arm: 9% 86% 43%

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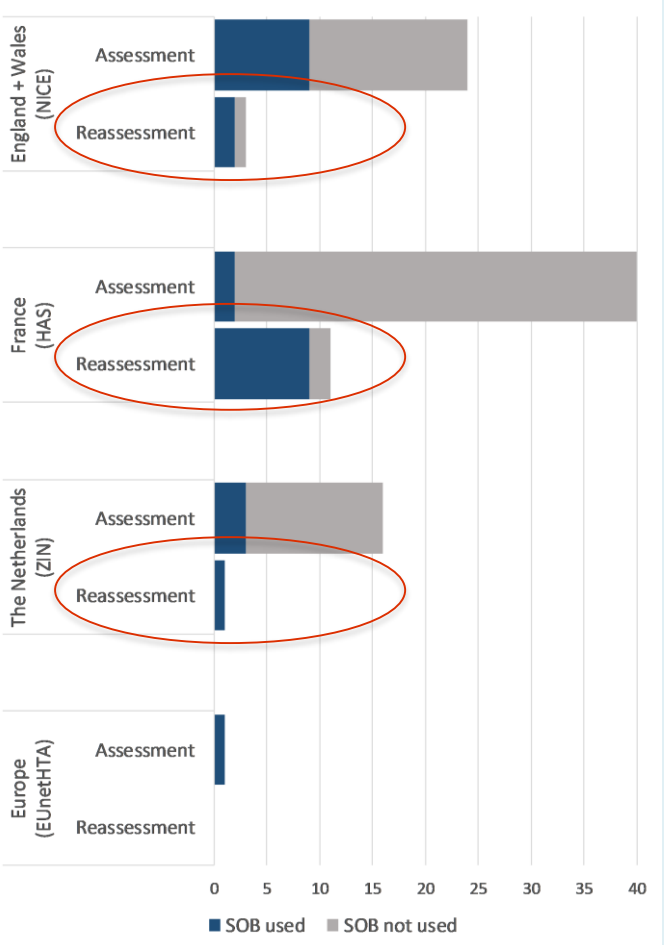
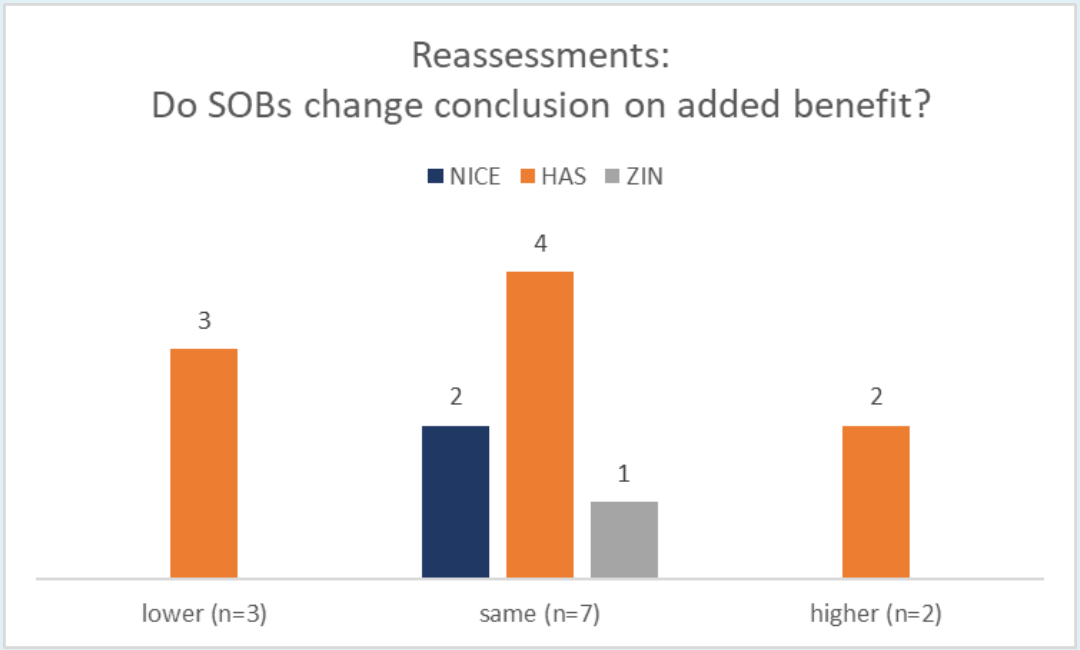
Conditional approval: impact of post-approval data in HTA





1. Content analysis needed!
2. Why not more reassessments?

   → …

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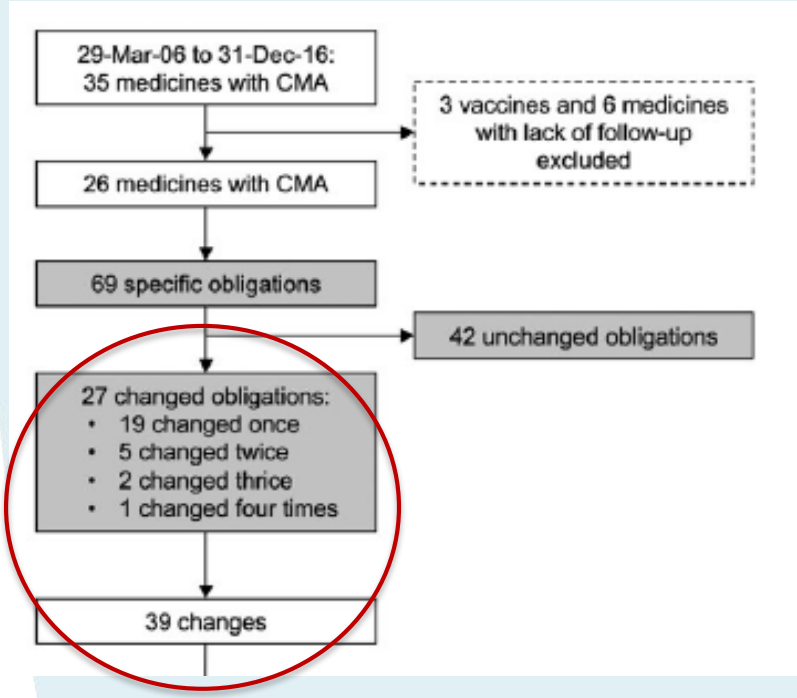
Post-approval data requirements may delayed and/or altered!



Bloem *et al.* Clin Pharmacol Ther 2019

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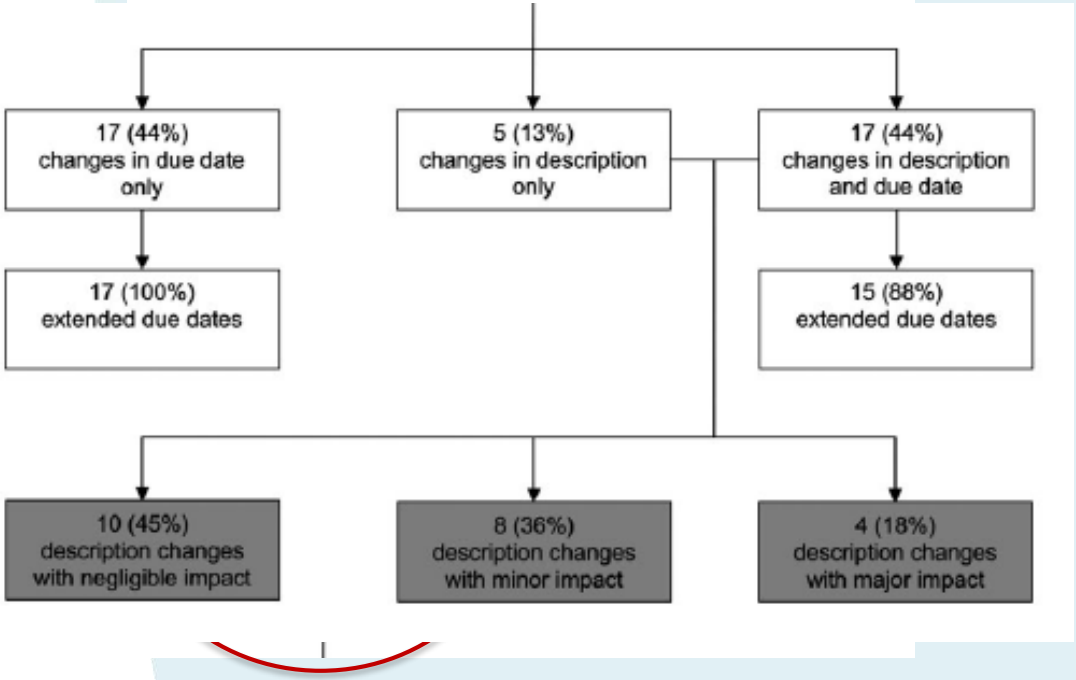

55% delayed + 6% substantial changes in study design

→ Could affect / limit downstream decision-making!

Bloem *et al.* Clin Pharmacol Ther 2019

Discussion

Regulatory uncertainty (EMA major objections / conditional approval) seems to trickle down to downstream stakeholders:

- HTA decision-making: negative recommendations
- Clinical decision-making: less often substantial clinical value at approval

However:

- May be dependent on indication → more positive HTA recommendations for conditional oncology medicines (definition of unmet medical need more straightforward?)
- More often substantial clinical value based on post-approval data

Policy conclusions

Involvement of stakeholders (HTA agencies, physicians) in setting evidentiary standards at regulatory approval is paramount to ultimately enable *timely patient access to innovative treatments*

HTA: early reg-HTA interactions could help by:

- Establishing a case by case uncertainty threshold
- Ensuring timely availability of relevant data post-approval

→ Right data at the right time!

Physicians: important role in EMA's Scientific Advisory Groups!

Patients!

Lessons for new monitoring and measurement technologies?

Building and acceptance of evidence: always uncertainty!

But: innovative evidence generation technologies → potentially more (downstream?) uncertainty, due to:

- Lack of (specific) expertise
- Lack of experience
- Lack of trust (?)

Effective application requires:

Early multi-stakeholder discussion: need + feasibility to generate evidence that increases knowlege / reduces uncertainty

→ Parallel reg-HTA Scientific Advice / Early Dialogues

Lessons for new monitoring and measurement technologies?

eunethta
EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 July 2019
EMA/410962/2017 Rev.2

Guidance for Parallel Consultation

uncertainty
→ Parallel reg-HTA Scientific Advice / Early Dialogues

Lessons for new monitoring and measurement technologies?

3.4. Other stakeholders

From an early stage, the EMA along with HTABs may consider the need for additional clinical experts in a given procedure and F2F meeting. The inclusion of patient representatives is expected on a routine basis.

Regulators' clinical experts are identified through National Competent Authorities (NCA) and SAWP members. A Health Care Professional (HCP) representative may also be invited by the EMA through the EMA HCP Working Party framework, as well as other stakeholders as appropriate.

Guidance for Parallel Consultation

uncertainty

→ Parallel reg-HTA Scientific Advice / Early Dialogues

Acknowledgements

Utrecht University
Prof. Olaf Klungel
Prof. Bert Leufkens
Prof. Aukje Mantel-Teeuwisse
Dr. Jarno Hoekman
Rick Vreman

Dutch Medicines Evaluation Board
Dr. Menno van der Elst

Students
Rosalinde Bot
Stijn van Oirschot
Niels Peeters

University of Copenhagen
Prof. Marieke de Bruin

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