IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Institute for Quality and Efficiency in Health Care

## Early benefit assessment of new drugs

# 5-year experiences of AMNOG (from IQWiG's point of view)

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Skipka G, et al. *Biom J* **58**: 43-58 (2016).

# IQWiG

- **IQWiG was founded as an independent scientific institute through a health care reform in 2004.**

- **Main task: Assessment of benefits and harms of medical interventions and production of independent, evidence-based reports**

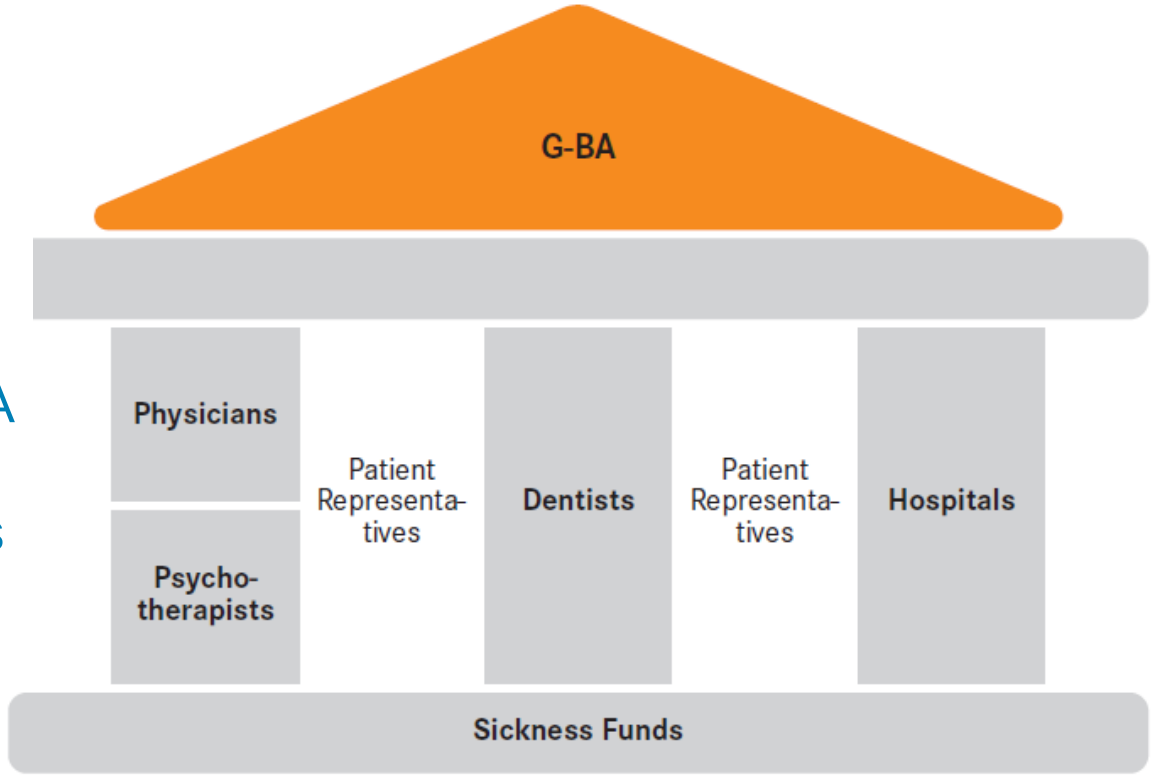

- **The legal basis of the work of IQWiG is the social code book V (SGB V)**

- **IQWiG is solely commissioned by the Federal Joint Committee or the Federal Ministry of Health (rather rarely), but can also cover topics on its own initiative under a general commission.**

# Federal Joint Committee (G-BA)

The Federal Joint Committee (G-BA) is the supreme decision-making body of the so-called self-governing system in Germany. Physicians, dentists, hospitals, sickness funds and patients are represented in the G-BA.

The G-BA issues directives and thus determines the benefit package of the statutory health insurance (GKV) covering about 70 million people. Finally, the G-BA is responsible for reimbursement decisions in the GKV.




Gemeinsamer Bundesausschuss

http://www.english.g-ba.de/downloads/17-98-2804/2010-01-01-Faltblatt-GBA_engl.pdf

## *Act on the Reform of the Market for Medicinal Products

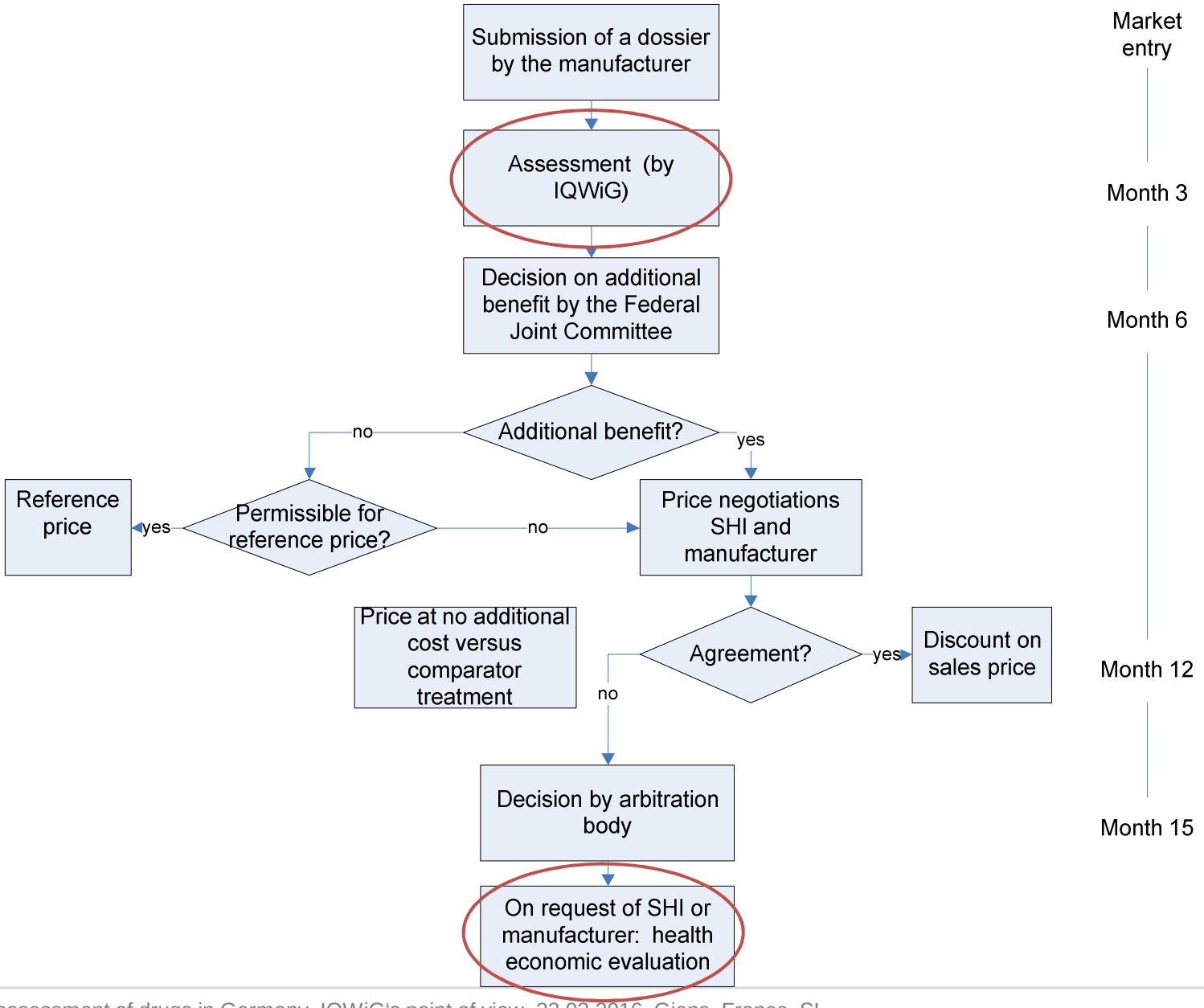
- Systematic early assessment of newly approved drugs
  - Assesses and quantifies (categories) additional benefit (vs. defined [appropriate] comparator → set by G-BA [not the ministry of health])
  - Forms the basis for price negotiations (→ discount on sales price)
  - Has no formal impact on prescription
  - 'must not contradict the statements on efficacy and safety by the drug regulation authorities' (German Social Code Book V)
  - Exception: orphan drugs – with the fiction of 'additional benefit by approval' – as long as sales volume < 50 Mio. € (otherwise: full assessment)
  - Assessment based on a dossier submitted by the manufacturer (at time of market access)

- No relevant role of health economics / cost-benefit-analysis

## Dossier

- information on the authorised indication
- all available evidence for the assessment of additional benefit (according to international standards of evidence-based medicine)
  - all studies sponsored by the pharmaceutical company
  - all available third-party studies
  - All information to study methodology and study results (of sponsors' studies) have to be made publicly available (no commercial-in-confidence data are acceptable)
- information on costs of the drug
- information on quality-assured use
- an incomplete dossiers means „no additional benefit"

# Process


Submission of a dossier by the manufacturer
Assessment (by IQWiG)
Decision on additional benefit by the Federal Joint Committee
Additional benefit?
no
yes
Reference price
yes
Permissible for reference price?
no
Price negotiations SHI and manufacturer
Price at no additional cost versus comparator treatment
Agreement?
yes
Discount on sales price
no
Decision by arbitration body
On request of SHI or manufacturer: health economic evaluation
Market entry
Month 3
Month 6
Month 12
Month 15

# Questions asked by AMNOG

- Does the drug under assessment have an additional benefit compared to the appropriate therapeutic alternative (appropriate comparator [set by the G-BA])?
- What is the extent of the additional benefit?
- What is the ‘probability‘ of the additional benefit (how certain are we about this additional benefit)
- Which patient groups experience a therapeutically important additional benefit?

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# Added benefit according to AMNOG

- Benefit = patient-relevant Effect
  (improving health state, shortening duration of illness, increasing survival, reducing adverse events, improving quality of life)
  (only validated surrogates may be considered → e.g. SVR for hepatitis C; however, PFS by Recist criteria has not been accepted in the past)

- Added Benefit = Benefit vs. appropriate comparator
  (Selection: evidence-base, practical experience, in case of comparable alternatives selection by manufacturer)

- Approval status has to be considered! (also for appropriate comparator)

# Multiple endpoints

**In principle, IQWiGs‘ methodology requires adjustment in case of a multiplicity issue …**

**In reality, however, IQWiG doesn‘t account for multiplicity in its assessments (up to now) …**

# ‘Probability’ (Certainty of conclusions)

| | | Number of studies | | | | |
|---|---|---|---|---|---|---|
| | | 1 (with statistically significant effect) | ≥ 2 | | | |
| | | | Homogeneous | Heterogeneous | | |
| | | | Meta-analysis statistically significant | Effects in the same direction[a] | | |
| | | | | Clear | Moderate | No |
| **Qualitative certainty of results** | High | Indication | Proof | Proof | Indication | – |
| | Moderate | Hint | Indication | Indication | Hint | – |
| | Low | – | Hint | Hint | – | – |

RCT with low risk of bias

RCT with high risk of bias

Non-RCT

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General Methods[a]

Version 4.2 of 22 April 2015

# Extent of added benefit (acc. to directive)

Major added benefit

Considerable added benefit

Minor added benefit

Added benefit not proven

Less benefit

*Added benefit not quantifiable*

Sustained and great improvement

Marked improvement

moderate and not only marginal improvement

# Extent of added benefit (acc. to directive)

| | Overall survival | Serious symptoms or events | *HRQoL*[#] | Non-serious symptoms or events |
|---|---|---|---|---|
| Major added benefit | Major increase | Long-term freedom or extensive avoidance | *Major improvement* | *N.a.* |
| Considerable added benefit | Moderate increase | Alleviation or relevant avoidance | *Important improvement* | Important avoidance |
| Minor added benefit | *Any increase* | *Any reduction* | *Any improvement* | Relevant avoidance |

= *Amendment to directive by IQWiG*

[#] *The condition is the use of a validated instrument and a validated response criterion. Values count for non-response.*

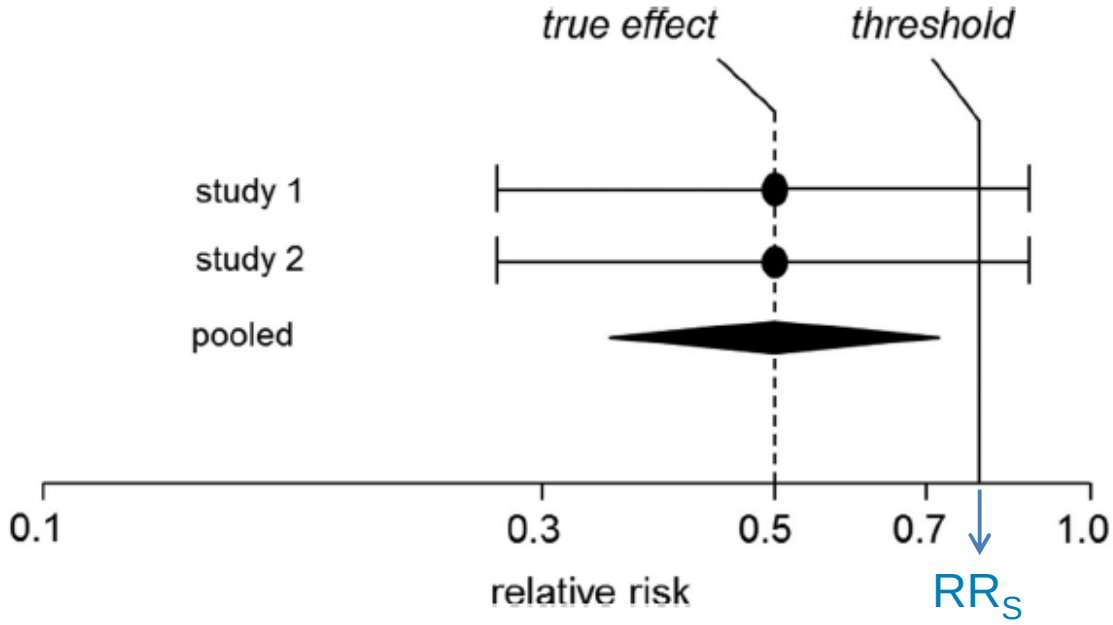
# What we would like to see …

| | Overall survival | Serious symptoms or events | *HRQoL* | Non-serious symptoms or events |
|---|---|---|---|---|
| Major added benefit | Major increase<br>$RR_o \leq 0,50$ | Long-term freedom or extensive avoidance<br>$RR_o \leq 0,17$ | *Major improvement*<br>$RR_o \leq 0,17$ | *N.a.* |
| Considerable added benefit | Moderate increase<br>$RR_o \leq 0,83$ | Alleviation or relevant avoidance<br>$RR_o \leq 0,67$ | *Important improvement*<br>$RR_o \leq 0,67$ | Important avoidance<br>$RR_o \leq 0,33$ |
| Minor added benefit | *Any increase*<br>$RR_o < 1,00$ | *Any reduction*<br>$RR_o < 1,00$ | *Any improvement*<br>$RR_o < 1,00$ | Relevant avoidance<br>$RR_o \leq 0,67$ |

*RRo = Observed relative risk*

# What we can expect to see …

**Suppose 2 reasonably powered studies with assumed ('true') effect RR (and conventional null-hypothesis $H_0$: RR ≥ 1 vs. $H_1$: RR < 1)**




**Select threshold $RR_S$ so that power for a test $H_0$: RR ≥ $RR_S$ vs. $H_1$: RR < $RR_S$ (pooled estimate) is the same as for the 2 single studies (with conventional null-hypothesis)**

Skipka G, et al. *Biom J* **58**: 43-58 (2016).

# What we have to test (shifted hypotheses)

| | Overall survival | Serious symptoms or events | *HRQoL* | Non-serious symptoms or events |
|---|---|---|---|---|
| Major added benefit | Major increase<br>RR < 0,85 | Long-term freedom or extensive avoidance<br>RR < 0,75[#] | *Major improvement*<br>RR < 0,75 | *N.a.* |
| Considerable added benefit | Moderate increase<br>RR < 0,95 | Alleviation or relevant avoidance<br>RR < 0,90 | *Important improvement*<br>RR < 0,90 | Important avoidance<br>RR < 0,80 |
| Minor added benefit | *Any increase*<br>RR < 1,00 | *Any reduction*<br>RR < 1,00 | *Any improvement*<br>RR < 1,00 | Relevant avoidance<br>RR < 0,90 |

*RR = Relative risk*

*[#] Risk must be at least 5% for at least one of the two groups compared*

Skipka G, et al. *Biom J* **58**: 43-58 (2016).

# What does this mean?

| | Overall survival |
|---|---|
| Major added benefit | Major increase<br><br>RR < 0,85 |

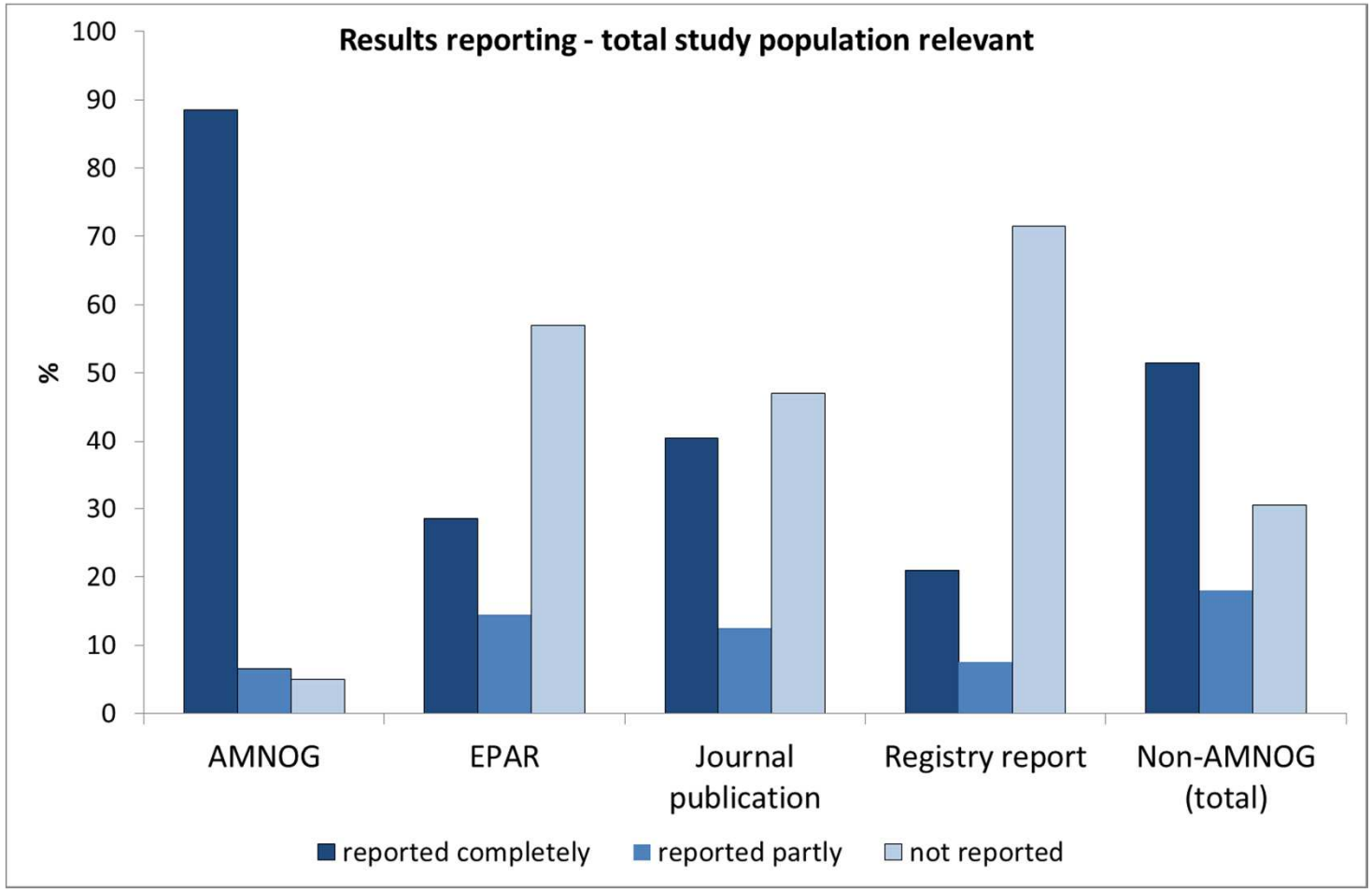
**If the upper limit of a 95% confidence interval for the effect estimate excludes 0,85**

**→ major increase in overall survival (major added benefit)**

Skipka G, et al. *Biom J* **58**: 43-58 (2016).

# ‘Added benefit’ of AMNOG

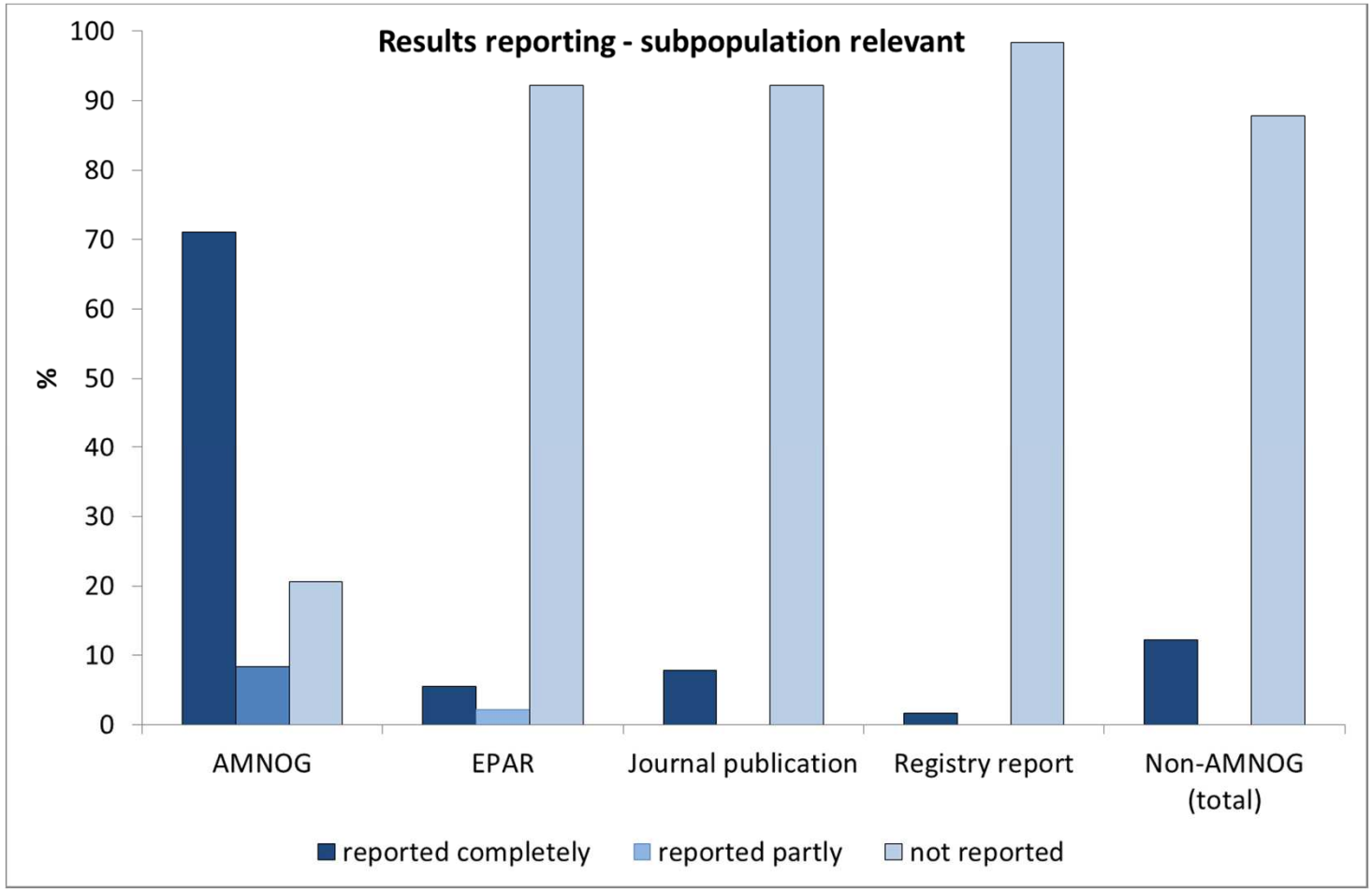
## Completeness of information of results with regard to patient-relevant endpoints




Köhler M. et al. Information on new drugs at market entry. BMJ 2015; 350; h796

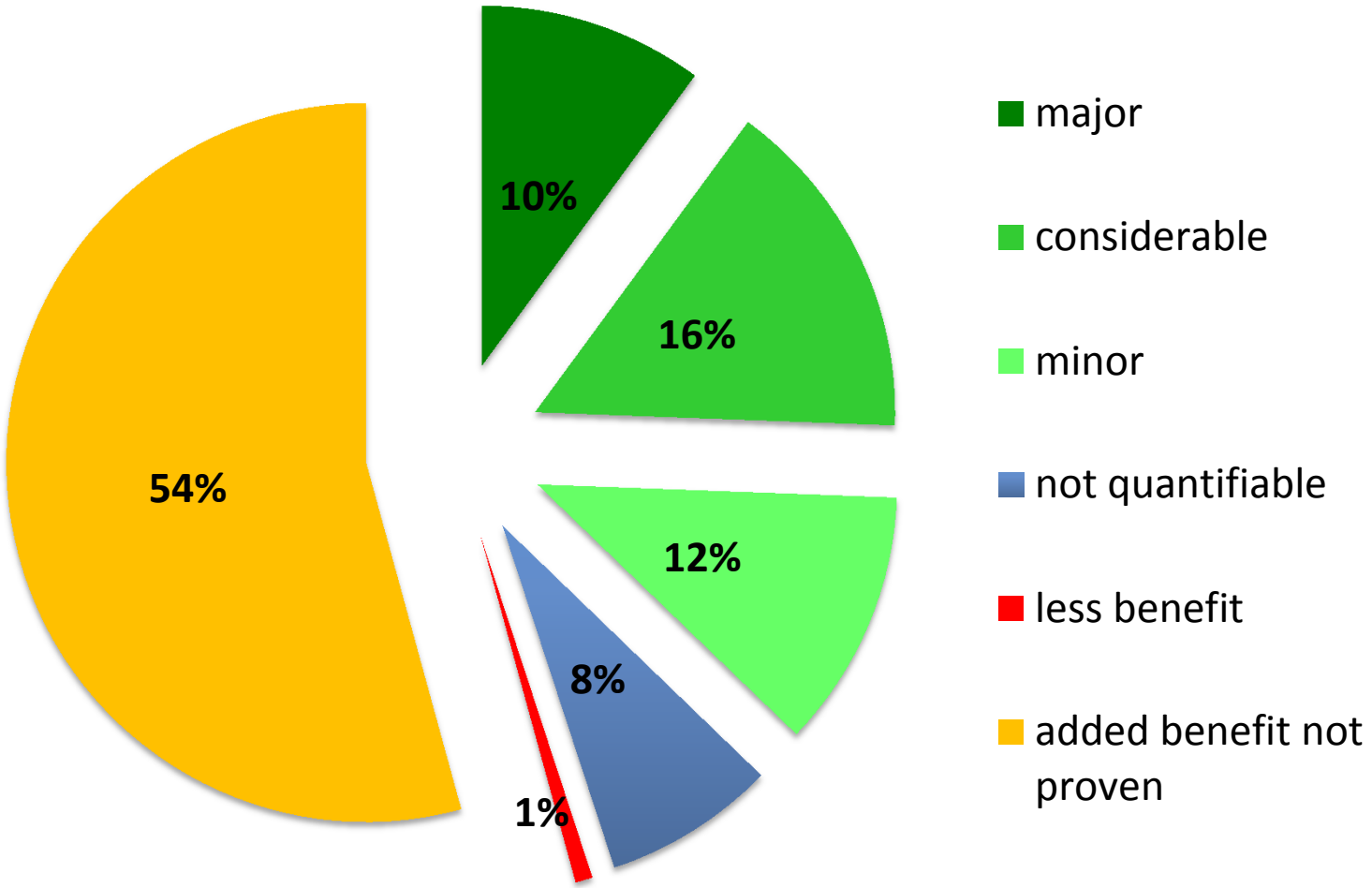
# ‘Added benefit’ of AMNOG

## Completeness of information of results with regard to relevant subpopulations/-groups




Köhler M. et al. Information on new drugs at market entry. BMJ 2015; 350; h796

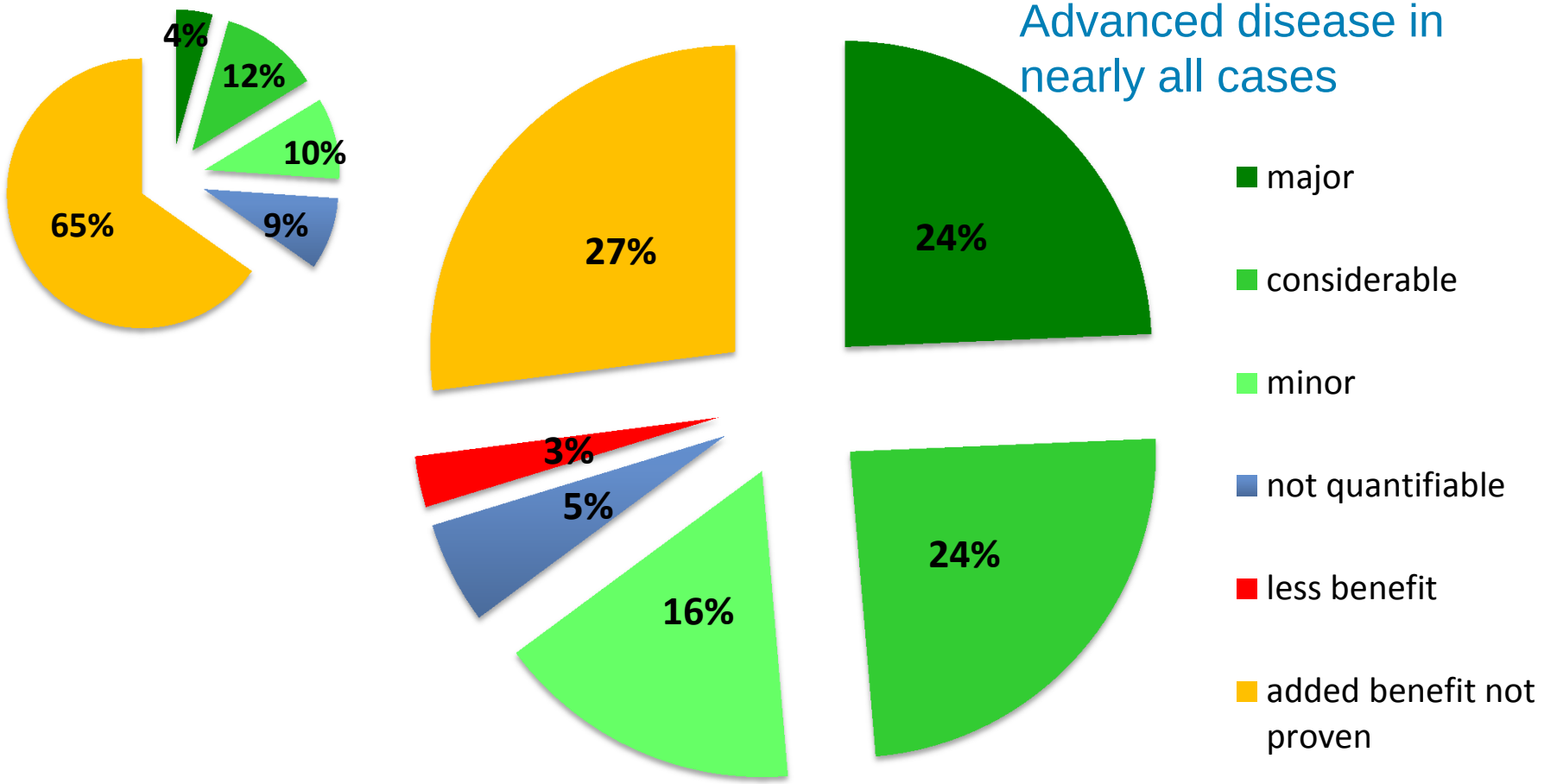
# Results (IQWiG, extent)




In each case best categorization of added benefit within one assessment

Status: 15/02/2016 129 assessments

# Results (IQWiG, extent)




In each case best categorization of added benefit within one assessment

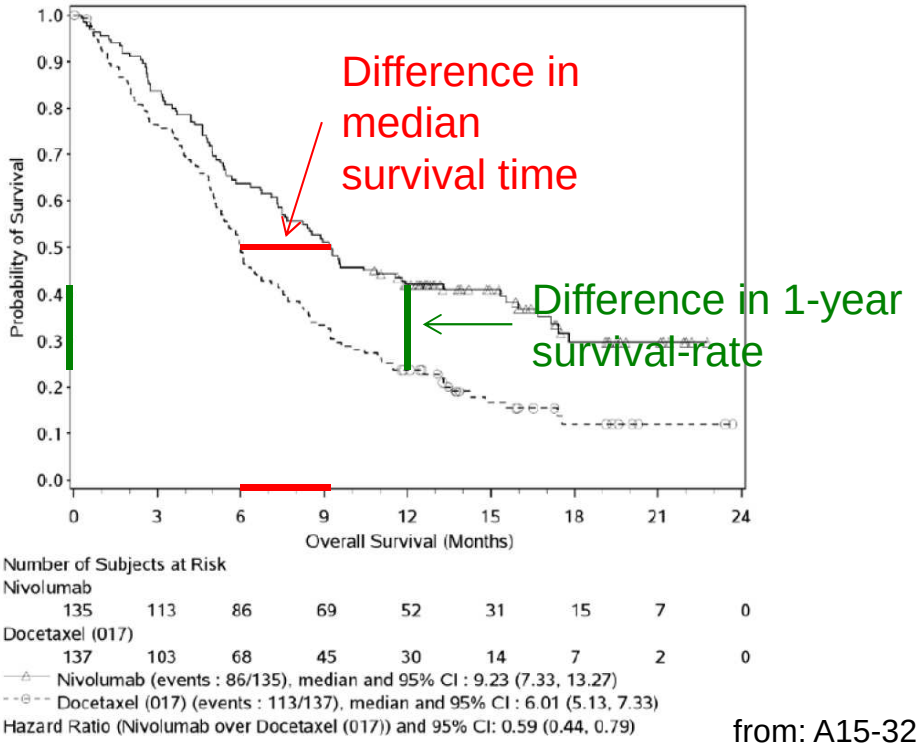
Status: 15/02/2016

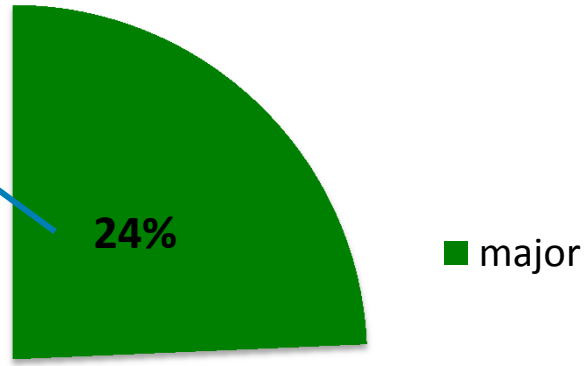
# Major added benefit?

## Oncology

Observed reduction in mortality (hazard ratio) always < 50% (HR > 0,5)

Example (HR: 0,59 [0,44; 0,79])



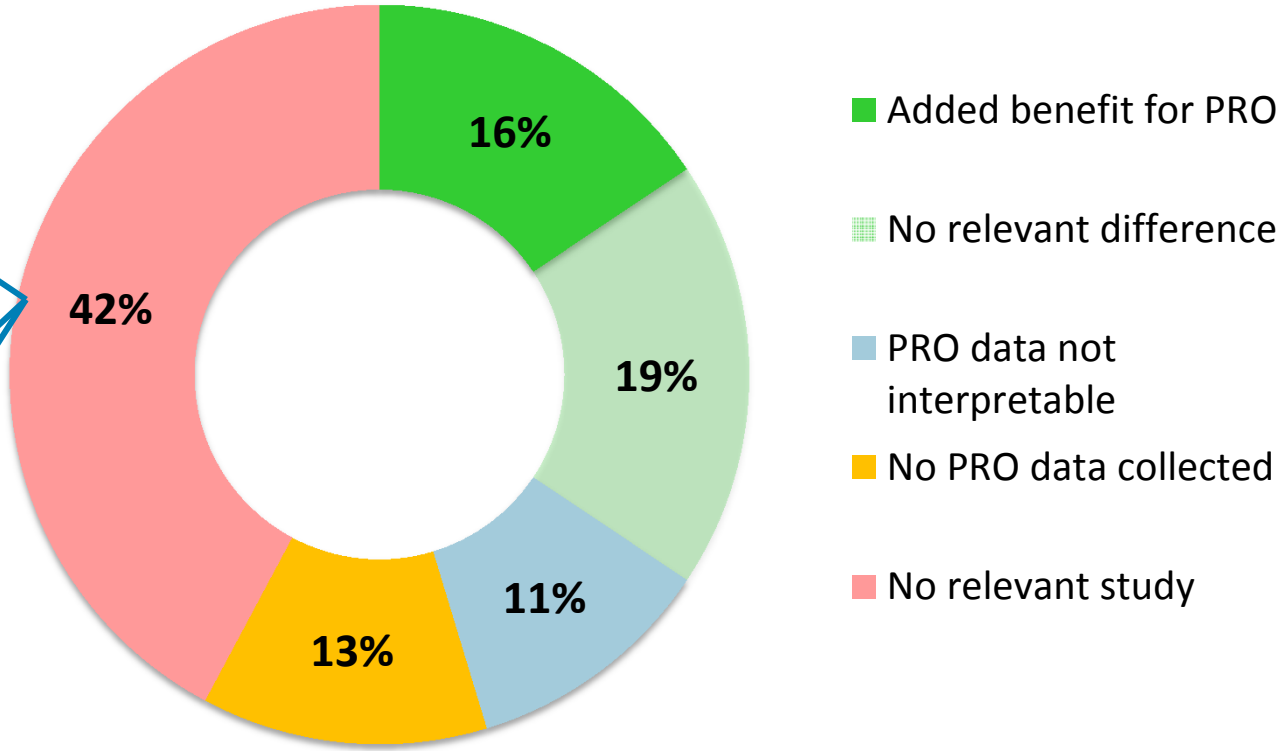

from: A15-32

# Results (IQWiG, PRO)

## Information with regard to patient reported outcomes (PRO, symptom scales or HRQoL)

Main reasons:

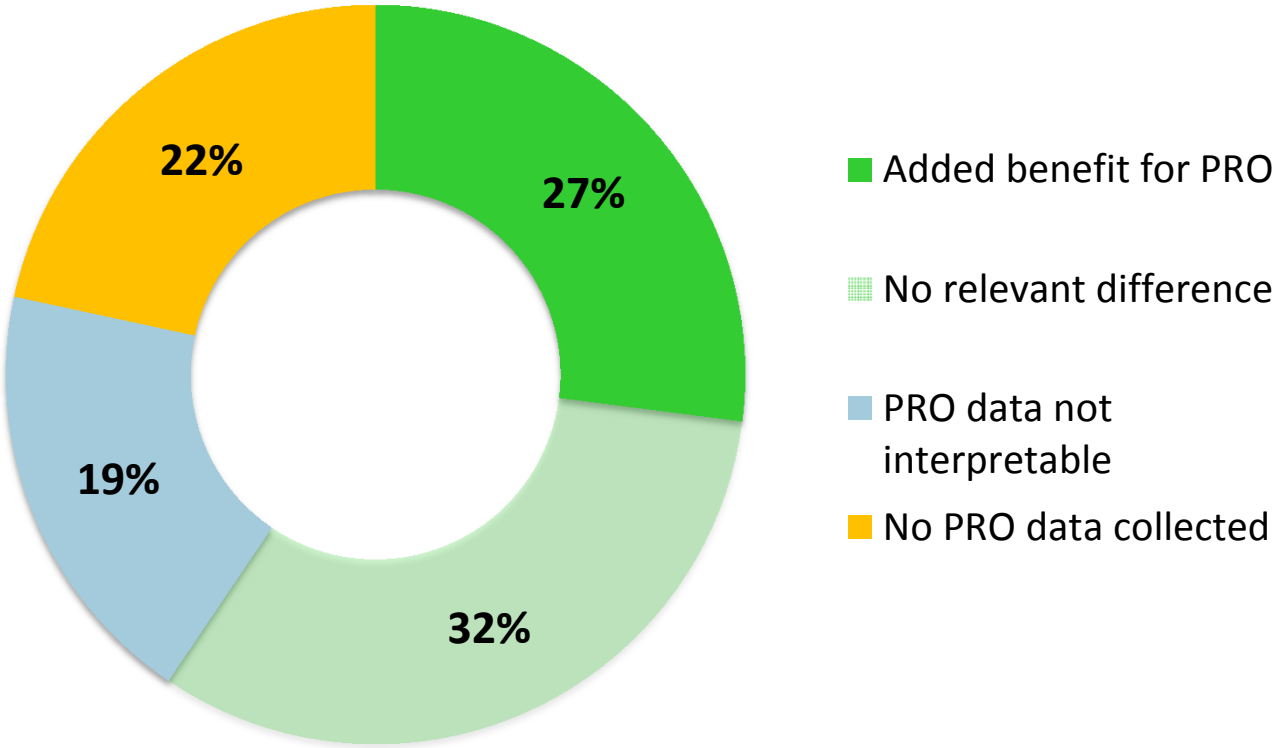
- Approval status not adequately considered
- Inappropriate comparator
- Unqualified indirect comparison




In each case best categorization of added benefit within one assessment

Status: 15/02/2016

## Information with regard to PRO, in case of relevant studies

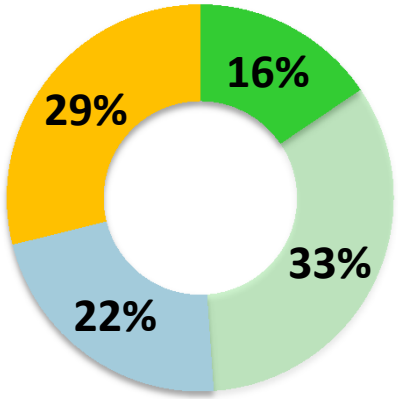



In each case best categorization of added benefit within one assessment

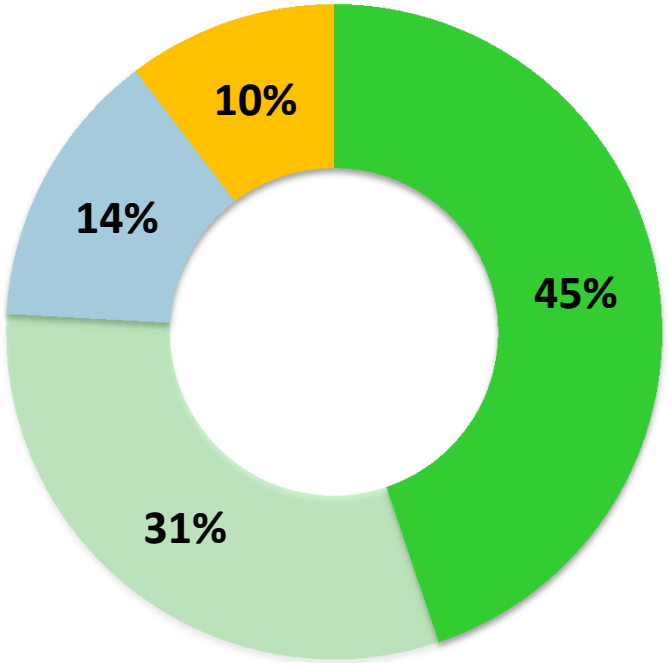
Status: 15/02/2016

## Information with regard to PRO, in case of relevant studies

### Others




### Oncology




- Added benefit for PRO
- No relevant difference
- PRO data not interpretable
- No PRO data collected

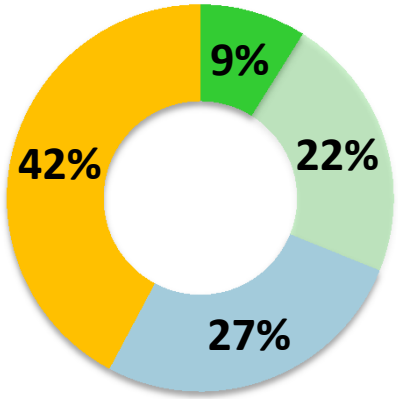
In each case best categorization of added benefit within one assessment

Status: 15/02/2016

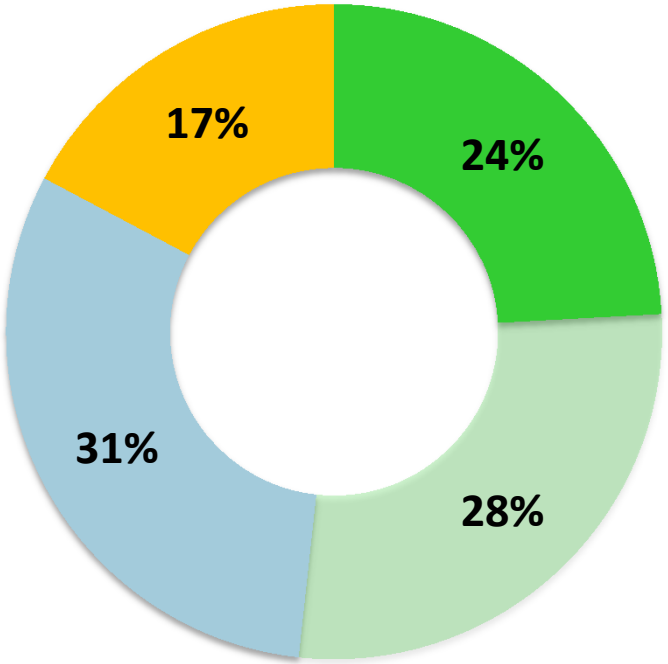
# Results (IQWiG, HRQoL)

## Information with regard to HRQoL, in case of relevant studies

### Others




### Oncology




- Added benefit for HRQoL
- No relevant difference
- HRQoL data not interpretable
- No HRQoL data collected

In each case best categorization of added benefit within one assessment

Status: 15/02/2016

# ‘Probability’ (in case of added benefit, IQWiG)

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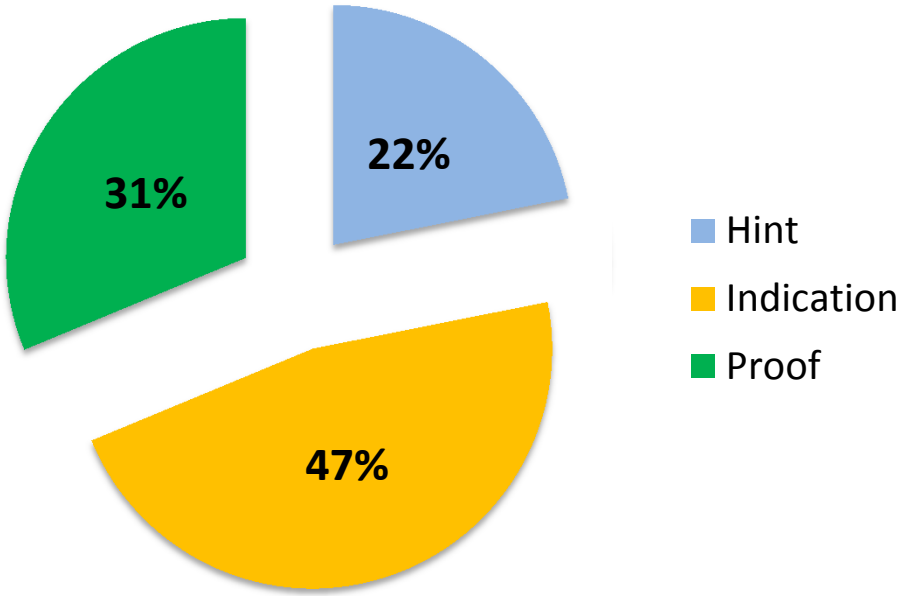
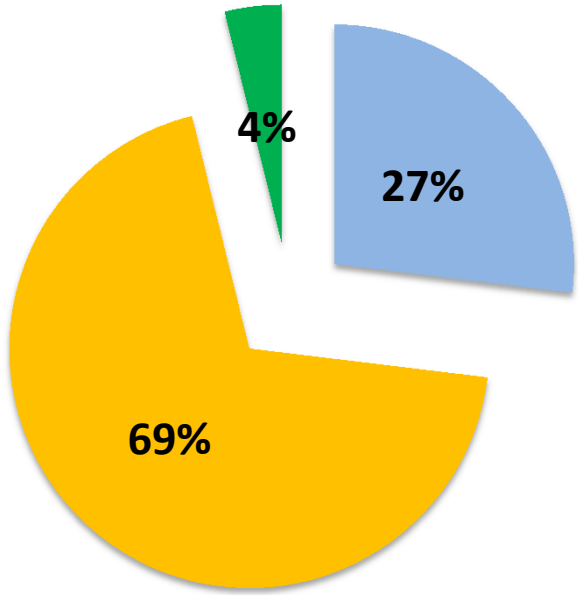
## Others




## Oncology




Hint
Indication
Proof

In oncology in general only one (pivotal, relevant) study available with about median 600 (suitable) patients

Status: 15/02/2016

# Agreement: Assessment (IQWiG) vs. decision (G-BA)

| IQWiG \ G-BA | Not proven | Not quantif. | Minor | Con-siderable | Major | Sum (IQWiG) |
|---|---|---|---|---|---|---|
| **Not proven** | 61 | 2 | 5 | 2 | 0 | **70** |
| **Not quantif.** | 0 | 3 | 0 | 6 | 0 | **9** |
| **Minor** | 0 | 0 | 11 | 2 | 0 | **13** |
| **Considerable** | 0 | 0 | 7 | 14 | 0 | **21** |
| **Major** | 0 | 0 | 2 | 10 | 2 | **14** |
| **Sum (G-BA)** | **61** | **5** | **25** | **34** | **2** | **127** |

In each case best categorization of added benefit within one assessment

# Thank you for your attention!

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