Towards an ecosystem of decision makers:

Etica approvazione e tempi CTIS – va bene cosi?

Nicola Magrini, MD

Direttore, UOC Innovazione, Sintesi Evidenze e Ricerca Clinica, IRCCS S.Orsola, Bologna

Professore di Farmacologia, DIMEC, Università di Bologna

Co-director, WHO Collaborating Centre for evidence synthesis and guideline development, Bologna

AIEOP

Lecce, 13 Ottobre 2026

Declarations

- Conflicts of interests – none
- Reflexivity statement: *I am deeply convinced essential medicines and vaccines have brought huge progresses and changed the world. Medicines and primarily essential ones are often used inappropriately or suboptimally (see antibiotics).*
- *I promote rigorous comparative evaluations mostly through RCTs and facilitate research and participation on advanced therapies like CAR-T and other ATMPs*
- *I am interested in research methodology and participation in clinical trials and in consents that make (some) sense*

- *I like cats, Joyce, classical music, jokes and peace.*
- *I have three daughters*
- *I have been Secretary of the WHO EML (2014-2020) and DG of the Italian Medicines Agency during Covid-19 (2020-2023)*

Pharmaceuticals – Medicines (drugs)

- The most regulated area/commodity in the world with a third party payer

"*Medicines are prescribed by people who don't take them,*

taken by people who don't pay for them,

and paid for by people who don't use them.«

La politica deve rendere possibile
ciò che è necessario

Ruth Dreyfuss

Presidente Confederazione Elvetica, 1999

Towards an ecosystem of decision makers

- An ecosystem of decision makers – are we slowly converging?
- How to avoid the current discrepancy/fracture
  - Evidence for approval vs evidence for reimbursement/HTA/guidelines
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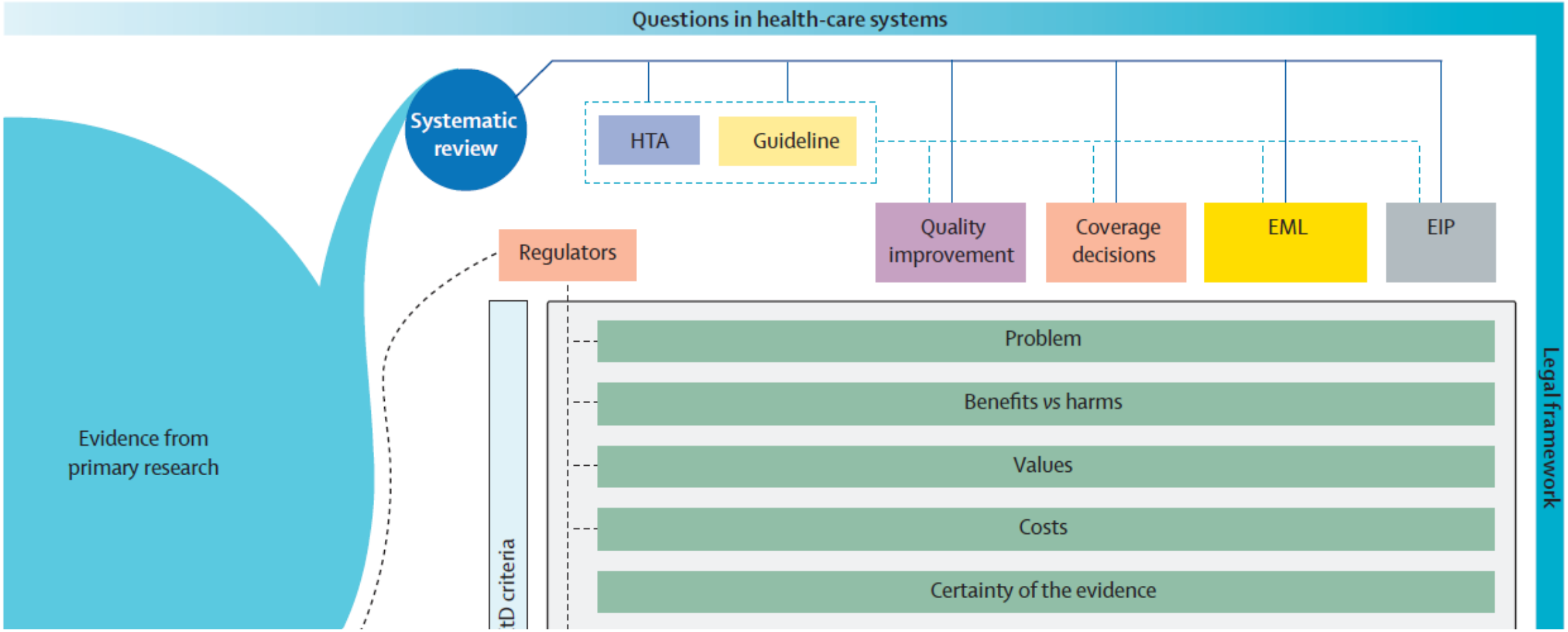
The ecosystem of health decision making: from fragmentation to synergy

Holger J Schünemann, Marge Reinap, Thomas Piggott, Erki Laidmäe, Kristina Köhler, Mariliis Põld, Brendalynn Ens, Alar Irs, Elie A Akl, Carlos A Cuello, Maicon Falavigna, Michelle Gibbens, Luciana Neamtiu, Elena Parmelli, Mouna Jameleddine, Lisa Pyke, Ilse Verstijnen, Pablo Alonso-Coello, Peter Tugwell, Yuan Zhang, Zuleika Saz-Parkinson, Tanja Kuchenmüller, Lorenzo Moja

Clinicians, patients, policy makers, funders, programme managers, regulators, and science communities invest considerable amounts of time and energy in influencing or making decisions at various levels, using systematic reviews, health technology assessments, guideline recommendations, coverage decisions, selection of essential medicines and diagnostics, quality assurance and improvement schemes, and policy and evidence briefs. The criteria and methods that these actors use in their work differ (eg, the role economic analysis has in decision making), but these methods frequently overlap and exist together. Under the aegis of WHO, we have brought together representatives of different areas to reconcile how the evidence that influences decisions is used across multiple health system decision levels. We describe the overlap and differences in decision-making criteria between different actors in the health sector to provide bridging opportunities through a unifying broad framework that we call theory of everything. Although decision-making activities respond to system needs, processes are often poorly coordinated, both globally and on a country level. A decision made in isolation from other decisions on the same topic could cause misleading, unnecessary, or conflicted inputs to the health system and, therefore, confusion and resource waste.

Lancet Public Health 2022; 7: e378–90

Department of Health Product Policy and Standards (L Moja MD) and Department of Research for Health (T Kuchenmüller MA), WHO, Geneva, Switzerland; Michael G. DeGroote Cochrane Canada Centre and McMaster GRADE Centres, Department of Health Research Methods, Evidence, and Impact, Department of Medicine, and WHO Collaborating Center for Infectious Diseases, Research



- *In conclusion, in appraising the evidence for health-care interventions, actors involved in decision-making should be aware that they do not exist with their responsibilities as single entities but as part of a complex system that has many commonalities.*

Politiche farmaceutiche tre livelli

EU EMA – indicazione approvata

AIFA – SSN - indicazione rimborsata

Regioni e aziende sanitarie: prescrizione/pazienti

Da EMA al PTN

- AIFA solo farmaci umani - PTN
- EMA umani e vet

- Quindi abbiamo già perso una parte della visione di sistema

One Health

journal homepage: www.elsevier.com/locate/onehlt

Evidence for the transmission of antimicrobial resistant bacteria between humans and companion animals: A scoping review

Mu Jin [a,b], Marwan Osman [a,c], Brianna A. Green [a], Yufan Yang [a], Aditi Ahuja [a], Zhengyu Lu [a], Casey L. Cazer [a,d,*]

[a] *Department of Public and Ecosystem Health, Cornell University College of Veterinary Medicine, USA*
[b] *Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, USA*
[c] *Cornell Atkinson Center for Sustainability, Cornell University, Ithaca, NY 14853, USA*
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ARTICLE INFO

Keywords:
Antimicrobial resistance
One health
Companion animals
Scoping review
Zoonotic disease

ABSTRACT

Objective: Transmission of antimicrobial resistant bacteria between people and household pets, such as dogs and cats, is an emerging global public health problem. This scoping review synthesized existing evidence of human-pet bacteria transmission to understand the magnitude and breadth of this issue.

Methods: The search included specific and generic terms for bacteria, resistance, transmission, pets, and humans. Searches were conducted through PubMed, Scopus, Web of Science, CABI Global Health, Networked Digital Library of Theses and Dissertations, Google Scholar. All studies published in English and Mandarin that isolated bacteria from pets (cats and dogs) and humans who had contact with the pets, and reported phenotypic or genotypic antimicrobial sensitivity test results, were included in this review. In cases of bacterial species that are commonly associated with pets, such as *Staphylococcus pseudintermedius* and *Pasteurella multocida*, we also included studies that only isolated bacteria from humans.

AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews

Check for updates

Clinical Microbiology | Review

Companions in antimicrobial resistance: examining transmission of common antimicrobial-resistant organisms between people and their dogs, cats, and horses

Benjamin Caddey,[1] Sibina Fisher,[1] Herman W. Barkema,[1] Diego B. Nobrega[1]

prescription in the companion animal setting. However, consensus between the WHO and the WOAH has not been reached on AMU classifications. For example, the WHO recently reclassified third- and fourth-generation cephalosporins as for human use only, while the WOAH classifies them as veterinary critically important antimicrobials for food-producing animals. Global guidelines for AMU in companion animals are urgently needed and should be developed within the context of both the WHO, its Global Action

March 2025 Volume 38 Issue 1

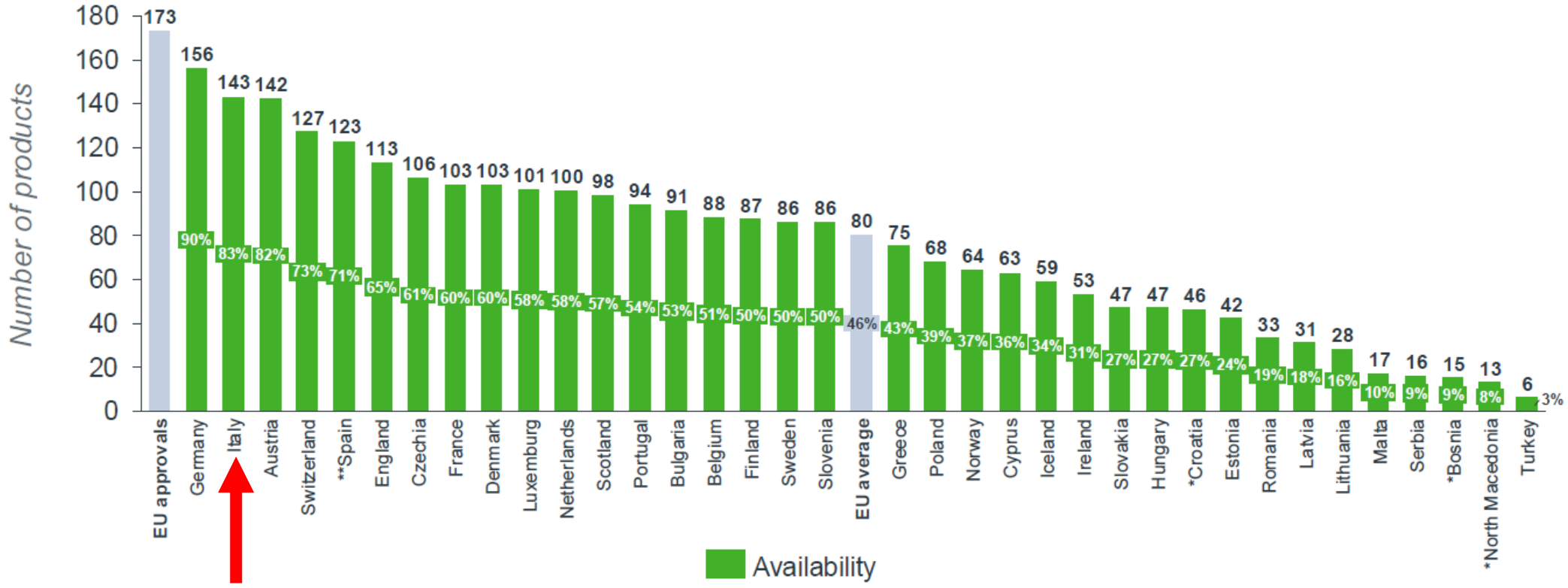
Da EMA al PTN - 2

- Non tutti i farmaci devono essere rimborsati se poco efficaci o con alternative preferibili
  - Italia rimborsa troppi farmaci?
  - Forse SI, se ci confrontiamo con Paesi EU più ricchi di noi e che spendono molto di più nel loro SSN (Olanda, Norvegia, …)

Italia ai primi posti per farmaci rimborsati (Efpia)

Rate of availability (2020-2023)

The **rate of availability**, measured by the number of medicines available to patients in European countries as of 5th January 2025. For most countries this is the point at which the product gains access to the reimbursement list†, including products with limited availability.



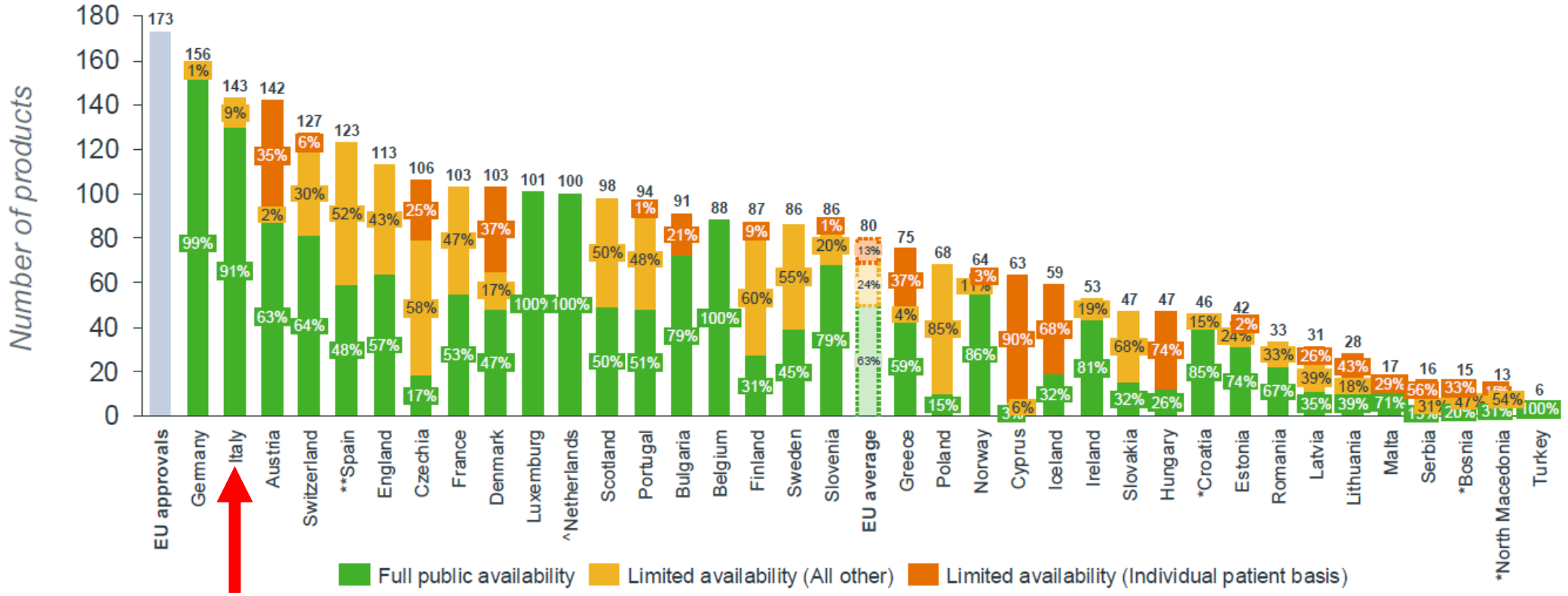
European Union average: 80 products available (46%) †Country specific definitions are listed in the appendix. *Countries with asterisks did not complete a full dataset and therefore availability may be unrepresentative. **In Spain, the WAIT analysis does not identify those medicinal products being accessible earlier in conformity with Spain's Royal Decree 1015/2009 relating to Medicines in Special Situations.

IQVIA

Italia ai primi posti per farmaci rimborsati (Efpia)

Breakdown of availability (2020-2023)

The **breakdown of availability** shows the proportion of medicines available to patients in European countries as of 5th January 2025 (for most countries this is the point at which the product gains access to the reimbursement list†) with full availability, via individual patient schemes, or with other restrictions.



European Union average: 80 products available (46%), Limited Availability (total) (37% of available products); ^Netherlands did not submit complete information on restrictions to available medicines meaning LA* is not captured in these countries. †Country specific definitions are listed in the appendix. *Countries with asterisks did not complete a full dataset and therefore availability may be unrepresentative. **In Spain, the WAIT analysis does not identify those medicinal products being accessible earlier in conformity with Spain's Royal Decree 1015/2009 relating to Medicines in Special Situations.

IQVIA

KONINKLIJKE NEDERLANDSE
AKADEMIE VAN WETENSCHAPPEN

SCIENCE IS THE PRESCRIPTION

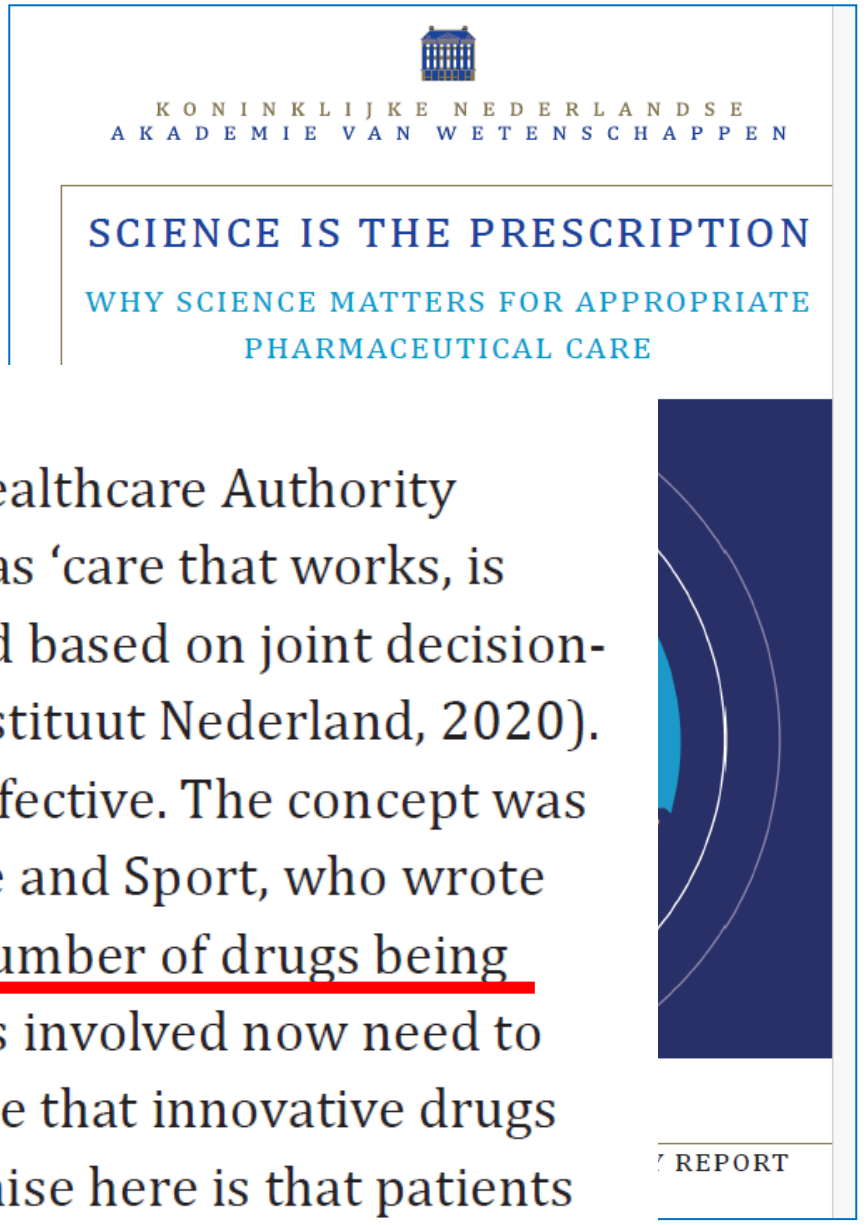
WHY SCIENCE MATTERS FOR APPROPRIATE PHARMACEUTICAL CARE



ADVISORY REPORT

Royal Netherlands Academy of Arts and Sciences

Feb 2026



Appropriate care

In 2022, the National Health Care Institute and the Dutch Healthcare Authority (NZa) introduced the concept of 'appropriate care', defined as 'care that works, is affordable, where possible arranged close to the patient, and based on joint decision-making by the patient and the care provider' (NZa & Zorginstituut Nederland, 2020). 'Care that works' refers to care that has been shown to be effective. The concept was well received, for example by the Minister of Health, Welfare and Sport, who wrote in 2023: 'In recent years, I have noticed an increase in the number of drugs being registered that offer only limited added value. All the parties involved now need to make choices so that we can manage expenditure and ensure that innovative drugs remain available and affordable for patients. The basic premise here is that patients should receive appropriate care.'[6]

L’OMS stima che più della metà dei farmaci sono prescritti in modo inappropriato e la metà dei pazienti li prende in modo non corretto

https://www.who.int/activities/promoting-rational-use-of-medicines

Quindi … si può fare molto per usarli meglio

in modo ottimale/appropriato

(parsimonioso, … dosi e durate)

Towards an ecosystem of decision makers

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  - Strenghten independent re-analysis of clinical trials
- Conclusions/proposals

Che una rivista così importante abbia pubblicato uno studio così **mal disegnato** e con **risultati irrilevanti** è un problema

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 5, 2023 VOL. 388 NO. 1

Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

Supported by Eisai (regulatory sponsor), with partial funding by Biogen.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Lecanemab - CLARITY AD: RCT dimensionato per una piccola differenza statistica NON clinicamente rilevante

- La dimensione dello studio è stata calcolata su una differenza attesa tra lecanemab e placebo di 0.337 punti alla scala CDR-SB, **ben al di sotto di quanto viene considerato la minimo clinicamente rilevante (almeno 1 punto nei pazienti con MCI) o la MID minimally important difference**

Cosa vuol dire efficacia nella demenza

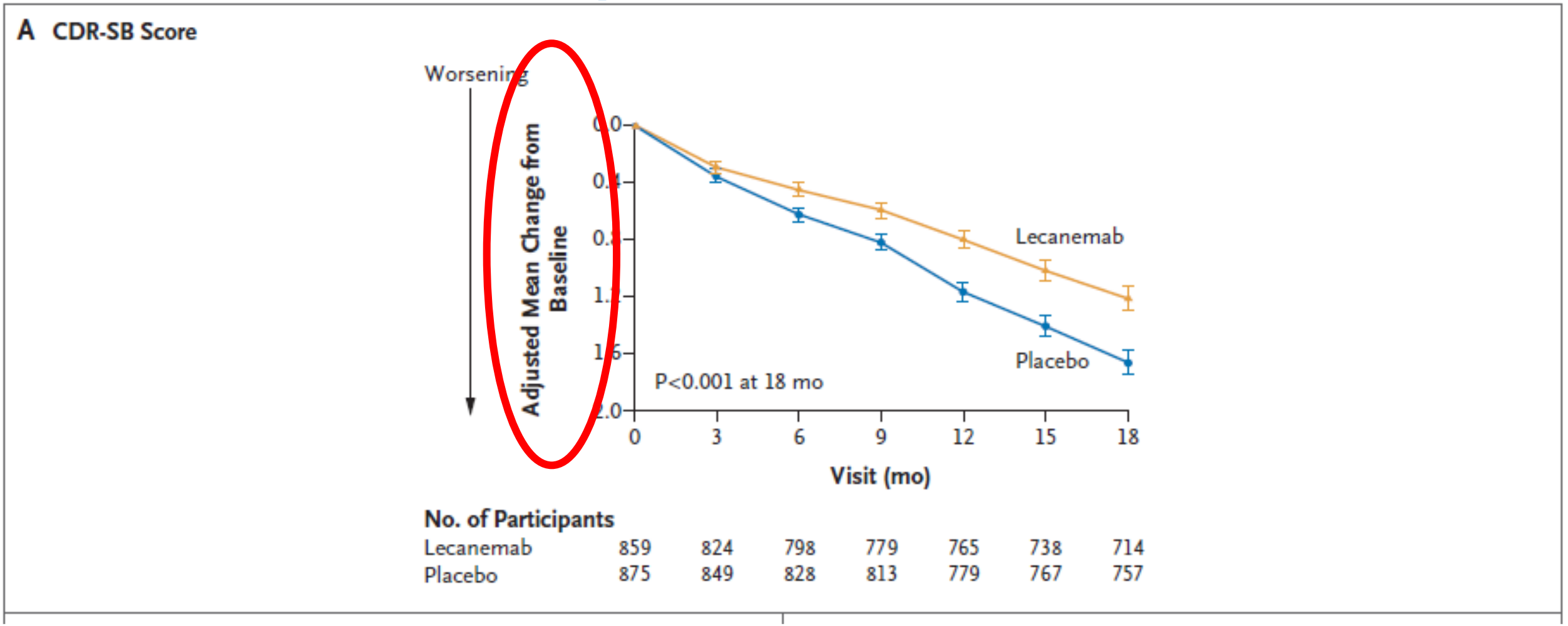
Clinical Dementia Rating - Sum of Boxes (CDR-SB)

- Intervista semi-strutturata **al paziente e al caregiver** (*informant-based* = componente di soggettività)
- Misura la gravità della demenza valutando la sfera **cognitiva** e **funzionale**
- **6 domini (Boxes):** Memoria, Orientamento, Giudizio e problem solving, Attività comunitarie, Cura della casa e hobby, Cura personale.
- **Punteggio massimo CDR_SB: 18 punti**
- A ogni dominio può essere assegnato un punteggio che va da 0 (normale) a 3 (grave)
- Maggiore è il punteggio, più e grave la demenza
- **Minimally Important Difference (MID)** = 1 punto (MCI), **1-2 punti (Mild dementia)** (Liu 2019, Muir 2023) **– aspetto più importante**

Efficacia: una differenza per il pointer …

ovvero una differenza clinicamente NON rilevante

e un possibile artefatto



MID

minimally important difference

Da anni le riviste internazionali hanno definito le modalità ottimali di presentazione dei risultati degli studi (molto spesso disattese):

differenze assolute (NNT e frequenze naturali) e differenze relative,

preferire i CI ai P value,

rilevanza clinica vs la significatività statistica e MID

Utilità della MID – *minimally important difference*

RESEARCH METHODS AND REPORTING

Check for updates

Core GRADE 2: choosing the target of certainty rating and assessing imprecision

Gordon Guyatt,[1,2,3,*] Linan Zeng,[3,4,5,6,*] Romina Brignardello-Petersen,[1] Manya Prasad,[7] Hans De Beer,[8] M Hassan Murad,[9] Alfonso Iorio,[1,2] Arnav Agarwal,[1,2,3] Liang Yao,[10] Thomas Agoritsas,[1,3,11] Jamie Rylance,[12] Reem A Mustafa,[1,13] Per Olav Vandvik,[3,14] Prashanti Eachempati,[3,15,16] Chunjuan Zhai,[17] Lingli Zhang,[4,5,6] Victor M Montori,[18,19] Monica Hultcrantz[20,21]

For numbered affiliations see end of the article

Correspondence to: G Guyatt guyatt@mcmaster.ca; (ORCID 0000-0003-2352-5718)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2025;389:e081904
http://dx.doi.org/10.1136/bmj-2024-081904

Accepted: 14 March 2025

This second article in a seven part series presents the Core GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to deciding on the target of the certainty rating, and decisions about rating down certainty of evidence due to imprecision. Core GRADE users assess if the true underlying treatment effect is important or not in relation to the minimal important difference (MID) or,

This is the second paper in a series describing the essentials of GRADE (Grading of Recommendations Assessment, Development and Evaluation) in rating certainty of evidence and grading recommendations, focusing on evidence addressing alternative care options from the perspective of the patient. In the first paper, we described our overall Core GRADE approach, noting that Core GRADE's certainty rating represents confidence that the true effect lies on one side of a threshold (such as an important difference) or in a particular range (such as an unimportant or little to no effect).[1] We further noted that randomised controlled trials start as high certainty evidence in Core GRADE's four category certainty approach (high, moderate, low, and very low), and non-randomised studies of interventions (observational) start at low certainty.

Utilità della MID – *minimally important difference*

CORE GRADE: IMPRECISION

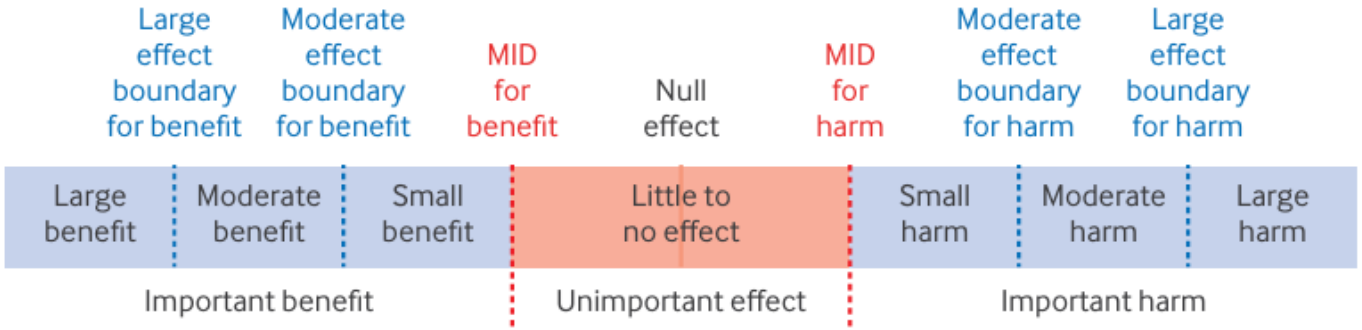
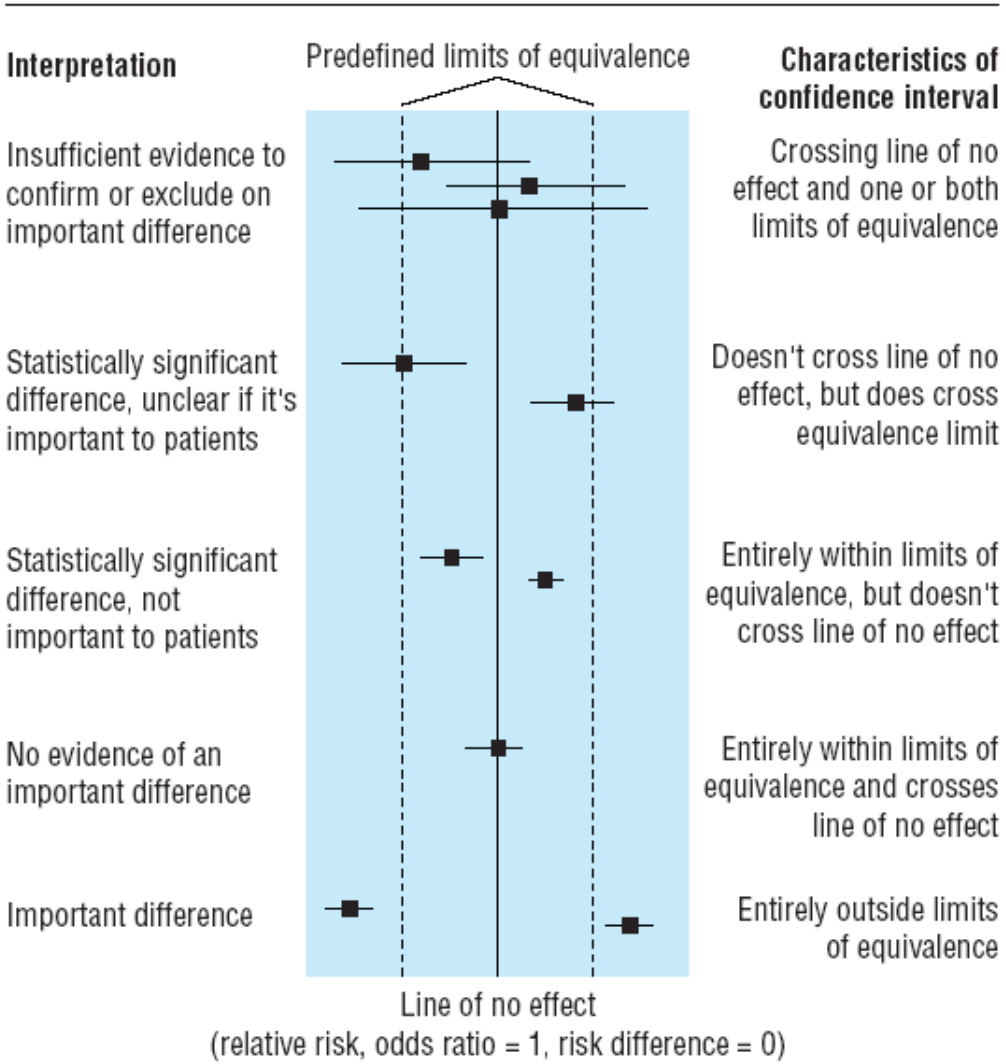


Fig 1 | Thresholds and ranges for rating certainty of evidence in Core GRADE. Besides the Core GRADE thresholds of null effect and MID, two other thresholds may be considered—the moderate effect threshold that demarcates small versus moderate effects, and the large effect threshold that demarcates moderate versus large effects. GRADE=Grading of Recommendations Assessment, Development and Evaluation; MID=minimal important difference

- users may assess their certainty in an important or unimportant effect (using the minimal important difference threshold), which often simplifies and clarifies ratings of imprecision and interpretation of results

Intervalli di confidenza: meglio dei P

Dove siamo?



Relation between confidence interval, line of no effect, and thresholds for important differences (adapted from Armitage, Berry, and Matthews[4])

Towards an ecosystem of decision makers

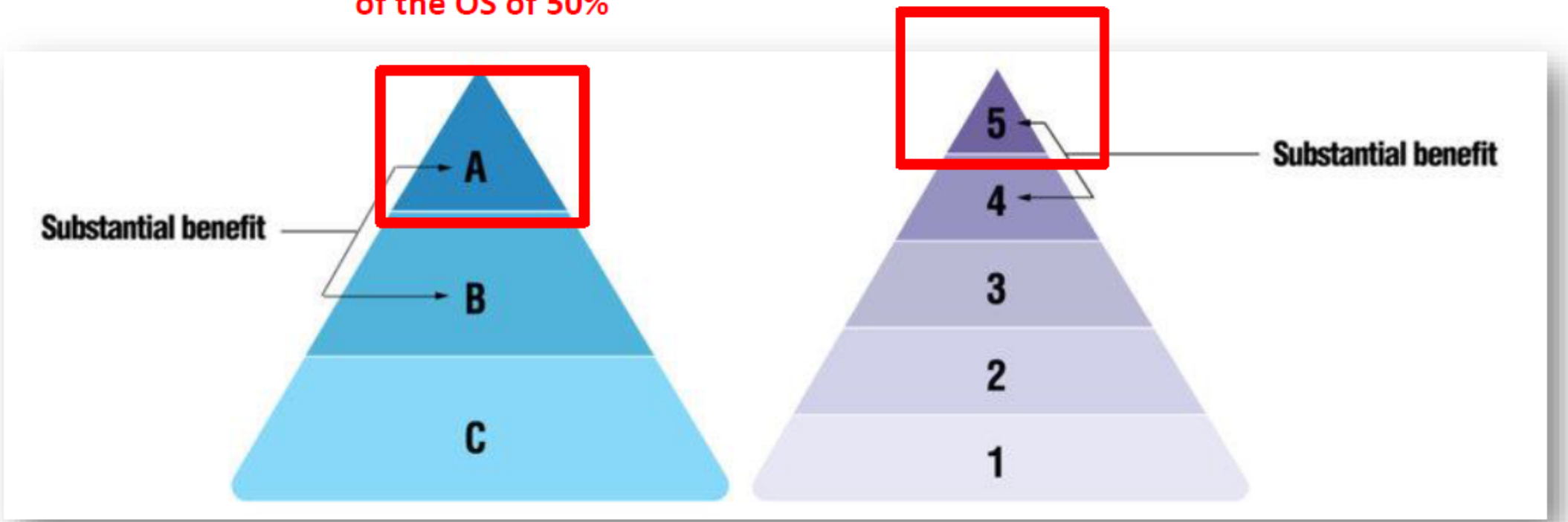
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THE ESMO MAGNITUDE OF CLINICAL BENEFIT SCALE

MCBS

Relative improvement of the OS of 50%

Absolute improvement of OS of 9 mo with better QoL

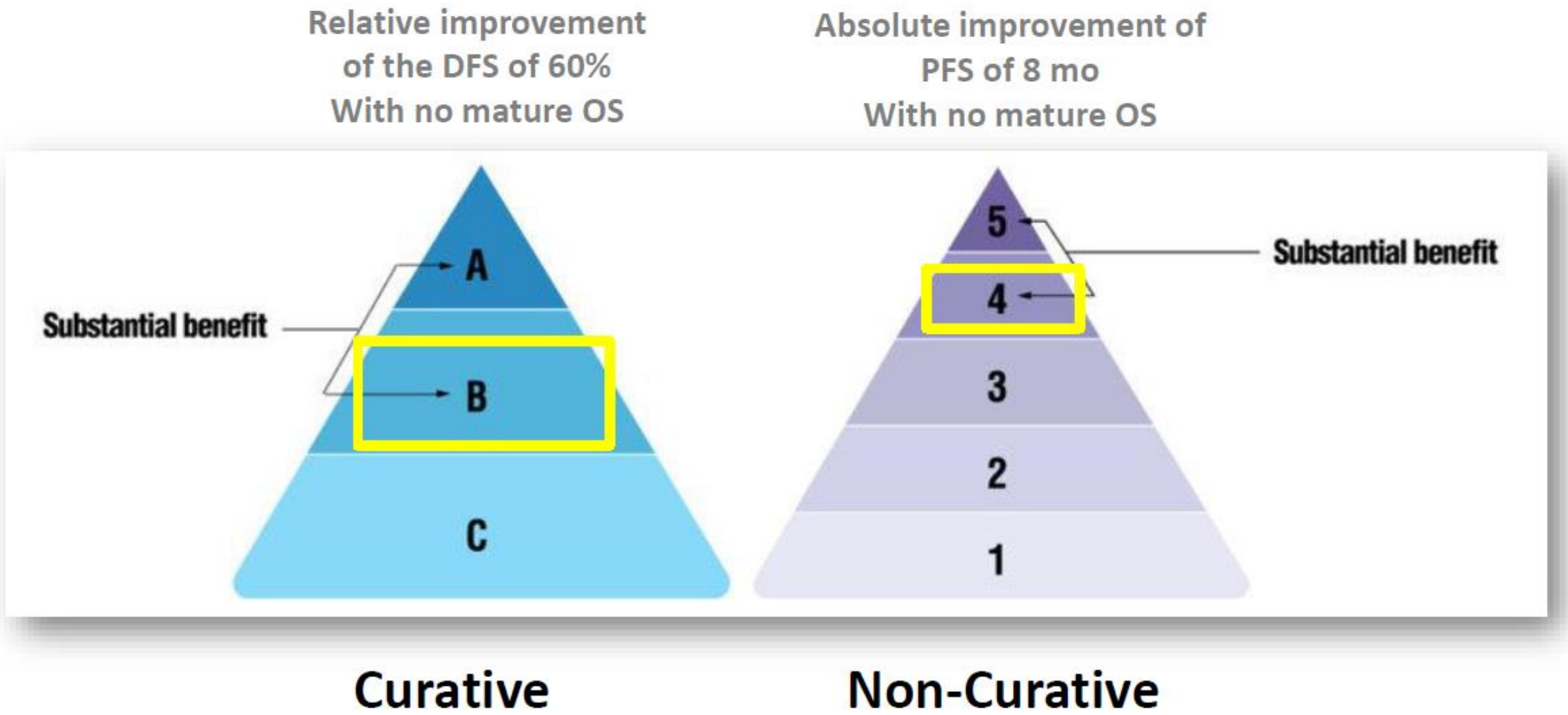


Curative **Non-Curative**

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THE ESMO MAGNITUDE OF CLINICAL BENEFIT SCALE

MCBS



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Prices and clinical benefit of cancer drugs in the USA and Europe: a cost–benefit analysis

Kerstin N Vokinger, Thomas J Hwang*, Thomas Grischott, Sophie Reichert, Ariadna Tibau, Thomas Rosemann, Aaron S Kesselheim*

Lancet Oncol 2020; 21: 664–70

See Comment page 609

*Joint first authors

Institute of Law (Prof K N Vokinger MD, S Reichert BMed) and Laboratory for Technology, Markets, and Regulation

Summary

Background Increasing cancer drug prices are a challenge for patients and health systems in the USA and Europe. By contrast with the USA, national authorities in European countries often directly negotiate drug prices with manufacturers. The American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) developed frameworks to evaluate the clinical value of cancer therapies: the ASCO-Value Framework (ASCO-VF) and the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS). We aimed to assess the association between the clinical benefit of approved cancer drugs based on these frameworks and their drug prices in the USA and four European countries (England, Switzerland, Germany, and France).

Prices and clinical benefit of cancer drugs in the USA and Europe:

*Kerstin N Vokinger**,

- Definizione di valore terapeutico
- Mancanza di associazione tra prezzo e valore?

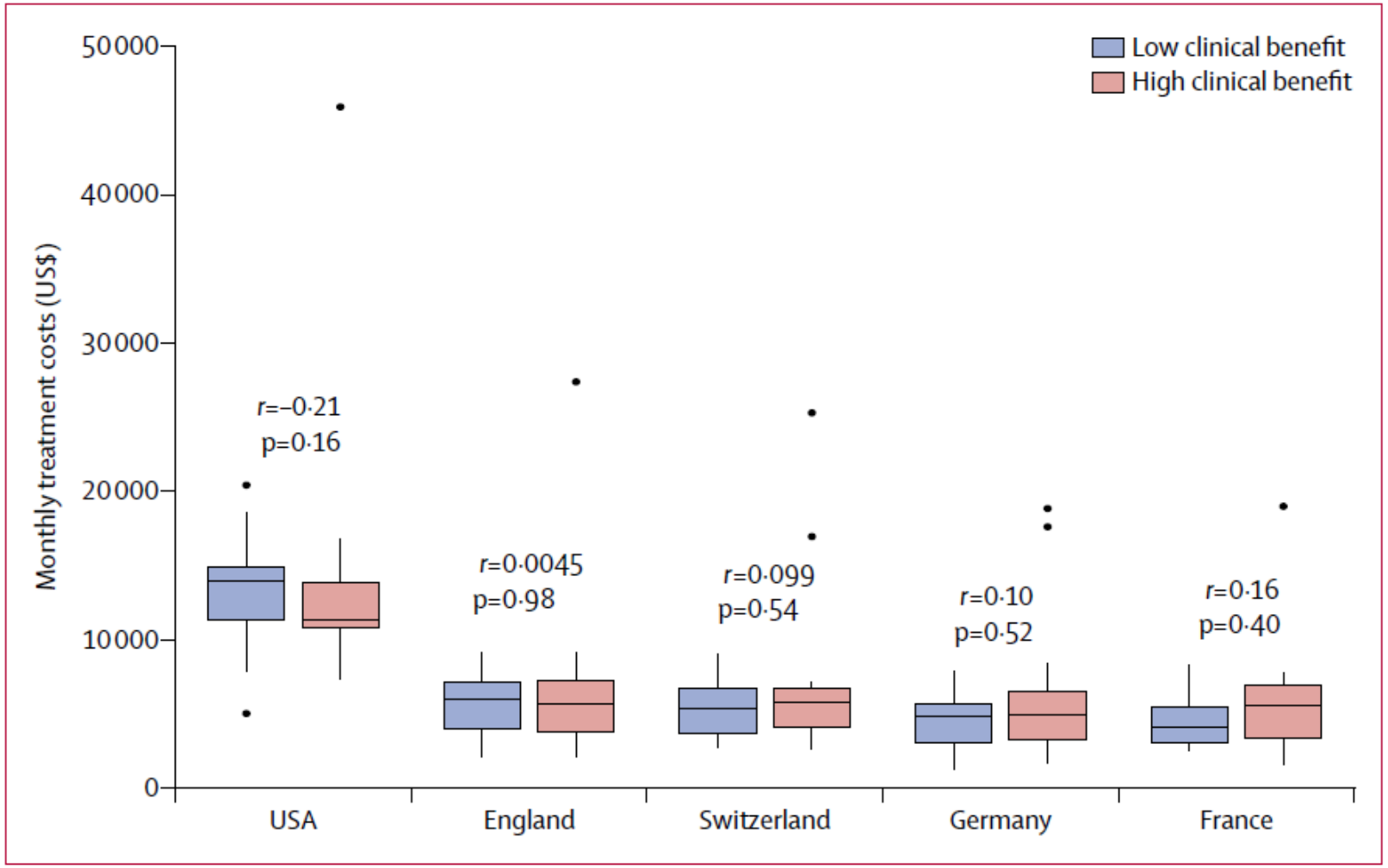


Figure 3: **Monthly drug treatment costs stratified by clinical benefit using the ESMO-MCBS**
Boxplots of monthly cancer drug treatment costs for solid tumours with low clinical benefit and high clinical benefit with Spearman's correlation coefficients *r* and asymptotic p values, based on the ESMO-MCBS in the USA, England, Switzerland, Germany, and France. Whiskers are drawn in Tukey style, and dots represent outliers. ESMO-MCBS=European Society for Medical Oncology-Magnitude of Clinical Benefit Scale.

Fragility Index degli RCT in oncologia

The fragility of phase 3 trials supporting FDA-approved anticancer medicines: a retrospective analysis

Joseph C Del Paggio, Ian F Tannock

Summary

Background The fragility index of trial results—ie, the minimum number of changes from non-events to events resulting in loss of statistical significance—can provide a measure of confidence that a positive effect reported in a randomised controlled trial is real. We aimed to calculate the fragility index of randomised controlled trials supporting US Food and Drug Administration (FDA)-approved anticancer drugs.

Methods This is a retrospective analysis of phase 3, randomised, controlled trials supporting anticancer drugs that were approved by the FDA between Jan 1, 2014, and Dec 31, 2018. Two-arm studies with 1:1 randomisation and significant positive results for a time-to-event outcome were eligible for the fragility index calculation, which involves the iterative addition of an event to the experimental group (defined as the group with the smaller number of events in positive trials) and concomitant subtraction of a non-event from that group, until positive significance (defined as $p<0\cdot05$ by Fisher's exact test) is lost.

Findings We identified 36 phase 3 randomised controlled trials, of which 17 (47%) were included in the fragility index analysis. The median fragility index was 2 (IQR 0–27). The fragility index was 2 or less in nine (53%) of 17 trials; for these trials, the fragility index was 1% or less of the total sample size. In five (29%) of 17 trials, the number lost to follow-up was more than the fragility index.

Interpretation Many phase 3 randomised controlled trials supporting FDA-approved anticancer drugs have a low fragility index, challenging confidence for concluding their superiority over control treatments. Although not a measure of effect, the fragility index might provide an additional means of assessing the robustness of clinical trial data.

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Department of Medical Oncology, Thunder Bay Regional Health Sciences Centre and Northern Ontario School of Medicine, Thunder Bay, ON, Canada (J C Del Paggio MD); **and Division of Medical Oncology, Princess Margaret Cancer Centre and University of Toronto, Toronto, ON, Canada** (Prof I F Tannock MD)

Correspondence to: Prof Ian F Tannock, Division of Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON M5G 2X9, Canada **ian.tannock@uhn.ca**

Fragility Index RCT in oncologia

Lancet Oncol, 2021

- The median fragility index for the 17 studies was 2 (IQR 0–27) —ie, a median of two events was required to change the results of the endpoint analysis from significant to non-significant
- Per metà degli studi bastava un paziente misclassified per rendere lo studio non più significativo
- Sono questi gli studi che desideriamo? Come comunità di decisori (ecosystem of decision-makers)?

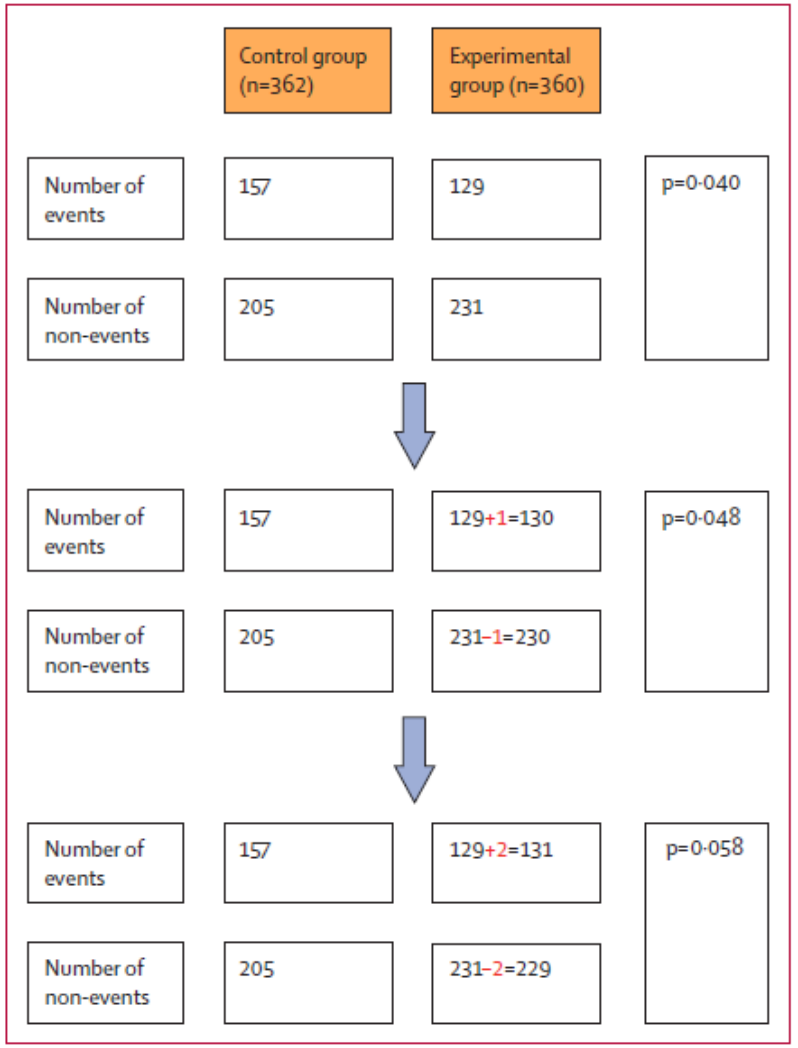


Figure: **Example of fragility index calculation for the phase 3 trial TOURMALINE-MM1[11]**

p values are calculated by Fisher's exact test, whereas the p value in the original study was calculated as 0·012 using the stratified log-rank test. The fragility index in this example is 2, which is the number of non-events required to convert to events so that the difference between the control and experimental groups no longer meets significance at the α=0·05 level using Fisher's exact test.

Towards an ecosystem of decision makers

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  - Metrics for value (for prices more proportional to value)
  - The role of journals and the recent withdrawal of avacopan
- What to simplify/streamline/change
  - CTIS - are 105 days too much? Probably yes
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EMA recommends revoking marketing authorisation for Tavneos

26 June 2026

Benefits no longer proven to outweigh risks of treatment

After reviewing the totality of the available data and new information on how the study data were handled, the CHMP concluded that the Advocate study was conducted in breach of good clinical practice (GCP) principles. Study data provided at the time of the assessment of the marketing authorisation application were found to be incorrect and misleading and could no longer be relied upon for demonstrating Tavneos' effectiveness. Supportive post-marketing data and other post-hoc analyses of the Advocate study are not considered sufficient to demonstrate the benefits of the medicine.

vedi commenti FDA e parere negativo CADT

As Tavneos is associated with an increased risk of drug-induced liver injury (DILI) and vanishing bile duct syndrome (VBDS, a rare condition where the small bile ducts inside the liver are gradually damaged and disappear over time), including cases with a fatal outcome, the liver function of patients treated with Tavneos should be closely monitored until treatment is permanently stopped.

Assessment for Noninferiority

As noted above, noninferiority but not superiority on remission was demonstrated at Week 26. Because both treatment arms received background therapy in the form of CYC or RTX and the benefit of glucocorticoids on top of CYC or RTX is not well-understood, it is difficult to determine if similar remission rates at Week 26 observed on both arms can support a conclusion that avacopan is effective or if such similarities can be primarily attributed to both arms receiving induction with RTX or CYC. In addition, the Applicant did not provide adequate data or information that would isolate the effect of prednisone when added to RTX or CYC induction to inform the margin of the non-inferiority comparison in this study.

entrambi i gruppi sono stati trattati con RTX e CYC e quindi la non inferiorità potrebbe essere legata alla efficacia di queste 2 molecole, visto inoltre che non sono stati forniti dati in grado di valutare l'effetto del solo cortisone nell'indurre la remissione

Interpretation of the non-inferiority comparison at Week 26 is further limited by the large number of patients (86%) who received glucocorticoids in the avacopan arm from Week 0 to 26. Therefore, the noninferiority assessment is not the intended comparison of avacopan vs. prednisone, but instead a comparison of avacopan plus lower dose glucocorticoids vs. higher dose glucocorticoids. Furthermore, based on the study design which specified the glucocorticoid use in the prednisone arm, it cannot be concluded that any differences in cumulative glucocorticoid use was due to a treatment effect of avacopan and not due to the specifications of the protocol. The use of glucocorticoids in AAV is evolving with more recent literature supporting that a lower dose steroid regimen may be sufficient for controlling disease activity compared to higher dose regimens (Walsh et al. 2020). In total, results of the efficacy analyses at Week 26 do not support the effectiveness of avacopan.

l'86% dei pazienti trattati con AVA ha ricevuto steroide nelle prime 26 settimane per cui la non inferiorità in realtà è tra AVA + steroide a bassa dose vs AVA + steroide ad alta dose. Inoltre, recenti dati suggeriscono che per controllare la malattia siano sufficienti dosi più basse di steroide

EDITORIAL

Retraction: Jayne DRW et al. Avacopan for the Treatment of ANCA-Associated Vasculitis, N Engl J Med 2021;384:599-609.

Eric J. Rubin, M.D., Ph.D.

The two academic authors of the article by Jayne et al., Avacopan for the Treatment of ANCA-Associated Vasculitis, N Engl J Med 2021;384:599-609,[1] request retraction of the article because, according to an ongoing Food and Drug Administration investigation conducted after publication, and without the knowledge of these two authors, the primary end-point assessments in nine patients were readjudicated after database lock and trial unblinding. This was not disclosed in the article and is inconsistent with proper research conduct. The editors therefore retract the article.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

This editorial was published on June 29, 2026, at NEJM.org.

1. Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med 2021; 384:599-609.

DOI: 10.1056/NEJMe2608684

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Avacopan lesson – July 2026

- First time, a registration trial is retracted

- Simple retraction seems insufficient to clarify what happened

Towards an ecosystem of decision makers

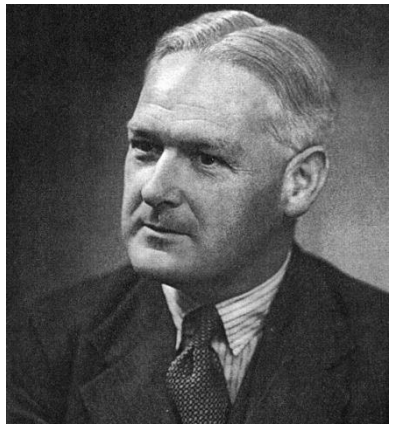
- An ecosystem of decision makers – are we slowly converging?
- How to avoid the current discrepancy/fracture
  - Evidence for approval vs evidence for reimbursement/HTA/guidelines – recent examples
  - Metrics for value (for prices more proportional to value)
  - The role of journals and the recent withdrawal of avacopan
- What to simplify/streamline/change
  - Clinical trials and CTIS EMA - are 105 days too much? Probably yes
  - Strenghten independent re-analysis of clinical trials
- Conclusions/proposals

RCTs 1948 Quando tutto è cominciato

Studi clinici randomizzati (RCTs): 3 principi

Sir Austin Bradford Hill

(disegnò e coordinò il primo RCT nel 1948 strepto nella TB)



- **Random division of the patients**
- selection of an appropriate primary outcome measure
- sample size calculation

1. **Randomizzazione per avere due gruppi simili/identici**
2. Scelta di una parametro appropriato di esito (clinicamente rilevante)
3. Dimensioni del campione e disegno

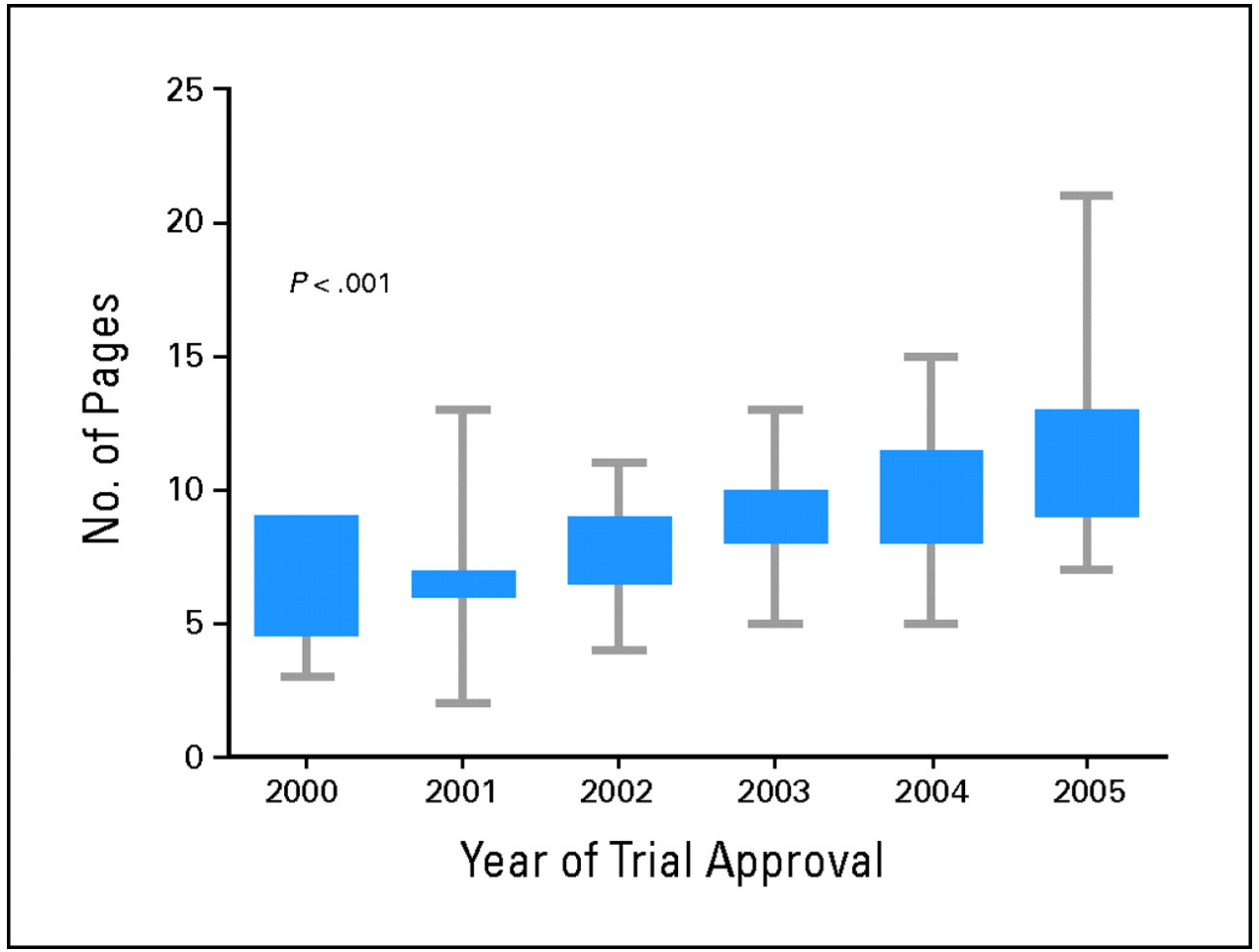
NB: se non puoi randomizzare – fase II o linee avanzate o ATMP – devi cercare un effetto grande del trattamento (magnitude of effect very large)

Comitati etici: teniamoli semplici e una occasione di confronto

Comitati etici – hanno due funzioni

- Proteggere i pazienti da rischi eccessivi
- Facilitare l’accesso alla ricerca e ai nuovi trattamenti

LUNGHEZZA DEI CONSENSI – chiaramente troppo lunghi e tuttora in aumento



Numero mediano di pagine dei consensi informati (N=214) in un arco di 6 anni (da 7 nel 2000 a 21 nel 2005)

Beardsley E. *Journal of Clinical Oncology* 2007;25:13-4

An official website of the European Union How do you know?

Clinical Trials Information System

Share

The Clinical Trials Information System (CTIS) supports the flow of information between clinical trial sponsors, European Union (EU) Member States, European Economic Area (EEA) countries and the European Commission. CTIS went live with a searchable public website on 31 January 2022.

Human Clinical trials

Page contents

Also on this topic

Searching for clinical trials: the public portal

CTIS serves to implement EU pharmaceutical law in the **Clinical Trials Regulation** (Regulation (EU) No 536/2014) .

The European Medicines Agency (EMA) maintains CTIS and the public website, together with the EU Member States, EEA countries and European Commission.

CTIS supports interactions between clinical trial sponsors (researchers or companies that run a clinical trial and collect and analyse the data) and regulatory authorities in the EU Member States and EEA countries, throughout the

https://www.ema.europa.eu/en/human-regulatory-overview/research-development/clinical-trials-human-medicines/clinical-trials-information-system

Clinical Trial Information System (CTIS) - EMA

Portale europeo (istituito dal regolamento europeo 536/2014) che funziona come:

- repository documentale
- mezzo di comunicazione tra regolatorio e CE

L'utilizzo del portale EMA-CTIS è **OBBLIGATORIO** per tutti gli studi interventistici di farmaco (fase I-II-II-IV)

Valutazione protocollo ed etica

106 giorni

Preparazione della documentazione, caricamento in CTIS e sottomissione **(click-day)**



11 December 2025
EMA/CHMP/ICH/778801/2022
Committee for Medicinal Products for Human Use

ICH M11 Clinical electronic structured harmonised protocol (CeSHarP) – Template

Step 5

Transmission to CHMP	3 October 2022
Adoption by CHMP	13 October 2022
Release for public consultation	26 October 2022
Deadline for comments	26 February 2023
Final adoption by CHMP	11 December 2025
Date for coming into effect	11 June 2026

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3 TRIAL OBJECTIVES AND ASSOCIATED ESTIMANDS

In this section, precisely define each trial objective and refine each trial objective into a precise clinical question of interest by defining the associated estimand. For considerations on estimands, refer to ICH E9(R1). Ensure alignment with every other section of the protocol.

Include additional level 3 headings (e.g., add a new level 3 heading for each secondary objective as needed). If there is more than one objective in a category (e.g., more than one secondary objective), number each objective consecutively as the level 3 heading (e.g., Secondary Objective 1, Secondary Objective 2, etc.).

No text is intended here (heading only).

3.1 Primary Objective(s) and Associated Estimand(s)

For all trials, precisely state each primary trial objective by providing a meaningful and concise description of the treatment effect of interest using natural, nontechnical language for clear understanding by sponsors, investigators, clinical site personnel, trial participants, ethics committees, and regulators.

For trials intended to estimate a treatment effect or test a hypothesis related to a treatment effect, use the table to precisely describe the associated estimand(s). This includes specification of the population targeted by the clinical question, the treatment condition(s), the endpoint (or variable), and the population-level summary. Precise specifications of treatment, population, and variable are likely to address many of the intercurrent events. Other intercurrent events not already addressed in the clinical question of interest by the aforementioned attributes should be described with their associated strategies. For other types of trials not intended to estimate a treatment effect or test a hypothesis related to a treatment effect, describe additional information relevant to the clinical question(s) of interest (at a minimum, present the endpoint(s) associated with each objective).

3.1.1 Primary Objective <#>

<Enter Primary Objective>

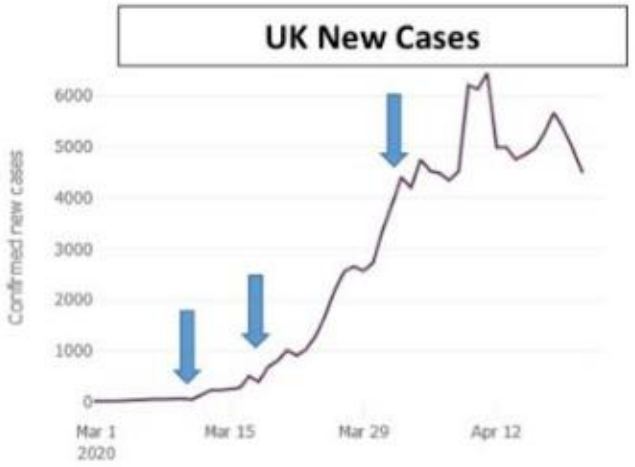
Enter information in table of estimand characteristics below including endpoint at a minimu

Estimand Characteristic	Description
{Population}	List of key characteristics, such as demographic characteristics (e.g., age, sex) and clinical characteristics (e.g., prior therapies, symptoms, severity, biomarker status) {<Enter Population>}
{Treatment}	List of key aspects of treatment regimens in each treatment group, including at least investigational agents, dosage, and administration route {<Enter Treatment>}
Endpoint	Definition of the endpoint <Enter Endpoint>
{Population-level Summary}	Description of the population-level summary (e.g., mean difference, relative risk) {<Enter Population-level Summary>}
{Other Intercurrent Event}	**{Strategy}**
{<Enter Description of Intercurrent Event>}	Description of the strategy to address the intercurrent event (e.g., a treatment policy strategy); cross reference the justification in Section 4 Trial Design. If there is >1 intercurrent event for an objective, add additional intercurrent event rows. {<Enter Intercurrent Event Strategy>}

In rosso le istruzioni di compilazione presenti nel template

Progress: Set-up

Taking the front-foot



10th March	First draft protocol
13th March	Joint regulatory & ethics (IRB) submission
16th March	Regulatory approval. Chief Medical Officer letter to all hospitals.
17th March	IRB committee meeting
18th March	IRB approval received in writing
19th March	First Patient Enrolled (1st protocol +9 days)
3rd April	1000 patients enrolled (FPE + 15 days)

Recruitment

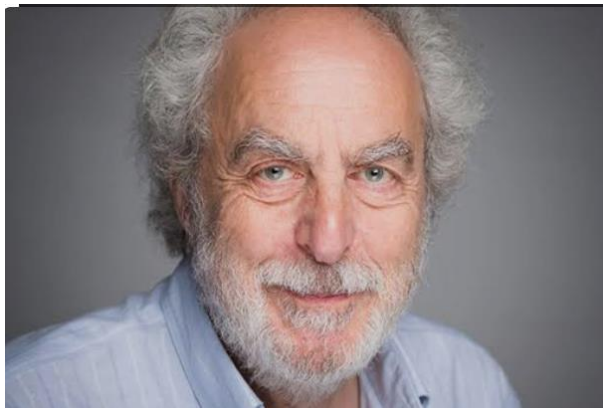
RECOVERY
Randomised Evaluation of COVID-19 Therapy

Timeline

2 weeks al primo paziente

Credibilità evidenze ed ecosistema decisori: cosa migliorare

- Le autorità regolatorie - FDA ed EMA - *debbono aumentare fortemente il sistema dei controlli e della ri-analisi degli studi clinici – vedi avacopan e altre ri-analisi*
- Responsabilità importanti del sistema delle riviste – *interamente privato e for profit- NON sorveglia abbastanza (vedi monoclonali demenza) la credibilità dei risultati degli studi e non è responsabile ne accountable di nulla*
- Occorre semplificare CTIS e consensi – *la ricerca ha bisogno di rapidità e chiarezza per i partecipanti/pazienti*.



We need less research, better research, and research done for the right reasons.

Doug Altman

The scandal of poor medical research. BMJ, 1994