NVTAG
Nederlandse Vereniging voor Technology Assessment in de Gezondheidszorg

NVTAG Webinar:
The GRADE framework and its application in reimbursement decision making

Date: Wednesday 13 February – 12:00-13:00

Time	Topic	Presenter
12.00-12.05	Introduction & Welcome	Maurice Driessen (NVTAG)
12.05-12.30	Introduction to the GRADE framework and its methodology	Miranda Langendam (Amsterdam UMC & GRADE Working Group)
12.30-12.55	Application of GRADE in reimbursement decision making	Rudy Dupree (Zorginstituut Nederland)
12.55-13.00	Closing	Maurice Driessen

Meeting will be recorded

The GRADE approach

NVTAG webinar 13 February 2025

Dr Miranda Langendam
Department Epidemiology and Data Science, Amsterdam UMC

Outline

- What is GRADE, why and when was it developed?
- GRADE approach overview
- Use of GRADE internationally and relevance for HTA

GRADE

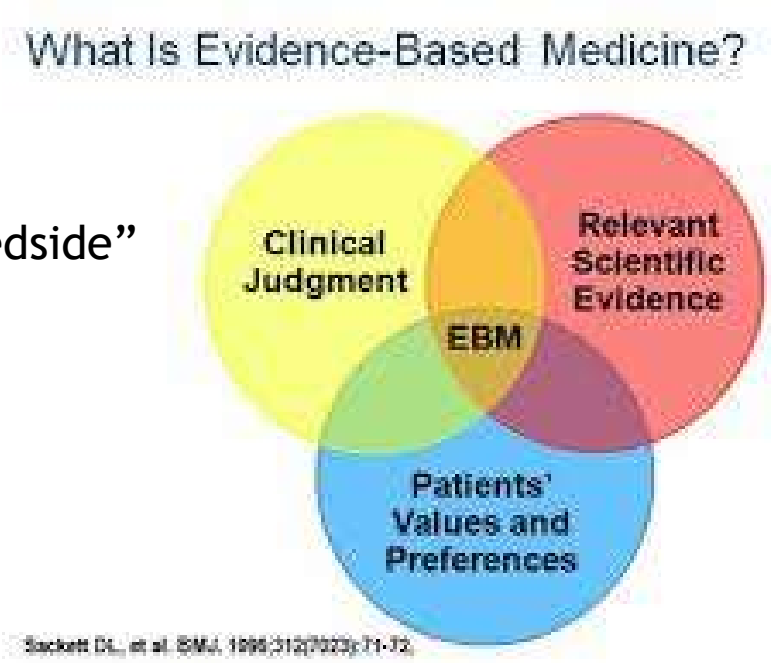
Grading of Recommendations Assessment, Development and Evaluation

Or, in other words:

Unifying, transparent and sensible system for grading the certainty of evidence and making decisions

Evidence-based medicine: fundament of GRADE

"Bringing the library to the bedside"



Judgments about evidence and recommendations are complex

‹ MedBlog *Heart*

Should I take blood thinners to control my atrial fibrillation?

August 24, 2015

Atrial fibrillation is one of the most common heart problems in the world. Patients with this condition have irregular heartbeats, which, in turn, can lead to the formation of dangerous blood clots that increase the risk of stroke.

Sharon Reimold, M.D., explains the risks of anticoagulants.

In the United States, an estimated 2.6 million people suffer from atrial fibrillation. Research conducted in the United States and Europe has found that one of every four people over 40 years old will develop the condition.

If you have atrial fibrillation – commonly referred to as AFib – it's important to understand that your greatest risk is having a stroke. Your physician can help you determine your personal risk. It's also important to ask your physician about the risks and benefits of taking medication for AFib.

Blood thinners have risks and benefits

Many people with AFib are prescribed blood-thinning medication (anticoagulants) to help prevent the formation of blood clots. Before 2010, warfarin (sold under the brand names Coumadin and Jantoven) was the only drug available for AFib

Which outcomes?

Which evidence to include?

Should we use new generation of blood thinners for atrial fibrilation?

More good than harm?
Worth the costs?

Certainty of the evidence?

Should all patients definitely be treated or probably be treated?

Certainty of evidence: pre-GRADE grading systems

AASLD	AGA	ACG	ASGE
I RCTs	I RCTs, well designed, n↑ for suff. stat. power	I Syst. review of RCTs	A. Prospect. controlled trials
II-1 Controlled trials (no randomization)	II 1 large well-designed clinical trial (+/- rand.), cohort or case-control studies or well designed meta-analysis	II 1+ properly desig. RCT, n↑, clinical setting	B. Obser-vational studies
II-2 Cohort or case-control analytical studies		III Publ., well-desig. trials, pre-post, cohort, time series, case-control studies	
II-3 Multiple time series, dramatic uncontr. experiments	III Clinical experience, descr. studies, expert comm.	IV Non-exp. studies >1 center/group, opinion respected authorities, clinical evidence, descr. studies, expert consensus comm.	C. Expert opinion
III Opinion of respected authorities, descrip. epidemiology	IV Not rated		

Summer 2000: first GRADE meeting in Andy Oxman's garden in Oslo

“We have developed a method to grade the level of evidence and strength of recommendations in clinical guidelines. There is a need for further work to develop a sensible approach that can be used for all the different types of evidence that must underpin healthcare recommendations. The method ought to be for general use and easy to understand for a larger group of users, including clinicians, patients and policy makers.”

Oxman AD et al. Tidsskr Nor Legefor 2000.


GRADE working group meetings anno 2025


GRADE Guidance Group

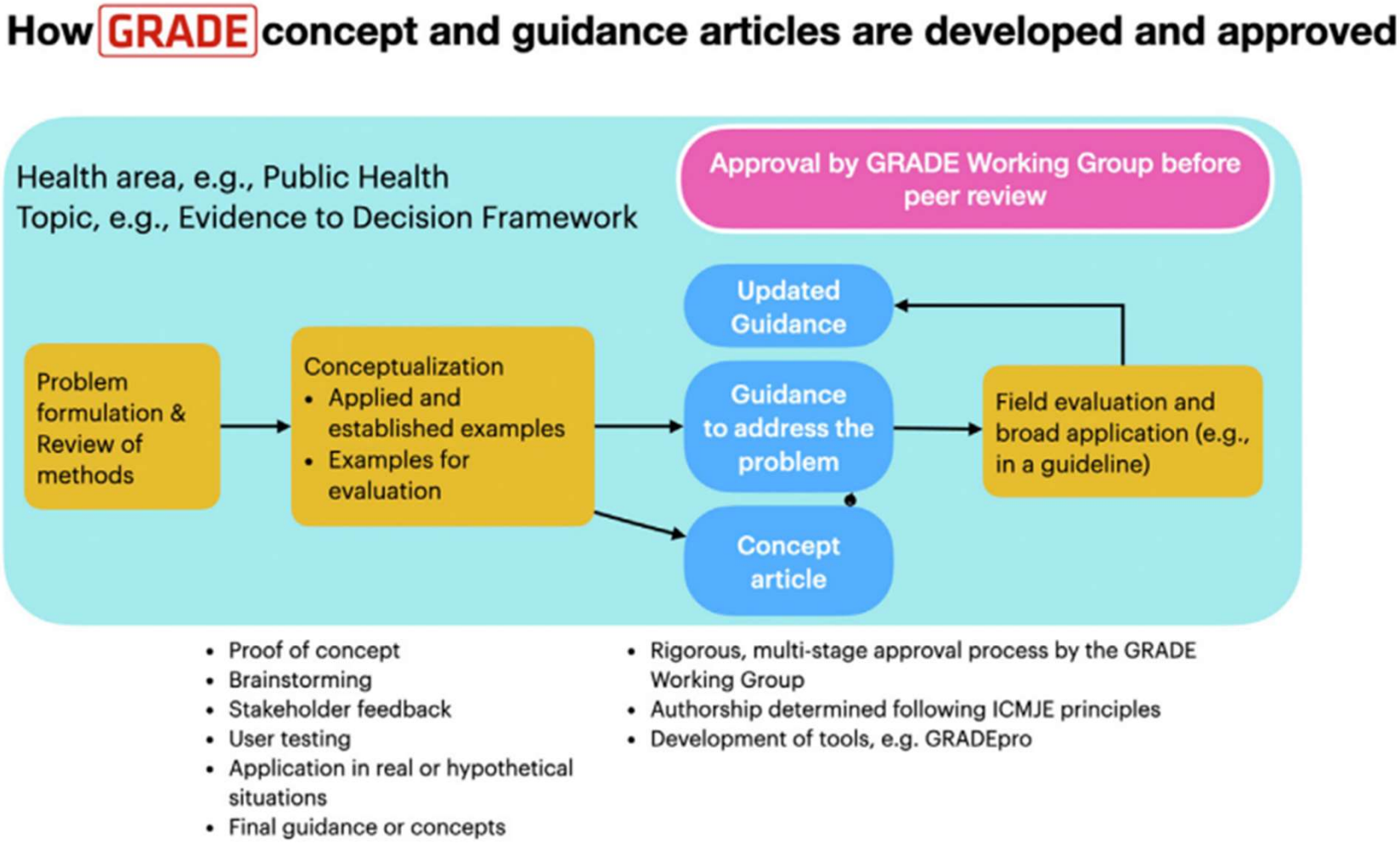


Fig. 1. Approach to developing GRADE Concept and Guidance articles.

www.gradeworkinggroup.org

Publications

A selected list of GRADE publications to get you started or to provide a deep-dive.

QUICK

Want to quickly find out what GRADE is all about? We suggest reading our BMJ series. Please note that the online text is the longer, full version of the submitted manuscript. The pdf's on BMJ's website are abbreviated print issues. Start with GRADE: an emerging consensus on rating quality of evidence and strength of recommendations, followed by What is "quality of evidence" and why is it important to clinicians? and Going from evidence to recommendations. You can also learn more about how diagnostic tests and strategies or resource use are considered in GRADE.

Learn more

IN-DEPTH

The JCE series and the GRADE handbook in GRADEpro provide a guide for systematic review and health technology assessment authors, guideline panelists and methodologists on how to apply the GRADE methodology framework in more detail: GRADE evidence profiles, framing the question and deciding on important outcomes, rating the quality of evidence, risk of bias, publication bias, imprecision, inconsistency, indirectness, rating up, resource use, overall rating, Summary of Findings tables (binary) and (continues), presentation of recommendations, and recommendation's direction and strength.

Learn more

Should we use new generation of blood thinners for atrial fibrilation?

Formulate question

Select outcomes

Rate importance

Outcomes across studies

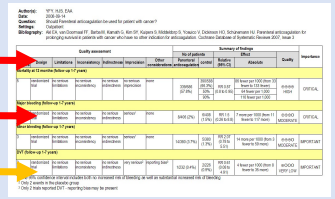
Create evidence profile with GDT

Rate quality of evidence for each outcome

Randomization raises initial quality
RCTs: high
Observational: low

P
I
C
O

Outcome Critical
Outcome Critical
Outcome Important
Outcome Not important



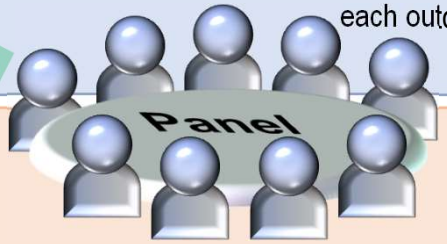
Summary of findings & estimate of effect for each comparison and each outcome

High ⊕⊕⊕⊕
Moderate ⊕⊕⊕◯
Low ⊕⊕◯◯
Very low ⊕◯◯◯

Grade down
1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up
1. Large effect
2. Dose response
3. Opposing bias & Confounders

Evidence synthesis/systematic review/HTA

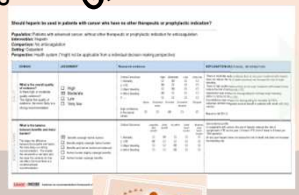


Recommendation/Decision

Grade recommendations (Evidence to Recommendation)
- For or against (direction) ↓↑
- Strong or conditional/weak (strength)

By considering balance of consequences (evidence to recommendations):
- ❑ Quality of evidence
- ❑ Balance benefits/harms
- ❑ Values and preferences
- ❑ Feasibility, equity and acceptability
- ❑ Resource use (if applicable)

EtD framework GRADEpro GDT

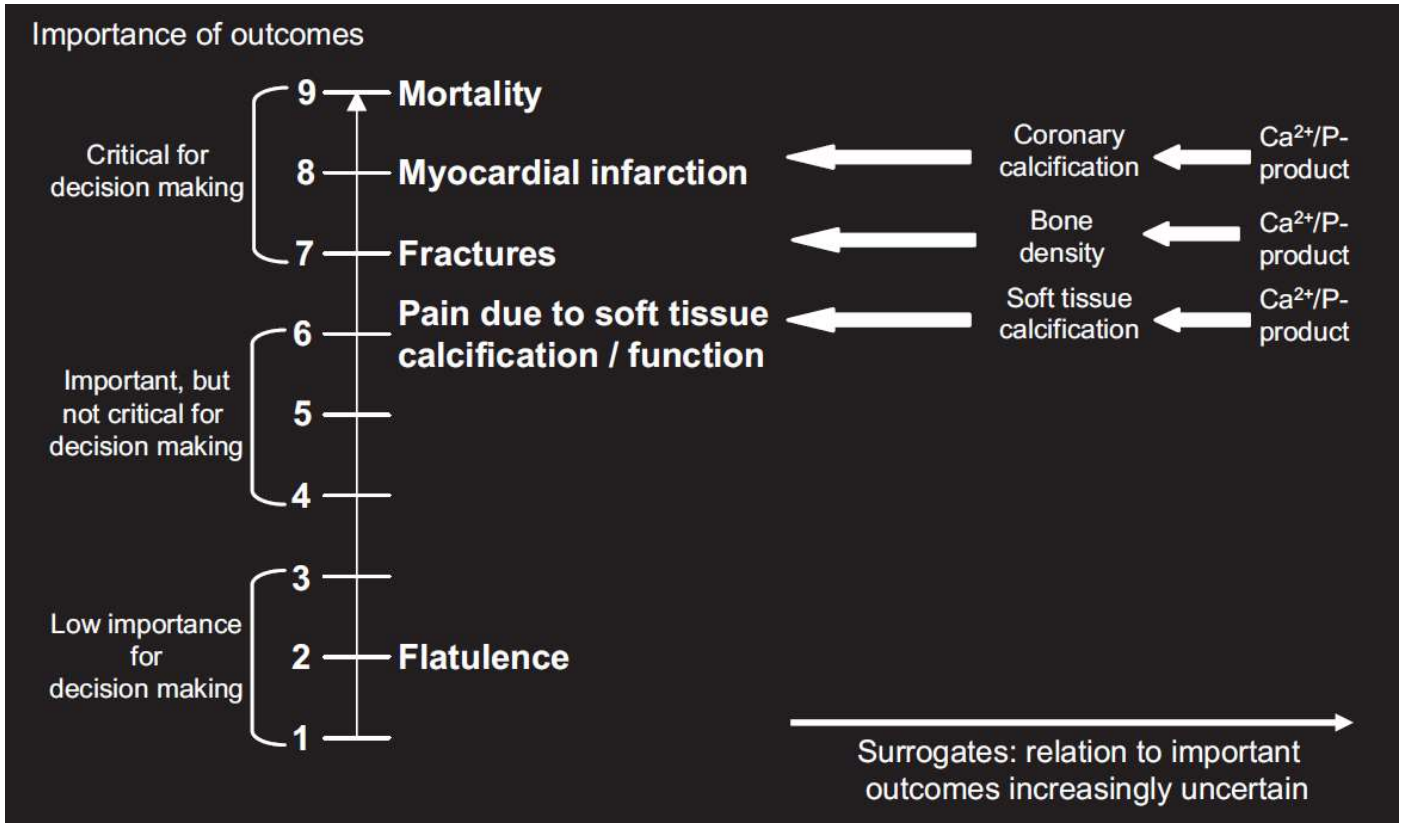


Guideline

Grade overall quality of evidence across outcomes based on lowest quality of ***critical*** outcomes

Formulate Recommendations (↓↑ | ⊕…)
"The panel recommends that ….should..."
"The panel suggests that ….should..."
"The panel suggests to **not** ..."
"The panel recommends to **not**..."
Transparency, clear, actionable
Research gaps

Define and prioritize outcomes…



Hierarchy of outcomes according to their importance to assess the effect of phosphate-lowering drugs in patients with renal failure and hyperphosphatemia (Guyatt GH et al. Journal of Clinical Epidemiology 64 (2011) 395-400)

… and clinical decision thresholds: minimally important difference or what you consider a trivial, small, moderate or large effect

Which outcomes?

Should we use new generation of blood thinners for atrial fibrilation?

GRADE evidence profile is based on a systematic review

- Baseline risk
- Absolute effects

Systematic Review

Author(s): Elie Akl & Holger Schunemann **Date:** 2008-09-11
Question: Should parenteral anticoagulation be used in prolonging survival of patients with cancer? **Settings:** Outpatient
Bibliography: EA Akl, FF van Doormaal, M Barba, G Kamath, SY Kim, S Kuipers, S Middeldorp, V Yosuico, H Dickinson, HJ S
anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation. CDSR Reviews. 20

Summary of findings					
No of patients		Effect		Quality	Importance
anticoagulation	control	Relative (95% CI)	Absolute		
339/586 (57.8%)	390/588 (60%)	RR 0.87 (0.8 to 0.95)	78 fewer per 1000 (from 30 to 120 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
477/586 (81.4%)	520/588 (85%)	HR 0.77 (0.65 to 0.91)	82 fewer per 1000 (from 28 to 141 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
1/232 (0.4%)	2/226 (4%)	RR 0.61 (0.08 to 4.91)	16 fewer per 1000 (from 37 fewer to 156 more)	⊕OOO VERY LOW	CRITICAL
8/406 (2%)	6/408 (1.5%)	RR 1.50 (0.26 to 8.8)	7 more per 1000 (from 11 fewer to 117 more)	⊕⊕OO LOW	CRITICAL
14/380 (3.7%)	5/380 (1.3%)	RR 2.07 (0.78 to 5.51)	14 more per 1000 (from 3 fewer to 59 more)	⊕⊕OO LOW	IMPORTANT

[1] Unclear concealment in one of the five trials did not lead to downgrading the quality of evidence.
[2] The studies used different LMWHs but indirectness is not likely given the similiarity in results across studies.
[3] The 95% CI includes both negligible effect and appreciable benefit or appreciable harm
[4] Out of 5 included studies, only 2 reported DVT. We assumed that this was based on selective reporting of outcomes. The authors of the study did not provide further information.
[5] Out of 5 included studies, only 3 reported major bleeding. We assumed that this was based on selective reporting of outcomes. The authors of the study did not provide further information.

Which outcomes?

Which evidence to include?

Should we use new generation of blood thinners for atrial fibrilation?

More good than harm?

Worth the costs?

1. Initial level of certainty	2. Consider lowering or raising level of certainty	3. Final level of certainty

Rating certainty of evidence by outcome

1. Initial level of certainty	
Study design*	Initial certainty in an estimate of effect
Randomized trials	High certainty →
Non-randomized	Low certainty →

* for interventions (treatment/prevention)

1. Initial level of certainty	
Study design*	Initial certainty in an estimate of effect
Randomized trials or non-randomized studies evaluated with ROBINS-I	High certainty →
Non-randomized studies not using ROBINS-I	Low certainty →

* for interventions (treatment/prevention)

1. Initial level of certainty		2. Consider lowering or raising level of certainty	
Study design*	Initial certainty in an estimate of effect	Lower if	Higher if**
Randomized trials or observational studies evaluated with ROBINS-I	High certainty →	Study limitations Inconsistency Indirectness Imprecision Publication bias downgrading	Large effect Dose response All plausible confounding & bias – would reduce a demonstrated effect or – would suggest a spurious effect when results show no effect upgrading
Observational studies not using ROBINS-I	Low certainty →		

* for interventions (treatment/prevention) ** usually applicable to observational studies only

1. Initial level of certainty		2. Consider lowering or raising level of certainty		3. Final level of certainty
Study design*	Initial certainty in an estimate of effect	Lower if	Higher if**	Certainty across those considerations
Randomized trials or observational studies evaluated with ROBINS-I	High certainty →	Study limitations Inconsistency Indirectness Imprecision Publication bias	Large effect Dose response All plausible confounding & bias – would reduce a demonstrated effect or – would suggest a spurious effect when results show no effect	High
				Moderate
Observational studies not using ROBINS-I	Low certainty →			Low
				Very low

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GRADE evidence profile

Certainty rating

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Bib ormaal, M Barba, G Kamath, SY Kim, S Kuipers, S Middeldorp, V Yosuico, H Dickinson, HJ
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Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	anticoagulation	control	Relative (95% CI)	Absolute	Quality	Importance
Survival at 12 months (study follow up)												
5	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	339/586 (57.8%)	390/588 (60%)	RR 0.87 (0.8 to 0.95)	78 fewer per 1000 (from 30 to 120 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Survival (overall - study follow up at 24 to 84 months)												
5	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	477/586 (81.4%)	520/588 (85%)	HR 0.77 (0.65 to 0.91)	82 fewer per 1000 (from 28 to 141 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
DVT												
2	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	1/232 (0.4%)	2/226 (4%)	RR 0.61 (0.08 to 4.91)	16 fewer per 1000 (from 37 fewer to 156 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding												
3	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[5]	8/406 (2%)	6/408 (1.5%)	RR 1.50 (0.26 to 8.8)	7 more per 1000 (from 11 fewer to 117 more)	⊕⊕OO LOW	CRITICAL
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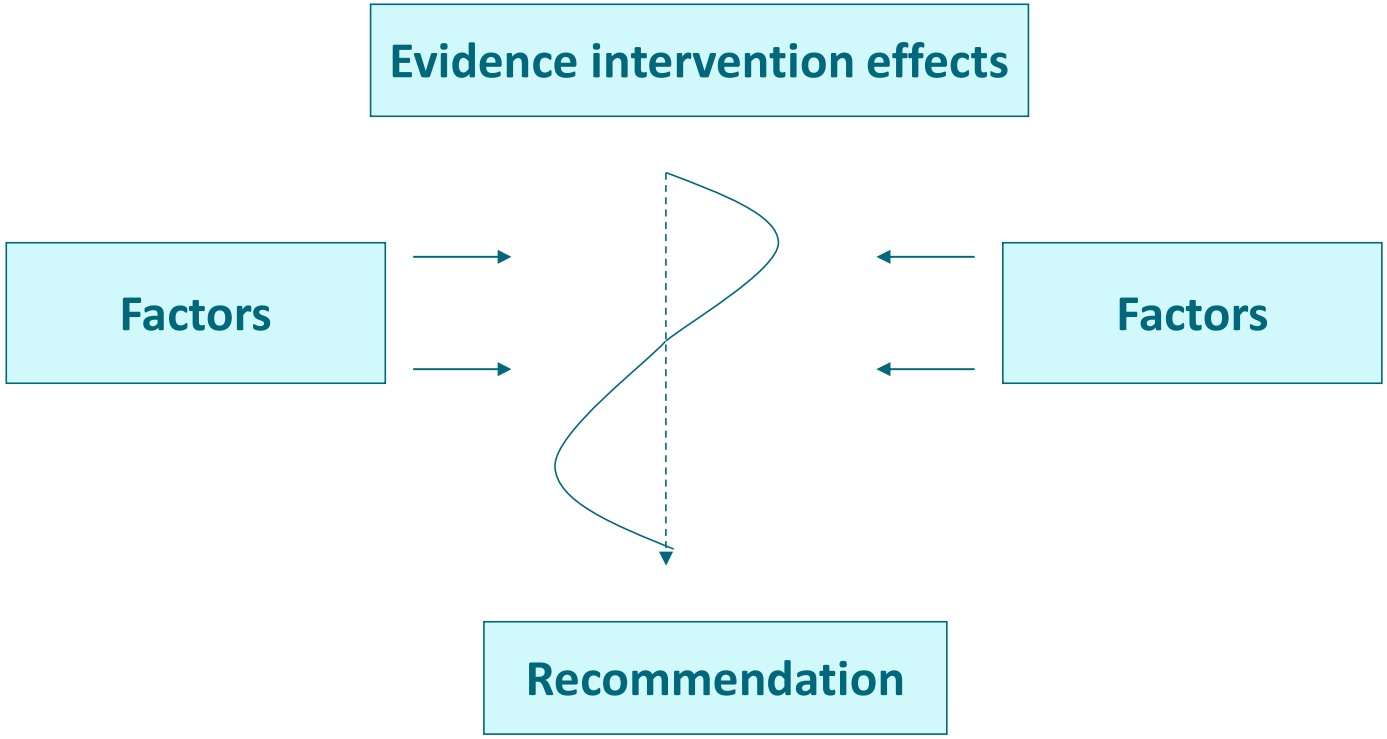
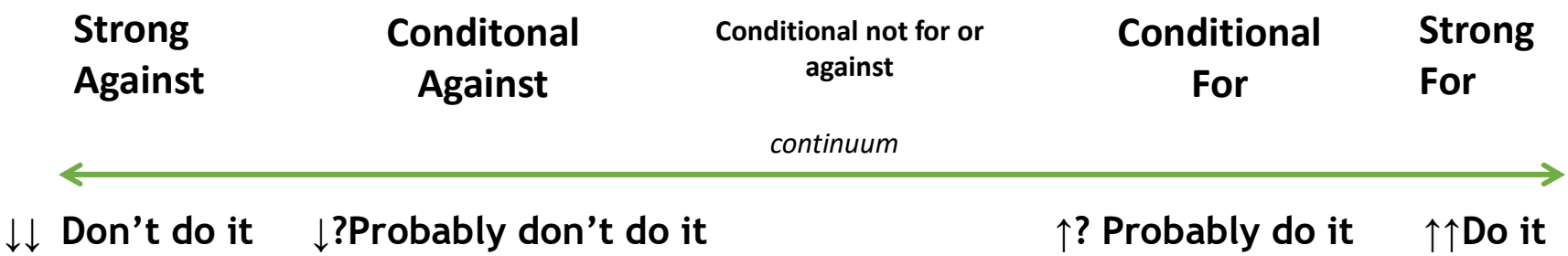
From Evidence to Decision (EtD)



Evidence to Decision (EtD) framework

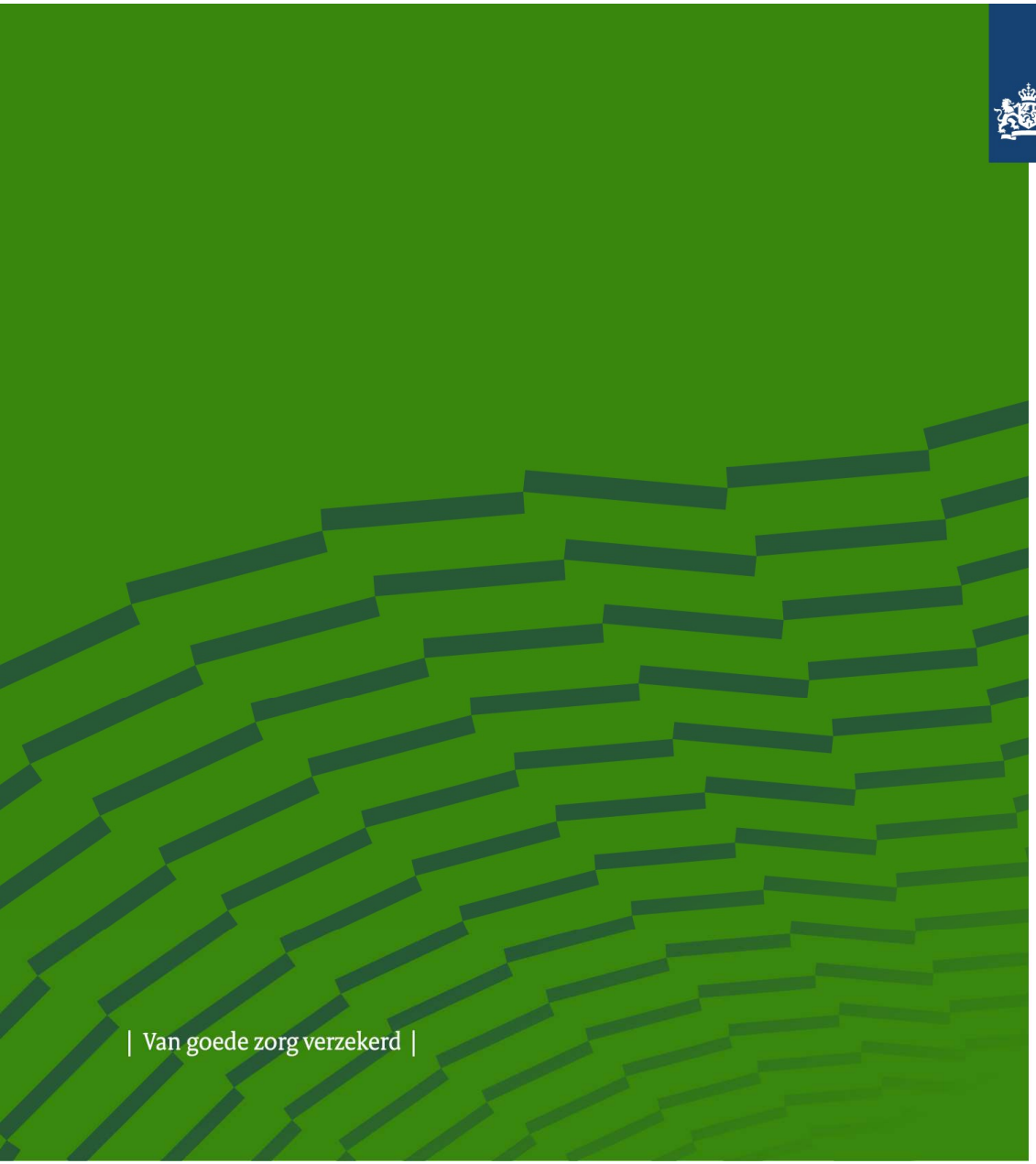
1. **Problem**
   Is the problem a priority?
2. **Desirable Effects**
   How substantial are the desirable anticipated effects?
3. **Undesirable Effects**
   How substantial are the undesirable anticipated effects?
4. **Certainty of evidence**
   What is the overall certainty of the evidence of effects?
5. **Values**
   Is there important uncertainty about or variability in how much people value the main outcomes?
6. **Balance of effects**
   Does the balance between desirable and undesirable effects favor the intervention or the comparison?
7. **Resources required**
   How large are the resource requirements (costs)?
8. **Certainty of evidence of required resources**
   What is the certainty of the evidence of resource requirements (costs)?
9. **Cost effectiveness**
   Does the cost-effectiveness of the intervention favor the intervention or the comparison?
10. **Equity**
    What would be the impact on health equity?
11. **Acceptability**
    Is the intervention acceptable to key stakeholders?
12. **Feasibility**
    Is the intervention feasible to implement?

Strength and direction of recommendation



Use of GRADE

- Certainty in the evidence is key step in systematic reviews
- Evidence to decision approach is state of the art method in developing clinical practice and public health guidelines
- Institutions making coverage decisions (e.g. Zorginstituut)



Zorginstituut Nederland

The use of GRADE in Dutch reimbursement decision making

Rudy Dupree

13 February 2025

HTA in the Dutch health care system

Criteria for reimbursement

- Statutary (Health Care Act):

Effectiveness - ‘established medical science and practice’ (SWP)

- Non-statutary:

Cost-effectiveness

Necessity

Feasability

Dutch National Health Care Institute (ZIN) assesses expensive drugs and some medtech

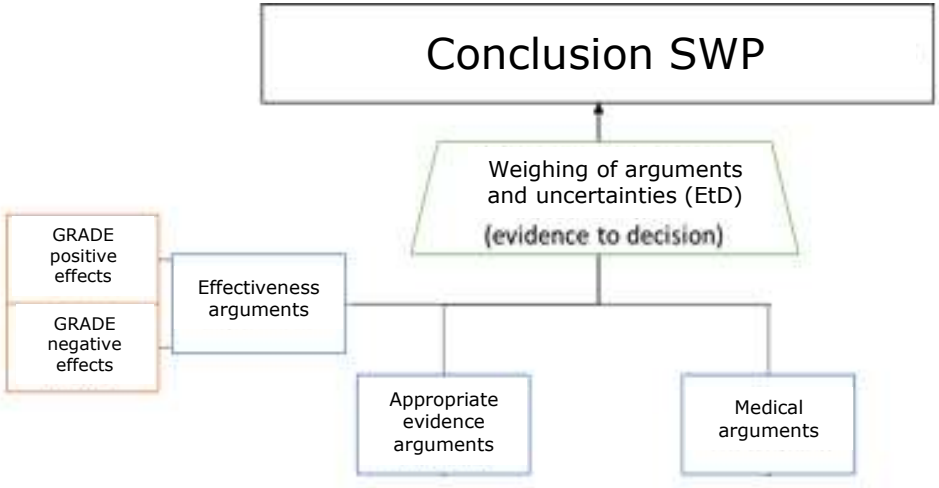
Established medical science and practice

- Assessment follows principles of evidence-based medicine
- Implementation of GRADE since 2015
- Follows GRADE guidances where possible

How do systematic reviews and ZIN HTA differ?

	Systematic review	HTA ZIN
Question	Research or clinical question	Policy question
Quality of evidence	GRADE quality of evidence	
Type of conclusions	• Strong and weak recommendations • 'Continuum'	• Meets SWP yes/no • Binary
Evidence to decision	Includes societal factors	Excludes societal factors (part of appraisal)
Process	Depends (e.g. Delphi, guideline panels, peer review, …)	• Includes stakeholder consultations and advice of scientific/appraisal advisory board • No full literature search in case of drugs (done by applicant)

Evidence to decision: context matters!



- EtD is not a strict normative framework, nor is it a checklist of arguments
- It merely describes place and cohesion of arguments
- The importance and weight of arguments are strongly context-dependent

Evidence to decision: examples of arguments

Category	Specification	Examples used in weighing towards positive decision	Informed by
Effectiveness	GRADE assessment positive effects	• Large effect • Sustained effect • Consistent effect over multiple studies • Effects on crucial outcomes	GRADE assessment
	GRADE assessment negative effects	• Risks are mild • Risks are controllable	GRADE assessment
Appropriate evidence (methodological)	Necessity for better evidence	• Better evidence not necessary (i.e. technical variant/me-too, well-established use) • (International) consensus / no clinical equipoise • Clear mechanistic relation between intervention and effect	Appropriate evidence framework
	Feasibility for better evidence	• Better research is not feasibile • E.g. blinding, randomization, …	Appropriate evidence framework
Appropriate evidence (medical)	Burden of disease	• High burden	Literature / appropriate evidence framework
	Availability of alternative treatments	• No good alternative treatments	Literature / appropriate evidence framework

Effectiviteitsargumenten

Door al bovengenoemde aspecten samen achten we het aannemelijk dat er door de inzet van PA-telemonitoring klinisch relevante effecten optreden ten aanzien van kwaliteit van leven en het aantal ziekenhuisopnamen.

Aantal studies	Studieopzet											
Kwaliteit van leven (vastgesteld met de KCCQ en de MLHFQ), follow-up 12 maanden												
1	gerandomiseerde trial								-	MD 7,13 (95% BI 1,51 tot	⊕⊕○○ Laag	cruciaal
Aantal ziekenhuiso												
1	gerandomiseerde trial											
Aantal SEH bezoek												
1	gerandomiseerde trial											
Aantal polikliniekb												
1	gerandomiseerde trial	ernstig[b]	niet ernstig	niet ernstig	niet ernstig	niet gevonden	176	172	-	MD -0,01 (95% BI -	⊕⊕⊕○ Redelijk	cruciaal
(Ernstige) complica												
1	gerandomiseerde trial						gerapporteerd en vijf niet-ernstige complicaties.					

Passend onderzoek argumenten

Uitkomsten worden bij voorkeur beoordeeld door een geblindeerde effectbeoordelaar; bij uitkomsten die door de patiënt zelf worden beoordeeld (zoals kwaliteit van leven) is dit in de in de MONITOR-HF studie gekozen opzet niet mogelijk. Het blinderen van behandelaars is voor deze interventie sowieso niet mogelijk omdat deze de drukmetingen moeten uitlezen en dus op de hoogte zijn van de toewijzing. Voor de andere uitkomstmaten dan kwaliteit van leven werd de beoordeling gedaan door een onafhankelijke commissie.

Medische argumenten

Hoewel er weinig complicaties optreden is er wel sprake van een invasieve procedure en de sensor blijft levenslang in het lichaam. Het dagelijks meten van de vullingsdrukken zou daarnaast belastend kunnen zijn voor patiënten. Tijdens de follow-up bleek echter dat de therapietrouw hoog was, de frequentie van (dagelijkse) metingen was 84,3%.

Afweging relevante aspecten

Op basis van het wetenschappelijke bewijs achten wij het voldoende aangetoond dat PA-telemonitoring leidt tot een verbeterde kwaliteit van leven, minder ziekenhuisopnamen en resulteert in weinig (ernstige) complicaties.

a. Risk of bias is beo[…] onduidelijk beoordeel[…] leven het risico op pe[…] door de fabrikant en […] ven. Hierdoor is het risico op selection bias (allocation concealment) als […]
b. Risk of bias is beo[…] onduidelijk beoordeel[…] de behandeling is het […] fabrikant en de onder[…]
c. Het 95% betrouwbaarheidsinterval doorkruist de klinische relevantiegrens.
d. Het 95% betrouwbaarheidsinterval doorkruist aan beide kanten de klinische relevantiegrens.

[Standpunt - Arteria Pulmonalis (PA) telemonitoring bij patiënten met chronisch hartfalen kan worden vergoed uit basispakket | Standpunt | Zorginstituut Nederland]

Towards European harmonization and cooperation on HTA

- Health care systems across Europe differ in **values**, **resource allocation**, and **policy / decision making**
- Still, most member states face the same challenges and much duplication exists

European collaboration on HTA evolved:

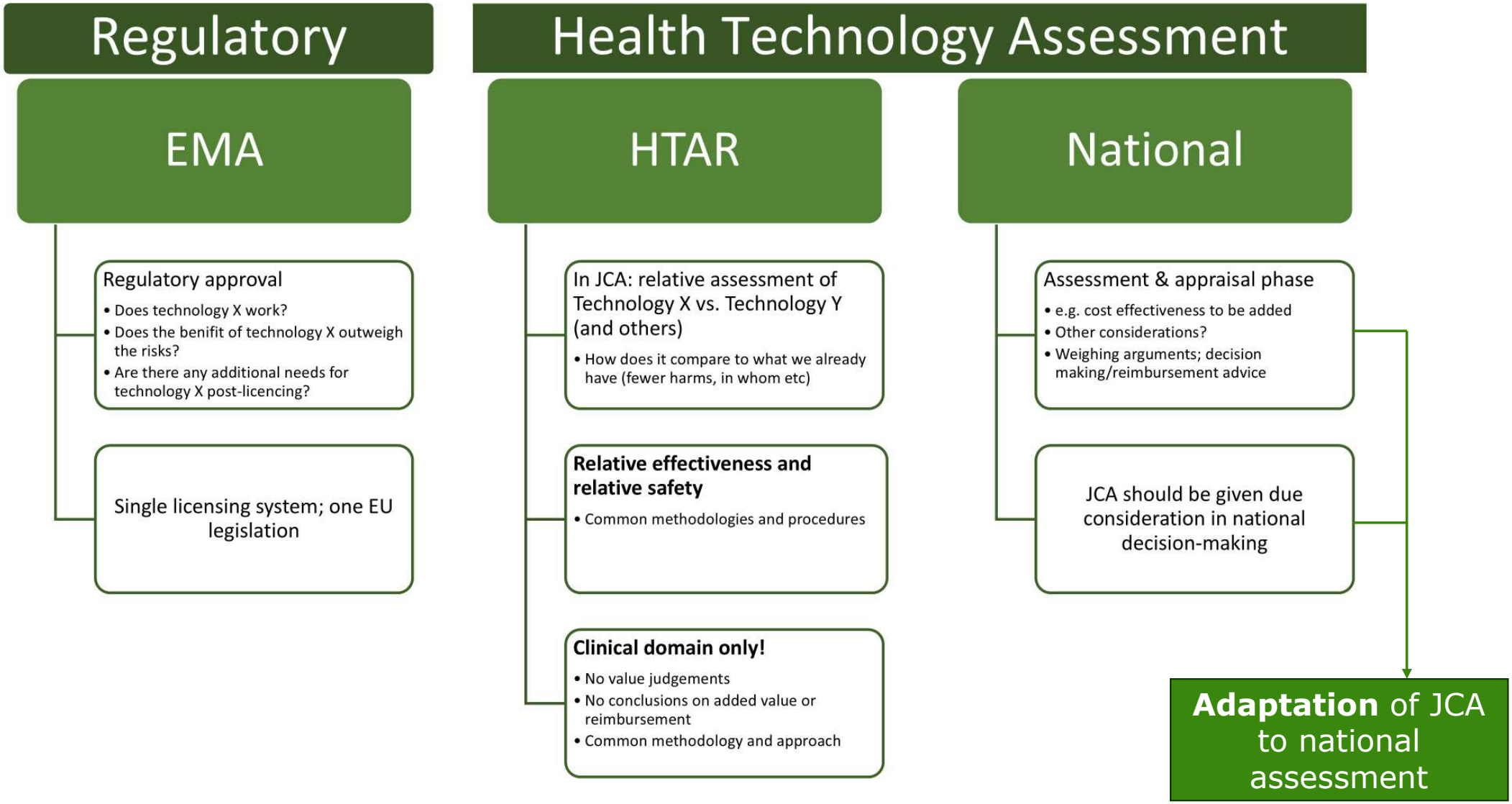
- EUnetHTA project, Joint Actions 1-3 and EUnetHTA21
- Beneluxa, Finose, Valetta, and others
- Horizon Scanning
- Early dialogues with stakeholders
- **EU HTA Regulation** (2022)

EU HTA Regulation

- Legislation for mandatory European cooperation on HTA
- Goals: efficiency, high quality, transparency and inclusivity
- Includes **Joint Clinical Assessments** and Joint Scientific Consultations
- Use of joint work in the national HTA process
- Progressive implementation of JCA's (oncology + ATMP in 2025; certain MedTech 2026; orphan drugs 2028, all 2030)

Member states will stay responsible for:

- drawing conclusions on added benefit
- decision making on pricing and reimbursement


Regulatory
Health Technology Assessment
EMA
HTAR
National
Regulatory approval
• Does technology X work?
• Does the benifit of technology X outweigh the risks?
• Are there any additional needs for technology X post-licencing?
Single licensing system; one EU legislation
In JCA: relative assessment of Technology X vs. Technology Y (and others)
• How does it compare to what we already have (fewer harms, in whom etc)
Relative effectiveness and relative safety
• Common methodologies and procedures
Clinical domain only!
• No value judgements
• No conclusions on added value or reimbursement
• Common methodology and approach
Assessment & appraisal phase
• e.g. cost effectiveness to be added
• Other considerations?
• Weighing arguments; decision making/reimbursement advice
JCA should be given due consideration in national decision-making
Adaptation of JCA to national assessment

JCA to Dutch assessment (SWP)

European assessment

- Systematic review based on Member States' needs (PICOs)
- JCA report summarizes available studies, results and assesses uncertainties around effects per PICO
- **No use of GRADE**
- *JCA report does not contain any value judgements nor conclusions on added benefit*

Dutch assessment SWP

- Refers to *relevant PICO* & results in JCA report
- **Adaptation of JCA into GRADE assessment** (contains value judgements)
- **'de novo' evidence to decision based on adaptation** (conclusion on added benefit)
- Needs to be supplemented with CEA, budgetimpactanalysis when appropriate (outside scope JCA)

Adaptation and contextualization from JCA to SWP

	JCA methods	Dutch SWP methods	Expected degree of contextualization
Scope	Informs member states	Reimbursement decision	Full
	Multiple PICOs (cater for many member states' needs)	Selection of PICO that fits with national policy question	Full
	No ranking of outcomes	Selection of crucial and important outcomes	Full
Uncertainties	Internal validity	GRADE Risk of bias	Limited
	External validity	GRADE Indirectness	Extensive
	Statistical precision	GRADE Imprecision (including national MCIDs)	Full
Other	Direct and indirect comparisons	GRADE Inconstistency / indirectness	Limited
Evidence to decision	None	ZIN EtD	De novo development
Appraisal	None	ZIN appraisal (CEA, budgetimpact, necessity, feasibility)	De novo development (non-GRADE)

Conclusion

Use of GRADE by ZIN's HTA…

- Leads to systematic and transparent assessment of the evidence
- Centers around a policy question (not data driven)
- Benefits from GRADE's continuous development
- Takes into account contextual factors in its conclusions (not 'just' the evidence)

European cooperation based on the HTA-R…

- Aimes at improving efficiency, transparency, quality and inclusivity
- As long as different health systems exist, adaptation to national HTA's is necessary
- JCA's are suitable to be used in Dutch HTA's with adaptation and contextualization

Want to know more?

Assessment framework SWP

https://www.zorginstituutnederland.nl/publicaties/publicatie/2023/04/11/beoordeling-swp-2023

(in Dutch, English translation in prep)

HTA Regulation

ZIN

https://www.zorginstituutnederland.nl/over-ons/programmas-en-samenwerkingsverbanden/eu-htar (Dutch)

https://english.zorginstituutnederland.nl/international-network/eu-htar (English)

European Commission

https://health.ec.europa.eu/health-technology-assessment/implementation-regulation-health-technology-assessment_en (English, other languages available)

https://health.ec.europa.eu/health-technology-assessment/key-documents_en (incl. methodological guidances, English)

Claim and policy question

- Claim: what is claimed by the applicant (pharmaceuticals)
- Policy question: PICO(ts) – not necessarily equal to the claim, incl. information on 'appropriate evidence'

Systematic literature search

- By ZIN (MedTech mostly)
- By applicant (pharmaceuticals)

Summary of the evidence

- Characteristics of included studies
- Meta-analyse if appropriate

Assessment of quality of the evidence

- "The confidence (high, moderate, low or very low) that the intervention, in comparison with standard or usual care, leads to a clinically relevant effect on patient-relevant outcomes"

Evidence to decision

- Weighing of quality of evidence with contextual factor (medical arguments en appropriate evidence)

Scientific advisory board and consultation

- Stakeholder consultation and scientific advisory board
- Appraisal committee in case other packet criteria are relevant (ACP)
- Final approval by board ZIN