



TARTU ÜLIKOOL

# Kliiniliste soovitude koostamine



**Eriline tänu:** Holger Schünemann ja GRADE working group

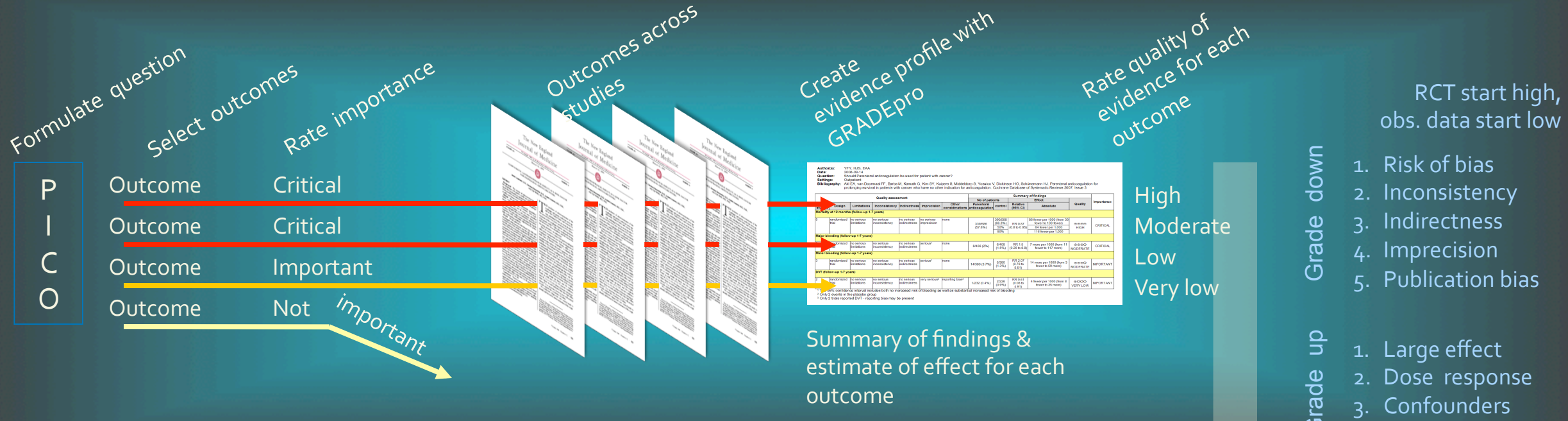
[www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)

Kaja-Triin Laisaar

TÜ peremeditsiini ja rahvatervishoiu instituut

[kaja-triin.laisaar@ut.ee](mailto:kaja-triin.laisaar@ut.ee)

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**Systematic review**

**Guideline development**

**Formulate recommendations:**

- For or against (direction)
- Strong or weak (strength)

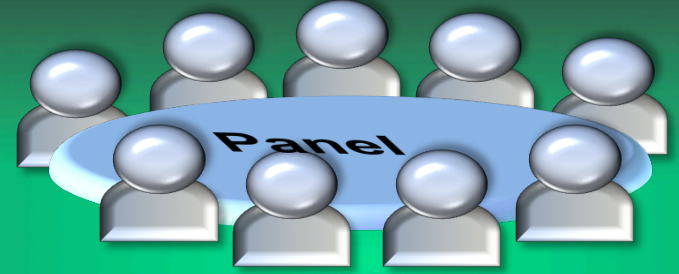
*By considering:*

- Quality of evidence
- Balance benefits/harms
- Values and preferences



Revise if necessary by considering:

- Resource use (cost)



- "We recommend using..."
- "We suggest using..."
- "We recommend against using..."
- "We suggest against using..."

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



# Kliinilise soovitus tugevus

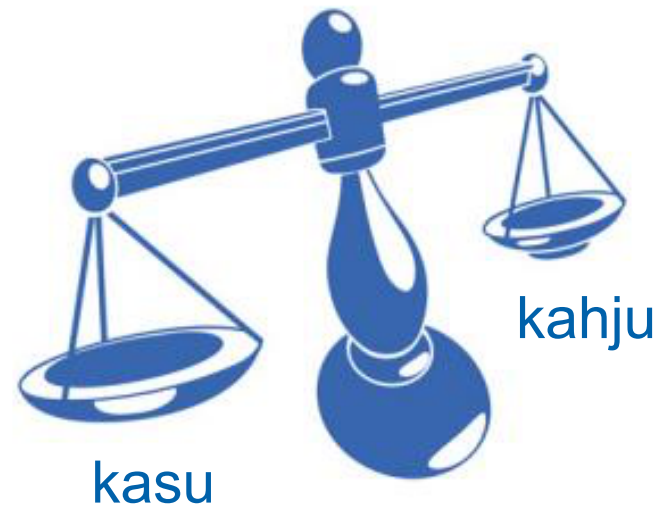
Soovituse tugevus näitab seda, mil määral saab olla kindel, et soovitus järgimisest tulenevad oodatavad mõjud ületavad soovimatuid mõjusid

Soovitus võib olla nii sekkumise poolt kui ka selle vast

## 2.1. Kaalule sekkumise soovitud ja soovimatud mõjud

- suremusele
- haiguse ja selle ravi kestusele
- ravikoormusele
- ravikulule
- elukvaliteedile

jmt-le



## 2.3. Kliinilise soovitusel tugevust mõjutavad tegurid

- tõenduse kvaliteet ingl *quality of evidence*
- soovitud ja soovimatute mõjude (kasu-kahju) tasakaal ingl *balance between desirable and undesirable effects*
- väärtushinnangud ja eelistused ingl *values and preferences*
- kulud (ressursikasutus) ingl *costs (resource allocation)*
- õigluse (võrdsuse) põhimõte ingl *equity*
- vastuvõetavus ingl *acceptability*
- teostatavus ingl *feasibility*



# Kliinilise soovitus tugevuse määravad (1)

## Tõenduse kvaliteedi üldine tase

... mis põhineb madalaimal (mistahes) kriitilise tulemusnäitaja tõenduse kvaliteedile antud hinnangul

Kõrge tõenduse taseme korral tugeva soovitus tõenäosus suurem

## Tasakaal soovitud ja soovimatute mõjude (kasu-kahju) vahel

# Tugeva kliinilise soovitusetõenäosus on suurem, kui

- tulem(id) on olulised (tõsised)
- (sekkumise) mõju on suur
- hinnang (sekkumise) mõjule on täpne
- eelnev risk ehk tulemi(te) tekke risk ilma sekkumiseta on kõrge



# Kliinilise soovitus tugevuse määravad (2)

## Patsientide eelistused ja väärtushinnangud

- uskumused ja arusaamad
- ootused ja eesmärgid nii tervise osas kui elus üldisemalt
- erinevate tulemi(te) väärtustamine
- hinnang kasudele-kahjudele

Eelistuste ja väärtushinnangute ühtsus ja kindlus suurendavad tugeva soovitus tõenäosust

## Kulud/ressursid

Kas saadav (puhas)kasu on kaasnevat kulu väärt?

Hinnagu kindlus suurendab tugeva soovitus tõenäosust



# Kliinilise soovitus tugevuse määravad (3)

Tervisesüsteemi vaatenurgast

**Õigluse (võrdsuse) põhimõte** ingl *equity*

Kas keegi (mingi patsientide rühm) jääks, pandaks ebavõrdsesse seisu?

Milline oleks selle mõju?

**Vastuvõetavus** ingl *acceptability*

Kas see soovitus on huvitatud osapooltele vastuvõetav?

**Teostatavus** ingl *feasibility*

Kas seda soovitust võimalik ellu viia?

# Tugeva soovituse tähendus

- **patsientidele:** valdav enamik\* sellises olukorras olevaid inimesi tahaks soovitatud sekkumist ning ainult vähesed ei tahaks
- **tervishoiutöötajatele:** valdava enamiku\* patsientide ravis peaks kasutama soovitatud sekkumist
- **tervishoiukorraldajatele:** soovitust on võimalik enamikes olukordades rakendada

\*  $\geq 85\%$

# Nõrga soovituse tähendus

- **patsientidele:** enamik sellises olukorras olevaid inimesi tahaks soovitatud sekkumist, kuid paljud siiski mitte
- **tervishoiutöötajatele:** peab olema valmis aitama patsiente otsuse langetamisel, mis oleks kooskõlas nende (endi) väärtushinnangutega; valmis jagatud vastutusega otsustusprotsessiks
- **tervishoiukorraldajatele:** on vajadus põhjaliku arutelu ja huvitatud osapoolte kaasamise järele



**Eriolukorrad, mil tõenduse kvaliteedi tase madal,  
kuid kliiniline soovitus tugev**

# Situation 1

Paradigmatic situation	Confidence in effect-estimates for health outcomes (Quality of evidence)		Balance of benefits and harms	Values and Preferences	Resource considerations	Recommendation
<b>Life threatening situation</b>	Benefits:  Low or very low confidence	Harms:  Immaterial (very low to high)	Intervention may reduce mortality in a life-threatening situation. Adverse events not prohibitive	A very high value is placed on an uncertain but potentially life-preserving benefit	Small incremental cost (or resource use) relative to the benefits justify the intervention	Strong recommendation in favor

*Example* Indirect evidence from seasonal influenza suggests that patients with avian influenza may benefit from the use of oseltamivir (low confidence in effect estimates). Given the high mortality of the disease and the absence of effective alternatives, the WHO made a strong recommendation in favor of the use of Oseltamivir rather than no treatment in patients with avian influenza.<sup>43</sup>

# Situation 2

Paradigmatic situation	Confidence in effect-estimates for health outcomes (Quality of evidence)		Balance of benefits and harms	Values and Preferences	Resource considerations	Recommendation
<b>Uncertain benefit, certain harm</b>	Benefits:  Low or very low	Harms:  High or Moderate	Possible but uncertain benefit. Substantial established harm	A much higher value is placed on the adverse events in which we are confident than in the benefit, which is uncertain	High incremental cost (or resource use) relative to the benefits may not justify the intervention	Strong recommendation against  <i>(or in favor of the less harmful/less expensive alternative when two are compared)</i>

*Example*

In patients with idiopathic pulmonary fibrosis, treatment with azathioprine plus prednisone offers a possible but uncertain benefit in comparison with no treatment. The intervention, however, is associated with a substantial established harm. An international guideline made a recommendation against the combination of corticosteroids plus Azathioprine in patients with idiopathic pulmonary fibrosis.<sup>44</sup>

<http://help.magicapp.org/knowledgebase/articles/369271-when-to-make-strong-recommendations-based-upon-low>

# Situation 3

Paradigmatic situation	Confidence in effect-estimates for health outcomes (Quality of evidence)		Balance of benefits and harms	Values and Preferences	Resource considerations	Recommendation
<b>Potential equivalence, one option clearly less risky or costly</b>	Benefits:  Low or very low	Harms:  High or Moderate	Magnitude of benefit apparently similar - though uncertain - for alternatives. We are confident less harm or cost for one of the competing alternatives	A high value is placed on the reduction in harm	High incremental cost (or resource use) relative to the benefits, may not justify one of the alternatives	Strong recommendation for less harmful/less expensive

*Example* H. pylori eradication in patients with early stage Extranodal marginal zone B cell (MALT) lymphoma with H. pylori positive. Low quality evidence suggests that initial H pylori eradication results in similar rates of complete response in comparison to the alternatives of radiation therapy or gastrectomy but with high confidence of less harm/morbidity/cost. Consequently, UpToDate made a strong in favour of H. pylori eradication rather than radiotherapy in patients with MALT lymphoma.<sup>45</sup>



## Situation 4



Paradigmatic situation	Confidence in effect-estimates for health outcomes (Quality of evidence)		Balance of benefits and harms	Values and Preferences	Resource considerations	Recommendation
<b>High confidence in similar benefits, one option potentially more risky or costly</b>	Benefits:  High or Moderate	Harms:  Low or very low	Established that magnitude of benefit similar for alternative management strategies. Best (though uncertain) estimate is that one alternative has appreciably greater harm.	A high value is placed on avoiding the potential increase in harm	High incremental cost (or resource use) relative to the benefits, may not justify one of the alternatives	Strong recommendation against the intervention with possible greater harm

*Example* In women requiring anticoagulation and planning conception or in pregnancy, high confidence estimates suggests similar effects of different anticoagulants. However, indirect evidence (low confidence in effect estimates) suggests potential harm to the unborn infant with oral direct thrombin (eg, dabigatran) and factor Xa inhibitors (eg, rivaroxaban, apixaban). The AT9 guidelines recommended against the use of such anticoagulants in women planning conception or in pregnancy.<sup>1</sup>

<http://help.magicapp.org/knowledgebase/articles/369271-when-to-make-strong-recommendations-based-upon-low>

# Situation 5

Paradigmatic situation	Confidence in effect-estimates for health outcomes (Quality of evidence)		Balance of benefits and harms	Values and Preferences	Resource considerations	Recommendation
<b>Potential catastrophic harm</b>	Benefits:  Immaterial (very low to high)	Harms:  Low or very low	Potential important harm of the intervention, magnitude of benefit is variable	A high value is placed on avoiding potential increase in harm	High incremental cost (or resource use) relative to the benefits, may not justify the intervention	Strong recommendation against the intervention  <i>(or in favor of the less harmful/less expensive alternative when two are compared)</i>

*Example* In males with androgen deficiency, testosterone supplementation likely improves quality of life. Low confidence evidence suggests that testosterone increases cancer spread in patients with prostate cancer. The Endocrine Society (USA) made a recommendation against testosterone supplementation in patients with prostate cancer.<sup>46</sup>



# GRADE's software for Summary of Findings tables, Health Technology Assessment and Guidelines

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# GRADE: tõendusest kliinilise soovituseni

## GRADE: Evidence to decision table (1)

### Question

Should parenteral anticoagulation be used in prolonging survival in patients with cancer?

<b>POPULATION:</b>	Patients with cancer
<b>INTERVENTION:</b>	Parenteral anticoagulation
<b>COMPARISON:</b>	No parenteral anticoagulation
<b>MAIN OUTCOMES:</b>	Survival at 12 months (study follow up) Survival (overall – study follow up at 24 to 84 months) DVT Major bleeding Minor bleeding
<b>SETTING:</b>	Outpatient

**GRADE: Evidence to Decision table (2)**

**Assessment**

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	<p><b>Is the problem a priority?</b></p> <ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>○ Yes</li>   <li>○ Varies</li> <li>○ Don't know</li> </ul>		
DESIRABLE EFFECTS	<p><b>How substantial are the desirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>○ Large</li>   <li>○ Varies</li> <li>○ Don't know</li> </ul>		
UNDESIRABLE EFFECTS	<p><b>How substantial are the undesirable anticipated effects?</b></p> <ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>○ Trivial</li>   <li>○ Varies</li> <li>○ Don't know</li> </ul>		

# GRADE: Evidence to Decision table (3)

CERTAINTY OF EVIDENCE	<p><b>What is the overall certainty of the evidence of effects?</b></p> <ul style="list-style-type: none"><li>○ Very low</li><li>○ Low</li><li>○ Moderate</li><li>○ High</li> <li>○ No included studies</li></ul>		
VALUES	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <ul style="list-style-type: none"><li>○ Important uncertainty or variability</li><li>○ Possibly important uncertainty or variability</li><li>○ Probably no important uncertainty or variability</li><li>○ No important uncertainty or variability</li></ul>		
BALANCE OF EFFECTS	<p><b>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</b></p> <ul style="list-style-type: none"><li>○ Favors the comparison</li><li>○ Probably favors the comparison</li><li>○ Does not favor either the intervention or the comparison</li><li>○ Probably favors the intervention</li><li>○ Favors the intervention</li> <li>○ Varies</li><li>○ Don't know</li></ul>		<p><i>GRADEPro GDT</i></p>

# GRADE: Evidence to Decision table (4)

ACCEPTABILITY	<b>Is the intervention acceptable to key stakeholders?</b> <ul style="list-style-type: none"><li>○ No</li><li>○ Probably no</li><li>○ Probably yes</li><li>○ Yes</li> <li>○ Varies</li><li>○ Don't know</li></ul>		
FEASIBILITY	<b>Is the intervention feasible to implement?</b> <ul style="list-style-type: none"><li>○ No</li><li>○ Probably no</li><li>○ Probably yes</li><li>○ Yes</li> <li>○ Varies</li><li>○ Don't know</li></ul>		

**GRADE: Evidence to Decision table (5)**

	JUDGEMENT							IMPLICATIONS
<b>PROBLEM</b>	No	Probably no	Probably yes	Yes		Varies	Don't know	
<b>DESIRABLE EFFECTS</b>	Trivial	Small	Moderate	Large		Varies	Don't know	
<b>UNDESIRABLE EFFECTS</b>	Large	Moderate	Small	Trivial		Varies	Don't know	
<b>CERTAINTY OF EVIDENCE</b>	Very low	Low	Moderate	High			No included studies	
<b>VALUES</b>	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
<b>BALANCE OF EFFECTS</b>	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
<b>ACCEPTABILITY</b>	No	Probably no	Probably yes	Yes		Varies	Don't know	
<b>FEASIBILITY</b>	No	Probably no	Probably yes	Yes		Varies	Don't know	



**Conclusions**

**Should parenteral anticoagulation be used in prolonging survival in patients with cancer?**

TYPE OF RECOMMENDATION	Strong recommendation against the intervention  ○	Conditional recommendation against the intervention  ○	Conditional recommendation for either the intervention or the comparison  ○	Conditional recommendation for the intervention  ○	Strong recommendation for the intervention  ○
RECOMMENDATION					
JUSTIFICATION					

# Kliinilise soovitus sõnastamine

Tabel 8. Soovituste sõnastuse näited (värvikoodisüsteemis)

	1. sõnastus	2. sõnastus	3. sõnastus
<b>Tugev soovitus teha</b>	Vajalik on...	Tervishoiutöötajad peavad ...	Tuleb...
<b>Nõrk soovitus teha</b>	Võiks ...	Tervishoiutöötajad võivad ...	Soovitame teatud tingimustel...
<b>Soovitus pigem mitte teha</b>	Ei tohiks...	Tervishoiutöötajad võiksid mitte...	Ei soovita teatud tingimustel...
<b>Tugev soovitus mitte teha</b>	Ei ole õige...	Tervishoiutöötajad ei tohi...	Kindlasti mitte kasutada/teha...

# Lisalugemist

- [www.decide-collaboration.eu](http://www.decide-collaboration.eu)
- Guyatt et al. Going from evidence to recommendations. *BMJ* 2008;336:1049-1051
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- Andrews J *et al.* GRADE guidelines: 15. Going from evidence to recommendations – determinants of a recommendations' direction and strength. *J Clin Epidemiol* 2013;726-735
- Alexander PE *et al.* World Health Organization strong recommendations based on low-quality evidence (study quality) are frequent and often inconsistent with GRADE guidance. *J Clin Epidemiol*. 2014 Dec 19. pii: S0895-4356(14)00417-X