SUMMARY OF FINDINGS TABLES

Cochrane Ireland conference, NUIG 2017

These slides are adapted from versions developed with the help of the UK Cochrane Centre (UKCC).

What are Summary of Findings tables?

- Want to go beyond giving summary statistic (e.g. risk ratio), number of studies, and little else.
- SoF table presents the main findings of a review in a transparent and understandable format.
- Gives information about:
  - The quality of the evidence
  - The magnitude of the effect
  - An overall summary of each outcome

Chapter 11.5 of the Cochrane Handbook

Why do we need to summarise findings?

- Cochrane reviews are complex and can be long:
- multiple outcomes with varying importance or relevance
- complex statistical discussions
- technical terms and abbreviations
- varying risk of bias among included studies

Magnitude of Effect and Quality of Evidence

Gordon H Guyatt et al. *BMJ* 2008;336:924-926

Cochrane review format and SoF

- Now required in MECIR standards: http://methods.cochrane.org/mecir
- Main Summary of Findings (SoF) table before the Background section
- Other SoF tables in Appendices

Sample SoF

Summary of findings (Explanation)

Summary of findings for the main comparison. Compression stockings compared with no compression stockings for people taking long haul flights

Does wearing compression stockings prevent deep vein thrombosis in people taking long haul flights?

Patient or population: passengers on a long haul flight (more than 4 hours)
Setting: long haul flights
Intervention: wearing compression stockings[1]
Comparison: not wearing stockings

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with not wearing compression stockings	Risk with wearing compression stockings				
Symptomatic deep vein thrombosis (DVT) Follow-up period	0 participants developed symptomatic DVT in these studies		Not estimable	2821 (9 studies)	Not estimable[2]	

Same comparison, different outcomes

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with not wearing compression stockings	Risk with wearing compression stockings				

2 If there are very few or no events and the number of participants is large, judgement about the quality of evidence (particularly judgements about precision) may be based on the absolute effect. Here the quality rating may be considered 'high' if the outcome was appropriately assessed and the event, in fact, did not occur in 2821 studied participants.

3 Two trials recruited high-risk participants defined as those with previous episodes of DVT, coagulation disorders, severe obesity, limited mobility due to bone or joint problems, neoplastic disease within the previous two years, large varicose veins or, in one of the studies, participants taller than 190 cm and heavier than 90 kg. The incidence for seven trials that excluded high-risk participants was 1.45% and the incidence for the two trials that recruited high-risk participants (with at least one risk factor) was 2.43%. We have rounded these off to 10 and 30 per 1000 respectively.

Symptomless DVT Follow-up period immediately post flight to 48 hours	Low-risk population[3]		OR 0.10 (0.04 to 0.25)	2637 (9 RCTs)	⊕⊕⊕⊕ HIGH
	10 per 1000	1 per 1000 (0 to 3)			
	High-risk population[2]				
	30 per 1000	3 per 1000 (1 to 8)			

Oedema Follow-up period immediately post flight Post flight values measured on a scale from 0 (no oedema) to 10 (maximum oedema)	The mean oedema score ranged across control groups from 6 to 9	The mean oedema score in the intervention groups was on average 4.7 lower (4.9 lower to 4.5 lower)	-	1246 (6 RCTs)	⊕⊕⊖⊖ LOW[5]	It was not possible to pool data from an additional 2 studies (Hagan 2008; Loew 1998). These both reported reduced oedema post flight in the stocking group[6]
Adverse effects arising from the use of compression stockings Follow-up period immediately post flight	The tolerability of the stockings was described as very good with no complaints of side effects in 4 studies		Not estimable	1182 (4 studies)	Not estimable	None of the trials reported adverse effects, apart from 4 cases of superficial vein thrombosis in varicose veins in the knee region that were compressed by the upper edge of the stocking in 1 trial. However, the meta-analysis of the data on this outcome from this trial and 7 others found a non-statistically significant difference (see above)

Outcomes

- Planning for SoF starts with the protocol
- All relevant outcomes should be selected for the review AND for the SoF tables
- The SoF tables are based on the importance of the outcomes, not the evidence in the review.
- How should importance of outcomes be determined?

- All important outcomes may not be assessed in randomised control trials.
  - e.g. adverse effects
- May need to use results of observational trials or even case reports (e.g. harms).
- Adds complexity to questions of quality of evidence.

GRADE: for making SoF tables

- A framework for assessing the quality of evidence, developed initially in the world of clinical guidelines:
  - As an improvement over existing study-design-based hierarchies of evidence
  - As an attempt to get a standardised approach across guideline developers
  - By an international working group over many years
- Used as the structure to prepare a Summary of Findings table.

Chapter 12.2 of the Cochrane Handbook

GRADE – the key features

- Within the context of a systematic review, GRADE reflects how confident we are that an estimate is close to the true effect.
- Judgments are made about the “quality of evidence” for each main outcome across all available studies.
- Clear separation between rating the evidence AND the process for making a recommendation (strength of recommendation).

Constructing SoF tables: Example from Airways Group

1 160/4.5 mcg BDF single inhaler therapy compared to current best practice for adult asthma that is not controlled on ICS

160/4.5 µg BDF single inhaler therapy compared to current best practice for adults with asthma that is not controlled on ICS

Patient or population: adults with asthma that is not controlled on ICS
Settings: community
Intervention: 160/4.5 µg BDF single inhaler therapy
Comparison: current best practice

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Current best practice	160/4.5 µg BDF single inhaler therapy				
Patients with exacerbations causing hospitalisation Follow-up: mean 6 months	**6 per 1000**	**5 per 1000** (3 to 8)	**OR 0.81** (0.45 to 1.44)	8841 (8 studies)	⊕⊕⊖⊖ **low**[1,2]	
Patients with exacerbations treated with oral steroids Follow-up: mean 6 months	**70 per 1000**	**59 per 1000** (50 to 69)	**OR 0.83** (0.70 to 0.98)	8841 (8 studies)	⊕⊕⊕⊖ **moderate**[1]	
Fatal serious adverse events Follow-up: mean 6 months	**1 per 1000**	**1 per 1000** (0 to 5)	**OR 1.95** (0.53 to 7.21)	8841 (8 studies)	⊕⊕⊖⊖ **low**[1,2]	
Serious adverse events (non-fatal) Follow-up: mean 6 months	**20 per 1000**	**24 per 1000** (18 to 32)	**OR 1.20** (0.90 to 1.60)	8841 (8 studies)	⊕⊕⊖⊖ **low**[1,2]	
Discontinuation due to adverse events Follow-up: mean 6 months	**7 per 1000**	**21 per 1000** (14 to 31)	**OR 2.85** (1.89 to 4.3)	8411 (7 studies)	⊕⊕⊕⊖ **moderate**[1]	

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[1] Unblinded trials

[2] Confidence interval cannot rule out important differences in either direction

BDF: budesonide plus formoterol; ICS: inhaled corticosteroids

Constructing SoF tables: Title & PICO

1 160/4.5 mcg BDF single inhaler therapy compared to current best practice for adult asthma that is not controlled on ICS

160/4.5 µg BDF single inhaler therapy compared to current best practice for adults with asthma that is not controlled on ICS

Patient or population: adults with asthma that is not controlled on ICS
Settings: community
Intervention: 160/4.5 µg BDF single inhaler therapy
Comparison: current best practice

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
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160/4.5 µg BDF single inhaler therapy compared to current best practice f

Patient or population: adults with asthma that is not controlled on ICS
Settings: community
Intervention: 160/4.5 µg BDF single inhaler therapy
Comparison: current best practice

Constructing SoF tables: up to 7 outcomes

1 160/4.5 mcg BDF single inhaler therapy compared to current best practice for adult asthma that is not controlled on ICS

160/4.5 µg BDF single inhaler therapy compared to current best practice for adults with asthma that is not controlled on ICS

Patient or population: adults with asthma that is not controlled on ICS
Settings: community
Intervention: 160/4.5 µg BDF single inhaler therapy
Co[illegible]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Current best practice	160/4.5 µg BDF single inhaler therapy				
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*The [illegible] group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
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Constructing SoF tables: up to 7 outcomes

Outcomes
Patients with exacerbations causing hospitalisation Follow-up: mean 6 months
Patients with exacerbations treated with oral steroids Follow-up: mean 6 months
Fatal serious adverse events Follow-up: mean 6 months
Serious adverse events (non-fatal) Follow-up: mean 6 months
Discontinuation due to adverse events Follow-up: mean 6 months

Constructing SoF tables: Treatment effects

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160/4.5 µg BDF single inhaler therapy compared to current best practice for adults with asthma that is not controlled on ICS

Patient or population: adults with asthma that is not controlled on ICS
Settings: community
Intervention: 160/4.5 µg BDF single inhaler therapy
Comparison: current best practice

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Current best practice	160/4.5 µg BDF single inhaler therapy				
Patients with exacerbations causing hospitalisation Follow-up: mean 6 months	**6 per 1000**	**5 per 1000** (3 to 8)	**OR 0.81** (0.45 to 1.44)	8841 (8 studies)	⊕⊕⊖⊖ **low**[1,2]	
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OR 2.85 (1.89 to 4.3)	8411 (7 studies)	⊕⊕⊕⊖ **moderate**[1]

Constructing SoF tables: Absolute treatment effects

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160/4.5 µg BDF single inhaler therapy compared to current best practice for adults with asthma that is not controlled on ICS

Patient or population: adults with asthma that is not controlled on ICS
Settings: community
Intervention: 160/4.5 µg BDF single inhaler therapy
Comparison: current best practice

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Current best practice	160/4.5 µg BDF single inhaler therapy				
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Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

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BDF: budesonide plus formoterol; ICS: inhaled corticosteroids

Constructing SoF tables: Absolute treatment effects

Outcomes	Illustrative comparative risks* (95% CI)	
	Assumed risk	Corresponding risk
	Current best practice	160/4.5 µg BDF single inhaler therapy
Patients with exacerbations causing hospitalisation Follow-up: mean 6 months	**6 per 1000**	**5 per 1000** (3 to 8)
Patients with exacerbations treated with oral steroids Follow-up: mean 6 months	**70 per 1000**	**59 per 1000** (50 to 69)
Fatal serious adverse events Follow-up: mean 6 months	**1 per 1000**	**1 per 1000** (0 to 5)
Serious adverse events (non-fatal) Follow-up: mean 6 months	**20 per 1000**	**24 per 1000** (18 to 32)
Discontinuation due to adverse events Follow-up: mean 6 months	**7 per 1000**	**21 per 1000** (14 to 31)

General process

- Synthesise the evidence (meta-analysis or narratively)
- Add the results into the text of the review
- Import RevMan file into GRADEpro (free software)
- Complete SoF table in GRADEpro, download file, and import it into RevMan
- Complete Results section: for each outcome, give GRADE assessment and quality comments
- Write Conclusion

http://gradepro.org

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Quality of evidence needs to be considered for each important outcome

- The quality of evidence may be different for different outcomes.
- Decision makers (and review authors) need to consider the relative importance of outcomes.
- Up to 7 important outcomes can be selected (including outcomes for which no data are available).
- The outcomes should be specified in your protocol.

What does GRADE assess?

- Early systems of grading the quality of evidence focused almost exclusively on study design.
- Randomised trials provide stronger evidence than observational studies.
- GRADE includes other factors that may decrease or increase the quality of evidence.

What you do

- Create a separate table for each comparison in your review.
  - Calculate manually or use GRADEpro software
  - free to download: https://gradepro.org/
  - imports data directly from RevMan
- Authors' input and judgement still required
- But…GRADEpro will not work on an Apple Mac
- Also… will not calculate for continuous outcomes – must be added manually.

Selecting comparison(s)

- Choose the most important comparison in the most important population.
- This should be the most important to decision-makers.
- This should not necessarily be the one with the most data.

Selecting comparison(s)

- Sometimes straight-forward
- But some reviews have more than one…
  - Intervention
  - Comparator
  - Population
    - Risk groups
    - Subgroups
  - Setting
  - Follow-up time

Different approaches

Summary of findings:

Compression stockings compared with no compression stockings for people taking long flights

Patients or population: Anyone taking a long flight (lasting more than 6 hours)

Settings: International air travel

Intervention: Compression stockings[1]

Comparison: Without stockings

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Without stockings	**With stockings**				
Symptomatic deep vein thrombosis (DVT)	See comment	See comment	Not estimable	2821 (9 studies)	See comment	0 participants developed symptomatic DVT in these studies.
Symptom-less deep vein thrombosis	**Low risk population** [2]		**RR 0.10** (0.04 to 0.26)	2637 (9 studies)	⊕⊕⊕⊕ **High**	
	10 per 1000	**1 per 1000** (0 to 3)				
	High risk population [2]					

[2] Two trials recruited high risk participants defined as those with previous episodes of DVT, coagulation disorders, severe obesity, limited mobility due to bone or joint problems, neoplastic disease within the previous two years, large varicose veins or, in one of the studies, participants taller than 190 cm and heavier than 90 kg. The incidence for 7 trials that excluded high risk participants was 1.45% and the incidence for the 2 trials that recruited high-risk participants (with at least one risk factor) was 2.43%. We have rounded these off to 10 and 30 per 1,000 respectively.

Constructing SoF tables: List all important outcomes (desirable and undesirable)

- Specify in the protocol how SoF tables will be constructed. Review may identify unexpected outcomes.
- Need to consider at the outset the relative importance of the outcomes (e.g., to policy makers, practitioners, patients, researchers)
- Your Review Group may have advice on primary outcomes and what to put into SoF.
- In one SoF table, outcomes are listed in order of importance.

http://gradepro.org

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Constructing SoF tables: Quality of evidence

Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
OR 0.81 (0.45 to 1.44)	8841 (8 studies)	⊕⊕⊖⊖ **low**[1,2]
OR 0.83 (0.70 to 0.98)	8841 (8 studies)	⊕⊕⊕⊖ **moderate**[1]
OR 1.95 (0.53 to 7.21)	8841 (8 studies)	⊕⊕⊖⊖ **low**[1,2]
OR 1.20 (0.90 to 1.60)	8841 (8 studies)	⊕⊕⊖⊖ **low**[1,2]
OR 2.85 (1.89 to 4.3)	8411 (7 studies)	⊕⊕⊕⊖ **moderate**[1]

GRADE approach to evidence quality

Methodology	Quality rating
Randomised trials; or double upgraded observational studies	High
Single downgraded randomised trials; or upgraded observational studies	Moderate
Double downgraded randomised trials; or observational studies	Low
Triple downgraded randomised trials; or downgraded observational studies; or case series/case reports	Very low

Grading the quality of evidence: factors that might **increase** the quality of evidence

1. Large magnitude of effect
2. All plausible confounding taken into account
3. Dose-response gradient visible

Grading the quality of evidence: factors that might **decrease** the quality of evidence

1. Study limitations (risk of bias)
2. Inconsistency of results
3. Indirectness of evidence
4. Imprecision of results
5. High risk of publication bias

GRADE evidence profile

- For factors that might decrease the quality of evidence has 3 scoring options:
- Not serious: no downgrade
- Serious: -1 level
- Very serious: -2 levels

GRADE assessment: 2016 revised wording for our confidence in the results

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate:

The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited:

The true effect may be substantially different from the estimate of the effect

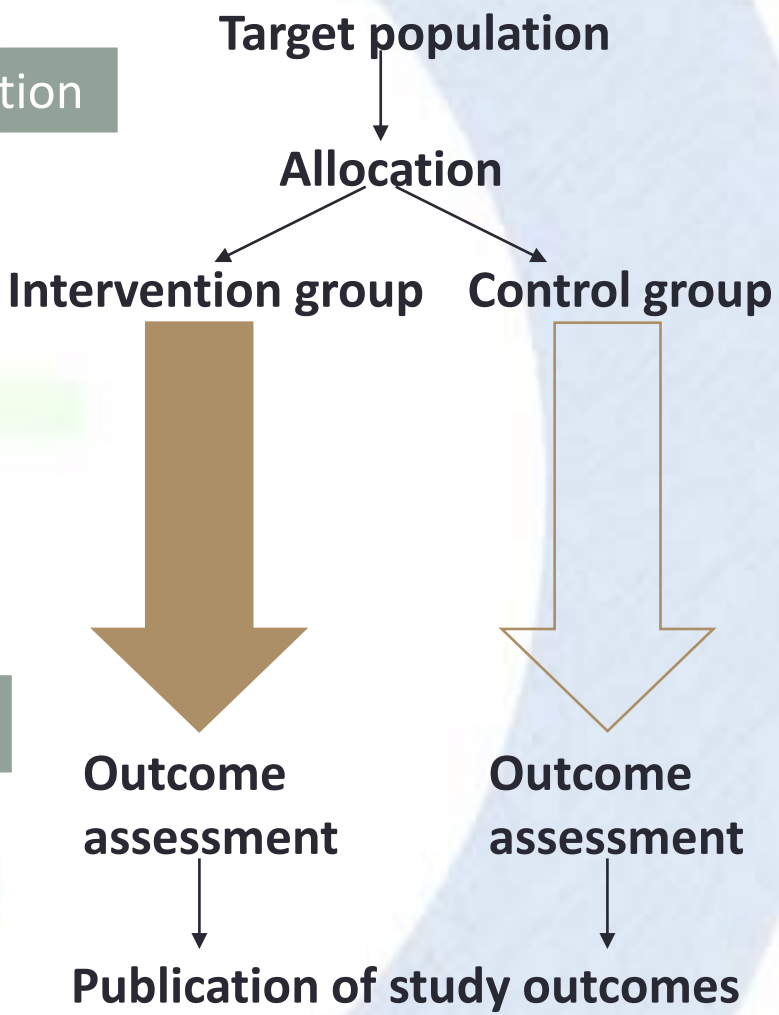
Very low quality: We have very little confidence in the effect estimate:

The true effect is likely to be substantially different from the estimate of effect

1. Summarizing study limitations for randomised trial

Sources of bias

Selection	Random sequence generation
	Allocation concealment
Performance	Blinding of participants, personnel
Detection	Blinding of outcome assessment
Attrition	Incomplete outcome data
Reporting	Selective reporting



1. Summarizing study limitations for randomised trials

- Assess the risk of bias across all the studies contributing to the outcome.
- Use the traffic light plot with the Forest plot.
- Reviewers make an overall judgment on downgrading.
- Most of the studies are not at obvious of important risk of bias – no downgrade.
- Enough studies are at obvious risk of important bias to alter the overall outcome – minus one.
- Most of the studies are at obvious risk of important bias so we really cannot trust the findings – minus two.

Risk of bias	Across studies	Interpretation	Considerations	GRADE Assessment
Low risk of bias	Most information is from studies at low risk of bias.	Plausible bias unlikely to seriously alter the results.	No apparent limitations	No serious limitations; do not downgrade.
Unclear risk of bias	Most information is from studies at low or unclear risk of bias.	Plausible bias that raises some doubt about the results.	Potential limitations are unlikely to lower confidence in the estimate of effect	No serious limitations; do not downgrade.
			Potential limitations are likely to lower confidence in the estimate of effect.	Serious limitations; downgrade one level.
High risk of bias	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.	Plausible bias that seriously weakens confidence in the results.	Crucial limitation for one criterion, or some limitations for multiple criteria, sufficient to lower confidence in the estimate of effect.	Serious limitations; downgrade one level.

2. Inconsistency of results

- Heterogeneity or variability in results across studies that has not been explained.
- Significant heterogeneity suggests that trials are not estimating a single common effect: patients, intervention, outcome, methodological

3. Indirectness of evidence

- Surrogate measures of outcome.
- The question being addressed by the systematic review is different from the available evidence regarding the population, intervention, comparator, or an outcome.
- Comparison is NOT head to head: A vs. placebo; B vs. placebo; but not A vs. B

4. Imprecision of results

- Numbers of events low: rule of thumb <300-400 events
- Number of participants is low
- Difficulties establishing a threshold
- Width of CI: How wide is too wide? Depends
  - For continuous data the 95% confidence interval includes no effect and the upper or lower confidence limit crosses the minimal important difference.

5. Publication bias

- Failure to report studies with no effect
- Selective outcome reporting
- How comprehensive was the search?
- Funnel plot

Decisions should be explicit and transparent

- Make judgements explicit and transparent to users
- Explain decisions in the footnotes
- Acknowledge borderline decisions

Space for comments

- Example of types of comments:
  - multiple outcomes with conflicting results
  - complex statistical discussion
  - technical terms and abbreviations
  - varying risk of bias among included studies

Resources

- Cochrane Handbook
  http://training.cochrane.org/handbook
  - Chapter 8: Assessing risk of bias in included studies
  - Chapter 11: Presenting results and Summary of Findings tables
  - Chapter 12: Interpreting results and drawing conclusions (GRADE)
- Cochrane Training:
  http://training.cochrane.org/path/grade-approach-evaluating-quality-evidence-pathway
- GRADE BMJ series: 2008;336;924-926 and following
- Journal of Clinical Epidemiology GRADE series:
  http://www.jclinepi.com/content/jce-GRADE-Series

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