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A core outcome set for multimorbidity research (COSmm)

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Abstract

Purpose
To develop a consensus based set of core outcomes for studies in multimorbidity.

Methods
Consensus study following the COS-STAR guidelines for the design and reporting of core outcome sets. An expert Delphi Panel completed a web-based survey with two Rounds. Panellists were presented with a range of outcomes that had been identified in previous workshops and a related systematic review. They indicated their level of agreement on inclusion of each outcome using a Likert scale and outcomes reaching a pre-specified consensus level were included.

Results: 30 panellists were invited to participate and 26 agreed, from 13 countries. All 26 completed both rounds of the survey. The Delphi Panel reached consensus on 17 core outcomes for multimorbidity. The highest ranked outcomes were health related quality of life, mental health outcomes and mortality. Other outcomes were grouped into overarching themes of patient reported impacts and behaviours (treatment burden, self-rated health, self-management behaviour, self-efficacy, adherence); Physical activity and function (activities of daily living, physical function, physical activity); consultation related (communication, shared decision making, prioritisation); and health systems (healthcare utilisation, costs, quality of healthcare).

Conclusions: This consensus study involved a wide range of international experts who identified a large number of outcomes for multimorbidity intervention studies. The results suggest that quality of life, mortality and mental health outcomes should be regarded as essential core outcomes. However, researchers should also consider the full range of outcomes when designing studies to capture important domains in multimorbidity depending on individual study aims and interventions.
Introduction
The COMET (Core Outcome Measures in Effectiveness Trials) is an initiative which aims to develop agreed standardised sets of outcomes, known as ‘core outcome sets’ (COS) (http://www.comet-initiative.org/). (1) COS represent the minimum that should be measured and reported in all clinical trials of a specific condition or conditions. (1)
Multimorbidity is commonly defined as the co-existence of two or more chronic conditions in an individual. (2) Its impacts include reduced health-related quality of life, increased psychological distress, functional difficulties, increased healthcare utilisation and heightened mortality risk. (3-8) Current randomised controlled trials tend to adopt a single-disease focus, resulting in a paucity of relevant evidence for the management of patients with multimorbidity. (9) There are a growing number of trials examining the effectiveness of interventions to address the specific experiences of patients with multimorbidity. (Cochrane review ref). The systematic review of these studies highlights challenges synthesising the evidence due to differences between studies including outcomes. The 2016 UK National Institute of Health and Care Excellence (NICE) Guidance on Multimorbidity stresses the need to design interventions and transform health services by addressing multimorbidity in both clinical guidelines and clinical practice. (10) This NICE Guidance and related systematic and clinical reviews (9-11), highlight the need for consensus regarding multimorbidity outcomes, so that evidence can be synthesised and is based on outcomes reflecting the priorities of all stakeholders, particularly patients.

The aim of this study was to identify a COS for multimorbidity research studies using a Delphi consensus process with an international panel of experts. The scope of this COS included studies of all intervention types targeting adults with multimorbidity and does not address the issue of patients with multimorbidity participating in single condition studies as these interventions are conceptually different. Research studies including a named index condition (e.g. hypertension, diabetes) plus another condition (referred to as co-morbidity studies) were excluded, as the aim was to develop a COS reflecting the heterogeneous nature of multimorbidity.

The specific objectives were:

1. To identify outcomes and outcome metrics that had previously been used in intervention studies for multimorbidity.
2. To develop a consensus based set of core outcome for intervention studies in multimorbidity.
3. To identify related outcome metrics potentially relevant for multimorbidity studies

Methods
A protocol of this project was registered with the COMET initiative and is available at: http://www.comet-initiative.org/studies/details/822?result=true . (12) The Core Outcome Set-STAndards for Reporting (COS-STAR) Equator Network guidelines were used for the reporting of this core outcome set. (1) COS can be considered in terms of what to measure, which we refer to as outcomes and how to measure them, which we refer to as metrics. (trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-1978-4)

**The Steering Group**

A Steering Group oversaw the development of the COS and consisted of academic family practitioners and primary care researchers with a specific interest in multimorbidity; all members are authors on this paper.

**The development of a preliminary set of core outcomes for multimorbidity: Information sources**

The Steering Group developed a list of relevant outcome for multimorbidity intervention studies using a comprehensive strategy of workshop discussions and review of outcomes in existing peer reviewed publication. This list of potential outcomes was developed over several years at academic primary care meetings and workshops attended by the author group and other experts in multimorbidity research. (13) (see Appendix 1) Members of the steering group also reviewed studies in the recently updated Cochrane review of the effectiveness of interventions for patients with multimorbidity and identified outcomes and related metrics reported in this review. (11) This approach was taken as the Cochrane systematic review involved a comprehensive systematic literature search across multiple databases and had been conducted relatively recently. These outcome and related metrics were compiled into an online survey using Survey Monkey© (Appendix 2). (14)

**Consensus process**

The Delphi technique is a commonly used consensus technique. (15) The Steering Group identified a panel of international experts with broad stakeholder representation. Participants were selected based on their interest in multimorbidity research or through their existing membership of patient panels supporting multimorbidity research in Ireland, the UK and Canada. The final panel included a multidisciplinary range of experts and stakeholders (see Appendix 3).

The survey containing the preliminary COS was first piloted (to test usability) by members of academic staff in the departments of the steering group and modified accordingly. Following formation of the Delphi panel, all potential members received the first round questionnaire via an on-line survey, SurveyMonkey©. (14) A full copy of this questionnaire including the instructions given to participants is included as Appendix 2.
Panel members were asked to rate the importance of each potential outcome and were also presented with a range of potential metrics. They were also given an opportunity to suggest additional outcomes or metrics if desired. A web link to the outcome metrics presented was also included to support the panel’s decision making. (See Appendix 2).

Sample size
Based on previous studies showing the range in sizes of Delphi panels, we anticipated that a purposively selected sample of at least 15 experts would adequately cover issues in the proposed outcome set. Only those responding to the first round were included in the second round. Based on previous Delphi studies a total of 30 panellists were invited, assuming an approximate response rate of 50%.

Round 1 analysis
Panellists were asked to indicate their level of agreement for the inclusion of each outcome domain using a 5-point Likert scale (1=strongly disagree, 2=disagree, 3=ambivalent, 4=agree, 5= strongly agree). For each statement, the median response and interquartile range (IQR) were calculated. Where the lower limit of the IQR was >3, the outcome domain was accepted as included in the core set. In statements where the upper limit of the IQR was <3, the outcome measure was rejected. If the IQR of a statement included 3, the language used in the statement was revised following recommendations from the panel and included in the second round. All members of the Steering Group were involved in reviewing statements and in refining the core outcomes included.

Round 2
The Delphi process underwent two rounds. Outcome remaining from the first Round were presented with the same definition of consensus as used for Round 1. Participants were not informed of the previous round scores but would have been aware that the remaining outcomes had not achieved consensus in Round 1. The wide range of potential outcome metrics included in Round 1 indicated that it was beyond the scope of the current study to reach agreement on metrics so these were not presented to the panellists for consideration for Round 2. All statistical analyses were performed using STATA version 13.0 (StataCorp LP, College Station, TX, USA).

Ethical considerations
Ethical approval for this study was granted by the Human Research Ethics committee at the Royal College of Surgeons in Ireland (RCSI) medical school. All participants were contacted by email with detailed information regarding the study. Patient and public representatives were contacted initially with a separate email invitation that included a specific public/patient participant information leaflet. For all panel members, once a signed consent form was received the panel member was sent another email with a link to the SurveyMonkey® questionnaire.
Results
An overview of the COS development process is provided in Figure 1. Of the 30 potential Delphi panel participants, 26 responded (87% response rate). Five panellists were patient or public representatives. Two people formally declined and two did not respond to several emails. (See Appendix 3).

Results: Round 1 Delphi Panel
Of the 30 preliminary outcomes presented to the panel, 11 had a median and IQR score >3 and were therefore included in the COS after round 1. (See Table 1) No outcomes were excluded following Round 1 and no additional outcomes were identified. A list of potential metrics was identified during Round 1 and is presented in Appendix 4.

Results: Round 2
The remaining 19 outcomes (IQR included 3) were presented to all 26 panel members for Round 2 of the Delphi process and all completed Round 2. A further six outcomes had median and IQR scores > 3 so were included, giving a total of 17 final outcomes in the COS. The steering group divided these 17 core outcomes into linked groups in an effort to clarify the key areas for consideration when choosing outcomes for individual studies from the COS. (See Table 2)

Discussion
Summary
A Delphi Consensus panel with 26 experts from 13 countries agreed on 17 core outcomes for multimorbidity intervention studies (COSmm). The highest ranked outcomes were health related quality of life (HRQoL), mental health outcomes and mortality. Given the number of outcomes we have grouped the remaining included outcomes into overarching themes of patient reported activities and behaviours, physical activity and function, consultation related outcomes and outcomes of importance to health systems including costs.

While the COSmm represents a large number of outcomes for consideration, this reflects the broad nature of multimorbidity and is consistent with the range of outcomes in studies included in the Cochrane systematic review on multimorbidity interventions.(11) Given the likely variation in intervention types for people with multimorbidity, individual studies will use outcomes that reflect their aims and underlying mechanisms.(13) Our results suggest that all studies should consider HRQoL, mental health outcomes and mortality as key outcomes and consider other outcomes within the COSmm based on their own individual study. While few individual studies will be designed or powered to detect changes in mortality, our panellists regarded it as an important outcome and inclusion of mortality in studies would facilitate its inclusion in meta-analyses in future systematic reviews. We
would also caution that if all outcomes in the COSmm were used in an individual study, it would likely lead to excessive burden on study participants and could lead to higher risk of Type 1 errors in interpreting results. We also acknowledge that many of the outcomes that were excluded could also be considered important, but the level of agreement amongst panellists was not sufficiently strong to include them and some may still be relevant in multimorbidity trials depending on the interventions involved.

One of the objectives of this study was to consider metrics which have been used previously for each of the core outcomes. The responses in Round 1 suggested that a consensus process for the use of these metrics would be very complex and challenging. However, the metrics identified during the process will likely be of interest to researchers and other stakeholders and have been included as an appendix. Methodology on the development of core outcome sets is evolving (17, 18), and we acknowledge that this COS will need to be updated regularly as new outcomes and metrics are developed over time.

Comparison with other COS
This COS was developed specifically for studies of interventions for patients with multimorbidity but other studies have used consensus approaches to develop outcomes to measure the quality of care for people with multimorbidity using the electronic healthcare record (Bayliss et al. JAGS 2016). A range of different consensus process methods have been used in the development of COSs.(1) We chose to use a Delphi Panel approach based on our previous experience and a review of COS literature.(16, 18, 19) Other potential approaches include expert panel groups, nominal group techniques, semi-structured group discussions and questionnaires.(18) Face-to-face approaches allow greater discussion but are restricted by limited accessibility for international stakeholders. Some elements of other approaches were employed through the use of workshops to identify the draft COS prior to the consensus process. This is an evolving area of research and there is no clear evidence suggesting benefit of one consensus approach over another.(16) We chose an online Delphi method as it allowed for involvement of clinicians, researchers and patients in multiple sites across continents. The method also allowed for purposive selection of a panel to ensure representation of a range of stakeholders from different countries and healthcare systems with both professional and patient representation.(20)

A high level of consensus was achieved after the first round for 11 outcomes. This is higher than might have been expected. There are clearly many important outcomes for evaluating care delivered to complex populations. After the first round we consulted the COMET group regarding the number of outcomes and they provided helpful feedback, which suggested that our COS is not unusual given the broad scope of multimorbidity.

We used a five-point Likert scale for outcome scoring. Other COSs have been developed using alternative outcome scoring methods, which may have been more appropriate.(1)
These alternatives include a higher number of options on the Likert scale or scoring based on average agreement scores. The methodology in core outcome sets has been developing rapidly over the last few years and there is no clear evidence as yet on which is the best scoring method. The COS Star Guidance was produced after we had published our protocol and secured ethical approval. (1) The potential to change our approach to outcome scoring was considered after Round 1 but we decided not to deviate from our protocol at that point.

**Strengths and weaknesses**

This multimorbidity COS was developed over a period of several years by an international group of researchers working in this area. It built on a number of workshops held with a wide range of participants at different international primary care meetings. We identified a Delphi Panel consisting of a broad range of experts with experience in multimorbidity research from 13 countries and with public and patient representation. Identifying appropriate public and patient representation was a challenge given the broad nature of multimorbidity, but we worked with experienced research groups to identify appropriate patient representatives from three different countries. A further strength was the very high response rate for the first round of the consensus process and 100% participation for the second round.

One potential limitation of this COS is the high number of outcomes identified by the panel. There was already a high number of included outcomes after Round 1 and we provided a cover letter for the Round 2 survey that stressed to panellists that there was not necessarily a need to identify further outcomes. Despite this, a further six outcomes were added. With hindsight, a greater number of Likert scale options might have allowed for more discrimination between outcomes and facilitated ranking of outcomes, though we had not intended to rank outcomes when designing the study. Another limitation may relate to our decision not to provide panellists with feedback on scores from other panel members for Round 2. We did this to ensure that panellists could make independent judgements and avoid moving towards a group average score. (20) Guidance on the use of Delphi techniques recommend that a measure of distribution around final scores should be reported, which we have done. Reporting of the final scores alone can mask major disagreement within the group, which might be the case if there was a wide distribution around scores (19) Our results do not suggest that this was the case.

Panel size and selection is always a key consideration and potential limitation for any Delphi process. We chose to identify a purposive sample of participants with some prior exposure to the concept of multimorbidity given the complexity of this topic. This could be seen as a limitation in that it did not open up the COS to a wider group. However, the broad nature of multimorbidity and the frequent debate about its definition and construct (add refs here) were repeated themes at all the workshops that led to the development of the preliminary
COS and these workshops were open to all attendees at the two largest primary care research meetings in North America and Europe. We therefore, felt it was appropriate to limit the Delphi panellists to those with prior exposure to multimorbidity as they had already considered issues as to whether multimorbidity itself represents a construct or not.

Other COS studies have used larger panel sizes to increase representation. However, there tends to be a lower response rate for larger panels. Some studies use snowballing techniques allowing open access to an online survey, which will lead to larger numbers of participants. However, this does not necessarily ensure broad and balanced representation of key stakeholders. Another potential limitation for our study is that while we included panellists from 13 countries, they were all based in high income countries. In addition, while we included patient representatives as Delphi panel members, like many previous COS studies, it is a limitation that they were not directly involved in the development of the initial COS.

**Conclusion**
This consensus study involved a wide range of international experts who identified a large number of core outcomes for multimorbidity intervention studies. Such studies are likely to vary depending on target populations and intervention types so given the scope of multimorbidity the large number of outcomes identified is not surprising. The results suggest that quality of life, mortality and mental health outcomes should be regarded as essential core outcomes. However, researchers should also consider the full range of outcomes in this COS for multimorbidity depending on their individual study aims and interventions.

**Ethical Approval**
**Research Ethics Approval**
Research Ethics Approval was granted by RCSI Research Ethics Committee, Dublin in July 2016.

**Acknowledgements**
The authors would like to acknowledge the input of the Delphi Panel members. See Appendix 3 for details of those acknowledged.

**Competing Interest**
All authors have completed the ICMJE uniform disclosure form and declare no support from any organisation for the submitted work and no other competing interests.

**Author contributions**
SMS, CS, LB and MF conceived the idea for this paper. All authors were involved in writing the protocol and the main paper including analysis of the Delphi Panel results and commenting on development of the COS at all stages as steering group members.

**Funding**

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Emma Wallace is Senior Research Fellow in the HRB Centre for Primary Care Research in Ireland (HRB Grant HRC-2014-1)

Martin Fortin holds the Research Chair on Chronic Diseases in Primary Care, Université de Sherbrooke, Canada

**References**


Figure 1: Overview of multimorbidity COS development process

Identification of 30 potential core outcomes as well as relevant metrics by the steering group

Delphi: Round 1 (n=26 panel members)
11 outcomes scored median and IQR >3 and were included in the final COS

Delphi Round 1
No new outcomes identified from respondents.
19 outcomes taken forward to Round 2 (IQR included score of 3).

Metrics removed for Round 2 and rewording of one Likert scale answer option, following feedback from one participant

Delphi: Round 2 (n=26 panel members)
6 outcomes scored median and IQR >3 and were included in the COS.

Final agreed multimorbidity COS
Scored by 26 panel members in Round 1 and 2
Final set: 17 core outcomes

Final 17 outcomes included in COS
1. Health related quality of life
2. Mental health
3. Mortality
4. Treatment burden
5. Self-rated health
6. Self-management behaviour
7. Self-efficacy
8. Adherence
9. Activities of daily living
10. Physical function
11. Physical activity
12. Communication
13. Shared decision making
14. Prioritisation
15. Healthcare utilisation
16. Costs
17. Patient rated quality of healthcare
Table 1: Results Round 1 and Round 2 Delphi process

<table>
<thead>
<tr>
<th>Domain</th>
<th>Number Responses</th>
<th>Median and IQR Round 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Round: Outcomes included</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Related Quality of Life (HRQoL)</td>
<td>25</td>
<td>5 (4-5)</td>
</tr>
<tr>
<td>Mental Health</td>
<td>25</td>
<td>5 (4-5)</td>
</tr>
<tr>
<td>Mortality</td>
<td>26</td>
<td>4.5 (4-5)</td>
</tr>
<tr>
<td>Activities of Daily Living (ADL)</td>
<td>25</td>
<td>4 (4-5)</td>
</tr>
<tr>
<td>Physical Function</td>
<td>23</td>
<td>4 (4-5)</td>
</tr>
<tr>
<td>Self Rated Health</td>
<td>25</td>
<td>4 (4-5)</td>
</tr>
<tr>
<td>Treatment Burden</td>
<td>25</td>
<td>4 (4-5)</td>
</tr>
<tr>
<td>Communication</td>
<td>25</td>
<td>4 (4-5)</td>
</tr>
<tr>
<td>Healthcare utilisation</td>
<td>24</td>
<td>4 (4-5)</td>
</tr>
<tr>
<td>Costs</td>
<td>24</td>
<td>4 (4-5)</td>
</tr>
<tr>
<td>Adherence</td>
<td>24</td>
<td>4 (4-4)</td>
</tr>
<tr>
<td><strong>Domains to exclude: None</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second round: Outcomes included</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shared decision making</td>
<td>25</td>
<td>4 (3-5)</td>
</tr>
<tr>
<td>Quality healthcare</td>
<td>24</td>
<td>4 (3-5)</td>
</tr>
<tr>
<td>Prioritisation</td>
<td>24</td>
<td>4 (3-4.5)</td>
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<tr>
<td>Self-management Behaviour</td>
<td>25</td>
<td>4 (3-4)</td>
</tr>
<tr>
<td>Self-Efficacy</td>
<td>25</td>
<td>4 (3-4)</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>24</td>
<td>4 (3-4)</td>
</tr>
<tr>
<td><strong>Second round: Outcomes excluded (no agreement)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic Symptom Measures</td>
<td>25</td>
<td>4 (3-4)</td>
</tr>
<tr>
<td>Social Role</td>
<td>25</td>
<td>4 (3-4)</td>
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<tr>
<td>Social Support</td>
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<tr>
<td>Patient Enablement</td>
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<td>System factors (continuity)</td>
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<tr>
<td>Treatment Satisfaction</td>
<td>24</td>
<td>4 (3-4)</td>
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<tr>
<td>Social Inclusion</td>
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<td>4 (2-4)</td>
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<tr>
<td>Smoking</td>
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<td>Alcohol</td>
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<td>Nutrition</td>
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<td>3 (2-4)</td>
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<td>Illness perceptions</td>
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<td>3 (2-4)</td>
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<tr>
<td>Self-Esteem</td>
<td>25</td>
<td>3 (2-4)</td>
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Table 2. COS for multimorbidity

<table>
<thead>
<tr>
<th>Domains (n=17)</th>
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<tr>
<td><strong>Highest scoring outcomes</strong></td>
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<tr>
<td>HRQoL</td>
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<tr>
<td>Mental Health</td>
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<tr>
<td>Mortality</td>
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<tr>
<td><strong>Patient reported impacts and behaviours</strong></td>
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<tr>
<td>Treatment Burden</td>
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<tr>
<td>Self-Rated Health</td>
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<tr>
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<tr>
<td><strong>Physical activity and function</strong></td>
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<td>Activities of Daily Living</td>
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<tr>
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<tr>
<td>Physical Activity</td>
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<tr>
<td><strong>Consultation related</strong></td>
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<tr>
<td>Communication</td>
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<tr>
<td>Shared decision making</td>
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<td>Prioritisation</td>
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<td><strong>Health systems</strong></td>
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<tr>
<td>Healthcare utilisation</td>
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<tr>
<td>Costs</td>
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<td>Quality healthcare (patient rated)</td>
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