## Title

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# Quality of control groups in randomised trials of multiple myeloma enrolling in the USA: a systematic review

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**To our knowledge, no study has evaluated the quality of control groups in randomised controlled trials of multiple myeloma. We aimed to do a systematic review of randomised controlled trials of multiple myeloma to ascertain the quality of the control groups used. PubMed (MEDLINE), Embase, Cochrane Controlled Register of Trials, and CinicalTrials.gov were searched for articles of randomised controlled trials of multiple myeloma based in the USA that initiated participant enrolment between Jan 1, 2010, and June 30, 2020. A control group regimen was considered to be inferior if a previous randomised controlled trial had shown an improved progression-free survival versus the control group before enrolment. Of 49 identified randomised controlled trials, seven (14%) began enrolling patients into inferior control groups after an existing superior regimen to the control had already been published. Nine (18%) of the 49 trials continued enrolment on substandard control groups after data emerged during the study enrolment period. The median time that newer data emerged regarding inferiority of the control group from the time a trial first enrolled a patient was 13 months (IQR 8–29 months). 12 (75%) of these 16 randomised controlled trials are published, and nine (75%) of the 12 published trials had overlapping investigators with trials that had previously shown the inferiority of the control group being used. Greater scrutiny on the quality of control groups in randomised controlled trials of multiple myeloma is needed.**

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## Introduction

Despite treatment advances in multiple myeloma, the disease is largely incurable and relapses are frequent.[1] The superiority of triplets versus doublets in first and subsequent lines of therapy has been shown across several studies.[1–4] However, trials testing novel treatments can be challenging to interpret because the control groups used might not reflect the standard of care at the time of the study.

The use of antiquated, questionable, or substandard control groups is a documented problem in registration trials in oncology;[5,6] however, to our knowledge, this problem has not been systematically explored in a cohort of trials in a single disease type. Assessing the extent of this problem is particularly relevant now, given the numerous new agents and combinations of treatment for multiple myeloma. Thus, it is important to assess whether the control groups of these trials were appropriate during the enrolment period, and whether the results of those studies can be applied to contemporary patients in the USA. The aim of this study was to do a systematic review of randomised controlled trials (RCTs) of multiple myeloma based in the USA, to ascertain whether such trials were enrolling patients onto appropriate control groups. For trials in which the control group was shown to be inferior after the RCT had already started enrolment, we assessed how long after study enrolment this was shown to occur and for how long enrolment continued after the discovery of the substandard control group.

## Methods

### Search strategy and selection criteria

Preferred Reporting Items for Systemic Reviews and Meta-Analyses guidelines were adhered to for the reporting of this systematic review.[7] This systematic review was not registered on PROSPERO. A clinical librarian with expertise in systematic reviews did the search. A systematic search of PubMed (MEDLINE), Embase, and Cochrane Registry of Controlled Trials for articles published between Jan 1, 2010, and Dec 1, 2019,

| | Trial in which control group was first shown to be inferior | Timepoint when inferiority was first shown |
|---|---|---|
| Lenalidomide–dexamethasone as front-line treatment for patients not intended for transplantation upfront | Bortezomib–lenalidomide–dexamethasone was shown to be superior in the SWOG 0777 trial[3] | December, 2015 |
| Bortezomib–dexamethasone for relapsed or refractory multiple myeloma | Carfilzomib–dexamethasone was shown to be superior in the ENDEAVOR trial[9] | May, 2015 |
| Lenalidomide–dexamethasone for relapsed or refractory multiple myeloma | Carfilzomib–lenalidomide–dexamethasone was shown to be superior in the ASPIRE trial[4] | December, 2014 |
| Observation as a maintenance strategy after transplantation | Lenalidomide showed increased overall survival compared with placebo in CALGB trial[10] | April, 2011 |
| Observation as a maintenance strategy in the non-transplantation setting | Continuous lenalidomide was superior to finite duration of treatment in the MM-015 trial[11] | May, 2011 |
| Pomalidomide–dexamethasone for relapsed or refractory multiple myeloma | Elotozumab–pomalidomide–dexamethasone was shown to be superior in the ELOQUENT-3 trial[12] | June, 2018 |

*Table 1:* **Evidence used to define an inferior control group by control regimen**

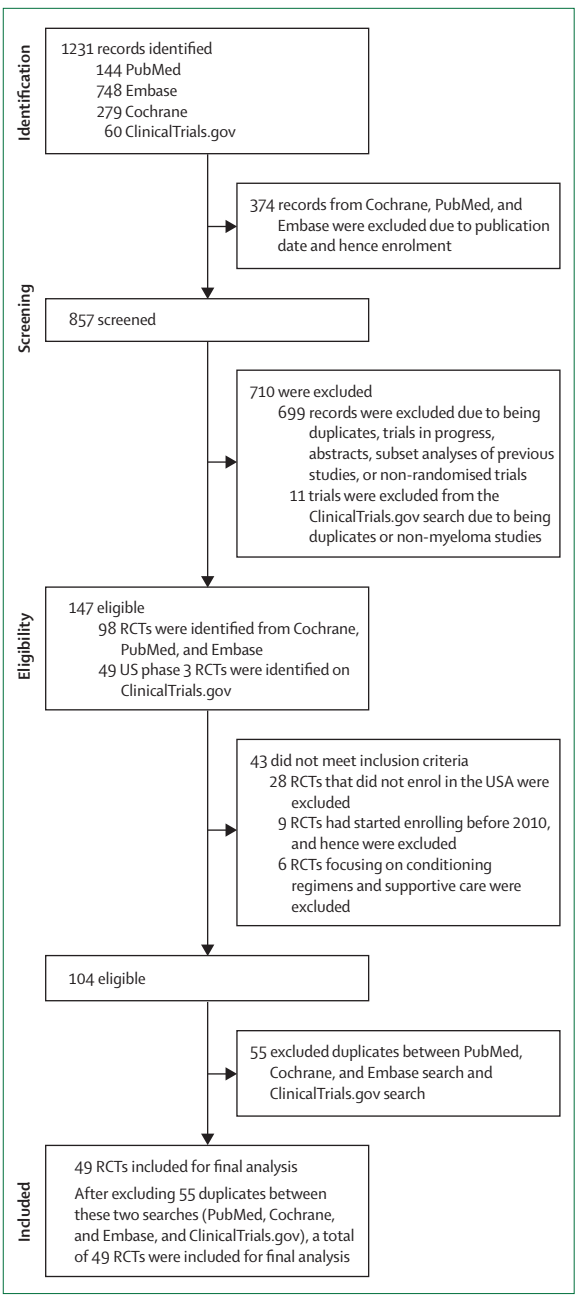


***Figure:*** **Flow diagram depicting our search strategy**
RCT=randomised controlled trial.

See Online for appendix

was done on April 1, 2020. An example search strategy is listed in the appendix (p 1). Two reviewers (GRM and KK) screened titles and abstracts, and created a shortlist of studies for further evaluation. We also cross-referenced citations of eligible articles to find additional studies suitable for inclusion. Studies were independently evaluated by two reviewers (GRM and KK), and any discrepancy was resolved through mutual discussion. We searched CinicalTrials.gov on Sept 15, 2020, using the key term "multiple myeloma". Filters were selected to choose only phase 3 trials recruiting within the USA, with an enrolment start date ranging from Jan 1, 2010, to June 30, 2020. Eligible studies on CinicalTrials.gov were selected on the basis of the following inclusion criteria: RCTs enrolling only US patients with multiple myeloma, with enrolment initiated between Jan 1, 2010, and June 30, 2020. Furthermore, the RCT had to include the assessment of active therapeutic interventions. Strategies comparing different conditioning regimens for transplantation, mobilisation strategies, or supportive care measures were excluded. The search was restricted to only RCTs, and all other studies (eg, observational, review articles, and case reports) were excluded. Our search strategy was not limited to any language. Trials that did not recruit any US patients with multiple myeloma were excluded, but a trial did not have to recruit exclusively in the USA to be included in our analysis. We chose to limit inclusion to US patients because the standard of care in the USA can substantially differ to elsewhere.[8]

For each control group, we evaluated the existing literature to see if data were already published showing superiority over the control regimen. A regimen was considered to be inferior in the front-line setting, relapsed or refractory setting, or maintenance in the non-transplantation setting if an RCT had previously shown an improved progression-free survival versus the control group that was used. In the setting of maintenance after a transplantation, an RCT would have had to have previously shown an improved overall survival versus the control group, for the control group to be determined inferior. Table 1 shows the studies that first showed superiority over the control groups used, as well as the time the results of these studies were first reported.

We examined four endpoints. First, the proportion of RCTs that began recruiting to a control group after an RCT had already shown inferiority of the control group. Second, the proportion of RCTs that continued to enrol to a control group after an RCT showed inferiority of the control group during enrolment. Third, we examined the median time an RCT continued enrolling after a new RCT emerged regarding inferiority of the control regimen after enrolment had already begun. Finally, we sought to determine the time an RCT had patients who were enrolled onto an inferior control group, and expressed this time as a percentage of the overall enrolment duration of the RCT.

## Data analysis

Two authors (GRM and KK) extracted and verified all data. Extracted data were tabulated by use of Microsoft Excel. We identified two characteristics of studies: disease phase (relapsed or refractory or front-line) and enrolment start and stop dates. We also collected information on the names of the authors, to assess for overlap between trials. The regimens used in the intervention groups and control groups of the studies were noted. Studies were also categorised on the basis of

| | Line of therapy | Primary funding source | Intervention arm | Control group | Start of enrolment | Were investigators part of the trial proving inferiority of control group? | Superior regimen to the control group at time of study initiation | Timepoint that the control regimen was shown to be inferior |
|---|---|---|---|---|---|---|---|---|
| NCT02516696 | Front-line | Pharmaceutical, collaborating with institution | Clarithromycin–lenalidomide–dexamethasone | Lenalidomide–dexamethasone | February, 2016 | No | Bortezomib–lenalidomide–dexamethasone | December, 2015 |
| NCT03110562 | One or more previous lines of treatment | Pharmaceutical | Bortezomib–selinexor–dexamethasone | Bortezomib–dexamethasone | May, 2017 | Yes | Carfilzomib–dexamethasone | December, 2015 |
| NCT02181413 | Maintenance | Pharmaceutical | Ixazomib | Placebo | July, 2014 | No | Lenalidomide | December, 2013 |
| NCT02312258 | Maintenance | Pharmaceutical | Ixazomib | Placebo | April, 2015 | Yes | Continuous lenalidomide | May, 2011 |
| NCT02755597 | One or more previous lines of treatment | Pharmaceutical | Venetoclax–bortezomib–dexamethasone | Bortezomib–dexamethasone | July, 2016 | Yes | Carfilzomib–dexamethasone | December, 2015 |
| NCT04162210* | Two or more previous lines of treatment | Pharmaceutical | Belantamab mafodotin | Pomalidomide–dexamethasone | April, 2020 | Not published | Elotozumab–pomalidomide–dexamethasone | June, 2018 |
| NCT03539744* | Two or more previous lines of treatment | Pharmaceutical | Venetoclax | Pomalidomide–dexamethasone | October, 2018 | Not published | Elotozumab–pomalidomide–dexamethasone | June, 2018 |

*Trial is still enrolling participants.

*Table 2:* **Randomised controlled trials that enrolled or are enrolling patients onto inferior control groups in which the control group was shown to be inferior before study initiation**

sponsorship (ie, whether the studies were industry-sponsored trials or co-operative group trials), by evaluating the funding source in the manuscript or by finding the publicly listed information. Because this study is a systematic review, and not a meta-analysis, no overall summary data were calculated.

## Results

We identified a total of 1231 records: 1171 records from PubMed, Embase, and Cochrane, and 60 from ClinicalTrials.gov. After excluding duplicates, trials in progress, abstracts, subset analyses of previous studies, non-randomised studies, or studies not recruiting patients with multiple myeloma, 98 studies were identified for further analysis from PubMed, Embase, and Cochrane, and 49 records were identified from ClinicalTrials.gov. After excluding duplicates between these search strategies and studies that did not enrol in the USA, 49 studies were identified for further analysis (figure).

Seven (14%) of 49 trials enrolled or are enrolling patients onto inferior control groups after an existing, superior regimen to the control had already been published or presented before the first patient was enrolled in these studies. These studies and their characteristics are listed in table 2. An additional nine (18%) of the 49 trials enrolled patients onto control groups after data emerged during the study enrolment period that showed inferiority of the control group. These studies and their characteristics are listed in table 3. The median time that newer data emerged regarding the inferiority of the control group from the onset of study enrolment was 13 months; however, this time ranged from 2 months (KEYNOTE-185,[13] NCT02579863) to 30 months (TOURMALINE-MM-2,[14] NCT01850524; IQR 8–29 months). The time that the nine trials enrolled onto an inferior control group as a percentage of the overall enrolment duration ranged from 90% (KEYNOTE-185) to less than 10% for other studies, such as the TOURMALINE-MM-2 study (table 3). The median time these nine trials continued enrolment after data emerged regarding inferiority of the control regimen was 8 months (IQR 5–21 months).

12 (75%) of the 16 trials (tables 2, 3) are published either as an abstract or a manuscript. For each of these 12 trials, we systematically assessed whether the authors of the study were also a part of the study that had previously shown the inferiority of the control group (table 1). Of these 12 RCTs, nine (75%) had at least one investigator involved in the RCT that had previously shown inferiority of the control group being used. We assessed the degree of overlap for each of these nine RCTs in which overlap was shown, by assessing what percent of the author list was shared, and whether the first or last author of the study had been a part of the study that previously showed inferiority. In seven (78%) of these nine studies, the first or last author had been a previous collaborator on a study that had shown inferiority (table 4).

## Discussion

Substantial improvements in the advances of care in myeloma have resulted in markedly improved overall survival over the past two decades,[1] owing to well designed RCTs of novel therapeutic agents. However, our results show a substantial minority of RCTs enrol patients on clearly inferior control groups.

Outside of a clinical trial, a fit, eligible patient in the USA is unlikely to be recommended a two-drug regimen

| | Line of therapy | Intervention group | Control group | Start of enrolment | Were investigators part of the trial that proved inferiority of control? | Superior regimen to the control group during the study | Timepoint that the control regimen was shown to be inferior | Timepoint that the trial stopped enrolling | Overall duration the trial enrolled for | Proportion of time trial enrolled onto inferior group, % |
|---|---|---|---|---|---|---|---|---|---|---|
| NCT01734928 | One or more previous lines of treatment | Pomalidomide–bortezomib–dexamethasone | Bortezomib–dexamethasone | January, 2013 | Yes | Carfilzomib–dexamethasone | May, 2015 | May, 2017 | 52 months | 48% |
| NCT02136134 | One or more previous lines of treatment | Daratumumab–bortezomib–dexamethasone | Bortezomib–dexamethasone | October, 2014 | Yes | Carfilzomib–dexamethasone | May, 2015 | January, 2016 | 15 months | 60% |
| NCT02076009 | One or more previous lines of treatment | Daratumumab–lenalidomide–dexamethasone | Lenalidomide–dexamethasone | May, 2014 | Yes | Carfilzomib–lenalidomide–dexamethasone | December, 2014 | July, 2015 | 14 months | 50% |
| NCT02252172 | Newly diagnosed | Daratumumab–lenalidomide–dexamethasone | Lenalidomide–dexamethasone | February, 2015 | Yes | Bortezomib–lenalidomide–dexamethasone | December, 2015 | January, 2017 | 23 months | 57% |
| NCT01850524 | Newly diagnosed | Ixazomib–lenalidomide–dexamethasone | Lenalidomide–dexamethasone | May, 2013 | Yes | Bortezomib–lenalidomide–dexamethasone | December, 2015 | February, 2016 | 33 months | 9% |
| NCT01564537 | One or more previous lines of treatment | Ixazomib–lenalidomide–dexamethasone | Lenalidomide–dexamethasone | August, 2012 | Yes | Carfilzomib–lenalidomide–dexamethasone | December, 2014 | August, 2015 | 36 months | 22% |
| NCT02579863 | Newly diagnosed | Lenalidomide–pembrolizumab–dexamethasone | Lenalidomide–dexamethasone | October, 2015 | No | Bortezomib–lenalidomide–dexamethasone | December, 2015 | June, 2017 | 20 months | 90% |
| NCT03151811 | Two or more previous lines of treatment | Melflufen–dexamethasone | Pomalidomide–dexamethasone | May, 2017 | Not published | Elotozumab–pomalidomide–dexamethasone | June, 2018 | September, 2020 | 40 months | 70% |
| NCT02726581 | Two or more previous lines of treatment | Nivolumab–pomalidomide–dexamethasone | Pomalidomide–dexamethasone | April, 2016 | Not published | Elotozumab–pomalidomide–dexamethasone | June, 2018 | September, 2018 | 29 months | 10% |

All trials were funded by pharmaceutical companies.

***Table 3:*** **Trials that continued to enroll patients onto inferior control groups in which the control group was shown to be inferior after study initiation**

| | Number of authors shared with previous study that showed inferiority (proportion of total authors on study, %) | Was first or last author part of the previous study that showed inferiority? |
|---|---|---|
| NCT03110562 | 4 (7%) | Yes |
| NCT02312258 | 4 (21%) | Yes |
| NCT02755597 | 2 (10%) | Yes |
| NCT01734928 | 4 (16%) | Yes |
| NCT02136134 | 5 (26%) | Yes |
| NCT02076009 | 4 (17%) | Yes |
| NCT02252172 | 1 (3%) | No |
| NCT01850524 | 1 (5%) | Yes |
| NCT01564537 | 3 (12%) | No |

***Table 4:*** **Overlap in authorship list and first or last author between published or presented studies with inferior control groups and a previous study that showed inferiority of the control group in question**

to treat myeloma in either the front-line setting or at first relapse.[1] Having clinical trials in which patients are systematically assigned to such control groups raises the question of whether these patients receive care that is inferior to the care they would receive had they not been participating in the study. Claims that the authors might not be aware of trials that show the inferiority of these regimens are weakened by the considerable overlap of authors in such trials.

We acknowledge that RCTs can face barriers to timely enrolment, and that the standard of care advances rapidly. It takes a substantial amount of time to make changes to an RCT;[15] however, continued enrolment onto substandard control groups for a long period of time represents a disservice to patients. As an example, the BOSTON study evaluating selinexor–bortezomib–dexamethasone versus bortezomib–dexamethasone for relapsed or refractory myeloma had bortezomib dexamethasone as a control group and began enrolling in May, 2017,[16] 2 years after the inferiority of bortezomib–dexamethasone had been shown even to another doublet in the relapsed or refractory setting.[9] As the BOSTON study was evaluating this regimen at first and further relapse, the trial had not established whether this regimen was superior to existing therapies administered at first relapse. During the enrolment period of the BOSTON trial, patients in the USA were routinely

administered a triplet at first relapse, and hence a triplet such as pomalidomide–bortezomib–dexamethasone or daratumumab–bortezomib–dexamethasone would have been a more appropriate control group. An appropriate control group for a doublet versus triplet in this setting would be carfilzomib–dexamethasone, versus the intervention of carfilzomib–selinexor–dexamethasone. This would have avoided repeating previously used therapies in the control group, as was done in the BOSTON trial.[16]

The strengths of our study are that we examined a cohort of studies in a single disease type by use of a prespecified definition of the inferior control group in a systematic manner, and, to our knowledge, we are the first to do so.

However, there are limitations. Our study uses time of trial enrolment, rather than trial conception, because the time of trial conception was not publicly recorded; considerable delays in this process can occur. We used the date of reporting of trial results as the timepoint at which superiority of a regimen was proven. Although this date often precedes formal US Food and Drug Administration (FDA) approval, we felt this was justified because myeloma treatments are rapidly adopted long before formal FDA approval. As an example, lenalidomide maintenance was used widely before the FDA approved its use,[17] and triplet induction was considered standard long before the SWOG 0777 trial[18] results were presented. As early as 2010, randomised trials were recruiting patients with bortezomib–lenalidomide–dexamethasone as standard induction therapy, 5 years before SWOG 0777 resulted.[18] We recognise that SWOG 0777 evaluated patients who were eligible for delayed transplantation, and hence its use as a criteria to establish superiority might not be fully applicable to studies evaluating transplantation-ineligible populations.[3] Manufacturers are aware that drugs can be prescribed for subsequent uses on the basis of trial data, and guidelines can endorse drugs before supplementary marketing authorisations. Notably, empirical analyses show a consistent delay from publication time to approval for subsequent approvals versus first approvals, which might reflect this incentive.[19]

We used progression-free survival as a criterion for evaluating a study, which is an imperfect surrogate for overall survival,[20] but because the trials themselves used progression-free survival as the primary endpoint, we believe our method was justified. However, we did use overall survival as a criterion for maintenance in the post-transplantation setting. We limited our study to focus on RCTs in the USA, and thus our study cannot be used to describe enrolment practices where the prevailing standard of care might differ substantially from that of the USA. Thus, the fixed criteria we used to define inferiority might not be applicable outside of the USA.[8] A control group can also be inferior by virtue of simply reusing treatments that patients were previously exposed to, and hence our methodology very likely underestimates the percentage of RCTs with inferior control groups in the USA. We also recognise that, for multiply relapsed multiple myeloma, not all patients have received drugs in the same sequence, and it might be difficult to design an ideal control group. This issue can be alleviated by having increased flexibility with regard to the control group, by allowing repeats of previously used regimens or unused regimens, or both, such as alkylator combinations, and comparing these regimens to a new agent. Given the poor prognosis of multiply relapsed multiple myeloma, such a trial would be expected to provide an overall survival result in a short period of time.[21]

Unfortunately, enrolment of trial participants onto inferior control groups persists. Numerous clinical trials (eg, NCT04162210 and NCT03539744) are currently enrolling patients onto a pomalidomide–dexamethasone control group long after its inferiority has been shown in multiple RCTs.[2,12,22]

We recognise that the use of a triplet or a more effective treatment regimen as a control group could take longer to produce results, given that the control arm would be expected to have better outcomes, hence resulting in a longer trial duration needed to show a difference between the intervention and control arm. However, the findings of such a study will be more applicable to real-world patients, and the patients enrolled onto the control group of the trial would be treated with similar therapies to those they would be receiving off-protocol. The accelerated drug approval pathway in the USA might be preferentially used while the results of confirmatory randomised trials are pending, because this approach provides access to the drug in question. This was the case in the approvals of selinexor and belantamab mafodotin.[23,24]

Our findings show a pattern of inferior control groups in a substantial minority of multiple myeloma RCTs. However, these findings are not unique to multiple myeloma. In an analysis of all RCTs that resulted in FDA approval of new cancer drugs between January, 2013 and July, 2018, 16 (17%) of 95 drugs were tested against therapy that was inferior to the standard of care. The use of chlorambucil repeatedly as a control group in chronic lymphocytic leukaemia RCTs,[25,26] sunitinib in advanced renal cell cancer,[27] and crizotinib for ALK-positive lung cancer[28] are important examples in this regard. By use of publicly available data on trial enrolment start dates, and reporting of trial results, we show that it is often well known that the control group is inferior before trial enrolment initiation.

Our findings show that most multiple myeloma RCTs in the USA enrol patients onto appropriate control groups in well designed trials. However, 14% of myeloma RCTs have had substandard control groups known to be inferior at the time of initiation of the trial. An additional 18% have continued enrolment onto inferior groups after newer data emerges, in some cases even if the data results within 2 months of initiation of study enrolment.[13] In most cases, the investigators for these trials were the same investigators who had, in previous studies, proven

the control group to be inferior. This finding highlights the need for stronger oversight from institutional review boards on the quality of control groups in RCTs, and increased flexibility and adaptability of control groups on RCTs.

#### Contributors

GRM, AMG, and VP conceived the research idea. GRM and KK did the literature search and finalised the list of studies. GRM and KK verified the source data. GRM did all statistical calculations. GRM wrote the first draft of the Review. BM, DS, A-OA, AMG, and VP all provided essential input on the Review and deliberated on the methodology of the project. All authors approved the final version of the manuscript. All authors had access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Declaration of interests

VP reports royalties from Johns Hopkins Press, Medscape, MedPage, consulting for UnitedHealthcare, and speaker's fees for Evicore. VP has a plenary session podcast that is supported by Patreon. VP is also funded to study low-value drugs via a grant from Arnold Ventures. AMG reports consulting for Seattle Genetics and EUSA Pharma. DS reports consulting for Janssen, SkylinDx, GlaxoSmithKline, Legend Biotech, Amgen, and Celgene. All other authors declare no competing interests.

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