PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Influence of Government Price Regulation and Deregulation on the Price of Antineoplastic Medications in China: A Controlled Interrupted Time Series Study
AUTHORS	Guan, Xiaodong; Wushouer, Haishaerjiang; Yang, Mingchun; Han, Sheng; Shi, Luwen; Ross-Degnan, Dennis; Wagner, Anita

VERSION 1 – REVIEW

REVIEWER	Jing Wu Tianjin University, China
REVIEW RETURNED	10-Jul-2019

GENERAL COMMENTS	Three major concerns should be further addressed for the study design. First, there are a bunch of polices that influence the drug price level in china. Among them, in my opinion, provincial bidding and procurement policy have stronger impacts on the price level than the maximum retail prices implemented by NDRC. The authors want to explore the effect of implementing or not maximum retail prices but without controlling the bidding policy. Although maximum retail prices policy was cancelled in 2015, but the provincial bidding and procurement policy still exist. So, the authored cannot conclude that “Neither government price regulation nor deregulation significantly impacted the ……” Second, the author should provide more information about the hospital samples and drug samples. Such as, the percent of tertiary hospital, secondary hospital and primary health facility. And also, how the drugs could be selected or identified? And their representative for different type of cancers. Third, for the new antineoplastic drugs that are not included in the national reimbursement drug list, most of them have patient access program (like buy 3 get 3 free). So, the listed price is not the real price. The dispense tunnel for some of these new drugs are the pharmacies with differential price compared with hospital price. These limitations should fully discussed in the paper.

REVIEWER	Dzintars Gotham Independent, UK I serve as a consultant for the World Health Organization, Treatment Action Group, and the Medicines Patent Pool.
REVIEW RETURNED	30-Jul-2019

GENERAL COMMENTS	Thank you for the opportunity to review this interesting manuscript. I commend the authors on the work. The analysis seems timely and a potentially important addition to the literature. I have concerns that would need to be addressed before acceptance. **Details on the price control policy** More detail is needed on how the maximum retail prices were set, i.e. what formula was used. MRP can describe a range of different policies. A range of formulae can be used for MRP setting – some will be more 'aggressive' and some will be less. Some MRPs, for example, are freely set by the drug manufacturer and serve chiefly to limit what the retailer may charge. Without knowing how the MRP was set by the government, it is hard to comment on the appropriateness of the Discussion section, and potentially also the Methods section. I would suggest the paper needs to be re-reviewed once the MRP formula is explained, chiefly for this reason. On superficial search, I see that in some cases Chinese MRP were set using a cost-plus calculation (cost of production declared by manufacturer plus a defined allowable margin) (e.g. https://www.healthaffairs.org/doi/full/10.1377/hlthaff.27.4.1042 and WHO Guideline on Pharmaceutical Pricing Policies 2015). WHO Guideline on Pharmaceutical Pricing Policies 2015 notes regarding China that "[Maximum Retail] Prices are set on the basis of declared costs submitted by manufacturers and are calculated as factory prices with duty/taxes and retail distribution profits incorporated. The prices submitted by manufacturers are not checked for accuracy." It is not clear whether this is necessarily the case for these 30 oncology drugs. This should be clarified in the text. **Characteristics of the included drugs** Similar to knowing how the MRP is set, it would be key to know how these 30 drugs were chosen by the government for price control.

	In addition, it is important to analyse the characteristics of the 'sample' (price-regulated drugs) and control groups. The authors should mention, for example: 1. whether all/most/none of these drugs are under patent protection in China 2. whether all/most/none are single-supplier 3. relatively niche use versus widely used 4. all in-patient or mix of in- and out-patient (looks like the answer is a mix). 5. how many are biologics 6. are any of the drugs used predominantly in China and neighbouring countries, and not widely used in other parts of the world e.g. the West? 7. Are the price-regulated drugs relatively 'important' (however this may be assessed)? (if some of these are not possible, e.g. patent status, this should be highlighted in Limitations). Especially the question of whether these drugs are single-supplier and/or originator, and whether this status changed during the period, is extremely key. How was the 'control' (unregulated) group chosen by the authors? If simply based on data availability, should be stated. Some of these medicines are likely (partial) therapeutic alternatives – e.g. there is no proven difference in overall survival, to my knowledge, for nilotinib over high-dose imatinib in CML. Perhaps some of the platinum-based compounds or anthracyclines are also (partially) alternatives to on another. This is of course especially important if (partially) substitutable drugs span both regulated and unregulated groups. It is surprising to see drugs like erlotinib, gefitinib, rituximab, trastuzumab, bortezomib, nilotinib, sorafenib, sunitinib, in the price-unregulated group, as these are medicines for which high, unaffordable prices have been widely described. Why were they not subject to price regulation? Page 9 line 54 asserts the selected medicines are likely representative of all price-regulated products. At least a sentence of explanation why the authors believe so should be added (this may

	also link to the explanation, which I've asked for above, on how the government chooses with drugs to price-regulate). **Explanation of statistical measures** Laspeyres index – if I have understood correctly from reading about this metric – an inherent limitation of Laspeyres index is that price increases may be underestimated, as the base volume weighting is used, and patients/buyers may switch away from higher-priced medicines. If the authors agree, this limitation should be noted. If data for procurement volumes for individual drugs were reported (e.g. in the appendix) this would also help assess the impact of this limitation. Additionally, the authors have not explained the point of Laspeyres index weighting the prices by the volume purchased in period 0. I.e. if a less procured drug had a large increase/decrease in price the effect of this on Lp would be diminished, compared to using a simple mean price index, for example. I agree that in the context of the study use of Lp strengthens the analysis compared to e.g. a simple price index – but then this should be explained. An intuitive interpretation for Lp should be provided. That is, what does a 10% decrease in Lp mean? Does it mean a 10% decrease in the price of the basket of medicines? In addition an intuitive interpretation of beta should be given, so that the reader can interpret whether or not, for example, an Lp decrease of beta = -0.013 is meaningful, or not. In ITS analysis, a key question is whether the policy intervention was expected (by the price-setters, in this case) or not. Please address. **Discussion and conclusions** The paper, broadly, will contribute to a body of literature on price controls for high-cost medicines in oncology. The Discussion should therefore analyse, at least briefly, whether the group of analysed medicines can be considered generalisable to a) oncology b) high-cost medicines c) originator medicines (and/or other groups). This

	of course will be influenced by how the government chose these 30 drugs to price-control. The authors find that the price of price-unregulated medicines decreased 'significantly' after deregulation. Though I do not doubt that the statically analysis was done correctly, looking at Figure 2, it is very difficult to visually convince myself that there was a price decrease for price the price-unregulated group. Some readers, without careful reading, may assume this (arguably surprising) finding is of a greater magnitude than it is. It would be good to note the absolute decrease in an intuitive format (e.g. percentage decrease rather than beta), and add discussion of whether this decrease is marginal/meaningful. Similarly, if the authors believe that it is marginal/not meaningful (as it seems from the Figure), this should even be mentioned in the Abstract, as without mentioning the implication is that there was a substantial decrease. Concluding that 'price regulation' has not been sufficient is greatly overgeneralises the findings. 'Price regulation' could include reference pricing, cost-plus pricing, supply chain mark-up controls, limits based on average pricing across manufacturers (such as the Federal Upper Limit for Medicaid in the US). At most, the conclusion would be that 'A price control policy based on XXXXX has not effectively lowered spending for selected oncology medicines'. (XXXX substitutes for the method of calculating MRP, whatever it is.) The Discussion should in general substantially discuss the specific price regulation policy – i.e. method calculating MRP. If the finding is that the MRP was insufficiently 'aggressive' to lower prices substantially, then why was it so? Could a 'more aggressive' MRP potentially work better, based on finding? A few more sentences setting the findings in context would be interesting – now that the Chinese government has reverted from the price-regulation policy, is a new one in the works? Or a different strategy for controlling oncology medicines expenditures? Page 9 line 10 – 'product quality' – what does this mean? Pharmacopoeial standards, purity? Or efficacy-based metrics? Discussion page 9 line 35 – 'prescribers may have preferred more expensive medications in the unregulated group' – the authors should be able to comment on whether or not this was seen in volume data for individual medicines.

	Page 9 line 36 – please clarify/rephrase 'volume and medication mix' – not sure what this means. Page 9 line 44 – 'zero mark-up policy' should be specified – what is this policy, zero mark up by manufacturer (I assume not), by retailer, hospital? I assume hospital – if so, does that mean hospitals now keep zero CNY from drug procurement? If so please state. Page 3, lines 48-57. I suggest this piece (from "However," to "regulation.") should be moved to Discussion. I see the dilemma of whether to have it in introduction or discussion, but it would be much more useful to the reader in the Discussion. Do the authors believe that this secondary level of price limits (hospital spending limit on insurance-reimbursed medications) could in fact explain the observed limited effect of the national price regulation policy? To the reader at least, this seems like a likely hypothesis and should be explored in the Discussion. Was the hospital-level price-regulation simply an overriding effect, and the national policy not 'aggressive' enough to 'overpower' the hospital level regulation? **Small wording points** 1. I was confused at points in the text with the group names 'price-regulated' and 'price-unregulated', as all 52 drugs are price-unregulated after the policy was reversed. I would prefer using the terms 'control' and 'intervention' (which indeed the authors use in first paragraph of Results), or if not, then adding a sentence in Methods along the lines of 'We use the term 'price-regulated medications' for the medicines that were under price regulation, although they are no longer price regulated'. 2. First line in Conclusion – as written implies price-unregulated products were not antineoplastic. Rewrite first sentence. 3. Page 8 line 24 and elsewhere – -1.57 – is there an intuitive way to explain what this number means? 4. Table 1 is very useful, but please clarify – does the situation shown in the Table represent a time before, during, or after the 'intervention' period?

REVIEWER	Marcell Csanádi Syreon Research Institute, Hungary
REVIEW RETURNED	05-Aug-2019

GENERAL COMMENTS	In general, I think this is a good piece of paper. I have however, two major issues as they are also described in the detailed

	comments below: 1) Authors do not differentiate between drugs (i.e. those under patent vs. those with expired patent) arguably the effect of any price regulation is highly dependent on the patent status of the drugs. 2) Discussing the volume does not make sense when the effect of price regulation is considered volume I believe should reflect on the patient needs and not on the introduced price measures Detailed comments: Abstract: 1) Why are the periods included to the results? This would be more appropriate to the methods. 2) Relative price should be explained. 3) It is a little confusing that in the results only the price is mentioned while in the conclusion the spending and the volume is mentioned. What where the specific findings on the spending and value? Why there is no conclusion based on the price? Introduction: 1) The second paragraph is very confusing. It oversimplifies the potential effects of regulation. It contrasts the government regulation to market competition in general to pharmaceuticals. I believe this can be misleading. What is market competition for original products when the patent is respected and no competitor can be present on the market? I would recommend to specify what types of drugs are considered here and more specifically I would include the literature that is strongly related to the research topic. 2) In the second paragraph when the favourable effects of market competition is stated the authors only refer to one publication from China. I would recommend to look for further, more theoretical work as well for instance those by Patricia M. Danzon. 3) In the third paragraph, again, it is not clear what types of pharmaceuticals are discussed. It is mentioned that central bidding and tendering was introduced, but was it only for generics and biosimilars? Or was it extended to originals from the same therapeutic groups? These are essential issues to describe to understand the introduced policies in China. 4) I do not see why it Table 1 that important. It could be better explained in the text. Again, it is quite oversimplification to call price-regulated medications and price-unregulated medications. Are these original drugs, generic drugs, biosimilars or what? 5) In the introduction please elaborate more on the specific regulation that is related to the investigated antineoplastic medications. I feel that the policies introduced in China are not detailed enough and not targeted well for the investigated group of medications. Methods: 1) Please explain whether all investigated drugs were under patent for the entire period. Same for the control group. 2) Please explain whether there was any further difference between the investigated and the control groups. Results: 1) Why is volume important here? Were the regulations targeted volume? Is the increase in the volume is good or bad? It should actually reflect on the needs so I am not sure this should be a scope of this study. It is a completely different issue. Conclusion: 1) Again, why is the purchased volume is mentioned here? Was it an intention to decrease the purchased volume by having a price regulation? This is I think a big mistake to include and to expect that hospitals will purchase less when the government is introduce

	a price regulation. I suggest to eradicate this issue from the entire paper.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1' Comments	Authors' Reply
1. There are a bunch of polices that influence the drug price level in China. Among them, provincial bidding and procurement policy have stronger impacts on the price level than the maximum retail prices implemented by NDRC. The authors explore the effect of implementing or not maximum retail prices but without controlling the bidding policy. So, the authored cannot conclude that "Neither government price regulation nor deregulation significantly impacted the ……"	Thank you for your comment. We agree that there are many policies that influence the drug prices in China, such as provincial bidding and procurement policies and insurance reimbursement policies. We provide a detailed introduction of these policies in the *Introduction* and *Discussion*. In this study, medications in the intervention group and in the control group were influenced by provincial bidding and procurement policies. While medications in the control group were not influenced by price regulation policies, medications in the intervention group were regulated and then deregulated. As we hypothesized, compared to price-unregulated cancer medications, the relative price of price-regulated medications decreased significantly, controlling for other policies, including bidding and procurement policies that were in effect during the study time frame for both intervention and control groups. The strength of the controlled interrupted time series (ITS) design we used lies in the fact that it controls for other factors that could influence the outcomes. We therefore believe that the strongest possible quasi-experimental study design we used, ITS with control, allows us to draw conclusions on the impact of governments of price regulation and deregulation.
2. The author should provide more information about the hospital samples and drug samples. Such as, the percent of tertiary hospital, secondary hospital and primary health facility. And also, how the drugs could be selected or identified? And their representative for different type of cancers.	Thank you for your suggestions. We added more information about the sample hospitals and drug selection in the *Methods* section and the *Supplement*. For example, we now note in the *Methods* section that that the data came from procurement records of "699 public hospitals, including 476 tertiary

	hospitals, 217 secondary hospitals and 6 primary health facilities in 28 provinces". Regarding the selection of the intervention and control group medicines, we provide detailed information in supplement materials.
3. For the new antineoplastic drugs that are not included in the national reimbursement drug list, most of them have patient access program (like buy 3 get 3 free). So, the listed price is not the real price. The dispense tunnel for some of these new drugs are the pharmacies with differential price compared with hospital price. These limitations should fully discussed in the paper.	Thank you for your comment. In this study, we used public hospital medication purchasing records on volumes and spending for procured products. Medicine sales in medical institutions account for about 70% medicine sales of the market[1]. While there may have been additional amounts provided through patient access programs directly to patients or their providers outside of hospital procurement, we believe that the hospital procurement data we used in this study were representative of majority of the market. We now also mention the point you raise in the *Limitations* section, saying "some new antineoplastic drugs not included in the NRDL and thus not price-regulated may be made available by manufacturers' access programs (like buy 3 get 3 free) for individual patients. These products would not be part of our price, volume, or spending analyses because they would be transacted directly between individual physicians, their patients, and the manufacturer (or an intermediary)."
Reviewer 2's Comments	**Authors' Reply**
1.Details on the price control policy：More detail is needed on how the maximum retail prices were set, i.e. what formula was used.	Thank you for your suggestions. We have provided more details on how the maximum retail prices were set in *Introduction*. "The maximum retail price was set, using a cost-plus calculation, according to generic name. Rules for price difference and price ratio of medicines were applied to convert a generic price into different prices for medicines with different dosage forms or specifications. From 1998 to 2015, the NDRC used price caps to reduce drug prices for 31 times, involving 1029 medicines (not

[1] Quan W , Yu-Hui Z , Xiu-Feng W . Results and Analysis of China National Health Accounts in 2013[J]. Chinese Health Economics, 2015.

	including traditional Chinese drugs) in terms of generic name.”
2.Characteristics of the included drugs：(A) It would be key to know how these 30 drugs were chosen by the government for price control.	Thank you for your comment. (A) The motivation for the Chinese government to implement price regulations was to limit pharmaceutical expenditures by the national medical insurance fund. All medicines listed in the National Reimbursement Drug List (NRDL) would receive price caps. According to the guidelines[2], medications listed in the NRDL were selected based on expert review according to their clinical value and cost-effectiveness. However, no detailed information about the process of NRDL medication selection was released to the public. For this reason, we unfortunately cannot provide more information on the process that led to inclusion of medicines in the NRDL or selection of medicines for price regulation.
(B) Why were medicines for which high, unaffordable prices have been widely described (like erlotinib, gefitinib, rituximab, trastuzumab) not subject to price regulation?	(B) New medicines with very high prices (like erlotinib, gefitinib, rituximab, trastuzumab) were so expensive that even the national medical insurance fund could not afford to include these medicines in the NRDL at that time. (Until September of 2017, after new policy approaches were implemented including National Drug Price Negotiations[3] in place of price regulation, these expensive medicines were subject to price negotiations and are now listed in the NRDL.)
(C) In addition, it is important to analyse the characteristics of the ‘sample’ (price-regulated drugs) and control groups. 1. whether all/most/none of these drugs are under patent protection in China 2. whether all/most/none are single-supplier 3. relatively niche use versus widely used 4. all in-patient or mix of in- and out-patient (looks like the answer is a mix). 5. how many are biologics	(C) We have provided more information about our drug samples in the *Supplement,* specifically we have now added information on 1,2,5. Unfortunately, for lack of public data, we are unable to provide information on 3,4,6,7. We have highlighted this fact in the *Limitations*.

[2] Wenbin Liu, Lizheng Shi, Monika Sawhney, Xiaoli Gu & Yingyao Chen.(2019). Evidence for the effectiveness of anti-hypertensive medicines included on the Chinese National Reimbursement Drug List.BMC Health Services Researchvolume 19, Article number: 112 .

[3] Hong, L. , Liu, G. G. , Jing, W. , Jiu-Hong, W. , Chao-Hui, D. , & Shan-Lian, H. . (2018). Recent pricing negotiations on innovative medicines pilot in china: experiences, implications, and suggestions. Value in Health Regional Issues, 15, 133-137.

6. are any of the drugs used predominantly in China and neighbouring countries, and not widely used in other parts of the world e.g. the West? 7. Are the price-regulated drugs relatively 'important' (however this may be assessed)?	
(D) How was the 'control' (unregulated) group chosen by the authors?	(D) We have provided more information about our drug selection in the *Methods*, including "We conducted a search of all antineoplastic medications in the database by ATC code (L01). We excluded those antineoplastic medications with missing data. Antineoplastic medications regulated in October 2012 were included as intervention group. Antineoplastic medications that were not listed in the NDRL and thus not subject to price caps during the study period were included as control group. We extracted procurement data for 52 antineoplastic medications (30 medications with retail price caps from October 2012 to June 2015 and 22 medications without any price caps from the year before to the year after the price poly changes, between October 2011 and June 2016)".
(E) Page 9 line 54 asserts the selected medicines are likely representative of all price-regulated products. At least a sentence of explanation why the authors believe so should be added	(E) We agreed with your comments, and finally deleted the expression 'the 30 price-regulated antineoplastic products studied are likely representative of all such products' in the limitation part.
3. Explanation of statistical measures： (A) The inherent limitation of Laspeyres index that price increases may be underestimated should be noted. If data for procurement volumes for individual drugs were reported this would also help assess the impact of this limitation.	Thank you for your suggestions. Laspeyres index: $$P_L = \frac{\Sigma(p_{c,t_n}) * (q_{c,t_0})}{\Sigma(p_{c,t_0}) * (q_{c,t_0})}$$ (A) Using Laspeyres index, price increases may be overstated while price decreases may be underestimated. [4] We agree that inherent limitation of Laspeyres index should be mentioned and we have added to the *Limitations* section that "Second, the inherent limitation of Laspeyres index may lead to underestimating the price decreases. However, the impact of this limitation was limited, since price elasticity of demand for medicines is relatively

[4] https://www.britannica.com/topic/Laspeyres-index

	small.". Due to the data owner's (CMEI) requirements for data confidentiality, we cannot provide price and volume data for individual drugs.
(B) The authors have not explained the point of Laspeyres index weighting the prices by the volume purchased in period 0.	(B) We have added an explanation in the *Methods* saying "the Lp is an index formula used in price statistics for measuring the price development over time of baskets of goods and services consumed in the base period 0 by weighting prices by the volume purchased in period 0."
(C) An intuitive interpretation for Lp should be provided. In addition an intuitive interpretation of beta should be given, so that the reader can interpret whether or not, for example, an Lp decrease of beta = -0.013 is meaningful, or not.	(C) We have added an interpretation for Lp in the *Methods*. As for beta, we have provided an interpretation in the *Statistical Analysis* section, saying "We used β_0 to estimate the baseline purchasing volume and spending; β_1 estimated the pre-regulation trend; β_2 estimated the change in level after the regulation policy; β_3 estimated the change in trend after the regulation policy; β_4 estimated the change in level after the deregulation policy; β_5 estimated the change in trend after the deregulation policy. Key coefficients were β_2, β_3, β_4 and β_5."
(D) In ITS analysis, a key question is whether the policy intervention was expected (by the price setters, in this case) or not. Please address.	(D) We have addressed it in *Methods,* saying "The first breakpoint, October 2012, served to assess the effects of the government retail price regulation that was announced on September 14th, 2012 and came into effect on October 8th, 2012 on the Laspeyeres price (Lp) index, monthly volumes of and spending on the study medications. ".
4. Discussion and conclusions: (A) The Discussion should analyse whether the group of analysed medicines can be considered generalisable to a) oncology b) high-cost medicines c) originator medicines (and/or other groups).	Thank you for your suggestions. (A) We have added this analysis in *Discussion*, saying "Our results indicate that, as expected, a price-cap policy was effective in decreasing the prices of selected antineoplastic medications. Most medicines in the intervention group were the products with intense market competition, possibly facilitating implementation of price caps. This might not be the case for originator products with only one supplier in the market."
(B) It is difficult to notice that the price of price-unregulated medicines decreased 'significantly' after deregulation from Figure 2. It would be good to note the absolute decrease in an intuitive format , and add discussion of whether this decrease is marginal/meaningful. Similarly, if the authors believe that it is marginal/not	(B) We noticed the point you questioned. Actually, China's government really endeavored many ways to control the medicine's price, and we also add related details in the discussion part. We don't think the decrease in the price of price-unregulated medicines is meaningful, so we used the 'difference group' to illustrate the price in the control group relatively decreased more. We have

meaningful (as it seems from the Figure), this should even be mentioned in the Abstract, as without mentioning the implication is that there was a substantial decrease.	revised the *Abstract* as you suggested.
(C) Concluding that 'price regulation' has not been sufficient is greatly overgeneralises the findings. At most, the conclusion would be that 'A price control policy based on XXXXX has not effectively lowered spending for selected oncology medicines'.	(C) We strongly agree with this and we have revised the *Conclusion* as suggested. "Unlike unregulated products, the prices of regulated medications decreased after setting price caps, but did not increase after deregulation. Neither of these policies affected volumes purchased or hospital spending on all antineoplastic medications. To control the rapid growth of oncology medication expenditures, more effective measures than setting price caps for selected (typically older) antineoplastic medications need to be taken."
(D) The Discussion should in general substantially discuss the specific price regulation policy –i.e. method calculating MRP.	(D) We have made a corresponding revision in *Discussion. "*In this study, we investigated the effects of maximum retail price regulation and subsequent deregulation for groups of antineoplastic medications in China. We found that after setting maximum retail prices, the relative price……"
5. Small wording points： (A) Page 9 line 10 – 'product quality'—Pharmacopoeial standards, purity? Or efficacy-based metrics?	We thank you for these detailed suggestions. (A) Both pharmacopoeial standards and efficacy-based metrics are taken into consideration. We have added this information.
(B) Discussion page 9 line 35 – 'prescribers may have preferred more expensive medications in the unregulated group'—the authors should be able to comment on whether or not this was seen in volume data for individual medicines	(B) We are unable to comment on this, because we are not able to identify suitable medication pairs that are substitutable drugs and span both regulated and unregulated groups in our samples to answer this question.
(C) Page 9 line 36 – please clarify/rephrase 'volume and medication mix'	(C) We are sorry for our carelessness. 'Medication mix' should be 'medication utilization mix'.
(D) Page 9 line 44 – 'zero mark-up policy' should be specified	(D) We have specified it, saying "the zero mark-up policy that canceled the mark-up by public health facilities"
(E) Page 3, lines 48-57. The piece (from "However," to "regulation.") should be moved to Discussion.	(E) We agree and have made the corresponding revision in Discussion.

(F) The group names 'price-regulated' and'price-unregulated' are confusing, as all 52 drugs are price-unregulated after the policy was reversed.	(F) We agree and have made the corresponding revision, saying "We use the term 'price-regulated medications' for the medicines that were under price regulation during the intervention period; these products are no longer price regulated."
(G) First line in Conclusion– as written implies price-unregulated products were not antineoplastic.	(G) We have made a corresponding revision.
(H) Page 8 line 24 and elsewhere – -1.57 is there an intuitive way to explain what this number means?	(H) We have responded to a similar comment in Explanation of statistical measures (C)
(I) Clarify that the situation shown in the Table 1 represent a time before, during, or after the 'intervention' period.	(I) We follow the Reviewer 3's comments (Introduction 4) and move this part of illustration to *Discussion* part and delete the table.
Reviewer 3's Comments	**Authors' Reply**
1. Authors do not differentiate between drugs (i.e. those under patent vs. those with expired patent) □ arguably the effect of any price regulation is highly dependent on the patent status of the drugs.	Thank you for your comments. We have provided additional information about selected drugs in the *Supplement* and made corresponding revisions in the manuscript.
2. Discussing the volume does not make sense when the effect of price regulation is considered.	Thanks for your comments. Price is the primary outcome in our study. But we are also curious about whether price control promoted access (using the proxy measure of increased volume purchased) or not and whether price control did curb increasing expenditures or not. We use volume and spending as secondary outcomes. Our data showed that price caps had no significant impact on volume and spending.
Detailed comments： **Abstract:** 1) The periods should be included to the methods. 2) Relative price should be explained. 3) It is a little confusing that in the results only the price is mentioned while in the conclusion the spending and the volume is mentioned. What where the specific findings on the	Thank you for your detailed comments. **Abstract:** 1) 2) 3) We thank you for highlighting these inconsistencies and have made corresponding revisions in the *Abstract.*

spending and value? Why there is no conclusion based on the price?	
Introduction: 1) The second paragraph oversimplifies the potential effects of regulation. It contrasts the government regulation to market competition in general to pharmaceuticals. I would recommend to specify what types of drugs are considered here and more specifically I would include the literature that is strongly related to the research topic.	Thank you for your suggestions. **Introduction:** 1) We have focused on the direct price-cap government regulation and its effect.
2) In the second paragraph when the favourable effects of market competition is stated the authors only refer to one publication from China.	2) We reconducted our literature search and now include more references on price regulation.
3) In the third paragraph, again, it is not clear what types of pharmaceuticals are discussed. It is mentioned that central bidding and tendering was introduced, but was it only for generics and biosimilars? Or was it extended to originals from the same therapeutic groups? These are essential issues to describe to understand the introduced policies in China.	3) We now better explain the policy environment in China. The central bidding and tendering policies apply to all medications, the same to control and regulated group. We have made corresponding revisions in the third paragraph of the introduction.
4) I do not see why it Table 1 that important. It could be better explained in the text.	4) Thanks for your suggestion, and we keep the explanations in the text and delete the table.
5) Again, it is quite oversimplification to call price-regulated medications and price-unregulated medications. Are these original drugs, generic drugs, biosimilars or what?	5) We have clarified this in *Methods* and provided more detailed information about selected medications in *Supplement.*
6) In the introduction please elaborate more on the specific regulation that is related to the investigated antineoplastic medications.	6) We have provided more information in *introduction.*
Methods: 1) Please explain whether all investigated drugs were under patent for the entire period. Same for the control group.	**Methods:** 1) 2) We have provided additional information about selected drugs in *Methods* and *Supplement.*

2) Please explain whether there was any further difference between the investigated and the control groups.	
Results: 1) Why is volume important here? Were the regulations targeted volume? Is the increase in the volume is good or bad? It should actually reflect on the needs so I am not sure this should be a scope of this study. It is a completely different issue.	**Results:** 1) Thanks for your comments. Price change is the primary outcome in our study. But we are also curious about whether price control promoted access (e.g., increased volumes procured) or not and whether price control could curb increasing expenditures or not. Therefore, we assessed volume and spending changes as secondary outcomes. Our results showed that price caps had no significant impact on volume or spending. Using these data, we cannot say whether procured volumes of the medications in question are either sufficient to treat patients for whom they are indicated or appropriately used. We mention this point in the limitations.
Conclusion: 1) Again, why is the purchased volume is mentioned here? Was it an intention to decrease the purchased volume by having a price regulation? This is I think a big mistake to include and to expect that hospitals will purchase less when the government is introduce a price regulation. I suggest to eradicate this issue from the entire paper.	**Conclusion:** 1) Thanks for your comments. We explain our thinking in the 2. Besides, we hypothesized that if prices were lower following the price caps, and were higher following lifting of the price caps, hospitals which operate on more constant budgets could adjust their purchasing by procuring more and less, respectively, of the cancer treatments.

VERSION 2 – REVIEW

REVIEWER	Marcell Csanádi Syreon Research Institute
REVIEW RETURNED	23-Oct-2019

GENERAL COMMENTS	Thank you for revising the paper. The changes reflect appropriately to the comments. One further recommendation would be to conduct sub-group analyses for the originator only / generic only / originator and generic categories. If this is possible (i.e. sufficient number of observation is available from the intervention group and from the control group) it would be nice to see whether the price regulations had any effect on the generics, which is more likely due to the competition among manufacturers.

	Another minor issue is that the title of the two tables in the supplementary material is the same. Supplement 1A and Supplement 1B has identical names. I suspect that one of them should include control group instead of intervention group.

VERSION 2 – AUTHOR RESPONSE

Reviewer 3's Comments	Authors' Reply
Thank you for revising the paper. The change s reflect appropriately to the comments.	We thank the reviewer for acknowledging our responsiveness to previous comments.
1. One further recommendation would be to conduct sub-group analyses for the originator only / generic only / originator and generic categories. If this is possible (i.e. sufficient number of observation is available from the intervention group and from the control group) it would be nice to see whether the price regulations had any effect on the generics, which is more likely due to the competition among manufacturers.	Thank you for your comment. For our study, we extracted from the CMEI data set procurement data for 52 antineoplastic medications: • 30 medications in the intervention group (3 drugs with only originator, 13 with only generic and 14 ones with both products), and • 22 medications in the control group (7 drugs with only originator, 10 with only generic and 5 ones with both products). We agree that it would be good to conduct sub-group analyses by generic/brand product type. However, since we only have aggregated data (across the intervention and control group medications), it is impossible to for us to separate individual medications by product type. We have added this point to the limitations section and will seek to fill this gap in a future study based on different data.
2. Another minor issue is that the title of the two tables in the supplementary material is the same. Supplement 1A and Supplement 1B has identical names. I suspect that one of them should include control group instead of intervention group.	Thank you for catching this oversight. We have corrected this mistake, saying "Supplement 1B. Antineoplastic medications samples of the control group"
	We proofread the paper one more time and hope it is easily readable now.