INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Unsupported Price Increase Assessment

Response to Public Comments on Draft Protocol

March 15, 2019

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Manufacturers		
Amgen		
1.	ICER should consider assessing price and net expenditure changes in the entire healthcare system, since this is an under researched area and is consistent with ICER's broader mission. If ICER insists on limiting its focus to medicines, the current proposal to focus only on the price for a handful of medicines with the highest system impact is inherently biased and will not meaningfully shed light on the reasons for changes in price or impact on overall healthcare expenditures. At a minimum, the report should look at all drug price changes that impact net prices in the entire sector. In a health system with constant innovation, robust and changing competition, frequent price collapses due to patent expiry, and other events which impact the competitive environment for medicines, ICER's currently proposed approach misses opportunities to help promote better understanding of this complex area.	Thank you, but we feel there are important public policy reasons to look at these drugs with the highest budget impact.
2.	One cannot determine whether a price increase is justified without looking at both the value being delivered and extrinsic effects that may have resulted in a price increase. There are many factors beyond the value of a drug that can explain price increases. The evidence base both in traditional clinical data and real-world evidence continues to evolve together with the addition of new indications, changing patterns of use, clinical care innovations, biomarkers and better understanding of patient sub-groups. In addition, various exogenous shocks to the market supply and demand curves can drive changes in the price. In unusual circumstances, this has sometimes included changes in prices for material costs and demand constraints from a given manufacturing plants capacity. The current draft protocol misses an opportunity for ICER to shed light on the reasons for price changes.	The proposal specifically allows manufacturers to submit information on other reasons for price increases.
3.	ICER should remove the term 'unsupported' from the title of the report. The use of the term 'unsupported' automatically suggests that all drugs in the assessment have unsubstantiated prices even before the analysis is performed. ICER can demonstrate greater impartiality and fair balance by starting with a title that does not make assumptions as to what the results of the report may be.	We expect the report to make it very clear which drugs on the list fall in the category of unsupported price increases.
4.	Net prices are difficult to discern given the complexity of the current system; should ICER decide to proceed with the analysis, it should account for uncertainty in the results. The walk from the wholesale average cost (WAC) to the actual price that manufacturers receive is exceedingly complex within a given payer, but this complexity grows in magnitude when taking into account	Manufacturers will be able to provide input on net price changes.

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	over 800 different payers in the US, all with different processes and payment mechanisms. Significant uncertainties accompany the move from the WAC to the net price with fundamental shortcomings inherent in the data sources used, wide variations across different diseases, drugs, delivery, payers, and methodological challenges for evaluating evidence and the subjective nature by which the value of this evidence is determined. These complexities require a robust and externally validated approach for reducing uncertainty.	
5.	Given extensive variability, ICER should provide greater detail on how it derives net price. There can be significant variation between net price and list price and the data used in this analysis will not account for this. Also, this approach is in contrast to how manufacturers capture these data.	ICER routinely describes how SSR calculates net prices.
6.	To enable a more fair-balanced assessment, ICER should also capture price changes in generics and biosimilars in addition to branded drugs. Some generic and biosimilar drugs have seen significant price growth, which is equally important in the U.S. Including these types of products in this pricing assessment enables a more accurate picture of historic U.S. price change.	ICER is not inherently excluding these agents, however, it is also not looking across all producers of a molecule to calculate budget impact.
7.	ICER should consider evidence for all indications regardless of population size. An indication may not reach 10% of a drug's use but may be 100% of the use in the indication, and as such, should be included due to its value in that indication. This would rule out certain populations. Pediatric evidence which provides valuable data for HCPs would likely fall under the 10% threshold. Identifying indications that form 10% or more of a drug's use can be difficult in some areas such as oncology, which have multiple tumor types, combinations and lines of therapy; this is also a significant issue in inflammation where one drug can have as many as 6 different indications.	Manufacturers will be able to provide input on percentage use by indication. ICER does not believe that infrequent indications for a drug's use could just a large increase in price.
8.	In addition to clinical data, ICER should include factors that determine price and other determinants of patient value. Amgen continues to invest in clinical trials, new indications, new formulations, new delivery methods, disease management programs and other ways to improve the patient experience. Continuous innovations like these require significant ongoing investment, which should be reflected in ICER's report. ICER should include wider components of benefit including improvements in disease-based patient life impacts, work productivity, and product enhancements to advance patient-centered care and improve utilization. These encompass better quality of life, adherence, unmet need, severity of disease, value of hope, ability of a treatment to extend life to give time for	New evidence demonstrating improvements in quality of life/patient value that had not previously been understood would be assessed as part of the analysis.

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	the development of a cure (real option value), scientific spillover and other contextual criteria that form the basis of a drug's benefit. These data should have: a). equal weight to clinical data, b). form a central part of the consideration of data and evidence that substantiates price, and c). be directly reflected in the determination of price substantiation.	
9.	ICER should ensure a robust, methodologically sound and impartial method for grading the quality of evidence and the magnitude of net health benefit. It is currently unclear from this draft protocol, how ICER will rate the quality of the new evidence and the level of additional net benefit. We suggest ICER adopt a 3-step process for this. (1). Identify a governance board to optimize credibility and validation of this process. To complete this analysis, the public should elect a governance board of impartial experts that will monitor and control the process of this assessment. ICER's press release states consultation with a multi-stakeholder advisory group but there is little information on membership and governance. (2). Rate the quality of new evidence (low, moderate, or high) using an external peer-review process to validate the methodology and application to this analysis. Subsequent to this, reviewers should report their findings publicly, subject to validation by the governance board. (3). Rate the additional net health benefit (none, small, or substantial for evidence that has been rated as of 'moderate' or 'high' quality from above): • The draft protocol should outline the criteria to determine 'small' versus 'substantial' benefits. • We recommend identifying a group of independent experts primarily from treating clinicians, experts in the relevant disease and affected patients. This group should be chosen by members of the public, industry and academic experts to ensure impartiality. This group and the criteria they will use to differentiate between 'small' and 'substantial' should be validated in a transparent manner by the governance board.	Thank you. Certain evidence ratings will likely require expert input, however, ICER has internal expertise in the general approach to grading evidence.
10.	To help minimize bias, ICER should remove the three additional subjectively chosen drugs. The addition of these extra products based on subjective criteria will compromise the scientific integrity of the work, invalidating the methodology and leaving the report open to criticism.	We disagree.
11.	We recommend ICER apply best practices in transparency and make their methodology, evidence model, data and data sources publicly available and replicable. Specifically, ICER should give greater detail as to the methodology for more complex areas that are open to interpretation and	Thank you. We believe that the GRADE methodology has been extensively described in the EBM literature.

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	assumption, including greater detail in the methodology for the evaluation of evidence and benefit.	
Boehringer Ingelheim Pharmaceuticals		
1.	ICER proposes to use the SSR health data (FSS for privately held companies) to determine the net price for each drug, with input from manufacturers and other sources that may also be taken into consideration. The SSR health data methods are a crude way to assess net price and do not take into account stocking and other supply chain issues. To ensure transparency of the process, detailed guidance on when and how manufacturer input will affect net price calculations should be provided in the protocol. Moreover, this guidance should clearly state how ICER will prioritize use of a manufacturer provided net price, if it will replace the SSR health net price, and what the criteria are for determining which price will be utilized in the UPI assessment.	ICER will accept manufacturer-submitted net prices and has now included suggested information that manufacturers should submit when they have concerns about the net price being used in the report. ICER will review these submissions and determine on a case-by-case basis the best estimate of net price.
2.	ICER provides a list of criteria that will be used for considering drugs to be added to the UPI list through public input, but does not specify the weight and rating that will be assigned to each criterion listed (i.e., "extremely high price increases" is listed as a criterion, but "extremely high" is not defined). In addition, there is no guidance on how these criteria are ranked respective to each other and the initial 10 drugs on the list. Boehringer Ingelheim requests increased transparency in the selection, methodology, calculations, and subsequent ranking, of all drugs included on the UPI assessment.	We do not feel we can provide precise definitions of all these terms, however, we feel that most stakeholders will be aware of drugs that have, for instance, experienced extreme price increases in the absence of new evidence. Such price increases would far exceed the cutoff (2x medical CPI) used for the 10 drugs. These three drugs would be distinguished from the 10 ranked drugs.
3.	Boehringer Ingelheim is concerned that 4 weeks is insufficient for manufacturers to receive notification that their product is on the UPI assessment list, gather the appropriate supporting evidence, carry out new analyses if needed, communicate any clarifying questions, and subsequently provide written and/or verbal comments to ICER. Boehringer Ingelheim strongly urges ICER to increase the timeline for manufacturer input.	ICER is seeking information that should generally be in the public domain. No new analyses should be required.
4.	In addition, it is unclear what criteria or restrictions are placed on the evidence that ICER will accept and consider. This includes questions around whether ICER plans to prioritize US data compared to global data, the acceptability and inclusion of evidence from non-US studies, consideration of patient-centered outcomes data, and the inclusion of other factors that weigh into the overall value of the drug (i.e., caregiver burden, quality of life data, patient perspective, and the potential impact on other costs). We request that ICER provide more detail around how evidence provided from manufacturers will be taken into account to increase methodological transparency and ensure manufacturer readiness.	All the forms of evidence listed would be considered if found in high quality studies/trials. Economic analyses will not be reviewed.

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5.	ICER references use of the GRADE rating system alone, rather than ICER's Evidence Rating Matrix (ERM). BI requests clarification of the rationale for not utilizing the ERM directly.	ICER's evidence matrix and GRADE assess evidence in very similar ways, but the evidence matrix has no rating for quality of evidence that is separate from the rating of improvement in net benefit. GRADE provides a way to separately report on quality of evidence.
6.	It is further unclear how ICER will account for single products that are prescribed and utilized in combination or otherwise may be perceived differently in the context of price compared to similar drugs in the class for the same indication. For example, drugs have increased in price due to competition from other products, but still remain at a lower total cost than competitors when taking into consideration total cost of care (i.e., combination therapy vs single therapy that requires add on drugs). One of ICER's guiding principles is "evidence on added benefits, price and insurance coverage." By failing to take into account the broader context of price increases, ICER is jeopardizing fostering innovation to create sustainable access to high-value care.	It is unclear why competition from other products in a free market should lead to higher prices.
7.	Further, BI recommends that ICER expand the type of evidence considered for the UPI assessment beyond efficacy and safety data. By overwhelmingly focusing on efficacy and safety evidence, the UPI assessment excludes an essential component of what brings value to patients. Even in ICER's own value assessment framework (VAF), "Other Benefits and Contextual Considerations" weigh into ICER's evidence ratings as they are recognized as very important aspects of a drug's value.	The UPI project is not a value assessment project. However, there is no intent to exclude any new information on patient-important benefits or harms.
8.	It is unclear what type of data are considered "non-clinical." For example, does this refer to anything collected outside of the randomized clinical trial? Specific objective criteria for data that will or will not be considered should be clearly outlined in the protocol.	ICER will have a broad view of clinical evidence as long as it relates to patient-important outcomes.
9.	Moreover, the nomenclature proposed by ICER alluding to "small" benefits and "unsupported" drug price increases are inherently subjective. To ensure the integrity of ICER's UPI report, it is essential that they clearly define and operationalize such terms.	These sorts of judgments are routinely made by HTA organizations and are similar to the judgments made in every ICER report.
10.	ICER's UPI assessment draft protocol does not support price increases in instances where indication specific pricing exists. The use of indication-based pricing is becoming more common, with the potential to progressively impact drug pricing in the future. ICER should consider specifying how the UPI protocol will account for products that have indication specific pricing, and if resulting price increases will be factored into UPI assessment results.	Should this occur, we will review our procedure on a case-by-case basis, consulting with companies to provide clarification on whether a price change pertains to any expanded indication.

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11.	We recommend ICER consider delineating a protocol for drugs that may have been included in previous UPI assessments. It is unclear if drugs may be included in the UPI assessment over 2 or more consecutive years, or if drugs will only be included in the annual UPI report once and then excluded from future versions of the UPI assessment. Further, a process in which subsequent assessments will address new evidentiary findings of drugs noted as unsupported in prior years should be considered.	If the same drugs show up in the report year after year, ICER may consider modifications to the protocol in the future.
Celgene		
1.	In assessing the value of an individual therapy, there must be some consideration for how the biopharmaceutical research ecosystem is expected to sustain, let alone enhance, innovation in the future. Tomorrow's breakthrough therapies are only made possible by the financial rewards for today's innovative products. In in an industry where only two in ten FDA-approved medicines produce revenues that exceed the average R&D investment, the value of a therapy should appropriately account for the great risks involved in biopharmaceutical innovation. Celgene fully supports the ongoing dialogue around how we as a country are allocating our healthcare resources, including spending on biopharmaceutical therapies. We believe that for consideration of our health system challenges to be a fruitful endeavor, it should be based upon a holistic examination of value, as opposed to a restricted assessment of price increases for one component of healthcare during a narrow timeframe. By focusing solely on the pricing of innovative medicines, combined with a limited analysis of value, ICER's UPI draft protocol is destined to underestimate the value of biopharmaceutical innovation.	It is unclear how the research ecosystem requires continued year over year price increases for agents already on the market.
Genentech		
1.	We encourage ICER to adopt a system-wide view to identify inefficiencies and optimize resource use by assessing health care beyond medicines… We recommend focusing on areas where resources can be used more efficiently to reduce the overall cost of care. Approximately $213 billion, or 8% of overall health care expenditures, was spent on avoidable costs in 2012. The largest sources of avoidable costs were additional resources required to manage negative health outcomes stemming from nonadherence, delays in applying evidence-based treatment in clinical practice, misuse of antibiotics and medication errors. An evaluation solely focused on the temporal price increases of prescription drugs will yield a limited perspective on potential improvement initiatives to support the goal of a better and more efficient system.	We agree that there are important problems in the health care system unrelated to drug costs.

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2.	An assessment of medicines should be value-based and comprehensively account for all available evidence to support the decision needs of patients, society and the health care system… Genentech is concerned that the designation of a supported or unsupported price increase is based on a limited view of available evidence and a rating system that lacks clear criteria. The proposed approach is agnostic to value and risks not accounting for important benefits and offsets obtained by the broad stakeholder base. As our healthcare system evolves to focus on value-based care, it seems remiss to ignore whether a drug's price is justified by the totality of health, economic and patient-reported outcomes it affords. Furthermore, a review of the totality of evidence will provide ICER with an indication of the level of post-approval investment a manufacturer is making to ensure the effectiveness, safety and value of a medicine, which may be one consideration in the decision to take a price increase.	The UPI report will be looking at changes in prices over time, with the expectation that broader considerations influenced the initial pricing decision.
3.	The evidence review should be expanded to include clinical, economic and patient-reported outcomes from both trial-based and observational settings. Per the draft protocol, only randomized trials, high quality comparative observational studies and uncontrolled large observational studies for low frequency harms are considered. However, we believe a limited focus on a subtype of clinical study designs will lead to inaccurate conclusions and underestimate a medicine's benefit and value to the national population. By only including clinical outcomes assessed in a highly selected group of patients, the UPI assessment will exclude important and relevant information on effectiveness, quality, patient-reported and economic outcomes. Public and policymakers are best served with a comprehensive understanding of all available evidence that reflects the outcomes most important to patients and society.	We are uncertain how the restriction that comparative observational studies be of "high quality" unreasonably restricts the evidence base that will be reviewed.
4.	We recommend that ICER provide additional clarification on how the GRADE system will be applied consistently and transparently in order to address known limitations of this framework. We are concerned that this may not be appropriate to inform population-level decision making for these specific reasons: • The GRADE system rates evidence quality as low, moderate or high quality based on reviewer opinion and risks subjectivity. • There is evidence to suggest that the framework is prone to inconsistencies and low interrater reliability. • Studies assessing outcomes with multiple endpoints are extremely difficult for reviewers to grade.	All grading systems involve reviewer judgments. GRADE has been used extensively to rate evidence from both observational studies and randomized trials.

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	• The grading system is limited by its lack of applicability to evidence generated from sources other than randomized clinical trials.	
5.	The rating of incremental net health benefit (NHB) is prone to significant subjectivity and variable interpretation. In the evaluation of incremental NHB, UPI raters will assess the magnitude of clinical benefit for a therapy as defined by the labeling information versus the additional benefit demonstrated from a "new" body of evidence in the prior three-year period. There are several risks associated with this approach that may result in misinforming policymakers and the general public. • The estimation of incremental NHB as none, small or substantial is not informed by a clear and validated rating system. • The risks and challenges are further compounded by the comparison of "previously understood net health benefit for a therapy versus placebo and/or comparators" and "any new, additional net benefit for that same therapy based on newer evidence." Therefore, this is an assessment of differences of differences which may be further complicated by varying comparators, differing study types, and divergent study objectives. • This approach is subject to significant variation based on the interpretation of a review panel and poses concerns around replicability.	These sorts of judgments are routinely made by HTA organizations and are similar to the judgments made in every ICER report.
6.	The 36-month time period offers a limited view on the totality of evidence. We suggest the evidence review encompass the entire body of available evidence for a product. ICER proposes to assess only evidence published in the prior 36 months against that described in the labeling information. The timeframe of 36 months is biased against therapies which have been on the market for several years. There may be meaningful evidence, such as post-approval subgroup analyses or long-term follow-up data, that may have been published prior to the time period of interest, but the value of which is not reflected in a product's price until a later time point. Additionally, this limited view may result in an underestimation of the quality or strength of evidence. Findings that are reproduced in multiple studies, which may be published at various time points, generally indicate a greater strength of evidence.	If this proves to be a significant concern about the first UPI report, ICER will reconsider the time frame for evidence for subsequent reports.
7.	The drug selection criteria proposed by ICER may result in an assessment that is biased, narrow in scope and repetitive. We believe that the current selection criteria may result in unintended consequences. The selection of final drugs starts with the top 100 drugs based on U.S.	We feel there are important public policy reasons to look at these drugs with the highest budget impact. We agree that the methodology could lead to the same drugs being reviewed year after

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	sales. Although ICER seeks to determine prescription drugs with the greatest U.S. budget impact, this criterion is inherently biased against chronic conditions, diseases of high prevalence and incidence and curative therapies. While sales are partially driven by drug price, other disease-related factors, including the number of treated patients, efficacy and treatment duration, are important drivers of total sales. Therefore, this criterion risks overlooking the evaluation of drugs that target smaller populations or acute conditions. Lastly, drugs with top dollar sales are unlikely to change significantly on a yearly basis. Annual reviews will thus likely be focused on a similar list of drugs, thereby limiting the scope and increasing redundancy in ICER's subsequent reviews. We advise ICER to reconsider the value in repeating this assessment on an annual basis.	year if they continue to experience very large price increases in the absence of new evidence.
8.	Rationale for the price increase threshold, based on the medical care Consumer Price Index (CPI), should be provided. To narrow the list of potential therapies to review, ICER proposes that drugs with Wholesale Acquisition Cost (WAC) increases greater than two times the medical CPI will be used. The rationale for the choice of two times the medical care CPI as an appropriate threshold for significant price increase is unclear, and as a key criterion in the selection process, should be further elaborated upon.	We feel that price increases at more than twice the rate of medical inflation for the highest budget impact drugs raise important public policy considerations.
GlaxoSmithKline		
1.	At a time when US health care expenditures has slowed, including slower growth for retail prescription spending, we believe that the UPI report's focus on drug prices and clinical evidence is misplaced. As proposed, ICER seeks to assess the temporal relationship between pricing increases relative to the public dissemination of clinical evidence. This approach suggests a simple, linear relationship between drug prices and clinical evidence, which is counter to the complexity of the US healthcare system and may mislead patient and policy stakeholders. We are concerned that this approach also fails to objectively value the significant commitment to extensive Phase IV evidence generation undertaken by manufacturers — not for label expansion or product differentiation but to improve appropriate clinical decision making or to ensure post-approval safety monitoring. Lastly, the UPI report's narrow focus on solely clinical evidence – underestimates the value and cost offsets that innovative therapies can deliver to the US health system, such as a reduction in non-drug related healthcare services or increased productivity.	Thank you, but we feel that large price increases for existing drugs in the absence of new evidence raise important public policy considerations.
2.	We recommend that ICER broaden the scope of its UPI report to include:	ICER will not be able to conduct such reviews for these therapies and so the methodology is

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	1. Detailed systematic literature reviews of both clinical and non-clinical evidence for included therapies and respective indications and, 2. More robust economic analyses of all therapies identified for the UPI report.	intended to be able to be sensitive to new evidence but not specific for evidence that would clearly justify price increases.
3.	We concur with ICER on the need for an independent systematic literature review (SLR) to support the intended aims of the UPI report. However, GSK is concerned about the potential impact that publication bias can have on SLR and the current body of knowledge at a cross-sectional point in time. Unfortunately, failed studies are less likely to be published in a timely manner or published at all. We are also mindful of the limitations of relying on published clinical data. Publication of a manuscript can often take between 6-12 months from journal submission. ICER proposes to accept manufacturer evidence under its academic in confidence policy to ameliorate this issue. However, the policy dictates that confidentiality will be maintained for 18-month period from the date of a public ICER meeting — a meeting that has not been included as part of the UPI protocol. We recommend that ICER further define their processes to adjust for publication bias in the proposed, independent SLR and UPI report.	Thank you, we will update the policy to reflect that for the UPI report information will be held confidential for 18 months after the public release of the report.
4.	As the UPI report results will rest heavily on the curation of evidence from SLR, we recommend that ICER provide all stakeholders with an opportunity to review the SLR protocol and results, including studies excluded by adjudication.	We have limited stakeholder review to protect the confidentiality of reviewed products prior to release of the report. Manufacturers will have the opportunity to provide comprehensive evidence.
5.	ICER proposes to use its existing Evidence Rating Matrix (EBM) to assess the quality and certainty of clinical evidence. While we concur with the need to assess curated studies from the SLR, we question the utility of the EBM to support the intended aims of the UPI report. The EBM's level of certainty is based on a "conceptual confidence interval" of existing evidence. The five domains that are used to anchor the "conceptual confidence interval" (Level of Bias, Applicability, Consistency, Directness, and Precision) handicaps any indications wherein evidence generation is challenged by the inherent uniqueness of the disease. For example, orphan diseases, in which evidence generation is challenged by small patient populations, misdiagnoses and poor surveillance as well as discontinuous access to specialty care centers, are at high risk of being systematically disadvantaged by the use of the EBM in UPI reports. We recommend that ICER reconsider the use of its EBM for assessment of orphan diseases and indications with small patient populations, to account for the challenges of evidence generation in these patient groups.	Actually, ICER proposes to use GRADE to assess the quality/certainty of clinical evidence. The ICER evidence matrix will be used to assess the magnitude of the additional net health benefit. On the broader point about orphan diseases, these are often very severe diseases where new therapies are capable of showing dramatic improvements in outcomes if effective. We do not think requiring at least moderate quality evidence showing a substantial benefit will disadvantage therapies for orphan diseases.

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6.	Lastly, as we have recommended the inclusion of non-clinical evidence in the UPI report, we believe that it is important to note that the EBM undervalues the meaningful, evidence drawn directly from patients, using mixed - methods or other socio-anthropologic approaches. These types of patient derived real-world data — often captured by studies using surveys, interviews, and focus group discussions — are unlikely to meet the UPI EBM criteria of "moderate/high quality" new evidence due to their study designs. We believe that ICER has a unique opportunity to expand its engagement and inclusion of patient perspectives in the UPI report. As highlighted by the recent NHC Roundtable on Patient Perspectives on Real-World Evidence, "patients would like to see RWE generated from patients' experiences be incorporated into value-driven decision making and policy discussions ensuring the outcomes most important to them are considered." GSK recommends ICER includes qualitative patient derived real-world data in the UPI report and prioritize the development of value assessment standards for qualitative evidence derived directly from patients.	There is nothing in the UPI protocol that is intended to disadvantage high-quality observational evidence.
Mallinckrodt Pharmaceuticals		
1.	Glossary of Key Terms: We continue to believe that a glossary defining key terms such as "budget impact," "largest budget impact increases," "harms" of Food and Drug Administration ("FDA")-approved therapies, "patient assistance programs," and "incremental clinical effect" would be helpful to readers of this report to ground them to ICER's approach and provide clarity regarding each term. These terms are often used imprecisely and in differing ways by industry, payers, and others, and thus, having clearly defined meanings will help to strengthen third-party understanding of ICER's methodology.	Thank you. This is a short document and we feel terms should be made clear where they are used rather than in a separate glossary. We are clarifying the description of budget impact and increases in budget impact. We do not believe "incremental clinical effect" appears in the document.
2.	To create a list of drugs with substantial price increases, ICER will rely on net prices obtained from SSR Health, which combines data on unit sales with publicly disclosed sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs. One outstanding question is whether discounts to pharmacies will be included in the net price calculations.	The SSR methodology relies on revenue coming back to the manufacturer, so these results are net of all discounts.
3.	We appreciate the addition of criteria to help guide the selection of the three additional drugs to be evaluated as part of this report in Section 2.2 of the draft protocol. It would also be helpful to clarify whether the methodology set out in Section 2.1 will be the same methodology used to evaluate drug price increases for the drugs publicly identified in Section 2.2. Further, please clarify that for the first report, ICER will be considering the same time frame	We have added this clarification.

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	as that identified in Section 2.1, from January 1, 2017-December 31, 2018, to assess price increases for the drugs identified in Section 2.2. We believe ICER should use the same methodology and time frame to evaluate price increases for drugs identified in each section in order to allow for meaningful comparisons between the two lists of drugs assessed.	
4.	Some of the data and information that would be helpful to ICER may be subject to intellectual property (IP) protections held by others, such as patents, copyrights, and trademarks. Under contractual arrangements to which manufacturers may be a party, such as clinical trial agreements or other arrangements, companies are bound by those IP protections often in the form of confidentiality provisions and would not be able to provide ICER the information sought without violating contractual obligations. Manufacturers would need additional time to work through those obligations in order to further share relevant information that may be useful to ICER in its evaluations.	We feel that if prices have increased as a result of new information, it should generally be possible to inform the public about that information. Manufacturers can refer to additional information they are holding confidential when they submit comments.
5.	The draft protocol does not sufficiently exempt from public disclosure data and information that is ordinarily protected as confidential commercial or trade secret information. For example, some data supporting a product's value proposition may result from interim analyses, unpublished data, or retrospective analyses of claims data. Each of these may be appropriate data sources. However, these data may not be available in the public domain for proprietary, competitive or other reasons meriting confidentiality and protection from public disclosure. Yet, ICER's draft protocol clearly states that any information submitted to ICER will be publicly released. As such, we believe that ICER should grant companies flexibility to provide abstracts of such data to maintain their confidentiality, without negative biases against such data. Further, ICER should clarify that information that is marked by the manufacturer as confidential commercial or trade secret information will not be publicly released.	We feel that for these price increases that have had the largest budget impacts on the US economy, manufacturers should either be able to provide public justification or accept ICER's review of public information.
Merck		
1.	The proposed title of the reports, “Unsupported Price Increase (UPI),” does not accurately reflect the content. • The reports will review evidence for all 13 drugs flagged due to a price increase threshold, regardless of whether their price increases are categorized as “unsupported” or not. • It is overly simplistic and misleading to determine price increases as “unsupported” only because no new clinical evidence was identified. Other than clinical	Thank you. We had already adjusted the protocol to make sure that drugs under review will not be publicly named before it is determined whether they have price increases with new clinical evidence and we hope that this will not disadvantage these drugs.

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	evidence, other value factors and business/market conditions may justify drug price changes (see the next comment). We suggest ICER uses a different title that more accurately reflects what the reports are intended to achieve, i.e., investigating whether drug price increases are associated with substantial new clinical evidence.	
2.	Other than clinical evidence, many other value factors (e.g., benefits for patients' caregivers, increased societal productivity) and certain business/market conditions (e.g., needs for raising additional resources to accelerate innovation development, production difficulties, supply shortages) may also justify price adjustments. It is important to identify and discuss these factors and conditions in the reports to present a fair and balanced view on drug price increases.	We did not intend to exclude information on benefits to caregivers or productivity from "new clinical evidence". We will be looking broadly at net health benefit.
3.	To reflect real-world price increases and budget impact, net prices should be used instead of WAC. The MCPI rate should be assessed over the same 24-month period, since this can fluctuate.	We have updated our language to reflect that the top 100 list will be determined using net sales revenue. We have updated our language to reflect that the top 100 list will be determined using net sales revenue. However, we will use the WAC change to identify top drugs with price changes and then apply the net price change to estimate change in budget impact over time. The same 24-month period will be chosen to derive price change and medical CPI change.
4.	Payers have their own mechanisms for negotiating net price that is not visible to the public or data vendors. SSR may not always have access to this sensitive price information. Using SSR data, ICER could end up with overestimating net prices. Using SSR and FSS data respectively for public and non-public companies could cause inconsistency and bias in identification of drugs for review.	Manufacturers can submit information on net price changes.
5.	1). SSR data may have significant variability for certain types of products, especially new products, LOE products, products with a low volume or shifting channel mix, and seasonal products- including vaccines. 2). SSR data combines products that are part of a product family, for example, Janumet/Janumet XR, MMR/Varivax/ProQuad, Recombivax HB / Vaqta (Hep A & B). 3). Some data are product-specific prior to mergers, which show the sales for each product and each manufacturer on a separate line. For example, Nexplanon data is reflected on the Schering line prior to the merger and on the Merck line after the merger, but there is a combined section further down the page	We are aware of some of the issues with the SSR dataset. We will consider other data sets such as FSS to obtain prices in such cases. For products belonging to a mix, SSR assumes the same discount when deriving net price for individual products that are part of the mix. The SSR data set accounts is able to reflect prices at a product level even for those products that are subject to manufacturer mergers/multiple manufacturer lines.

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6.	Concern: ICER's approach to prioritizing drugs for review (e.g., ranking drugs by multiplying the current annual sales by change in net price over 24 months). Using this approach, the ICER reports will focus primarily on drugs with larger patient populations. However, some of the most controversial price increase cases occurred for drugs treating rarer conditions (e.g., Daraprim, Deflazacort). We suggest ICER sheds more light on these cases and the irrational behavior behind it.	This is the rationale behind having three additional drugs reviewed.
7.	The criteria for additional drugs selection are generally vague – e.g., what metric is used to determine "drugs used by millions...," what does it mean to have "important affordability implications" or "concerns about the fairness of price increases"? Why is MCPI benchmark arbitrarily changed for additional drugs? ICER should provide more specifics to minimize potential biases or unfair scrutiny in the drug selection process.	We will consider revising after the first version of the UPI report as ICER and stakeholders have more information on how this plays out.
8.	Please clarify at what point of the review process ICER will reach out to manufacturers for input.	ICER will reach out as early as the list of drugs is known and no later than May 6 this year.
9.	Please clarify how ICER intends to incorporate this information into the price increase reports. As previously commented, we believe it is crucial to discuss these "other justifications" in the reports to present fair and balanced views on drug price increases.	As stated in Section 5, this information will be provided as a component of the report.
10.	While ICER expects manufacturers to submit commercial information to justify price increase, this information may not be protected under the ICER academic-in-confidence policy. This would discourage manufacturers from sharing sensitive information. For example, when the SSR data on net prices aren't accurate, manufacturer wouldn't be able to share that information with ICER. So, we suggest ICER clarifies whether its academic-in-confidence policy also applies to commercial information.	ICER is not planning to accept commercial in-confidence data as part of the UPI report.
11.	If indications are relatively new, they might not have yet met the 10% threshold, but there could be significant clinical data to support their use. We suggest ICER reviews all available data, whether the indication meets the 10% threshold or not. If the evidence supports the product, it should be part of the review.	We have added language to deal with an indication that is rapidly increasing as a portion of a drug's use.
12.	Concern: Use of evidence from FDA labeling information to determine a baseline of known safety and clinical effectiveness. For drugs that have been on the market for several years, ICER should use more current evidence to establish the baseline.	Our understanding is that the label would typically be updated with new evidence. If we had an outdated baseline, this would be favorable to the manufacturer as evidence might appear new that was not.
13.	Some evidence may get a low GRADE rating due to single-arm design, small study sample sizes, or short follow-ups, but shows substantial health benefits (e.g., in the CAR-T cases). This type of evidence should not be ignored. We	The GRADE system is capable of dealing with a situation such as CAR-T. Large magnitude of benefit increases certainty under GRADE.

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	suggest ICER assesses net health benefits from all evidence bases rated as high, moderate, or low using GRADE.	
14.	Concern: Drugs found to have moderate/high quality new evidence of a substantial improvement in net benefit will be categorized as having a "price increase with new clinical evidence." Based on the last comment, we suggest ICER revises the categorization criterion so that drugs found to have low quality evidence of substantial net benefits will be further assessed for more appropriate categorization.	We do not feel that prices should increase rapidly based on low quality evidence.
15.	We believe ICER should maintain certain flexibility to accept information that emerges at a late stage of the review process. Some new information (e.g., safety alerts) could be too important to be ignored.	The price increases that ICER is reviewing will have occurred in the past. The information justifying those price increases should already be available when the review is initiated.
16.	Please clarify how manufacturers review will be incorporated into the final reports.	These will be published as public comments along with the UPI report.
17.	Concern: Reporting on factors other than clinical evidence that may justify price increases. As previously commented, we believe these other factors are just as important to discuss as clinical evidence to justify drug price changes. This information should be presented appropriately in the main sections of the reports, not simply attached as an appendix.	Our intent was that these would be included in the discussion of each drug with an unsupported price increase.
Novartis		
1.	ICER plans to obtain a list of 100 drugs with the largest dollar sales in the US. However, it is not clear whether it refers to gross or net sales and what year of sales will form the basis for the list.	This refers to net sales revenue.
2.	Consistent methodology should be applied when the price or budget increase, and the rate of medical consumer price index (CPI) are calculated. Specifically, if net price is calculated by taking a difference in two time points during a 24 months period, the rate of medical CPI increase should be calculated the same way.	This is how we will calculate the increase in medical CPI.
3.	The methodology for net price derived by SSR Health is not transparent and Novartis recommends ICER provides additional information about their methodology, including the data source.	ICER routinely describes how SSR calculates net prices.
4.	Regarding the assessment of clinical effect size, transparent criteria for determining "small" and "substantial" should be provided.	These sorts of judgments are routinely made by HTA organizations and are similar to the judgments made in every ICER report.
5.	In addition, any threshold chosen for the report should be supported by a strong rationale. For example, it is not clear why 2 times the rate of medical CPI was chosen as a threshold for price increase.	We feel that price increases at more than twice the rate of medical inflation for the highest budget impact drugs raise important public policy considerations.
6.	The title of the report may suggest that the drugs included have unsupported price increase determined by ICER. Novartis recommends ICER to consider using a different title such as "Evidence-based price increase assessment"	We expect the report to make it very clear which drugs on the list fall in the category of unsupported price increases.

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	to reflect its suggested methodology and stated intent of the report	
7.	A more detailed and clear methodology regarding additional 3 drugs to be reviewed is needed. For example, currently provided criteria do not clarify how "extremely high price increases," and "important affordability implications" are determined.	We will consider revising after the first version of the UPI report as ICER and stakeholders have more information on how this plays out.
8.	Novartis recommends that ICER provides a hypothetical example that permits manufacturers to use as framework and examine the calculations thoroughly. The example will illustrate the methodologies more clearly and help provide transparency.	We have updated our description of the calculations and we believe it should now be clear.
9.	"ICER recognizes manufacturers may have more precise data on net prices changes than SSR or FSS, and plans to work with manufacturers to gain this information." However, without the protection of this confidential information, manufacturers may be unable to have a full exchange of information with ICER during the review.	ICER will then need to use the data sources available.
10.	ICER plans to perform systematic reviews for "information from randomized trials, high quality comparative observational studies, and, for information on low frequency harms, from large uncontrolled studies." Novartis recommends that ICER consider other types of evidence such as non-comparative observational studies, and evidence presented in forms of posters, manuscripts, and grey literature.	Except when looking at low frequency events, non-comparative observational studies typically do not provide moderate or high quality evidence and so our systematic reviews will not look for such data. Manufacturers may submit such data and also information from posters and grey literature.
11.	ICER states in the report that "UPI reports are not intended to determine whether a price increase is fully justified by new clinical evidence...Instead, we will focus the analysis on whether or not substantial new evidence exists that could justify its price increase." Whether the evidence fully justifies or could justify price increases seems to be a subjective assessment without clear and established criteria. Novartis recommends that ICER interprets the evidence in an objective manner.	An objective assessment would involve a cost-effectiveness analysis. However, that will not be possible as part of the UPI project and so ICER will not be making this determination when moderate or high quality evidence exists for substantial added net health benefit.
Pfizer		
1.	ICER's approach is not patient-centric. In several prior comment letters, we have highlighted how ICER's approach to value assessment does not fully adopt the perspective of the patient. In the case of the UPI project, ICER has again failed to take a patient-centric approach, notably with respect to its selection of price metrics. ICER's use of list and net pricing in its analysis ignores what patients are most concerned about: their out of pocket healthcare costs. For most, these expenditures are directly impacted by their insurance premiums, deductibles, co-payments and co-insurance. The amounts paid by most patients for pharmaceuticals differ vastly from the list prices set by manufacturers and net prices paid by	The UPI project is not a value assessment project.

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	insurers. Yet, ICER continues to measure drug prices in a manner that is not relevant to most patients in the US. As such, the outputs of UPI report will not aid policymakers in their understanding of one of the issues that matter to patients most. We continue to encourage ICER to meaningfully engage patients, their families and their caregivers to understand the most important challenges they face, and to seek to address those critical and pragmatic questions.	
2.	ICER excludes important factors related to pharmaceutical pricing. Yet ICER's proposed framework for the determining whether a price increase is 'unsupported' specifically excludes all other considerations that may factor into drug pricing decisions. ICER does not offer any rationale for excluding factors it explicitly acknowledges may be relevant to pricing decisions. While ICER notes that it intends to ask manufacturers for "other potential justifications for a price increase," it is unclear whether and how this information will be used by ICER given that its proposed framework intends to exclude this information. We urge ICER to include in its framework all factors proposed by manufacturers in response to its inquiry. ICER's rejection of additional factors reflects its bias and unwillingness to meaningfully consider pricing decisions in full context. This again raises significant concerns regarding the value of ICER's UPI report in a policymaking context.	Thank you, but we feel that large price increases for existing drugs in the absence of new evidence raise important public policy considerations.
3.	The scope of ICER's draft UPI protocol is limited to the assessment of price increases of pharmaceutical products. This narrow focus is a missed opportunity to contextualize changes in drug prices relative to changes in other sectors of healthcare. For example, recent data suggest that the prices of hospital services and physician visits have increased dramatically in recent years. Understanding price increases across all sectors of healthcare would provide critical context for whether the increases observed in pharmaceuticals are 'supported' from a value perspective. Prior analysis suggests that over time, innovation in pharmaceuticals has offered the greatest value with respect to impact on patient outcomes. Given ICER's interest in value and sustainability, a broader examination of healthcare pricing is warranted.	Thank you, but we feel that large price increases for existing drugs in the absence of new evidence raise important public policy considerations.
4.	ICER's net pricing data have not been validated: Net pricing data are central to ICER's UPI methodology. ICER proposes to use net pricing data from SSR Health in its analysis. Because net prices are confidential, SSR Health has developed its own estimates of net prices through proprietary calculations. The use of net pricing data that	Manufacturers can submit information on net price changes.

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	have not been empirically validated will significantly diminish the validity of ICER's findings.	
5.	ICER's threshold rationale is unclear: ICER proposes to establish a threshold of two times the medical consumer price index (mCPI) as an initial cutoff for its determination of 'unsupported' increases.' CPI measures are used in economic analysis as a measure of inflation; ICER offers no rationale as to why the use of an inflation-based measure is appropriate in its UPI project, and further does not establish why twice the mCPI is the right value for its analysis. The use of arbitrary thresholds limits the value of ICER's output.	We feel that price increases at more than twice the rate of medical inflation for the highest budget impact drugs raise important public policy considerations.
6.	ICER's focus on individual pricing decisions ignores true patient impact: in section 2.1.2 of the draft protocol, ICER notes that it will focus on individual pricing decisions only and will exclude price increases for a single product observed across multiple manufacturers. These kinds of multi-manufacturer pricing actions may have a significant impact on patient expenditures. Given ICER's objective to assist policymakers, we believe that these types of price increases should be included in the framework.	We agree that price increases of this sort are important to multiple stakeholders, however, they will not be part of this initial UPI report.
7.	ICER offers no rationale for proposed timeframes for evidence gathering: ICER is interested in new clinical data developed in the 36 months preceding a price increase. ICER offers no justification or rationale for its approach in the selection of this time frame. The lack of a clear conceptual framework and vetted rationale for the relationship between evidence and price significantly undermines the overall quality of the project.	The time frames were suggested by a multi-stakeholder group that worked on the draft proposal.
8.	ICER's proposed net health benefit metric is not objective: A critical element of the UPI methodology is ICER's determination of the relative value of the clinical evidence for a given product. ICER proposes to assess the net health benefit demonstrated by the clinical evidence using its own Evidence Matrix (EM) rating system. The EM system was developed in 2007 by a workgroup convened by America's Health Insurance Plans. We have significant concerns about the subjective nature of the EM system, especially given that ICER notes that "judgment remains an important component of the rating system." We strongly believe that the evaluation of the relationship between clinical evidence, value, and price should be objective, and not subject to bias.	Judgments about evidence and net health benefit are inherently subjective, but using formal systems such as the Evidence Matrix and GRADE tends to make them more reproducible.
9.	ICER's binary rating system applies a subjective approach: At the end of its assessment, ICER will label the price increases observed for the products under review as (a)"having price increase with new clinical evidence" or (b) "having unsupported price increases." This categorization does not allow for any price increase to be deemed	In the absence of cost-effectiveness analysis ICER will not be able to state whether a price increase is supported.

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	'supported,' even with compelling evidence, and pre-determines the findings of the framework in a biased manner.	
Sanofi		
1.	The report's exclusive focus on prescription medicine products and pricing and the perspective of insurers provide a limited and incomplete view of pricing and value issues in the health care system, and do not address patients' key concerns... Thus, if the underlying objective of the UPI Report is to contribute positively to efforts to address medical care spending, the exclusive focus of the report on prescription medicines and drug pricing seems misplaced, does not constitute a holistic assessment of value, and is poorly conceived to support this aim.	The UPI project is not a value assessment project.
2.	The proposed narrow focus of the UPI Report is also in conflict with good principles of health technology assessment, which call for comprehensive evaluation of different types of health care technologies and explicit consideration of tradeoffs between alternative types of interventions, and facilitate differentiation between high- and low-value health care. Such tradeoffs cannot be readily considered within the current proposed framework of the UPI Report. The selective focus only on drugs also conflicts with ICER's own stated organizational purpose of serving as a nonpartisan evaluator of all types of health care interventions, i.e., an institution that "objectively evaluates the clinical and economic value of prescription drugs, medical tests, and other health care and health care delivery innovations."	The UPI project is not a value assessment project.
3.	Informative evaluation of pricing decisions after launch for prescription medicines necessarily requires a long-term perspective, because an understanding of clinical benefits and harms and economic value evolves over time, and uncertainty is difficult to quantify. Moreover, drug pricing trajectories are typically unique in comparison to other non-drug health care services because of the impact of patent expirations and loss of exclusivity. For example, Fendrick and George emphasize this point by contrasting the relative pricing histories of statins vs. coronary stents, both introduced approximately three decades ago.10 A selective focus on a limited time span of pricing decisions distorts the specific assessment of a drug as well as comparisons to non-drug alternatives. Methods exist to measure and evaluate long-term costs and cost offsets of drugs, but the UPI Report protocol does not consider or incorporate such approaches.	Thank you, but we feel that large price increases for existing drugs in the absence of new evidence raise important public policy considerations.
4.	The payer's perspective is exclusively represented in the proposed report, in contrast to the recommendations of good assessment practices for a broader focus on societal	The use of changes in list price and the three additional drugs are intended to help capture

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	and patient interests. We are especially concerned that the proposed protocol makes minimal reference to the specific concerns of patients, and does not specify types of evidence included in the evaluation process that will be meaningful to patients.	price changes that have implications for patients as well as payers.
5.	ICER's proposal to use the consumer price index (CPI) for medical care to establish a standard against which to gauge the magnitude of drug prices changes is insufficiently described. Please clarify how the CPI benchmark will be calculated over the proposed 24 month period.	We have added language to clarify this.
6.	We are also concerned that reliance upon SSR Health data to estimate and inform net price is problematic and may lead to erroneous conclusions. SSR data is based on a set of assumptions; if these assumptions are in error, recommendations will be similarly flawed. Moreover, SSR provides multiple net prices; it is not clear from the draft protocol which approach ICER will utilize.	Manufacturers can submit information on net price changes.
7.	ICER's use of estimated budget impact as part of the product selection process is flawed. It is inappropriate to evaluate a product's budget impact on US health care spending in isolation from its potential impact on savings for other health care services. ICER's proposed approach also penalizes drugs for highly prevalent conditions such as diabetes or cardiovascular disease, skewing the initial list to such therapies.	Thank you, but we feel that large price increases for existing drugs in the absence of new evidence raise important public policy considerations.
8.	ICER's proposed selection process to identify up to 3 additional drugs (Section 2.2) to review in addition to the primary list is informal and appears largely arbitrary, and is inconsistent with the process outlined for the primary list identification process. The few parameters listed for this portion of the report are remarkably broad and appear to encompass virtually any potential selection decision. This open ended approach is also in conflict with good technology assessment practices, which call for explicit, systematic, and transparent evaluation objectives. This informality undercuts the overall premise of the report.	We will consider revising after the first version of the UPI report as ICER and stakeholders have more information on how this plays out.
9.	ICER's protocol should clearly state the types of evidence that will be accepted as the basis for improved clinical or economic outcomes and the relative weighting of such evidence for the objective of the assessment. For example, will the assessment include data from all of the following: randomized controlled trials, observational studies or cohorts, real world studies based on claims/administrative databases or electronic health records or registries, and cost-effectiveness models?	Cost-effectiveness models are not a type of evidence. The other types of evidence could be submitted and if judged moderate or high quality evidence would contribute to the review.
10.	Statistical procedures to combine findings from systematic reviews and compare drugs are not identified in the protocol. How will meta-analyses be completed? Will	We cannot describe a protocol ahead of a review question.

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	network meta-analyses be conducted? Will pairwise indirect comparisons be included?	
11.	How will outcomes for the comparisons be chosen to avoid selected outcome reporting biases? Outcomes have different clinical value, for example improvement on cardiovascular outcomes or mortality/survival is clinically more important than sole improvement in lipid levels or HbA1c in metabolic disorder trials. For other diseases, this hierarchy in outcome clinical value is more difficult to determine. When comparing two drugs, better efficacy can be statistically demonstrated for some of the outcomes while not for others. Therefore, guidance on the way outcomes will be chosen to evaluate evidence is needed in the protocol to avoid a bias when selecting the outcomes to undergo analysis.	The types of factors described in this comment will relate to judgments around whether substantial additional benefits have been demonstrated.
12.	GRADE is not an optimal assessment tool for observational and real world research, and thus is of questionable utility for a report designed to evaluate the evolving value of products in current clinical settings. GRADE's evidence hierarchy privileges data from randomized clinical trials (RCTs) at the beginning of the rating process and down weights evidence from observational/real world studies. The two types of studies of course provide answers to different questions: RCT answers the efficacy in a controlled clinical trial setting, observational studies (comparative) effectiveness in a real world setting. How this will be balanced to rate the overall additional net benefit in ICER's UPI Report? For example, take the example of a drug A with slightly but significantly better efficacy in RCTs than drug B, while poor adherence/persistence in real world leads to a better effectiveness of B compared to A. By process, GRADE will tend to favor drug A over B with potential consequences for the conclusions of the Unsupported Price Increase Assessment. ICER has previously shown substantial interest in incorporating real world evidence in its assessments, so it is disappointing that this protocol does not sufficiently address this issue.	Real world evidence can be of high or moderate quality. If it is not, we do not feel it can justify rapid price increases.
13.	Will the final categorization proposed in the report ("price increase with new clinical evidence" vs. "unsupported price increase") be based on GRADE criteria, or after applying ICER's matrix ratings for additional net health benefit? The translation from GRADE to ICER matrix ratings should be more clearly stated in the protocol.	The judgment on whether there is moderate or high quality evidence will rely on GRADE. The judgment of whether this evidence show a substantial additional net health benefit will be based on the ICER evidence matrix.
14.	There is no mention of sensitivity analyses or other efforts test the validity and reliability of the conclusions. This may give a false impression of precision to the findings. It is critical to evaluate the uncertainty associated with conclusions.	The UPI report will be transparent about uncertainty.

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15.	In general, we are concerned that the UPI report's designations will be characterized by high levels of uncertainty and inconsistent quality, given its reliance on the creation of a large, heterogeneous list of up to 13 products using diverse methods, limited assessment period and abbreviated appraisal process. It is important that ICER appropriately characterize this uncertainty and qualify findings, to avoid over interpretation of the report's conclusions when it is released.	The UPI report will be transparent about uncertainty.
UCB		
1.	ICER's undertaking to inform the public and policymakers of drugs with substantial price increases with no evidence generated or published in the previous 36 months would be a relatively simple process. It is where ICER attempts to then determine whether the evidence provided could justify the price increase that is seemingly more complex. Does ICER intend on creating committees with experts, including patients, that have direct experience with the drugs and indications identified for review?	There will be no attempt to judge whether the evidence justifies a given price increase as part of the UPI report. Only whether there is new evidence.
2.	The GRADE and ICER evidence matrix currently do not capture assessment of economic outcomes. How will this be integrated in the overall evaluation if the tools available do not allow for non-clinical elements to be assessed as low/high quality of evidence?	Economic outcomes are not part of the UPI evidence assessment.
3.	It appears that new evidence, specifically, clinical evidence, is most important factor in determining whether an increase in price is justified or not. For other 'potential justifications,' (page 7) how is each factor weighted and can these factors alone warrant a price increase?	There will be no attempt to judge whether the evidence justifies a given price increase as part of the UPI report. Only whether there is new evidence. The other factors will be reported on but will not be used to determine categorization in the UPI report.
4.	How does ICER plan to assess evidence and/or manufacturer commitments related to improving patient experience and/or satisfaction? This can include evidence related to innovative delivery mechanisms or less frequent dosing, both of which can lead to improved adherence and enhanced disease control.	Appropriate evidence for these outcomes would be considered.
5.	In ICER's review for new information, via systematic review or manufacturer input, will both prospective and retrospective observational studies be considered for review?	Yes.
6.	How will ICER review and rate studies that indirectly inform efficacy for a specific therapeutic area? For example: randomized trials, PK studies, or retrospective observational studies that provide insight into specific patient segments that may experience an incremental benefit in efficacy or safety versus the general population with the disease in question.	These will necessarily be subjective judgments.
7.	For any given indication, there may be several outcomes/endpoints that inform the incremental efficacy	In some situations, ICER may need to involve clinician experts.

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	or safety of a drug. How will ICER consolidate information across several outcomes and potentially across several GRADEs of evidence to make an informed decision on whether the evidence could justify a price increase? Will clinical physician specialists review and provide GRADEs for evidence submitted? How will discrepancies be reconciled?	
8.	Typically, ICER's evidence matrix ratings are using when comparing a common outcome across several comparators. How will the matrix be adapted to account for several outcomes with variability in GRADEs to provide a consistent rating?	If there is moderate or high quality evidence for any outcome or outcomes that lead to substantial additional net health benefit, the price increase will not be considered unsupported.
9.	Does ICER intend on publishing dichotomous results as "price increase with new clinical evidence" or "price increase with no new clinical evidence?" Given the levels of GRADEs that could be attribute to the evidence provided in addition to the levels captured in the evidence matrix, should there be a scaled response based on the certainty or uncertainty of the type of evidence provided and its proposed impact on the population of interest?	We intend to provide dichotomous results.
10.	Although a full cost-effectiveness analysis is out of scope, will there be any economic modeling considered? Especially since economic outcomes are being considered.	Economic outcomes are not part of the UPI evidence assessment once drugs are under review.
11.	While economic studies are considered as new evidence, the draft framework states that "nonclinical rationales will not be evaluated by ICER." Can ICER provide a clear framework on how economic information will or will not be reviewed and included in the assessment?	An economic study that collected new evidence could be reviewed. For instance, a trial that demonstrated a therapy allowed patients to earn more money because of less sick time would be reviewed.
Advocacy and Research Organizations		
Aimed Alliance		
1.	Study Design May Not Identify Most Egregious Price Increases. The Protocol proposes to assemble a list of the top 100 medications, determined by sales revenue in the United States. ICER will then identify the medications that have experienced a list price increase "over two times the medical Consumer Price Index over a two-year period." ICER will then analyze the net price increase that these medications experienced and select the top 10 medications whose price increases would generate the "largest increase in budget impact at the national level." We believe that this approach is flawed because it will not necessarily identify the medications that experienced the most unreasonable price increases. For example, several generic manufacturers have increased the prices of their products significantly, including products that have been in the market for many years. This protocol would exclude these price increases from the scope of ICER's review. We find this troubling because generic medications should offer the most promise for increased competition and	Generics are not inherently excluded from the review, but for this initial ICER report we will not be reviewing therapies that only have had large increase in budget impact in aggregate across multiple manufacturers. The three additional drugs could include generics for which a company has monopoly pricing power.

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	lower prices for patients. When generics fail to provide this benefit, the manufacturers are likely exploiting market forces to achieve unjustified profits. We recommend that ICER adjust its Protocol in order to identify the top bad actors in the industry, regardless of sales revenue.	
2.	Study Design Should Include Critical Actors in the Supply Chain. The Draft Protocol, by design, only analyzes data from manufacturers and excludes information from other actors in the supply chain who have a significant influence on the prices that consumers pay for their medications at the pharmacy counter. Without considering the behavior and trade practices of these entities, ICER's review will be incomplete. We recommend that ICER solicit data from insurers, PBMs, distributors, hospitals, and pharmacies, which could provide additional context for the prices that consumers pay for medications, inefficiencies or waste in the supply chain, whether drug prices are reasonable, and which entities are most responsible for high prices.	While there are many other participants in the delivery system, the UPI report is focusing on one piece.
3.	Wholesale Acquisition Costs Are Likely to Lead to Inaccurate Assessments. ICER's Protocol proposes to compare the wholesale acquisition cost ("WAC") and Consumer Price Index ("CPI") to determine the theoretical budget impact that a reference medication has on the national level. We recommend against using WAC as a variable in this calculation because other factors, such as rebates, discounts to PBMs, best price mandates, discounts to hospitals and health systems, wholesaler fees, copay assistance programs, and administrative fees to group purchasing organizations ("GPOs") and PBMs account for a significant portion of a medication's price. These factors are included in a medication's net price, but not the WAC. Determining whether a price increase is reasonable based on the WAC ignores the true cost of medications and may produce misleading results. For these reasons, we recommend that ICER only use net price as a reference and exclude WAC from these calculations.	We have modified our description of the process of identifying the top 10 drugs in our list. We will use the WAC only to filter drugs with list price change >2x medical CPI price change. Thereafter, we will use these drugs' net price change to derive budget impact.
4.	Length of Time on the Market Can Impact Drug Pricing. The Protocol does not account for fluctuations in price that are typically associated with the length of time that a product has been available on the market. When medications are introduced in the market, prices are often high, but they usually come down as patent and exclusivity protections expire. Therefore, depending on the situation, a price increase after the drug has been on the market for several years may be less justified than a price increase for a medication that is new to the market. Drug prices may also increase right before patent and exclusivity periods are scheduled to run out. We do not support tactics to keep drug prices artificially high and prevent generic drug	We agree that time on the market may influence drug pricing, but this will be beyond the scope of the UPI report.

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	entry into the marketplace, such as patent evergreening and other strategies that extend the life of patents without providing new clinical benefits to patients. These tactics are bad for patients and the health system overall. Therefore, investigating the length of time the drug is on the market, especially in relation to its patents and exclusivities could be helpful in assessing whether a pricing increase is justified or not. We recommend that ICER incorporate this data into its review to account for secondary factors that could influence pricing decisions.	
5.	Manufacturers May Not Be able to Share Requested Information. ICER proposes to solicit information from manufacturers about their medications and competitor medications that could justify a substantial price increase. Notably, ICER proposes to publish this information publicly in the final report. We caution that some of the data that ICER seeks from manufacturers may be prohibited. For example, the Food Drug and Cosmetics Act prohibits manufacturers from sharing certain data with the public if such data is not listed on the product's FDA-approved labeling because the information could be considered false and misleading. As such, manufactures may be prohibited from sharing information on potential new clinical indications or uses with ICER. However, such information may be critical in assessing a pricing increase.	Data may be submitted under ICER's academic in-confidence policy.
6.	The FDA recently released guidance titled "Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities – Questions and Answers" ("Guidance"). The Guidance notes that manufacturers may share health care economic information, including information on different dosing or use regimens, different endpoints, more-limited or targeted patient populations, with payers, formulary committees, and "other similar entities with knowledge and expertise in the area of health care economic analysis." Therefore, we recommend that ICER request an advisory letter from the FDA that would confirm that ICER is a "similar entity with knowledge and expertise in the area of health care economic analysis" in accordance with the Guidance. ICER should delay its implementation of this Protocol until it receives this confirmation from the FDA.	The UPI report is not an economic analysis.
7.	Non-Clinical Factors Do Not Receive Proper Consideration. In the Protocol, ICER indicates that it will request "other potential justifications for a price increase, including . . . a large increase in costs of production . . . large price savings attributable to the drug in other parts of the health system . . . [and] all other reasons deemed relevant by the manufacturers." Yet, the Protocol also states that "non-clinical rationales will not be evaluated by ICER as a	These justifications will be discussed in the report, but the UPI report is looking at whether there is new clinical evidence to support a price increase.

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	determinant in whether the drug is categorized as having its price increase unsupported by clinical evidence." It is unclear why ICER is requesting other potential justifications for a price increase when such information will not be incorporated into the final assessment of drug price increases. Considerations should be given to valid business practices that could contribute to increased drug prices, such as drug shortages due to shortages of raw materials or unanticipated demand, and manufacturing issues. This information should be given weight because unexpected increases in production costs are a legitimate reason to increase the price of a medication.	
8.	Orphan Drugs. As ICER acknowledged in its Orphan Drug Assessment published in November 2017, orphan drugs should be treated differently. For individuals with rare diseases, it is typical for very few medication options to be available. Pharmaceutical manufacturers do not prioritize developing these types of medications because generally there is little-to-no return on investment. Without being able to charge prices for these medications that could potentially generate at least some level of return on investment, there would be no incentive to bring these medications to the market. Due to these factors, we recommend that ICER exclude these types of medications from its assessment.	It is not clear why drugs used for orphan conditions should experience more rapid price increases than other drugs.
Biotechnology Innovation Organization		
1.	We believe the dichotomy between "possibly justified by new clinical evidence" or "unjustified" is inappropriate. This draft protocol fundamentally fails at accurately – and in a way that is helpful to policymakers and the public – describing when a price increase is "justified." How prescription drugs are priced is an incredibly complex process. Clinical considerations, supply chain dynamics, payor preferences, research and development, and market conditions all factor into how the price of a medicine is set. Yet nearly all these considerations are disregarded in the draft protocol.	Thank you, but we feel that large price increases for existing drugs in the absence of new evidence raise important public policy considerations.
2.	ICER's approach to seeking feedback and information from manufacturers as part of this process clearly illustrates the flaws in this methodology. Many of the considerations critical to prescription drug pricing are, and have long been considered, proprietary and confidential. However, ICER states that with the exception of its standing Academic-In- Confidence policy (in which ICER will not publish data provided by manufacturers that is awaiting peer review or public presentation), any information provided by manufacturers as part of this process will be included in the final report. This necessarily limits the types of information that manufacturers could provide to	We feel the UPI report will provide important information to policy makers, however obviously there is other information that stakeholders could choose to consider.

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	ICER as part of the UPI process. By definition, then, this methodology cannot provide a complete picture when it comes to how prices for prescription drugs are determined. Yet ICER seems to be framing this report as a tool for policymakers to do just that.	
National Health Council		
1.	We appreciate ICER's inclusion of a patient representative on the multi-stakeholder advisory committee. We encourage the consideration of additional patient representatives and engagement in the process. ICER should also outline a role for patient representatives within the individual reviews. For example, patient perspectives from those with experience in a particular disease area would provide useful insights within the scope of individual reviews. The draft protocol contains a detailed explanation of how manufacturers can submit information but is lacking in detail on how patients and patient organizations can contribute to the process in a similar fashion as ICER's therapeutic reviews.	Because this is not a value assessment, but an evidence assessment, there will be less stakeholder input than in an ICER report on a new drug or technology. In part, this is to address concerns from manufacturers about having drugs listed as being under review before a determination has been made about the existence of new evidence. However, there may be circumstances where for individual assessments in the UPI process that ICER will need to seek input from clinicians or patients to better judge whether an additional benefit is or is not substantial.
2.	Additionally, greater clarity on how ICER will identify "important affordability implications for individual patients even if not for the health system" is needed. Greater clarity on the intended meaning of "affordability implications" would be needed for operationalizing the program and improve transparency. The scoping document also does not describe whether or not the Advisory Committee will participate in the selection of the (up to) three additional drugs. If not, how will the drugs be selected? Since many patients struggle with the costs of drugs and only up to three public-identified drugs will be considered, transparent and detailed selection criteria would help facilitate the process.	We will consider revising the protocol after the first version of the UPI report as ICER and stakeholders have more information on how this plays out. Currently, we want to keep this flexible to deal with various issues that may arise. Examples of affordability issues may include drugs that typically are not covered or that require co-insurance and have experience large price increases that would then be passed along to individual patients.
3.	Additional details on how the independent systematic reviews will be performed would also be useful. For example, the scoping document refers to "high quality comparative observational studies." We recommend that ICER provide a definition or characteristics of "high quality" in this context.	ICER typically looks at USPSTF criteria in judging study quality.
4.	ICER's decision to categorize drug-price increases as either "price increase with new clinical evidence" (those with moderate/high quality new evidence of a substantial improvement in net benefit) or unsupported is a reasonable approach. However, it may be important to consider what is included under the "clinical evidence" umbrella. For example, we recommend consideration of other factors that typically fall into the "contextual considerations" category of ICER's therapeutic reviews, such as impact on adherence, social factors, productivity, quality of life, or other outcomes not typically considered	We did not intend to exclude this sort of evidence from consideration.

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	"clinical." Determination of impacts to consider would be greatly benefitted by engaging with patients and patient organizations	
5.	Finally, the NHC recommends greater clarity on the format of the pubic reports. We recommend that ICER publish a report that can be understood by individual patients and include information that explains what the potential impact may be for them. For example, our 2017 recommendation calls for a report that "offer[s] context around the selected drugs' pricing and attempt to characterize its health, economic, and societal benefits, measured through both short- and long-term patient outcomes, adherence, productivity, quality of life, and/or life expectancy."	The UPI report is not an economic analysis and so will not be able to provide this level of detail.
National Pharmaceutical Council		
1.	Value assessments should focus broadly on all aspects of the health care system, not just on medications. (Guiding Practice VII). Optimizing our health care resources by shifting our health care system from a volume-based focus to a value-based focus requires an examination of the entire system. Medications account for only 16% of health care spending, yet ICER puts almost 100% of its resources towards examining medications. NPC recommends that ICER shift resources to meaningfully examine the rest of the health care system.	Thank you, but we feel that large price increases for existing drugs in the absence of new evidence raise important public policy considerations.
2.	Sufficient time, staff and resources should be dedicated to support a thorough and robust assessment process. (Guiding Practice VI). What ICER hopes to accomplish with this report — in a relatively short timeframe — is an incredibly time-intensive and unprecedented undertaking. ICER notes in its draft protocol that "ICER does not have the capacity to perform full economic analyses on the large number of therapies that will be subject to analysis as part of this new report process. Therefore, these UPI reports are not intended to determine whether a price increase for a drug is fully justified by new clinical evidence." Considering these resource constraints, ICER should avoid making determinations, or at least add extensive caveats and acknowledge limitations. NPC recommends that ICER add caveats to any determinations and acknowledge their limitations.	We agree that the report should be transparent about limitations.
3.	ICER notes it does not have the resources to answer the question of whether price increases are supported by new evidence and, hence, does not seek to answer this question. This approach is only designed to identify cases where ICER believes the price increases are unsupported; it does not seek to identify supported price increases. This one-sided methodology will only present the biopharmaceutical industry in a negative way without	Thank you, but we feel that large price increases for existing drugs in the absence of new evidence raise important public policy considerations.

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	highlighting any positives. Taking a one-sided approach runs contrary to ICER's previously stated mission: "Our aim is not to support one side in a negotiation; it is to provide what our health care system has lacked for so long: an independent, trustworthy source of information that can bring all voices into the discussion on value." This one-sided approach does not contribute to a constructive discussion about drug prices and health care spending. NPC recommends that ICER undertake more comprehensive reviews that can identify cases where price increases are aligned with value.	
4.	Patients and society value more than clinical outcomes, including economic and humanistic types of outcomes. Ignoring non-clinical information such as health care resource utilization, medical cost offsets, work productivity, patient preference and/or caregiver burden dismisses these factors. We should encourage investment in all aspects of the patient experience and not place emphasis solely on clinical development. NPC recommends that ICER expand its analyses to include non-clinical information.	We did not intend to exclude evidence relating to productivity, patient preference, or caregiver burden from consideration.
5.	Sensitivity analyses should be performed, taking into account input from external stakeholders. (Guiding Practice XI). Whether a product's price increases are labeled as unsupported hinges on ICER's subjective assessment of the size of the clinical effect demonstrated by new evidence — if the effect is deemed "small," the increase is labeled unsupported; if the effect is considered "substantial," the unsupported label is not applied. There are no transparent criteria to differentiate between "small" and "substantial" effects — the categorization process lacks specificity and is not replicable. Further, there are no sensitivity analyses to explore the range of effects that lie between the binary choices of "small" and "substantial." NPC recommends that ICER use transparent and replicable ratings criteria and incorporate sensitivity analyses.	These sorts of judgments are routinely made by HTA organizations and are similar to the judgments made in every ICER report.
6.	ICER's proposed methodology lacks specificity. As noted above, the categorization of evidence scoring is subjective, and no complete definition or academic references have been provided by which to assess best-use cases. It is unclear how ICER will weight outcomes (overall survival vs. progression-free survival, for example), or whether evidence related to a new indication will be weighted more or less than additional outcomes or safety evidence for an older indication.	Thank you. We believe that the GRADE methodology has been extensively described in the EBM literature.
7.	ICER should avoid using terminology and phrases that are imprecise or lack objectivity, e.g., "extremely high price increases"; "fell just below"; and "raise concerns about	We do not feel we can provide precise definitions of all these terms, however we feel that most stakeholders will be aware of drugs that have, for

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	fairness." Such terms may potentially alienate stakeholders, particularly in the absence of transparent and clearly stated assumptions. The normative basis of "fair," "unsubstantiated," "substantial," etc., should be made explicit and transparent. NPC recommends that ICER clarify methods and terminology to facilitate transparency and reproducibility.	instance, experienced extreme price increases in the absence of new evidence. Such price increases would far exceed the cutoff (2 x medical CPI) used for the 10 drugs.
8.	Stakeholders should be given the opportunity to submit relevant evidence, such as clinical trial and real-world evidence beyond the public literature. (Guiding Practice XXI). While ICER does give manufacturers the opportunity to submit relevant evidence, only some of this evidence will be protected. Proprietary clinical information will be protected under the ICER's "academic in confidence" policy; proprietary confidential financial information, however, will not be protected. Manufacturers' confidential commercial and trade secret information have significant trade protections under law and regulations in many contexts. These protections should be recognized by ICER and extended to information manufacturers may choose to submit in response to an ICER inquiry. Failure to provide complete protection will limit the types of information that manufacturers can submit and, therefore, provide an incomplete picture of value. NPC recommends that ICER fully protect the confidentiality of manufacturer information.	We feel that if large price increases are not supported by new evidence, the public has the right to know how manufacturers are justifying such price increases. However, manufacturers are welcome to submit "We are increasing our prices based on confidential internal information" and we would report on this in the UPI report.
9.	In addition, the evidence review limits the amount of evidence considered by an arbitrary cutoff of approximately 10% or more of the drug's use. There is a huge need for better treatment of rare conditions and many pediatric indications, and this arbitrary cutoff appears to disregard important areas such as these. This disadvantages products with multiple indications and is in opposition to Food and Drug Administration incentives to research and invest in smaller, yet high burden, disease areas. NPC recommends that ICER reconsider the 10% utilization threshold when examining new data.	We feel the approximate 10% cut point addresses situations where price changes are implemented due to expanded indication in or use in a very small population. The drugs on the list will have had increases in price at more than twice the increase in medical CPI, and this seems hard to justify if new evidence does not apply to 90% of a drug's use.
Patients Rising Now		
1.	The process described in the Draft Protocol document is limited in several ways that could lead to inaccurate assessments and conclusions because of the restricted scope of the analyses and data that will be considered. By self-limiting this process, ICER is leading itself – and any individuals or organizations that may use the output from reports generated in this process – towards warped understandings of prices and value. While it is certainly true that no research can be entirely comprehensive because of time, resource, and data constraints, wise researchers and analysts know how to carefully frame	We do not understand why an organization purportedly worried about patient access and patient care would not support a report looking at large unsupported increases in drug prices.

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	their conclusions and insights within the context of those limitations – including in their public presentations of their findings, and particularly when conveyed to the media and lay audiences. We are concerned about the limitations of the Draft Protocol because of ICER's history in this area, and the utilization of ICER's reports – including draft reports – for sensationalizing to the public and the resulting limits to patient access.	
2.	We are once again disappointed that ICER continues to minimize the importance to patient's perspectives in their proposed analytical methodology. For example, while the Draft Protocol does include a process for determining net prices to manufactures, it does not recognize that those net prices may have only limited connection to what patients actually pay. That is one of the driving forces behind the Federal government's proposal to shift such discounts from going to health plans to going directly to patients, as mentioned above.	The proposal uses both list price increases and net price increases in getting to the list of 10 drugs for this reason.
3.	We are also concerned about the Draft Protocol limiting itself to only economic analyses, which appears to preclude looking at offsetting savings related to productivity or other aspects of patients' lives such as transportation, caregiver time, and other family burdens. This is particularly perplexing since those factors are an area that ICER routinely requests input for other assessments, yet the Draft Protocol specifically states that it will not consider non-clinical factors in its analysis. We believe ICER should explain in greater detail why it is circumscribing the range of inputs for its analysis in this area – and by doing so explicitly limiting the information important to patients.	The UPI project is not a value assessment project.
4.	We are concerned about the limited scope of information the Draft Protocol will include and how that could prevent consideration of larger changes to overall care protocols in a disease area. For example, as precision medicine continues to expand with greater accuracy of diagnostics and treatments, more specific diagnoses can lead to methods or criteria that would affect treatment decisions that may not be reflected in product labels or be specific to a single product. We would like ICER to explain how such information would be considered in its process, particularly if a company would be precluded from providing ICER such information because it is not reflected in any changes to an FDA approved label.	We do not believe manufacturers are precluded from providing such information to ICER.
5.	Another aspect that is missing from the Draft Protocol is how treatments for ultra-rare conditions will be assessed. Because ICER has a modified value framework for those diseases, we recommend ICER provide insights about how any analyses and reports based upon the Draft Protocol	It is not clear why drugs used for orphan conditions should experience more rapid price increases than other drugs.

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	(or a Final Protocol should one be issued) will address the differential nature of ultra-rare diseases.	
6.	The Draft Protocol says that it will not consider multi-source generics, but a recent report showed that generics with three or fewer manufacturers can have greater than average price increases over time – particularly when there is a shortage of that medicine. We would like ICER to respond to the findings of this study and explain why price increases in generic medicines should be beyond the scope of its activities.	This is a choice for this initial UPI report.
7.	As you know, biosimilars are an emerging type of medicine that are expected to decrease the overall cost of care. However, the Draft Protocol does not address how biosimilars will be incorporated into ICER's process. We believe that biosimilars – whether declared interchangeable or not – should be considered along with the original biologic medicine that they are "similar" to when evaluating overall cost changes in a therapeutic area. We would like ICER to respond and provide an explanation about how biosimilars will be treated by ICER in potential analyses in this activity.	Biosimilars and the drugs they are similar to can both be reviewed as part of the UPI project. It is unclear why the emergence of a biosimilar would lead to rapid unsupported price increases.
TruDataRx		
1.	First, what is the practical purpose of the UPI reports, and how does ICER intend for them to be used? ICER's comparative effectiveness analyses allow the public - including patients, providers, payers, and policy makers - to determine the economic value of a drug. This can practically impact decisions such as which drugs a provider prescribes, or which drugs a payer chooses to cover. Alternatively, an ICER report can influence a manufacturer's pricing decisions, as occurred when the price of evolocumab was reduced partly in response to ICER's value assessment for PCSK9 inhibitors. It is unclear whether the new UPI reports would have a similar influence, as they will be comparing a drug's current value to its historic value without offering a clear picture of what alternatives may be available. In a press release, the president of ICER mentioned that "several states have already passed laws that will generate lists of drugs with substantial price increases so that policy makers and the public can seek greater transparency," but some critics have pointed out that these laws don't empower states to take action against price increases. Instead, they mainly provide an avenue for shaming manufacturers who raise prices too quickly. It seems that ICER's UPI reports may help to focus that shame where it is most deserved, but it is not yet clear that manufacturers will actually respond to that shame.	It is difficult to judge the impact of the UPI report at this point in time.

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2.	Second, although the UPI report draft protocol states that it will seek new evidence about both benefits and harms of the drugs being reviewed, it seems to assume that overall, new evidence will primarily provide information about added health benefits. However, it is possible that new clinical evidence will bring to light safety issues that are infrequent or only occur after long term use of a drug. It is also possible that a drug that is meant to be used chronically and was approved on the basis of relatively short-term data, such as RCTs lasting 2 years, are shown to have lackluster long-term efficacy data. Has ICER considered the possibility that a drug's overall net health benefit may have actually decreased in light of new information about the long-term safety and efficacy of a drug? What conclusions about price increases might be drawn for a drug with new safety concerns or poorer than expected long-term efficacy?	A decrease in net health benefit would be interpreted as failing to show additional new net health benefit.
3.	Third, does ICER intend to include generic drugs in its UPI reports? If so, how? The draft protocol states "a rise in price across multiple manufacturers of a generic medication that in combination had a large change in budget impact would not be included in the review." Although the background section of the protocol states that both brand and generic drug prices are a matter of concern, it is unclear how the UPIs will be able to assess price increases for the vast majority of generic drugs, as generics typically have multiple manufacturers. In light of the December 2018 news about 16 generic drug companies being investigated over allegedly price-fixing more than 300 drugs, the question of a rise in price across multiple generic manufacturers should be given stronger consideration in the UPI protocol.	Generics are not inherently excluded from the review, but for this initial ICER report we will not be reviewing therapies that only have had large increase in budget impact in aggregate across multiple manufacturers. The three additional drugs could include generics for which a company has monopoly pricing power.
4.	Fourth, does ICER intend to ensure that the UPI reports cover a range of drugs that represent different aspects of the pharmaceutical market? Pharmaceutical drugs may fall into different categories, including but not limited to generic vs. brand, biologic vs. non-biologic, hospital administered vs. self-administered drugs, drugs that are delivered via a patented device such as inhalers or "pens" for subcutaneous injection, and so on. If, by chance, the top 10 drugs whose net price increases have had the largest impact on US spending over the prior two years happen to include drugs that are very similar to each other and may reflect the same market trend - e.g., if most of the 10 drugs are biologics - will an effort be made to include less similar drugs - e.g. non-biologics - in the selection of the up to 3 additional drugs?	If the same drugs show up in the report year after year, ICER may consider modifications to the protocol in the future. We do not currently think we will consider the categorizations of the 10 drugs in deciding which three additional drugs should be evaluated.

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Individual Researchers		
Dan Ollendorf, PhD, Center for the Evaluation of Value and Risk in Health, Tufts University		
1.	The decision to use the medical care CPI as a measure of drug price inflation is not clear to me. All components of the CPI are based on a "market basket" approach to measurement that aligns most closely with out-of-pocket expenditures. While these are certainly significant (and growing) for prescription drugs, the majority of a drug's list or negotiated price is borne by third parties. Other publicly-available indices include third-party payments, such as the Personal Health Care (PHC) index published by CMS or the Personal Consumption Expenditure health (PCEhealth) index available from the Bureau of Economic Analysis. The CPI has also been found to overstate inflation as individuals substitute away from goods or services with rapid price increases.	We feel that price increases at more than twice the rate of medical inflation for the highest budget impact drugs raise important public policy considerations. While other measures could be used, CPI is generally well known to the public.
2.	There is likely to be a need to use an alternate (FSS or other) schedule for more than just prescription drugs produced by privately-held companies. Several drugs with highly specialized distribution systems (bypassing agents for hemophilia come to mind) are also not well-captured by the SSR dataset.	Thank you, we have added text to reflect this.