

June 11, 2021

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates this opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report regarding treatments for atopic dermatitis (AD). AD is a lifelong, chronic condition with no current cure that impacts more than 9.6 million children and 16.5 million adults in the United States. It can have a huge impact on patients' quality of life causing severe itching and pain, which can lead to difficulty sleeping and lost productivity.¹ It is imperative that the needs of these patients and the value treatments bring to them are being considered in any value assessment for AD. We encourage ICER to consider the following comments on its draft evidence report.

ICER's model is not sensitive to or reflective of the outcomes that matter most to patients.

In ICER's *Patient and Caregivers Perspective* section of the draft evidence report, it is clear that the primary symptom of concern for AD patients is itch. Patients express that itch can lead to a host of additional problems including skin pain and infections, as well as disrupting sleep and causing anxiety and depression. It is primarily through itch and pain, that AD can have a profound impact on life activities, interpersonal relationships, and the ability to be productive at work. Patients highlighted the need for therapies to address itch and pain that work quickly, provide sustained relief, and are safe for long-term use.

Other than discontinuation rate, none of these aspects of importance raised by patients was incorporated into the model. The cycle in the model was 16-weeks, so any benefit from a therapy that resulted from a quick response as compared to a slower or delayed response would be missed in the ICER model. Similarly, long-term data was not used in the construction or execution of the ICER model. We would encourage ICER to rework the model to ensure the benefit of expedient relief is captured.

¹ <https://nationaleczema.org/eczema/types-of-eczema/atopic-dermatitis/>

Despite the emphasis patients put on the importance of itching on their quality of life, the ICER model is structured solely around Eczema Area and Severity Index (EASI) score, which combines coverage, location and severity weighted equally by clinicians – not patients. Recent studies have suggested that itch-specific measures have weak-to-moderate correlations with EASI.² There are more sensitive resources available that do capture a more accurate picture of the patient’s experience with itch and pain, and we would encourage ICER to look to these for its model. For example, the model could be built on a combination of EASI and PP-NRS or used patient itch questionnaire - numerical rating scale and verbal rating scale (PIQ NRS, VRS)³ or frequency of itch.⁴

For example, ICER states that more patients achieved a ≥ 4 -point improvement in PP-NRS with upadacitinib 30 mg than dupilimumab (55% vs. 36%).⁵ But since the ICER model is based solely on response as defined by change in EASI score, upadacitinib is considered to be ‘less effective’ than dupilimumab. Subsequently upadacitinib has almost twice the efficacy of the comparator in terms of the one outcome that matters most to patients but still the model shows these two treatments to at best be equal in efficacy, and at worse, less effective than the comparator. We would highly encourage ICER to rework its modeling to ensure it is capturing the outcomes that matter most to patients.

ICER’s model continues to use the discriminatory Quality-Adjusted Life Year (QALY) and relies on population averages and does not take into account patient heterogeneity.

We would like to reiterate that the QALY innately discriminates against people with disabilities and chronic illnesses and is an inappropriate tool for assessing value.⁶ We would encourage ICER to look to more sensitive mechanisms that do not rely on population level averages and do a better job incorporating the outcomes that matter to the specific patient population in question.

In addition to its reliance on the QALY, ICER compares all treatments it is assessing to placebo or dupilimumab, under the assumption that both the index and comparator drugs are similarly effective for each patient. This is an example of when the value assessments only looking at the “average” patient will not reveal accurate or useful information on actual efficacy of treatments. For many patients dupilimumab will not

² Silverberg JI, Lai JS, Patel KR, Singam V, Vakharia PP, Chopra R, Sacotte R, Kantor R, Hsu DY, Cella D. Measurement properties of the Patient-Reported Outcomes Information System (PROMIS®) Itch Questionnaire: itch severity assessments in adults with atopic dermatitis. *British Journal of Dermatology*. 2020 Nov;183(5):891-8.

³ Phan NQ, Blome C, Fritz F, Gerss J, Reich A, Ebata T, Augustin M, Szepietowski JC, Ständer S. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. *Acta dermato-venereologica*. 2012 Sep 1;92(5):502-7.

⁴ Oosterhaven JA. How to measure itch in atopic dermatitis?. *The British Journal of Dermatology*. 2020 Nov 1;183(5):802-3.

⁵ RINVOQ™ (upadacitinib) Achieved Superiority Versus DUPIXENT® (dupilimumab) For Primary and All Ranked Secondary Endpoints in Phase 3b Head-to-Head Study in Adults with Atopic Dermatitis [press release]. 2020

⁶ NCD Report

work, will stop working after treatment initiation, or will be discontinued due to side effects. For all three of these groups, the comparison to dupilimumab is irrelevant. We would encourage ICER to abandon its reliance on population level averages and address the question of value from the perspective of patients who have very particular needs from their treatments.⁷

ICER's inputs are opaque, and we would encourage more transparency.

The cost-effectiveness calculations in ICER's model are largely driven by the choice and application of the health utility weights within the QALY. In the past ICER has been urged by various stakeholders to be more transparent.⁸ Unfortunately, this specific report seems to take a step backwards and is less transparent than many previous reports, as many of its inputs are blacked out. It is very difficult for stakeholders to make comments on data choices we cannot clearly see. We would encourage ICER to be transparent about its choice of utilities and make a concerted effort to share more, not less, data with stakeholders as it continues performing assessments.

ICER uses randomized clinical trial data when real world estimates of utilities for health states, particularly for active disease, are likely to be more representative of the population of need.

As a general rule, real-world cohort-based estimates of utilities, especially for active disease states (non-response) will provide more accurate data than relying on randomized clinical trial data. Clinical trials are known to recruit healthier patients than those people who make up the real-world population of need.^{9,10} There is also the problem of the placebo effect in randomized clinical trials on patients in the comparator arm.^{11,12} Finally, patients in RCTs tend to receive far more non-treatment specific care and attention; symptom management, and interaction with clinicians than the average patient in a real-world setting.¹³ As such, quality of life measures in patients non-

⁷ Basu A, Grieve R, Pritchard D, Stevens W. One size does not always fit all in value assessment. *Am J Manag Care*. 2019 Nov 1;25(11):540-2.

⁸ Hay JW. Now is the time for transparency in value-based healthcare decision modeling. *Value in Health*. 2019 May 1;22(5):564-9.

⁹ Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, Dieppe P. The causes and effects of socio-demographic exclusions from clinical trials. *Health Technology Assessment (Winchester, England)*. 2005;9(38):iii-152.

¹⁰ Shrier I, Boivin JF, Steele RJ, Platt RW, Furlan A, Kakuma R, Brophy J, Rossignol M. Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. *American journal of epidemiology*. 2007 Nov 15;166(10):1203-9.

¹¹ Hussain-Gambles M, Atkin K, Leese B. Why ethnic minority groups are under-represented in clinical trials: a review of the literature. *Health & social care in the community*. 2004 Sep;12(5):382-8.

¹² Glasziou PP, Simes RJ, Gelber RD. Quality adjusted survival analysis. *Statistics in medicine*. 1990 Nov;9(11):1259-76.

¹³ West J, Wright J, Tuffnell D, Jankowicz D, West R. Do clinical trials improve quality of care? A comparison of clinical processes and outcomes in patients in a clinical trial and similar patients outside a trial where both groups are managed according to a strict protocol. *BMJ Quality & Safety*. 2005 Jun 1;14(3):175-8.

response states are often higher for patient in randomized clinical trials than in real world cohort studies.

Given the availability of real-world estimates of utilities, we would encourage ICER to use this available data instead of relying on utilities from randomized clinical trials. Literature based values for utilities have been preferred in the vast majority of AD models produced in the last decade.^{14,15,16} A recent review of studies measuring health utility weights in AD patients showed a fairly consistent conclusion that untreated moderate to severe AD had a fairly consistent estimate of 0.61.¹⁷

Conclusion

PIPC echoes some of our consistent feedback in this comment letter urging ICER to be more transparent, incorporate outcomes that truly matter to patients, and account for patient heterogeneity.

Sincerely,



Tony Coelho
Chairman
Partnership to Improve Patient Care

¹⁴ Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, Ong PY, Fuxench ZC, Simpson EL. Health utility scores of atopic dermatitis in US adults. *The Journal of Allergy and Clinical Immunology: In Practice*. 2019 Apr 1;7(4):1246-52.

¹⁵ Lundberg L, Johannesson M, Silverdahl M, Hermansson C, Lindberg M. Quality of life, health-state utilities and willingness to pay in patients with psoriasis and atopic eczema. *British Journal of Dermatology*. 1999 Dec;141(6):1067-75.

¹⁶ Schmitt J, Meurer M, Klön M, Frick KD. Assessment of health state utilities of controlled and uncontrolled psoriasis and atopic eczema: a population-based study. *British Journal of Dermatology*. 2008 Feb;158(2):351-9.

¹⁷ Capucci S, Hahn-Pedersen J, Vilsbøll A, Kragh N. Impact of Atopic Dermatitis and Chronic Hand Eczema on Quality of Life Compared With Other Chronic Diseases. *Dermatitis*. 2020 May 1;31(3):178-84.