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**Sir,
Response to: Comment on 'Cost effectiveness of collagen crosslinking for progressive keratoconus in the UK NHS'**

We thank Dr Godefrooij and his colleagues¹ for their interest in, and their thought-provoking comments regarding, our work. We are aware of the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study,² which was a repeated measures evaluation of 1209 patients recruited from 16 centres in the USA and followed up for 8 years beginning in the mid to late 1990s.² All except two centres recruited over 60 patients. The patients' mean age at enrolment was around 39 years, with around 250 aged under 30.² Patients were not specifically selected according to any progression rate criteria. All patients completed the SF36 at baseline but not so far as we are aware, thereafter, although NEI VFQ scores were measured year on year.² The SF36 raw scores have not been published. There are also some practical problems using this data for our type of analysis. These are, first, the fact that it has a multi-centre structure that might lead to difficulties modelling the correct uncertainty.³ Second, the number of patients in the set who correspond to our decision problem criteria might be very small.

Dr Godefrooij and colleagues have provided valuable further insight into the difficulties of estimating utility values from clinical data. We are not surprised by the poor association between keratometry values and utility values, as these represent opposite ends of the proximal–distal continuum of outcome measurements. Their findings with regard to utility *vs* keratometry on the SF36 are certainly perplexing, and would imply that not even corneal grafting could be offered to keratoconus patients. Quality of life is obviously modulated by many factors apart from simple clinical measurements. However, cost effectiveness studies are essentially of a comparative nature. The comparison in this case is between collagen crosslinking (CXL) and standard treatment, including corneal transplantation. We find that if Dr Godefrooij's keratometry-derived utility values are modified so that any increments in utility associated with obvious disease worsening are amended to no change, as seems reasonable, then our model predicts that CXL would be cost effective at willingness to pay thresholds greater than around £14 000 per QALY in our base case scenario. Utilities based on

visual acuity are therefore likely to give similar results to our own. It seems that the present need is for progress on how utility is measured in keratoconus.

The correlation between visual acuity in the better eye and utility has been demonstrated many times^{4–7} and seems to persist in multivariate regression models.⁶ It has also assumed a central role in cost effectiveness modelling. The most vivid example of this, perhaps, remains the decision by the UK National Institute of Health and Care Excellence regarding licencing of treatment for age-related macular degeneration.⁸ We note that the correlation appears well demonstrated on vision-specific scales^{4,5} (absolute values of Pearson's *r* of the order of 0.4–0.67), but may be less on generic health-related quality of life (HRQoL) scales such as the SF6D and EQ-5D,^{6,7,9,10} as Dr Godefrooij's absolute value of 0.113 also suggests. The square of Pearson's *r* is equal to the proportion of measured variance in an outcome variable that is explained by the predictor variable in a univariate regression model.¹¹ This result means that better eye visual acuity 'explains', at best, up to around 45% of the overall variance in patients' utility scores. Dr Godefrooij and his colleagues' result thus corresponds to around 1.3% of the total variance in the SF36 scores in CLEK.² These estimates perhaps partly explain why not all are convinced that better eye visual acuity should be accorded such importance,¹² and that other correlations for example with worse eye visual acuity and visual field defects may also be relevant. We feel confident that Dr Godefrooij and many others would welcome a reappraisal of the situation, especially with regard to generic HRQoL *vs* vision specific scales, patient *vs* public elicitation, and disease specific factors.¹² Dr Godefrooij and his colleagues' suggestion that the SF36/SF6D is a poor instrument for measuring disutility in visual disease is very likely to be correct.^{9,10} The implications with regard to the EQ-5D and decision-making have been highlighted previously.¹³ Their further suggestion that patients show adaptation to their condition over time also seems very plausible. We would also propose that the patients in the CLEK data are subject to a variety of confounding factors such as chronic disease, age, economic status etc. For example, there were 99 reports of coexisting cardiovascular disease, diabetes, or cystic fibrosis.² On the other hand, the numerous additional reports of asthma and other atopic conditions,² which have been linked to keratoconus,² suggest that even if the disutility of diminished visual function is adequately measured, the overall disutility of keratoconus has additional dimensions.

At the present time, we still feel that the largest degree of parameter uncertainty is to be found in the duration of treatment effect, which is also clearly illustrated in our results. In this context, the recently published follow up results of the Wittig-Silva RCT¹⁴ (for example) are welcome, but it will be sometime before the results of more substantial follow-up are available.

Conflict of interest

The authors declare no conflict of interest.

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