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LETTERS TO THE EDITOR

TIDI Addresses Uncertainty But Not Indeterminism

To the Editor—Transparent interactive decision interrogator (TIDI) [1] allows decision makers to run advanced statistical models under different scenarios in real time, increasing transparency and avoiding problems associated with preprepared analyses. It will be particularly useful in circumstances (similar to the examples in the article) in which there is evidence to inform the model structure and parameters, but that evidence is subject to uncertainty.

For some pharmaceuticals, however, there will be some parts of an economic model where no evidence is available at all. This is *indeterminism*, rather than *uncertainty* [2]. For example, imagine that an adjuvant therapy has been developed for use in a subgroup of melanoma patients (e.g., those in whom the cancer has spread to regional nodes). Further imagine that the randomized controlled trial (RCT) for marketing approval has a median follow-up of 24 months and that the point estimate of the hazard ratio (HR) for overall survival (OS) is 0.70 (which is considered clinically important), but that follow-up is not long enough to estimate median or mean OS.

For cost-utility analysis, an estimate of difference in mean OS (i.e., life-years gained) is needed. Given the available evidence, this will require modeling (extrapolation) of the OS beyond the time horizon of the RCT. One option is to assume constant HRs. This is possibly reasonable in this circumstance because, for colon cancer, there is good evidence that the HR for OS for some adjuvant treatments is constant (~0.7) out to 8 years [3].

A competing assumption is to allow the HRs to approach 1.0 and then exceed 1.0. This is the case for some adjuvant treatments for breast cancer [4], and is explainable in terms of selection bias [5]. That is, patients with the poorest prognosis die at different rates in the two groups, so that although the two groups were balanced at the start of the RCT, they become increasingly unbalanced as the RCT progresses [5].

Unless the requested price is only slightly higher than current standard treatment (best supportive care), these two competing assumptions (i.e., constant vs. nonconstant HR) will produce completely divergent conclusions about the adjuvant treatment for melanoma (i.e., cost-effective vs. dominated). From a value-of-information perspective, the decision maker could conclude that the long-term HR is critical information that should be collected before a subsidy decision is made. Such information, however, would take at least 5 years to reach maturity, during which time there will be inequitable access to a potentially life-prolonging drug (i.e., only those affluent enough to afford the drug will have access).

In any case, a decision about whether to subsidize or wait for further evidence needs to be made now, on the basis of the currently available evidence. Given that a critical piece of evidence (long-term HR for OS) is indeterminate, a full-blown economic model would not provide any more information than a cost consequence analysis. In fact, it could be argued that the cost consequence analysis is a clearer, more precise, and more elegant way to help decision makers use the available (imperfect) evidence to make a decision they cannot avoid [6].

In short, TIDI will be helpful in some circumstances, but not all. In all jurisdictions, the resources for health care technology assessment are finite (and in some jurisdictions they are scarce). Therefore, judgments will be needed about when it is useful to allocate resources to developing a full-blown economic model with TIDI-like output and flexibility and when a simpler approach would be as informative.

Coproduction of research for decision making is essential [7]: prudent subsidy decisions require early and frequent interactions between experts in clinical medicine and experts in modeling. Often, several iterations will be required to identify the critical inputs. This will avoid the unnecessary expense of constructing a model with an abundance of detail in some aspects, while a critical piece of evidence is indeterminate [8].

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Transparent Interactive Decision Interrogator—Reply to Letter to the Editor by Michael Coory

To the Editor—We thank Prof. Coory for his comments on our work on the transparent interactive decision interrogator (TIDI). We agree that TIDI cannot be applied to all scenarios in medical decision making, certainly not in the form exactly presented in our article in *Value in Health* [1]. This first version of TIDI was developed as a proof-of-concept for an illustrative example in antenatal care. Subsequently, a version of TIDI has been developed for a real technology appraisal of biopharmaceuticals in the treatment of psoriatic arthritis [2] to be test run within a real reimbursement decision-making process by the National Institute for Health and Clinical Excellence in the United Kingdom. In both cases, the illustrative example and the real-life technology appraisal, there was evidence available to populate the health-economic model including the effectiveness data. TIDI was tailored to the specific needs of these models. The software was, and still is, however, at a proof-of-concept stage and it does not address all the modeling issues. TIDI certainly does not have the ability to make up for the lack of data; it can only facilitate the model interrogation by using available evidence.

Despite its limitations, TIDI has a potential to be a useful tool in exploring the boundaries of evidence. When long-term outcomes, such as the 5-year survival rates in melanoma, are not available, it is very difficult to make reimbursement decisions, we agree. Systems such as TIDI, however, can enable decision makers to carry out deterministic sensitivity analyses, for example, of alternative extrapolation techniques to investigate the effect of alternative assumptions on the estimates of cost-effectiveness. Existing analogous evidence and/or background knowledge can be built into TIDI to carry out analyses that would help decision makers to make judgments about the relative plausibility of different assumptions.

The version of TIDI presented in *Value in Health*, for the example in antenatal care, focused mostly on the parameter uncertainty. It can be tailored, however, to address other sources of uncertainty such as structural uncertainty. The interrogator developed for the psoriatic arthritis model allowed for sensitivity analyses of some modeling assumptions, for example, alternative ways of modeling utility and cost, alternative stopping rules for the Markov model, or some subgroup analyses. TIDI can certainly be tailored to suit a number of purposes and ways of dealing with uncertainty. For example, methods of parameterizing structural uncertainty have been developed that allow for a direct representation of the uncertainty in the model, which can facilitate inferences about the value of further research by estimating the expected value of information [3]. TIDI can be adapted to facilitate this kind of analysis. TIDI-like tools can also be designed to facilitate elicitation of expert opinions, which can then be integrated in the model in the form of prior distributions. Methods of elicitation of experts' opinions have been already developed, for example, to parameterize the structural uncertainty related to unknown long-term treatment effects [4] and also to account and adjust for biases in evidence synthesis [5]. Our future research will be focused on designing TIDI methods for a range of commonly occurring challenges in modeling in health technology assessment.

Prof. Coory is certainly making a valid point in saying that discussions between experts of multidisciplinary teams are required prior to obtaining the final model and "often several iterations will be required to identify the critical inputs." The version of TIDI developed for the technology appraisal by the National Institute for Health and Clinical Excellence was developed at the final stage of the modeling process when the academic group commissioned to carry out the analysis achieved consensus on the model structure following discussions between clinical and statistical experts and health economists. It was created with decision makers in mind to allow them to make formal judgments about model assumptions, evidence, and uncertainty. When analysts present the results to decision makers, they are constrained to a limited number of scenarios based on alternative modeling assumptions. TIDI facilitates the construction of a potentially infinite number of scenarios, hence avoiding limitations of the preprepared analysis. It can be tailored to the needs of a specific decision problem regardless of how small or big the problem is.

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