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"Stick or Twist?": Negotiating Price and Data in an Era of Conditional Approval

Running title: Negotiating in an era of conditional approval

Abstract

Background: Changes in the regulatory context enable faster approval of transformative medicines. They also lead to HTA agencies having to make decisions with less evidence. In response HTA agencies have also initiated forms of conditional approval. When the evidence base for a new oncology treatment leaves substantial uncertainty, the new Cancer Drugs Fund allows the National Institute for Heath and Care Excellence to give the manufacturer two options: (i) offer a low price based on conservative assumptions and obtain immediate approval ("stick"); or (ii) wait until the evidence base has further matured before finalising a potentially higher agreed price ("twist").

Objectives: The purpose of this article is to explain how, using the theoretical framework of the expected value of sample information, simulation methods can help inform manufacturer's decisions when faced with the option to "stick" or "twist".

Methods: We first summarise a general model to help frame the manufacturer's negotiating strategy. We then use a motivating case study, based on a hypothetical immunotherapy, to illustrate how manufacturers can use simulation methods to robustly characterise the uncertainty inherent to further data collection and incorporate this uncertainty within their decision making.

Results: Our approach allows us to estimate the commercial value of generating additional data (the difference between "stick" and "twist's" estimated net present value). We test the sensitivity of the results to different assumptions via scenario analyses.

Conclusions: This article shows that simulation methods can be used to help pharmaceutical managers make informed strategic decisions in contexts of uncertainty.

Highlights

- The changing regulatory and HTA context means it will be increasingly important to estimate the value of collecting further information. Expected Value of Sample Information (EVSI) provides a framework for this
- To date EVSI has predominantly been applied from the perspective of the HTA organisation rather than the manufacturer. Our contribution is to use a motivating case study to explain how simulation methods can be used to estimate the expected *commercial* value of sample information
- We show that the uncertainty inherent in collecting further data can be characterised. This allows pharmaceutical managers to make decisions that formally incorporate this uncertainty

Introduction

Background

The context for the development, approval and reimbursement of new medical interventions is evolving rapidly. Companies are increasingly focussing on areas with high unmet need[1,2]. The development of immunotherapies, including the chimeric antigen receptor T-cell therapies, mean that some patients who would have previously been considered at the "end of life" may now have a prognosis similar to the general population[3]. This changing development landscape has been accelerated by changes in the regulatory context. For interventions addressing areas of high unmet need the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have launched initiatives to lower the regulatory hurdle[4–6]. Conditional, or accelerated, approval may be granted to these interventions to allow earlier access. Manufacturers then need to return to the regulators with further data in order to be granted "standard" marketing authorisations following re-assessment[4–6].

Though the regulators' increased flexibility may increase the speed with which patients can access "breakthrough" medications it will likely increase the competition for scarce resources[7]. Health Technology Assessment (HTA) bodies may have to make an initial assessment on a sparser evidence base[8,9]. Some bodies such as the Italian Medicines Agency (AIFA) have long been comfortable with the need to *repeatedly* assess the link between an intervention's observed effectiveness and its reimbursed price[10]. Until recently many bodies, including NICE, have adopted a binary approach – relying on the evidence available at launch, to assess whether an intervention is an effective use of public funds. The re-launched Cancer Drug's Fund (CDF) changes this for oncology interventions. Under the revised arrangements a new therapy may now be approved, rejected or *approved with research*.

When attempting to launch an oncology intervention a manufacturer now faces a more complex decision. Previously it could either de facto withdraw by keeping the price at a level the company knows is un-approvable within the cost-effectiveness framework, or reduce the price in order for the intervention to be considered cost-effective. Now it can either: (i) withdraw; (ii) permanently reduce the price and access baseline commissioning ("Stick"); or (iii) seek approval with research with the expectation that the additional data supports a higher price ("Twist"). Into this context the recent DSU guidance by Grimm et al. provides advice to the NICE decision makers but how can manufacturers make informed decisions when faced with high levels of uncertainty[11]?

Estimating the value of information

Value of Information (VoI) methods provide an approach for assessing the value of further evidence collection [8,9,12,13]. Changes in the regulatory context are likely to result in these methods having greater relevance for HTA bodies. However, HTA bodies will need to not only consider the maximum benefit that could be accrued from further research, the expected value of perfect information (EVPI), but also the expected value of information from concrete proposals for further data collection - the expected value of sample information (EVSI) [8].

To date, there has been little consideration of how *manufacturers* can use VoI methods to address the commercial uncertainties they face in this era of conditional approval. The changing context increases the importance of considering the *commercial* value of collecting further information, and thus the rationale for 'twisting'. In this paper we consider the commercial value of 'twisting' to primarily be captured through any increase, relative to 'sticking', in the estimated net present value (NPV) - the time discounted flow of revenues associated with a strategy minus its costs).

EVSI provides a coherent framework for informing a company's negotiating position during the reimbursement process. It enables the manufacturer to combine the divergent sources of information they possess in their different functions within one integrated analysis. We demonstrate how this analysis can be undertaken to identify the estimated NPV of a specific data collection plan (with limited patient numbers and a limited follow-up period). To increase clarity we illustrate our approach using a pertinent but hypothetical case study – an immune oncology therapy under assessment by NICE.

Methods

General model

If a new intervention is initially judged by an HTA body to be not cost-effective the pharmaceutical company may: (i) lower the price permanently and get immediate approval; (ii) lower the price temporarily while collecting further data under "approval with research"; or (iii) abort their attempt to launch in that market. A range of factors influence this decision including: profit maximisation; relationships with key stakeholders; and the pharmaceutical company's internalised values. In the face of this complexity we adopt an approach similar to NICE. For each of available strategies we formally derive an estimate for one dominant metric and expect the decision made to be *informed* by this metric but not determined solely by it. For the pharmaceutical company the single metric of greatest relevance is not the incremental cost-effectiveness ratio (ICER) but the NPV of each of the potential strategies, i.e. each strategy's expected time-discounted cash flow[14].

The methods we adopt are applicable in any value-based or outcome-based reimbursement setting. However, for clarity, we assume that the manufacturer is launching the drug in a market where cost-effectiveness analysis is the primary metric used by the HTA body to assess the value of the new intervention.

As such the HTA body can be assumed to decide to reimburse the intervention with the greatest net health benefit. Formally:

$$D_{Reimb} = \underset{d}{arg\,max}\, E_{\theta_{HTA}}(\lambda Q_d - C_d) \quad (1)$$

where D_{Reimb} is the intervention the HTA body chooses to reimburse, λ is their threshold, the maximum cost the HTA body would be willing to pay for one QALY when coming to a reimbursement decision (under the assumption that the net monetary benefit maximazation at a given threshold is the only rule for acceptability). Q_d and C_d are the quality-adjusted life years (QALYs) and costs estimated for each decision option (*d*) given the parameters (θ_{HTA}) judged most plausible by the HTA body for each of the possible treatment strategies, and $E_{\theta_{HTA}}$ denotes the expected (i.e. mean) value, averaged over the distribution of θ_{HTA}[1]. From here on, in order to simplify the notation we describe the method for a decision problem when there are only two options, the current intervention (option 1) and the manufacturer's new product (option 2). The method extends naturally to more than two decision options.

The company knows the decision rule of the HTA. To maximise revenue, the price (P_2^*) is selected by the manufacturer at the highest they still achieve reimbursement, more formally:

$$P_2^* = \underset{P_2}{arg\,max}\, [P_2 \times I\,\{E_{\theta_{HTA}}\left(\lambda Q_2 - C_2(P_2)\right) > E_{\theta_{HTA}}(\lambda Q_1 - C_1)\}] \quad (2)$$

where *I (A > B)* is an indicator function that takes the value 1 if *A* is greater than *B*, and zero otherwise.

[1] Strictly speaking, the HTA body defines the *distribution* $p_{HTA}(\theta)$. We write θ_{HTA} as shorthand for θ that has distribution $p_{HTA}(\theta)$.

We call P_2^* the *economically justifiable price* (EJP) – the maximum at which the mean ICER, based on the HTA body's belief concerning their specification of θ_{HTA}, remains below their threshold and achieves reimbursement (causing *I* to take a value of 1 rather than 0). If $P_2^* < P_F$, where P_F is the manufacturer's floor price, the lowest price the manufacturer is willing to provide the new product for, then the intervention is not launched in the jurisdiction governed by the HTA body.

As discussed, the metric of greatest relevance to the company is the estimated NPV. For our analysis we make the simplifying assumption that the commercial decision as to whether to "stick" or "twist" are taken at the country level and that the NPV for that country is independent of the novel intervention's reimbursement in other countries.

The NPV for the strategy to "stick", and therefore be reimbursed at the EJP the current evidence base supports is formally summarised below:

$$NPV_S = \sum_k \left(\frac{V_{2,S} \times (P_{2,S}^* - C_M)}{(1+r)^k} - \frac{C_{N,S}}{(1+r)^k} \right) \quad (3)$$

Where $V_{2,S}$ is the anticipated volume of sales for the manufacturer's intervention under strategy "stick" (where the subscript *s* denotes stick), C_M are the marginal costs associated with each unit of the intervention sold, $C_{N,S}$ are the non-marginal costs associated with the stick strategy, *r* is the manufacturer's discount rate and *k* is the year the revenue or costs are generated.

Estimating the Expected Commercial Value of Sample Information

Equation (2) and (3) summarise the price and discounted cash flows that can be achieved by strategy "stick", but what if the manufacturer wishes to consider the commercial impact of collecting more data ("twist")?

We cannot know with certainty the parameter values that will be supported by the new sample. Simulation methods do allow the manufacturer to characterise the data (*X*) that could plausibly arise from a trial of some specified follow up duration and number of patients. Suppose the manufacturer believes the HTA body is over-cautious in its assessment of the evidence base and therefore that the HTA body's specification of the distribution for $\theta_{HTA,}$ is "conservative" - the manufacturer's beliefs about θ may be less conservative, and we represent the parameters defined according to the manufacturer's distribution as θ_M.[2] They would use their belief distribution when considering what plausible data from a new study would look like. To generate plausible data the manufacturer would sample from the sampling distribution of the data, conditional on θ_M, $X \sim P(X|\theta_M)$. See Ades et al. for a general discussion on generating plausible trial data[15].

Any new data would be critically reviewed by the HTA body. New information could lead to a revision in the HTA body's beliefs about the true underlying parameter values, and this would have consequences for the manufacturer's EJP. By modifying equation (2) we can define the EJP for the "twist" strategy (demarcated using subscript *t*) as:

$$P_{2,t}^{*}|X \;=\; \underset{P_{2,t}}{arg\,max}\,[P_{2,t} \times I\,\{E_{\theta_{HTA|X}}\left(\lambda Q_2 - C_2(P_2)\right) > \; E_{\theta_{HTA|X}}(\lambda Q_1 - C_1)\}] \qquad (4)$$

[2] Again, strictly speaking, the manufacturer defines the *distribution* $p_M(\theta)$. We write θ_M as shorthand for θ that has distribution $p_M(\theta)$.

Similarly, by modifying equation (3) the expected NPV of the twist strategy can be defined as:

$$NPV_t(X) = \left\{\sum\left(\frac{V_{2,t} * \left(P^*_{2,t}(X) - C_M\right)}{(1+r)^k} - \frac{C_{N,t}}{(1+r)^k}\right)\right\} \quad (5)$$

The expected NPV for the twist strategy is then $E_x(NPV_t(X))$. The expected commercial value of sample information (ECVSI) is the difference between the expected net present value of strategy "twist" and the estimated net present value of strategy "stick", more formally:

$$ECVSI = E_x(NPV_t) - NPV_s \quad (6)$$

As previously discussed, within published literature, EVSI is typically presented in relation to the expected value to the payer rather than the manufacturer. Using a case study, we now illustrate how EVSI can be used in commercial practice.

Case study

Rationale for the case study

We select a specific managed access process for the case study in order to make the approach more concrete and clearer. We choose the new CDF, which is integrated into the NICE process, because of: (i) the relative transparency of the process; and (ii) NICE's reputation for technical rigour[16]. Figure 1 illustrates how the CDF fits within the NICE process for assessing oncology interventions.

<Figure 1 about here>

With oncology interventions it will commonly be the case that an important area of uncertainty concerns the longer-term extrapolation of observed survival benefit. With immune oncology therapies in particular, it will often be the case that there is: (i) a strong rationale for believing a proportion of the treated population will have an excellent long-term

prognosis; while (ii) having insufficient follow-up data at the time of initial assessment to demonstrate this. We anticipate that the additional data collected to reduce this uncertainty will often rely on continuing follow-up in the interventions' ongoing pivotal study - a "hunch" that is supported by the high proportion of interventions covered by the CDF where this has been the case to date [18].

Data available at initial NICE assessment

We have used a hypothetical example for the illustrative case study. Figure 2 presents Kaplan-Meier's (KMs) summarising the overall survival data available at the date of the initial NICE assessment.

<Figure 2 about here>

While the intervention's KM curve is beginning to plateau towards the end of the initial follow-up period the (hypothetical) appraisal committee deemed the current evidence insufficient to demonstrate the existence of a population of "long term survivors" (patients who are "cured"). When coming to a decision as to the ICER they judge most plausible, the committee decide to adopt an assumption they see as "conservative" - i.e. an extrapolation approach that does not assume a proportion of the treated population are long term survivors (and therefore chose the extrapolation based on the solid rather than the dotted red line in Figure 2). In order to obtain immediate reimbursement on baseline commissioning the manufacturer would need to give the treatment a price per vial justified by this conservative assumption (in our hypothetical case study the intervention is packaged in 50mg vials). Assuming this initial price is above the manufacturer's floor price they are left with the decision as to whether to "stick" (accept immediate reimbursement) or "twist" (with the assumption that further data collection will demonstrate the existence of a population of "long term survivors").

The manufacturer estimated the cost-effectiveness of the intervention using a three-state partitioned survival model, with health states for progression-free, progressed and death (as would typically be used for oncology interventions). Below we outline the 'base case' approach for this model. Parameters for the model are outlined in appendices 3 and 4; in appendix 5 we present the results of scenario analyses which explore the effect of varying important base case assumptions.

As well as medication costs values for monitoring costs, adverse event costs, administration costs and utilities were included in the model. A sub-module to estimate the NPV and EJP of each strategy (stick or twist) via equations 2-5, and the ECVSI via equation 6, was added to the cost-effectiveness model. The sub-module included parameters for: (i) the manufacturer's discount rate; (ii) the incident population; (iii) each strategy's market share over time (assumed in the base case to be equivalent for each strategy); (iv) the marginal costs per unit of intervention sold; (v) the fixed marketing costs; and (vi) of relevance only to the twist strategy, the cost of further data collection.

Estimating the EJP and NPV of the 'stick' strategy.

For the "stick" scenario, parametric survival models were fitted to the overall survival data available at the time of initial assessment by the (hypothetical) appraisal committee (i.e. models were fitted to the data presented in Figure 2 that did not assume a proportion of the population were long term survivors). For the intervention and comparator groups, log-logistic models were selected (details presented in Appendix 1). These models were therefore used to define the survival parameters for $\theta_{HTA,s}$. In line with equation 2, the "stick" EJP was derived using the mean of 1,000 probabilistic sensitivity analysis iterations, in which parameters relating to patient characteristics, overall survival curve parameters, relative PFS efficacy, utility values and cost and resource use were varied within their distributions. The

resultant EJP was calculated by multiplying the incremental QALYs by the willingness-to-pay (WTP) threshold (£30,000 was used for this case study), and then calculating the price required to match this value. Using equation 3 the NPV of the 'stick' strategy was estimated from the EJP.

Estimating the EJP and NPV of the 'twist' strategy.

In order to estimate the EJP and NPV of the 'twist' strategy it is first necessary to simulate plausible (to the manufacturer) datasets that a new study may generate, and then interpret how this additional sample information would be interpreted by the HTA body. Doing so requires three key steps to be followed: (1) determination of the manufacturer's beliefs about θ, which may be less conservative than the HTA body's beliefs (i.e. to characterise θ_M); (2) simulation of plausible future survival data, X, for the patients in the pre-existent study who are yet to experience an event (note because the trial is already underway there is a fixed number of these patients, and given the need to return to NICE for the final assessment, there is also a fixed period of time for additional follow-up); and (3) fitting of parametric *mixture-cure* survival models (to represent the manufacturer's belief that there is a proportion of patients who will be "cured") to the "full" dataset comprising the observed data up to the time of appraisal, plus the simulated data from step (2)[3]. Steps '2' and '3' are then repeated for a sufficient number of iterations to characterise the manufacturer's expectation of their NPV, conditional on the sampled data. An algorithm summarising the overall simulation approach for steps '1' to '3' is presented in Figure 3.

[3] In a full Bayesian treatment we would compute the posterior distribution of the parameters, conditional on the follow up data simulated in step (2). This can be computationally challenging, so instead we generate an approximation to this posterior distribution by fitting (via maximum likelihood) a standard survival model to the "full" dataset comprising the observed data plus the data simulated in step (2). If the observed survival data represent our only information about the survival model parameters at the time of the appraisal (i.e. there is no other strong prior information), and if the posterior distribution of the survival model parameters is approximately Normal, then this approximation will be reasonable.

<Figure 3 about here>

Figure 4 shows the data observed at the initial assessment and for the intervention arm, for one simulation with and without assuming the treatment has a curative effect for some. In the base case we assume that there is a 75% chance that the intervention has a curative effect. In those simulations where it does have a curative effect we assume 75% of the patients yet to experience an event have a life expectancy equivalent to the general population (are "cured"). We vary the values of ρ and π from 75% in sensitivity analysis.

<Figure 4 about here>

A series of Weibull mixture-cure models were fitted to the combined observed and simulated data. The Weibull mixture-cure model was chosen as a suitable extrapolation technique for this hypothetical case study given: (i) its prior use in studies of immune oncology therapies; and (ii) the ability to directly account for the dichotomous population considered in this example[20,21].

Having simulated the expected sample information (X) it is possible to use the cost-effectiveness model to estimate the expected EJP for the twist strategy using the approach outlined in equation (4). For the comparator, distributions for efficacy parameters in the cost-effectiveness model were derived from parametric curves fitted to the observed data shown in Figure 2. For the intervention mixture cure models were fitted to the simulated trial data. For each simulation, the estimated efficacy parameters were used to populate the cost-effectiveness model and the EJP was calculated. As with the estimation of the 'stick' strategy the per simulation EJP was estimated using the justifiable price derived from the 1,000 PSA iterations undertaken for each of the 1,000 trial simulations. Doing so allows the HTA body's

uncertainty that remains following further data collection to be accounted for in line with NICE's preferred approach [22].

Using equation 5 for the 'stick' strategy, the *distribution* of EJPs is generated, and from each EJP, a corresponding NPV is estimated. For realism, we assume a minimum price below which the company would not launch after the CDF (which we set at £300). Where the EJP resulting for a given simulation is below the floor price the NPV estimate only incorporates revenue over the first two years (as we assume the intervention is not reimbursed after this period). As noted above, the NPV estimate for the twist strategy incorporates an additional cost for data collection. In this hypothetical example we assume this to be £1,000,000, split equally across the two years. Because we draw from the distribution of EJPs per simulated trial we are able to estimate the probability that the additional data collection results in a sample that leads to a higher EJP, and therefore a higher NPV, than would result from pursuing the 'stick' strategy.

Results: the expected commercial value of the sample information

Table 1 summarises the anticipated commercial consequences of the pharmaceutical company deciding to either "Stick") or "Twist".

<Table 1 about here>

As shown in Table 1 the simulation exercise indicates that the decision to "Twist" would result in an estimated net financial benefit of £8,006,677. It is not only important to identify which strategy is most likely to generate the higher revenues but also assess risk. The probability that "twist" is the optimal strategy is higher than 75%, the prior expectation that a plateau would be demonstrated by the extended follow up data. This is a result of two factors in combination. Firstly, it is to be expected that the observed sample can either be more optimistic or pessimistic than the hypothesised value. Secondly, however, if we assume that a

proportion of patients are cured, this will always lead to more favourable outcomes on average, than an alternative "no cure" assumption. We may not see a lower EJP than for the "no cure" assumption in any simulation, even when there is sampling variability Therefore, combining these factors, a substantive proportion (13%) of the "no cure" samples support a higher price than justified in the "stick" base case as do all (100%) the "cure" samples.

Figure 5 also illustrates that there is a high probability that further data collection will support a higher price, benefiting revenue. However, it additionally presents the consequences of a substantially negative outcome. 15% of simulations resulted in the EJP being below the floor price, leading to the drug not being reimbursed and a mean net loss of revenue of -£2,275,693 for these samples. The area under the curve to the left or to the right of the y-axis illustrates the probability that the twist decision will be negative or positive, respectively.

<Figure 5 about here>

Prior to making a decision the manufacturer would likely wish to consider how the results would vary depending on the assumptions adopted. Some important areas of uncertainty to explore include: the extent to which the sales volume during the interim funding period would be worse than if the intervention was reimbursed via baseline commissioning; and the estimated probability that the intervention truly has a "curative" effect. Indeed, conditional upon the assumption of "curative effect" being validated it would also be important to explore: the estimated proportion of "long term survivors"; and the prognosis of these "long term survivors" relative to the age matched general population. Scenarios exploring these areas uncertainty are presented in appendix 4.

Discussion

EVSI provides a framework through which different facets of knowledge, held across a pharmaceutical company, can be formally integrated to estimate the commercial value of

collecting further information. It allows a considered, analytically grounded investigation of whether NICE's (or another HTA body's) "most plausible ICER" is likely to be sufficiently pessimistic to be worth challenging through further data collection. To the best of our knowledge, when considering whether to accept conditional reimbursement or lower the price to gain immediate approval, pharmaceutical companies currently lean heavily on the judgement of senior managers. Anecdotally it would seem that rarely, if ever, do they formally draw together all their cross-functional knowledge into one coherent analysis to quantify each option's probability, risks and rewards. Borrowing from Culyer, we acknowledge that the role of the economist is not to determine the optimal course of action for the legitimate decision maker[23]. However, we do believe the analyst has a role to play in facilitating the decision makers coming to a more informed decision; particularly when there is considerable uncertainty regarding the data that will be accrued by further follow up, for example when the data at the time of initial submission is less mature than in our hypothetical case study.

When a treatment is being assessed by an HTA body there are three very real options. The manufacturer can "stick", "twist" or *withdraw* their application. When faced with both numerous organisational constraints and uncertainty about the outcomes that will emerge from continuing follow-up, it may be the case that managers will tend to make decisions which, while judicious for the individual's interests, are suboptimal for either the company and society. Specifically, they may prefer to select the options with known consequences and therefore either: (i) accept a permanently lower price than would be supported by further follow-up data (of benefit to society but suboptimal for the company); or (ii) withdraw the intervention because the price the HTA body is currently willing to offer is below the floor price and they are less confident of the likely outcomes of the follow-up study than they could be (a decision that would be suboptimal for both society and the company). The

demands to meet senior managers' or external investors' requirements may at times make a detailed quantification of the benefits and risks of further data collection redundant. We do, however, believe there are many instances where the magnitude of the consequences involved justify the use of advanced analytics.

This manuscript has focussed on an oncology case-study in a cost-effectiveness HTA context. We acknowledge it would be beneficial if future methods research worked to apply these simulation methods in a broader range of negotiation manufacturer/HTA negotiation contexts.

Conclusion

Changes in the wider drug development, regulatory and HTA context are leading to it being increasingly important to consider the value of collecting further information. Simulation methods, informed by the theoretical framework of EVSI, can facilitate pharmaceutical managers making more informed decisions in contexts of uncertainty.

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Figures

Reference: Adapted from the NHS England Board paper February 2016, Appendix 2[17]

Note: The dotted red line represents a mixture-cure model fitted to the KM data, whereas the solid red line represents an alternative standard parametric extrapolation. Shading indicates the 95% CI around the KM for each arm.

Tables

Table 1: expected commercial value of postponing the final decision until further data are collected

Supplementary material

Appendix 1: Survival applied in "stick" scenario

Six distributions were considered (exponential, Weibull, Gompertz, generalised gamma, log-normal and log-logistic). The log-logistic provided a reasonable extrapolation for both treatment arms, and so this model was considered appropriate to apply in the cost-effectiveness model base case in the "stick" scenario. An overview of these models is provided in Figure 6.

Figure 6: Survival models applied in "stick" scenario

Appendix 2: Parameters incorporated in the cost-effectiveness model

Appendix 3: Parameters incorporated in the eNPV submodule

Appendix 4: Results of the exploratory scenarios

Note that for each scenario where a different assumption is made for the time to event data each of the parameters are also re-simulated (two of the columns in the table below draw attention to the differing simulated values for two of these parameters below).