Can Life Expectancy and QALYs Be Improved by a Framework for Deciding Whether to Apply Clinical Guidelines to Patients With Severe Comorbid Disease?

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Can Life Expectancy and QALYs Be Improved by a Framework for Deciding Whether to Apply Clinical Guidelines to Patients With Severe Comorbid Disease?

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Background: *Guidelines with short-term harms and long-term benefits are often applied to chronically ill patients who may not benefit. The payoff time framework has been proposed (i.e., do not apply a guideline if a patient's life expectancy (LE) is shorter than when a guideline's cumulative incremental benefits first exceed its cumulative incremental harms), but its health impact is unclear.* ***Objective:*** *To investigate whether the payoff time framework improves LE and/or quality-adjusted life-years (QALY) for chronically ill patients.* ***Methods:*** *I evaluate impact of the payoff time framework on LE and QALYs, assuming (1) high and constant background mortality rate from chronic illness (≥ 10% per year), (2) immediate guideline-related harm with probability < 1, and (3) constant guideline-related benefit that occurs over an extended time. I apply the framework to questions of whether to screen chronically ill 50-year-old women for colorectal cancer using colonoscopy, and whether to advocate intensive glucose control for chronically ill diabetics.* ***Results:*** *If a guideline's payoff time is greater than a patient's LE, then withholding that guideline will increase LE and QALYs for that patient. For a 50-year-old chronically ill woman with background mortality > 0.15 per year (corresponding to LE < 6.5 years), withholding CR screening will increase LE. For a diabetic with background mortality > 0.11 per year (corresponding to LE < 9.4 years), withholding CR screening will increase QALYs.* ***Conclusion:*** *The payoff time framework may indicate when withholding a guideline with short-term harms and long-term benefits may increase LE and/or QALY.* ***Key words:*** *geriatric medicine; internal medicine; performance measurement.* ***(Med Decis Making 2011;31:582–595)***

An increasing number of clinical guidelines trade off the risk of a short-term harm against the reward of a long-term benefit.[1–6] Individuals undergoing screening colonoscopy accept a short-term risk from procedural complications in order to gain a longer term benefit from lowering colorectal cancer incidence.[1,5] Individuals receiving surgery for a stable aortic aneurysm accept a short-term risk of perioperative mortality in order to gain a longer term benefit from reducing the risk of aneurysm rupture. Clinical guidelines that trade off short-term harms against long-term benefits are typically evaluated on healthy populations yet are often generalized in practice to patients with severe comorbid chronic diseases[2–4,6,7] (e.g., colorectal cancer screening for severely ill patients with short life expectancies). Because chronic disease may magnify short-term harms and may attenuate benefits through increased competing risks, it is often unclear when guidelines with short-term harms and long-term benefits should be applied to patients with severe chronic disease.

A framework has been developed based on the ''payoff time,'' the earliest time when cumulative incremental benefits attributable to a clinical guideline exceed cumulative incremental harms attributable to that guideline.[8] The payoff time framework stipulates that a guideline should only be implemented if its payoff time is shorter than a patient's

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life expectancy. This framework has the advantage of embedding a concept that is intuitive for clinicians (i.e., do not use a guideline if its benefits take longer to exceed its harms than a patient is likely to live) and therefore may be likely to be understood, accepted, and used for clinical decision support.

Regardless of its intuitive appeal for clinicians, it would be imprudent to recommend applying this framework if it does not improve quality or quantity of life. In the current report, I investigate whether applying the payoff time framework may lead to increases in LE or quality-adjusted life years (QALYs) and demonstrate how it may be used to inform decisions regarding colorectal cancer screening and intensive glucose control.

METHODS

I first outline a generic decision model for a clinical guideline. Second, I outline assumptions that adapt this decision model to the particular case in which a patient has severe chronic disease, the risk of guideline-related harm would occur immediately, and guideline-related benefit would accrue gradually and cumulatively. Third, I further adapt this decision model to the situation where the outcome of interest is LE and show that LE is increased by applying the following heuristic: Only implement a clinical guideline if a patient's LE is greater than the guideline's payoff time (i.e., earliest time when attributable cumulative benefits exceed attributable cumulative harms). Fourth, I adapt this decision model when the outcome measure of interest is QALYs and show that QALYs are increased by applying the same heuristic. Fifth, I address the particular circumstances when the outcome measure is discounted and when the onset of accumulating benefit is delayed. Sixth, I demonstrate how these heuristics may guide practical decisions in clinical care (i.e., colorectal cancer screening decisions in populations with chronic disease and intensive glucose control in patients with diabetes).

Generic Model

Consider the simple and generic decision analytic model (Figure 1) in which there is a choice between electing to follow a clinical guideline and electing not to follow that guideline. If the guideline is not followed, the patient's outcome (θ) will be unaffected by the guideline's benefits or harms (θ_o). If the guideline is followed, there is a probability of harm (P_h), which will result in a poorer outcome θ_h. However, if the guideline is followed and the harm does not occur (probability $1 - P_h$), then the outcome will improve to θ_b.

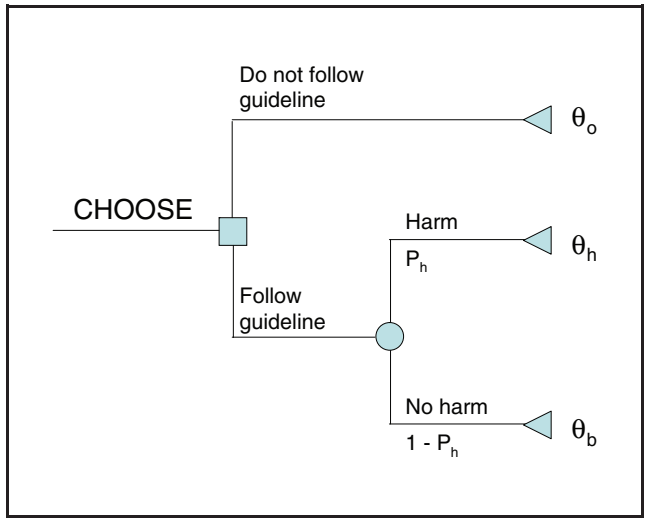

Figure 1 Generic decision model.

The best decision would be not to follow the guideline, if the expected value of not following the guideline is greater than the expected value of following the guideline. This will occur if

$$\theta_o > \theta_h \cdot P_h + \theta_b \cdot (1 - P_h). \quad (1)$$

Rearranging, it will be preferable not to follow the guideline when P_h meets

$$P_h > \frac{(\theta_b - \theta_o)}{(\theta_b - \theta_h)}. \quad (2)$$

Because $(\theta_b - \theta_h)$ is the sum of $(\theta_b - \theta_o) + (\theta_o - \theta_h)$, the inequality can be rewritten again as

$$P_h > \frac{(\theta_b - \theta_o)}{(\theta_b - \theta_o) + (\theta_o - \theta_h)}, \quad (3)$$

which gives an intuitive result. A guideline should not be followed if the probability of harm P_h is greater than its incremental benefit $(\theta_b - \theta_o)$ divided by the sum of its incremental benefit $(\theta_b - \theta_o)$ and incremental harm $(\theta_o - \theta_h)$. If the incremental benefit is large compared with the incremental harm, the probability of harm from the guideline would have to be great to prevent it from being the preferred choice. In contrast, if the incremental

benefit is small compared with the incremental harm, then the probability of harm from the guideline would have to be small in order to prevent the guideline from being the preferred choice.

Adapt Model to Immediate Harms and Gradually Accumulating Benefits

Now consider the more particular situation in which a patient has severe chronic disease and in which guideline-related harms occur immediately whereas guideline-related benefits accumulate gradually. This situation can be specified by the following assumptions while preserving the model's applicability to a large array of guidelines and clinical circumstances:

A. The patient has severe chronic disease, with a high background mortality rate $\lambda_o(t)$ of at least 10% per year.

Patients with lower background mortality rates (i.e., LEs >10 years) will often live long enough to sustain benefit from guidelines with immediate harms and are therefore not suitable candidates for the payoff time framework.

B. This background mortality rate $\lambda_o(t)$ will change little over the analysis time horizon (≤ 10 years) and therefore may be assumed to be a constant value (λ_o).

This assumption is a simplification to enhance mathematical tractability. However, it does not restrict inferences from the payoff time framework. If the background mortality rate were to change, it is more likely to increase than to decrease, in which case the estimated LE would exceed the true LE. If the payoff time is greater than the estimated LE, it will also be greater than the true LE, and inferences would remain valid.

C. The harm that may result from the guideline (P_h) occurs immediately.

This simplifying assumption closely mimics reality for the many guidelines that involve medical procedures (e.g., colonoscopy, aneurysm surgery), as harms occur during or soon after the procedure.

D. The probability of harm from the guideline, while clinically significant, is much lower than 1 ($P_h \ll 1$).

A guideline will generally not involve a high likelihood of clinically significant harm, so this assumption is likely to be valid in most circumstances, particularly for guidelines that target prevention.

E. The benefit that may result from the guideline occurs over a long time period and therefore may be considered constant over the analysis time horizon.

This simplifying assumption mimics many different clinical circumstances, such as the reduction in colorectal cancer incidence after screening colonoscopy. When the outcome of interest is mortality, this benefit can be expressed as an attenuation of baseline mortality rate (λ_o) to a lower value ($\lambda_o - \lambda_b$), where $\lambda_b < \lambda_o$. Because λ_b is the amount by which the mortality rate is reduced, it can be thought of as the magnitude of benefit from intervention.

Also note that the benefit that may result from a guideline is likely to wane over time. However, even when the benefit wanes it may still be possible to make valid inferences using Assumption E because the estimated payoff time would be less than the true payoff time. Therefore, if the estimated payoff time is greater than a particular LE, then the true payoff time would also be greater than that LE, and it would remain valid to infer that the guideline may be harmful.

Applying Model When Outcome Is Life Expectancy

Now replace the generic outcome measure (θ) with the particular outcome measure LE. Returning to our generic decision model, using a clinical guideline will lower the expected value of a generic outcome if

$$(2)P_h > \frac{(\theta_b - \theta_o)}{(\theta_b - \theta_h)}.$$

Because our outcome of interest is now life expectancy (*LE*), we now substitute the corresponding terms:

$$P_h > \frac{(LE_b - LE_o)}{(LE_b - LE_h)}. \quad (4)$$

Because Assumption A specifies a high baseline mortality rate ($\geq 10\%$), life expectancy can be approximated using the declining exponential approximation of life expectancy (DEALE).[9] Correspondingly, LE_b can be approximated by $1 / (\lambda_o - \lambda_b)$, and LE_o can be approximated by $1 / \lambda_o$. Because our outcome of interest is mortality, the relevant

harm would be death, and therefore LE_h is equal to 0. Consequently, Equation 4 becomes

$$P_h > \frac{\left(\frac{1}{\lambda_o - \lambda_b} - \frac{1}{\lambda_o}\right)}{\left(\frac{1}{\lambda_o - \lambda_b}\right)}. \quad (5)$$

Equation 5 reduces to

$$\frac{P_h}{\lambda_b} > \frac{1}{\lambda_o}. \quad (6)$$

The right side of this equation is simply the DEALE approximation of a patient's life expectancy in the absence of that guideline. I will demonstrate that the left side of this equation is the guideline's payoff time. Therefore, this inequality implies that if the life expectancy of a patient in the absence of a clinical guideline is less than the guideline's payoff time, then applying the guideline will reduce that patient's life expectancy. Because guidelines usually should not be used in situations in which they reduce life expectancy, this implies what I set out to demonstrate (i.e., if a patient's life expectancy is lower than a guideline's payoff time, then the guideline should not be used for that patient).

Payoff Time Can Be Approximated by $\frac{P_h}{\lambda_b}$

The payoff time has been defined as the earliest time when cumulative benefits attributable to a guideline first exceed cumulative harms.[8] When the outcome of interest is life expectancy, we are considering those benefits and harms that affect mortality. Recall that we denote the rate at which a guideline's benefits incrementally lower the mortality rate as $\lambda_b(t)$, and we denote the rate at which a guideline's harms incrementally raise the mortality rate as $\lambda_h(t)$. Therefore,

$$\text{Payoff time} = \text{earliest } t > 0 \text{ such that } \int_0^t \lambda_b(t)dt > \int_0^t \lambda_h(t)dt. \quad (7)$$

Because the integrated mortality function, $\lambda(t)$, is simply the cumulative mortality, $\Lambda(t)$, we can rewrite the payoff time inequality in terms of cumulative mortality:

$$\text{Payoff time} = \text{earliest } t > 0 \text{ such that } \Lambda_b(t) > \Lambda_h(t). \quad (8)$$

To evaluate the right side of the inequality, note that $\Lambda_h(t)$ is equal to $-\ln(S_h(t))$, where $S(t)$ denotes a survival function. Because guideline-attributable harm occurs immediately with a probability P_h (Assumption C), this implies that $S_h(t)$ is equal to 1 at $t = 0$ and is equal to $1 - P_h$ for any $t > 0$. Therefore, the cumulative incremental mortality hazard, $\Lambda_h(t)$, for any $t > 0$ will be equal to

$$\Lambda_h(t) = -\ln(1 - P_h). \quad (9)$$

To evaluate the left side of Equation 9, note that the magnitude of mortality decrease is constant and equal to λ_b (Assumption E). Therefore, the cumulative incremental mortality decrease at any time $t > 0$ will be equal to

$$\Lambda_b(t) = \lambda_b t. \quad (10)$$

Substituting Equations 9 and 10 into Equation 8,

$$\text{Payoff time} = \text{earliest } t > 0 \text{ such that } \lambda_b\, t > -\ln(1 - P_h). \quad (11)$$

Because P_h is very small compared with 1 (Assumption D), $-\ln(1 - P_h)$ may be approximated by P_h. Consequently, we can rewrite Equation 11 as

$$\text{Payoff time} \approx \text{earliest t} > 0 \text{ such that } \lambda_b t > P_h. \quad (12)$$

The payoff time is therefore

$$\text{Payoff time} \approx \frac{P_h}{\lambda_b}. \quad (13)$$

Consequently, the payoff time may be estimated by the simple ratio $\frac{P_h}{\lambda_b}$ when life expectancy is the outcome of interest.

Applying Model When Outcome Is QALY

Now replace the generic outcome measure (θ) with the particular outcome measure QALY. We address QALYs separately from LE rather than treating LE merely as a special case of QALYs when utilities are set equal to 1, because more assumptions are necessary when the outcome is QALYs:

F. Any impact of the guideline on utility is much greater than the impact of the guideline on life expectancy.

This assumption implies that we can ignore the mortality impact of the guideline if we consider the utility impact. Therefore, our analysis is only applicable to guidelines that have frequent and/or substantial impacts on quality of life compared with their impact on quantity of life.

G. The patient has an expected utility function, $u(t)$, in the absence of the guideline, that can be approximated by a constant value, u_o, over the duration of the analysis.

This assumption is a simplification to enhance mathematical tractability. Because our analysis is driven by incremental changes in utility, rather than by the baseline utility function itself, this assumption is unlikely to restrict inferences from the payoff time framework.

H. The harm that may result from the guideline occurs immediately and lowers utility by an amount u_h, where $u_h < u_o$.

This simplifying assumption closely mimics reality for the many guidelines that involve medical procedures (e.g., colonoscopy, aneurysm surgery), as harms occur during or soon after the procedure. Because we have chosen to focus on the outcome of QALY, reduction in utility is the relevant harm.

I. The benefit that may result from the guideline increases the baseline utility (u_o) to a higher value ($u_o + u_b$), where $u_b < (1 - u_o)$ and occurs with an incidence of λ_b, which is much less than 1. λ_b can be thought of as reflecting the likelihood that any benefit occurs, and u_b can be thought of as the amount of benefit that is conferred.

This simplifying assumption mimics many different clinical circumstances, such the increase in utility (compared with baseline) associated with preventing colorectal cancer. In this particular case, λ_b would be the reduction in colorectal cancer incidence attributable to the guideline, and u_b would be the reduction in utility if colorectal cancer were to occur.

Note that the decision model (Figure 1) does not explicitly represent the possibility that harm and benefit may both occur. It implicitly assumes that if harm is known to occur, its impact on the outcome of interest will be much greater than the impact of any benefit that may occur simultaneously. Because λ_b is much less than 1 (Assumption I), this implicit assumption is reasonable.

Starting with Equation 2,

$$(2)\ P_h > \frac{(\theta_b - \theta_o)}{(\theta_b - \theta_h)},$$

we now substitute the corresponding expressions for our outcome measure of interest (QALYs).

If utility over time remains constant, as it does in the absence of the guideline and for those who are harmed by the guideline, we can just multiply life expectancy by utility:

$$QALY_o = \left[\frac{1}{\lambda_o}\right] \cdot u_o \tag{14}$$

$$QALY_h = \left[\frac{1}{\lambda_o}\right] \cdot (u_o - u_h) \tag{15}$$

As before, because Assumption A specifies a high baseline mortality rate, we use the DEALE to approximate LE_o as $\frac{1}{\lambda_o}$.

If utility varies over time (as it does for those who are not harmed by the guideline), then we have to integrate the survival function multiplied by the utility. The survival function for those not harmed by the guideline is $e^{-\lambda_o t}$. The utility function for those not harmed by the guideline is the proportion not benefited ($e^{-\lambda_b t}$) multiplied by the utility for those not benefited (u_o) plus the proportion benefited ($1 - e^{-\lambda_b t}$) multiplied by the utility for those benefited ($u_o + u_b$). Therefore, the utility function for those not harmed by the guideline is

$$u_o\ e^{-\lambda_b t} + (u_o + u_b)(1 - e^{-\lambda_b t}). \tag{16}$$

To estimate QALYs for those not harmed by the guideline, we need to integrate over time the product of the survival function multiplied by the utility function:

$$QALY_b = \int_0^\infty (e^{-\lambda_o t})\left[u_o e^{-\lambda_b t} + (u_o + u_b)(1 - e^{-\lambda_b t})\right] dt. \tag{17}$$

Because λ_b is small compared with 1 (Assumption I), we can approximate $1 - e^{-\lambda_b t}$ as $\lambda_b t$. Therefore, we can rewrite the equation as

$$QALY_b = \int_0^\infty (e^{-\lambda_o t})[u_o(1 - \lambda_b t) + (u_o + u_b)(\lambda_b t)]dt, \tag{18}$$

solving the integral,

$$QALY_b = \frac{u_o}{\lambda_o} + \frac{u_b \lambda_b}{\lambda_o^2}. \tag{19}$$

Now that we have expressions for $QALY_o$, $QALY_h$, and $QALY_b$, we can prepare to substitute into Equation 1, which specifies that the guideline should not be implemented if

$$(1)\ \theta_o > \theta_h \cdot P_h + \theta_b \cdot (1 - P_h).$$

Now, substituting the corresponding QALY terms for the θ terms, the guideline should not be implemented if

$$\frac{u_o}{\lambda_o} > \left[\frac{1}{\lambda_o}\right] \cdot (u_o - u_h) \cdot P_h + \left[\frac{u_o}{\lambda_o} + \frac{u_b \lambda_b}{\lambda_o^2}\right] \cdot (1 - P_h). \quad (20)$$

This equation reduces to

$$\frac{P_h u_h}{u_b \lambda_b (1 - P_h)} > \frac{1}{\lambda_o}. \quad (21)$$

Because $P_h \ll 1$ (Assumption D), we can approximate Equation 21 as

$$\frac{P_h u_h}{u_b \lambda_b} > \frac{1}{\lambda_o}. \quad (22)$$

Therefore, a guideline will lower QALYs if Equation 22 is true. As before, the right side of the inequality is a patient's life expectancy in the absence of the guideline (approximated by the DEALE). I will demonstrate that the left side of this equation is the guideline's payoff time if its probability of harm is P_h, the magnitude of harm is u_h, the incidence of benefit is λ_b, and the magnitude of benefit is u_b. Therefore, this equation suggests that if the life expectancy of a patient in the absence of a clinical guideline is less than the guideline's payoff time, then the QALYs will be reduced. Because guidelines usually should not be used in situations in which they reduce QALYs, this equation implies what we set out to demonstrate (i.e., if a patient's life expectancy is lower than a guideline's payoff time, then the guideline should not be used for that patient).

Payoff Time $= \frac{P_h u_h}{u_b \lambda_b}$ *When the Outcome Is QALY*

Recall that the rate of a harmful event occurring is $\lambda_h(t)$, the rate of a beneficial event occurring is $\lambda_b(t)$, and u_h and u_b are the decrement and increment in utility, respectively, from the harmful and beneficial events.

Consequently, the cumulative incremental harm at time t is equal to

$$\int_0^t S(t)\lambda_h(t)u_h dt \quad (23)$$

where $S(t)$ is the survival function. Analogously, the cumulative incremental benefit at time t is equal to

$$\int_0^t S(t)\lambda_b(t)u_b dt. \quad (24)$$

The payoff time is the earliest time when cumulative incremental benefits exceed cumulative incremental harms and is therefore the earliest time when

$$\int_0^t S(t)\lambda_b(t)u_b dt > \int_0^t S(t)\lambda_h(t)u_h dt. \quad (25)$$

Recall that P_h is the probability of harm from the guideline. Because the harm is assumed to occur instantaneously at $t = 0$ (Assumption C), we can therefore approximate Equation 25 by the following:

$$\int_0^t S(t)\lambda_b(t)u_b dt > \int_0^t S(t)P_h u_h dt. \quad (26)$$

Because we are assuming the rate of benefit from the guideline is constant with a value λ_b (Assumption E), we can rewrite Equation 26 as

$$\int_0^t S(t)\lambda_b u_b t dt > \int_0^t S(t)P_h u_h dt, \quad (27)$$

At very small values of t, the left side of the equation being integrated is small, whereas the right side of the inequality is close to $P_h\ u_h$ (for small t, $S(t) \approx 1$), and therefore the inequality is not met. For Equation 27 to be met at a particular time t (i.e., the cumulative incremental benefits exceed the cumulative incremental harms), the instantaneous incremental benefits must exceed the instantaneous incremental harms for at least some prior time t. Therefore, the earliest time at which the cumulative incremental benefit can exceed the cumulative incremental harm (i.e., the payoff time) may be later, but not earlier, than the earliest time at which the instantaneous incremental benefits exceed the instantaneous incremental harms. Consequently, the earliest time at which the instantaneous incremental benefit exceeds the instantaneous incremental harm may be viewed as a lower bound estimate for the payoff time. A lower bound estimate for the payoff time would be the smallest t such that

$$S(t)\lambda_b u_b t dt > S(t)P_h u_h. \quad (28)$$

Dividing both sides of Equation 28 by $S(t)$, the condition would be met when

Table 1 Summary of Formulas for Payoff Time and Estimated Life Expectancy

		Payoff Time	Life Expectancy
LE payoff time	No delay, no discounting	$\frac{P_h}{\lambda_b}$	$\frac{1}{\lambda_o}$
	Delay in benefits (t_d years)	$\left(\frac{P_h}{\lambda_b}\right) \cdot e^{\lambda_o t_d}$	$\frac{1}{\lambda_o}$
	Discount rate of r	$\frac{P_h}{\lambda_b}$	$\frac{1}{(\lambda_o+r)}$
QALY payoff time[a]	No delay, no discounting	$\left(\frac{P_h}{\lambda_b}\right) \cdot \left(\frac{u_h}{u_b}\right)$	$\frac{1}{\lambda_o}$
	Delay in benefits (t_d years)	$\left(\frac{P_h}{\lambda_b}\right) \cdot \left(\frac{u_h}{u_b}\right) \cdot e^{\lambda_o t_d}$	$\frac{1}{\lambda_o}$
	Discount rate of r	$\left(\frac{P_h}{\lambda_b}\right) \cdot \left(\frac{u_h}{u_b}\right)$	$\frac{1}{(\lambda_o+r)}$

Note: LE, life expectancy; QALY, quality-adjusted life expectancy. If the payoff time is less than the estimated life expectancy, then a guideline will reduce life expectancy (LE payoff time) or QALYs (QALY payoff time).
a. Lower bound.

$$\lambda_b u_b t > P_h u_h. \quad (29)$$

Dividing both sides of the equation by $\lambda_b\ u_b$, the earliest t at which the instantaneous incremental benefits could exceed the instantaneous incremental harms would be

$$t^* = \text{QALY payoff time} \geq \frac{P_h u_h}{\lambda_b u_b}. \quad (30)$$

Therefore, Equation 30 is a lower-bound estimate of the QALY payoff time. The true payoff time (earliest time when cumulative incremental benefits exceed cumulative incremental harms) may be longer but not shorter. This bounded estimate may be viewed as the mortality payoff time $\left(\frac{P_h}{\lambda_b}\right)$ multiplied by an adjustment factor that reflects the ratio of harm to benefit $\left(\frac{u_h}{u_b}\right)$.

Special Cases Incorporating Discounting and Delays in Benefits

In particular circumstances, it may be appropriate to discount future benefits, or it may be known that there is a particular delay before any guideline-associated benefits start to accumulate (Appendix). In these cases, the same clinical heuristic applies (''only implement a clinical guideline if a patient's life expectancy is greater than the guideline's payoff time''), but the formulas used to approximate the payoff time and estimated LEs may vary (Table 1). The payoff time can be adjusted for delays in the onset of benefits by adding a delay term $e^{\lambda_o t_d}$ that multiplies the payoff time based on the length of the delay. The life expectancy estimate can be adjusted for discounting by replacing λ_o with $\lambda_o + r$, which has the effect of lowering life expectancy based on the amount of discounting.

Informing Clinical Care Decisions

To demonstrate the feasibility of the payoff time heuristic, I apply it to 2 clinical guidelines in which short-term harms may offset long-term benefits. First, I ask when colorectal cancer screening may lower the life expectancy of 50-year-old women who have varying levels of background mortality from chronic disease (λ_o ranging from 0.1 [life expectancy of 10 years] to 0.5 [life expectancy of 2 years]). Second, I ask when intensive glucose control may lower the QALY of 50-year-old diabetic patients, who also have varying levels of background mortality from chronic disease (λ_o ranging from 0.1 [life expectancy of 10 years] to 0.5 [life expectancy of 2 years]).

Colorectal cancer screening. Consistent with our prior analyses,[10] I estimated the harm from screening colonoscopy (probability of colonoscopy-related death, 25 per 100,000 patients; probability of serious complication from colonoscopy, 250 per 100,000 patients) and the benefit from screening colonoscopy (reduction in death from colorectal cancer, relative risk reduction, 0.70; absolute risk reduction, 8.6 per 100,000 patient-years; reduction in colorectal cancer incidence, relative risk reduction, 0.70; absolute risk reduction, 26 per 100,000 patient years).[11-13] Also consistent with our prior analyses, I assume a 5-year delay until the mortality benefits from colorectal cancer screening are clinically manifest.[10] I assume that the screening method used is

colonoscopy once every 10 years. In sensitivity analyses, I perform comparable analyses for patients with risk factors that magnify benefits or harms. As an example of patients with magnified benefits from screening, I consider those with an increased risk of colorectal cancer (relative risk of 2.3, corresponding to the risk associated with HIV).[14] As an example of patients with magnified harms from screening, I consider those with increased risk of serious complications from colonoscopy (relative risk of 4.3, corresponding to the risk associated with severe systemic disease).[10]

Intensive glycemic control. Based on prior reports, I estimated the absolute risk reduction of microvascular disease (i.e., nephropathy, retinopathy, neuropathy) from intensive glycemic control at an annual rate of 0.011.[15] I assumed no direct impact of intensive glycemic control on macrovascular complications of diabetes or on mortality. I calculated an average disutility of microvascular complications of 0.096, based on a weighted average of disutilities for each complication multiplied by their relative frequency.[16] In sensitivity analyses, I performed comparable analyses for patients with risk factors that magnify guideline-attributable benefits and/or harms. As an example of patients with magnified benefits from screening, I consider those with increased risk of microvascular complications (relative risk of 2.0). As an example of patients with magnified harm from screening, I consider those who have a greater disutility from complying with the burden of intensive glycemic control (–0.02 utility units, the greatest utility decrement compatible with intensive glycemic control being a preferred choice).[17]

RESULTS

I first describe generic results and then describe results when the payoff time framework is applied to particular guidelines for colorectal cancer screening and intensive glucose control.

Generic Results

The payoff time varies depending on background mortality and delay in onset of benefits but is always at least equal to $\frac{P_h}{\lambda_b}$ (when life-years is the designated outcome) or $\left(\frac{P_h}{\lambda_b}\right) \cdot \left(\frac{u_h}{u_b}\right)$ (when QALY is the designated outcome) (Table 3). These terms can be thought of as harm-to-benefit adjustors since their numerators reflect magnitude of harm and their denominators reflect magnitude of benefit, and they bound the minimum value of the payoff time. As background mortality increases and/or delay in onset of benefit increases, the payoff time rises above the harm-to-benefit adjustor, frequently exceeding estimated life expectancy (Table 3).

Applying Payoff Time to Colorectal Cancer Screening

For 50-year-old women with average risk for colorectal cancer and average risk of complications from colonoscopy, the payoff time for the mortality effect of colorectal cancer screening is 2.9 years, unadjusted for delays in benefits (Table 3). Adjusting the payoff time for the 5-year delay before mortality benefits become evident from colorectal cancer screening increases the payoff time to between 4.8 years (if background mortality is 0.1 per year) and 35.4 years (if background mortality is 0.5 per year).

For women with risk factors that magnify guideline-associated benefits (i.e., higher risk for colorectal cancer), the payoff time for the mortality effect of colorectal cancer screening is 1.3 years, unadjusted for delays in benefits (Table 2). If we adjust the payoff time for the 5-year delay before mortality benefits become evident from colorectal cancer screening, the payoff time increases to between 2.1 years (if background mortality is 0.1 per year) and 15.4 years (if background mortality is 0.5 per year).

For women with risk factors that magnify guideline-associated harms (i.e., higher risk of complications from colonoscopy), the payoff time for the mortality effect of colorectal cancer screening is 12.2 years, unadjusted for delays in benefits (Table 2). If we adjust the payoff time for the 5-year delay before mortality benefits become evident from colorectal cancer screening, the payoff time increases to between 20.1 years (if background mortality is 0.1 per year) and more than 100 years (if background mortality is 0.5 per year).

Intensive Glucose Control in Diabetes

For diabetic patients with typical harm-to-benefit profiles (small disutility from intensive glucose control [–0.01 utility units] and average risk of microvascular complications), the payoff time for the quality-of-life effect of intensive glucose control is 9.4 years, unadjusted for delays in benefits (Table 4). If a 5-year delay were to occur before quality-of-life

Table 2 Generic Results for the Payoff Time of a Hypothetical Guideline

Background Annual Mortality Rate	Delay (years)	Payoff Time (years)			
		Harm-to-Benefit Adjustor 1.0	Harm-to-Benefit Adjustor 2.0	Harm-to-Benefit Adjustor 5.0	Harm-to-Benefit Adjustor 10.0
0.1	0	1.0	2.0	5.0	**10.0**
	1	1.1	2.2	5.5	**11.1**
	2	1.2	2.4	6.1	**12.2**
	5	1.6	3.3	8.2	**16.5**
0.2	0	1.0	2.0	**5.0**	**10.0**
	1	1.2	2.4	**6.1**	**12.2**
	2	1.5	3.0	**7.5**	**14.9**
	5	2.7	**5.4**	**13.6**	**27.2**
0.5	0	1.0	**2.0**	**5.0**	**10.0**
	1	1.6	**3.3**	**8.2**	**16.5**
	2	**2.7**	**5.4**	**13.6**	**27.2**
	5	**12.2**	**24.4**	**60.9**	**121.8**

Note: The table shows generic results for the payoff time of a hypothetical guideline, as a function of background mortality rate, delay until onset of guideline's benefits, and the guideline's harm-to-benefit adjustor $\left(\frac{P_h}{\lambda_b}\right)$ when using life-years or $\left(\frac{P_h}{\lambda_b}\right) \cdot \left(\frac{u_h}{u_b}\right)$ when using QALYs). Payoff times become longer when time until onset of benefits is delayed and/or background mortality rate increases. Boldface signifies circumstances in which payoff times are greater than probable life expectancies (based on applying the declining exponential approximation of life expectancy to background mortality rates) and therefore are circumstances in which the guideline should not be applied.

Table 3 Payoff Time for Colorectal Cancer Screening

Background Annual Mortality Rate	Delay (years)	Payoff Time (years)		
		High Cancer Risk, Normal Complication Risk $\frac{P_h}{\lambda_b}$= 1.3	Normal Cancer Risk, Normal Complication Risk $\frac{P_h}{\lambda_b}$= 2.9	Normal Cancer Risk, High Complication Risk $\frac{P_h}{\lambda_b}$= 12.2
0.1	0	1.3	2.9	**12.2**
	1	1.4	3.2	**13.5**
	2	1.5	3.6	**14.9**
	5	2.1	4.8	**20.1**
0.2	0	1.3	2.9	**12.2**
	1	1.5	3.6	**14.9**
	2	1.9	4.3	**18.2**
	5	3.4	**7.9**	**33.2**
0.5	0	1.3	**2.9**	**12.2**
	1	**2.1**	**4.8**	**20.1**
	2	**3.4**	**7.9**	**33.2**
	5	**15.4**	**35.4**	**148.8**

Note: The table shows the payoff time for colorectal cancer screening, as a function of risk of complications from screening colonoscopy (relative risks of 1.0 [normal] and 4.3 [high] evaluated) and risk of colorectal cancer (relative risks of 1.0 [normal] and 2.3 [high] evaluated). Payoff times become longer as the risk of complications increase. Payoff times become shorter as the risk of colorectal cancer increases. Boldface signifies circumstances in which payoff times exceed probable life expectancies. The payoff time may precede the delay in onset of benefits when a minority of patients sustain a sufficiently large enough increase in life expectancy to offset a decline in life expectancy for the majority. In these situations, an alternative heuristic is to only implement a guideline if life expectancy exceeds the minimum of the payoff time and the delay in onset of benefit.

benefits become evident, the payoff time would increase to between 15.5 years (if background mortality is 0.1 per year) and more than 100 years (if background mortality is 0.5 per year).

For diabetic patients with risk factors that magnify guideline-associated benefits (higher risk of microvascular complications), the payoff time for the quality-of-life effect of intensive glucose control is 4.7 years, unadjusted for delays in benefits (Table 4). If a 5-year delay were to occur before quality-of-life benefits became evident, the payoff time would increase to between 7.7 years (if background

Table 4 Payoff Time for Intensive Glucose Control in Diabetes

Background Annual Mortality Rate	Delay (years)	Payoff Time (years)		
		Disutility 0.01; High Vascular Risk $\left(\frac{P_h}{\lambda_b}\right) \cdot \left(\frac{u_h}{u_b}\right) = 4.7$	Disutility 0.01; Normal Vascular Risk $\left(\frac{P_h}{\lambda_b}\right) \cdot \left(\frac{u_h}{u_b}\right) = 9.4$	Disutility 0.02; Normal Vascular Risk $\left(\frac{P_h}{\lambda_b}\right) \cdot \left(\frac{u_h}{u_b}\right) = 18.8$
0.1	0	4.7	9.4	**18.8**
	1	5.2	**10.4**	**20.7**
	2	5.7	**11.5**	**22.9**
	5	7.7	**15.5**	**30.9**
0.2	0	4.7	**9.4**	**18.8**
	1	**5.7**	**11.5**	**22.9**
	2	**7.0**	**14.0**	**28.0**
	5	**12.8**	**25.5**	**51.0**
0.5	0	**4.7**	**9.4**	**18.8**
	1	**7.7**	**15.5**	**30.9**
	2	**12.8**	**25.5**	**51.0**
	5	**57.2**	**114.3**	**228.7**

Note: Table shows the payoff time for intensive glucose control in diabetes, as a function of disutility from intensive glucose control (disutilities of 0.01 and 0.02 evaluated), and relative risk for microvascular complications compared with typical diabetes (relative risks of 1.0 [normal] and 2.0 [high] evaluated). Payoff times become longer as disutility from intensive glucose control increases and can exceed life expectancies even when the disutility is small. Payoff times become shorter as microvascular risk increases but still can exceed life expectancies when background mortality is high. Boldface signifies circumstances in which payoff times exceed probable life expectancies.

mortality is 0.1 per year) and more than 57.2 years (if background mortality is 0.5 per year).

For diabetic patients with risk factors that magnify guideline-associated harms (more disutility from intensive glucose control [–0.02 utility units]), the payoff time for the quality-of-life effect of intensive glucose control is 18.8 years, unadjusted for delays in benefits (Table 4). If a 5-year delay were to occur before quality-of-life benefits became evident, the payoff time would increase to between 30.9 years (if background mortality is 0.1 per year) and more than 100 years (if background mortality is 0.5 per year).

DISCUSSION

In this report, I formally evaluated the payoff time framework,[8,10] stipulating that a guideline should only be implemented for a patient with severe chronic disease if its payoff time is shorter than the patient's life expectancy. I demonstrated that applying this framework increases life expectancy and QALYs. The payoff time framework is increasingly feasible to apply to clinical care because an increasing array of validated generic and disease-specific models are available to estimate life expectancy based on comorbidity burden, and their use may be facilitated by electronic medical record systems.[18,19] It advances prior work because other frameworks for adapting clinical guidelines based on comorbidity burden are qualitative and more subjective[1-4] and therefore are less subject to application in electronic medical records (EMR) or informing quality of care measures.

Based on these results, the payoff time can be thought of as a clinically intuitive framework for coupling a simple decision analytic model together with bounding arguments, to yield clinical inferences that are limited in scope but have high certitude. The payoff time framework only seeks to identify a subset of circumstances when implementing a guideline is harmful and therefore would be undesirable, rather than seeking to classify correctly each time whether guideline implementation would be desirable. This approach may enhance the generalizability of the payoff time framework, because criteria for desirable use (e.g., willingness to pay for health benefit) may vary greatly from clinician to clinician or from health system to health system, whereas a particular criterion for undesirable use (harm) should be stable across clinicians and health systems.

Applying the payoff time framework suggests that 50-year-old women at average risk of colorectal cancer should only be screened for colorectal cancer if their expected mortality rate is approximately 0.15 per year or less (corresponding to a life expectancy of

at least 6.5 years) and that diabetic patients should only be urged to maintain intensive glucose control if their expected mortality rate is approximately 0.11 per year or less (corresponding to a life expectancy of at least 9.4 years). Given that clinicians often apply aggressive measures to patients at high risk of mortality, these results may have broad impact for patient care and medical decision making.

Because the payoff time framework embeds concepts that have face validity for clinicians, it may be more likely to be adopted and used for clinical decision support than a life-expectancy or QALY-maximizing decision analytic model alone. Anecdotally, clinicians have a difficult time thinking in terms of maximizing QALYs but readily think about when patients are ''too sick'' because of competing risks to gain from an intervention with delayed benefits. The payoff time harnesses these clinically intuitive concepts, using them to frame the decision analytic model and its bounding arguments.

It is conceivable that EMR-based clinical decision supports may facilitate comparison of a patient's life expectancy with a guideline's payoff time (adjusted, if necessary, when a patient's comorbidities modify guideline-specific risks or benefits). If the payoff time exceeds the life expectancy, then the guideline will lower life expectancy and quality-adjusted life expectancy and therefore may be unadvisable. The EMR could prompt the clinician with this information, who could then use it to inform a shared decision with the patient. It may also inform the evaluation of patient care quality (e.g., pay for performance, report cards) by helping to arbitrate circumstances under which clinicians' noncompliance with a guideline is appropriate. At the time of writing, the payoff time framework is being pilot tested within an EMR-based decision support to personalize colorectal cancer screening recommendations at the point of care.

The current generation of clinical guidelines were designed to reduce variation in practice patterns in settings where practice variation could be harmful. It is widely understood that practice variation is desirable when it reflects personalization of care based on patient-specific risk factors and preferences, but reducing this desirable practice variation was implicitly viewed as a price worth paying in order to reduce undesirable practice variation (e.g., culture, inertia, payment incentives), which could harm patients or waste resources. The payoff time framework can be thought of as part of a next generation of guidelines that will use EMR-based risk calculators and other algorithms to reinsert and reward desirable sources of variation in practice patterns.

The payoff time heuristic will not give clear-cut advice if a patient's life expectancy exceeds the payoff time by a small amount or if the rank order of the life expectancy and the payoff time is not robust when assumptions are varied (i.e., the life expectancy only exceeds the payoff time under select discounting assumptions or under assumptions that are uncertain because of statistical variation or weak evidence). In these cases where there is not a definitive answer, it may be especially important to incorporate patient preferences into decision making. Indeed, results of applying the payoff time framework could be used in discussions with patients about implementing guidelines and could allow patients to incorporate their context and preferences.

Limitations of the Payoff Time Heuristic

The payoff time heuristic does not address cost but rather assumes infinite willingness to pay for mortality benefits. If the payoff time heuristic were modified to reflect willingness to pay thresholds, numerically lower (more restrictive) willingness-to-pay thresholds would lead to progressively longer payoff times. A basic limitation of the payoff time heuristic is that it can delineate circumstances under which a guideline is likely to be harmful but cannot delineate circumstances under which a guideline is likely to be helpful. Finally, the payoff time assumes that guideline-related benefits do not wane and that comorbidity-related mortality does not increase. However, both of these assumptions make the life expectancy more likely to exceed the payoff time. Therefore, if the life expectancy is lower than the payoff time using these simplifying assumptions, the life expectancy would remain lower than the payoff time without using these simplifying assumptions (and applying the guideline would remain inappropriate).

Limitations of How the Payoff Time Heuristic Was Applied to Clinical Examples

One may argue that it is inappropriate to model screening colonoscopy as a one-time event, because screening colonoscopies are intended to be repeated at regular intervals. However, the recommended periodicity of screening colonoscopy (10 years) is longer than the life expectancies of patients whose decisions would be affected by the payoff time

heuristic (<10 years), so this consideration is unlikely to affect inferences. It may be argued that mortality from colonoscopy complications is not instantaneous, as is assumed by the payoff time heuristic. However, colonoscopy complications serious enough to confer mortality (e.g., perforation of the colon, life-threatening-bleeding) are generally acute events requiring hospitalization, and therefore the mortality burden would likely occur within time frames (days or weeks) that are extremely short compared with relevant time horizons relevant to the payoff time framework (years).

It may be argued that delays before benefits accrue are shorter than 5 years in the case of colorectal cancer screening and are longer than 5 years in the case of intensive glucose control. However, the payoff time framework allows incorporation of any alternative assumption regarding delay times (t_d in Table 1). Similarly, the framework can be applied to any desired age group if the appropriate age-specific and comorbidity-adjusted life expectancies are incorporated (λ_o in Table 1). Finally, it may be argued that our estimation of mortality from colonoscopy was pessimistic (we assumed that 10% of serious complications were fatal, yielding an attributable mortality rate of 25 per 100,000 colonoscopies; whereas a recent US Preventive Services Task Force analysis assumed that 4% of serious complications were fatal, yielding a lower attributable mortality rate of 10 per 100,000 colonoscopies).[13] However, it is important to observe that any alternative complication rate can be incorporated into the heuristic (P_h in Table 1).

CONCLUSIONS

The payoff time heuristic may be used to delineate specific circumstances under which a guideline with short-term harms and long-term benefits may decrease life expectancy and/or QALYs. Using the payoff time to inform care decisions may be increasingly feasible with the advent of electronic medical record systems and has the theoretical potential to add to the short list of care innovations that simultaneously lower costs while improving outcomes.

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APPENDIX
Special Circumstances in Which Benefits Are Delayed

I first address the circumstance when life expectancy is the outcome of interest, and then I address the circumstance when QALYs are the outcome of interest

Life Expectancy Is Outcome of Interest

From Equation 4, we are interested in the scenario when

$$(4)\ P_h > \frac{(LE_b - LE_o)}{(LE_b - LE_h)}.$$

Because LE_o and LE_h are not affected by a delay in benefits, their formulas remain unchanged.

$$LE_o = \frac{1}{\lambda_o} \qquad (A1)$$

$$LE_h = 0 \qquad (A2)$$

However, LE_b is affected by a delay in benefits. Consider now the scenario in which there is a delay (t_d) before guideline-associated benefits begin to accrue. The equation for LE_b will now have two functional forms, one before t_d and one after t_d:

$$LE_b = \int_0^{t_d} e^{-\lambda_o t}\,dt + \int_{t_d}^{\infty} e^{\left(-\lambda_o t + \lambda_b\left(t - t_d\right)\right)}\,dt. \qquad (A3)$$

We are interested in detecting a subset of conditions when life expectancy in the presence of the guideline is less than life expectancy in the absence of the guideline. *LE* in the absence of the guideline (LE_o), as before, is simply equal to $\frac{1}{\lambda_o}$. However, life expectancy in the presence of the guideline is more complicated. Integrating Equation A3,

$$LE_b = \frac{1}{\lambda_o} - \frac{e^{-\lambda_o t_d}}{\lambda_o} + \frac{e^{-\lambda_o t_d}}{(\lambda_o - \lambda_b)}. \qquad (A4)$$

If we define d as the proportion of deaths before t_d without the guideline $\left(1 - e^{-\lambda_o t_d}\right)$, then we can rewrite the expression more simply as

$$LE_b = \frac{d}{\lambda_o} + \frac{(1-d)}{(\lambda_o - \lambda_b)}. \quad (A5)$$

Because life expectancy with the guideline reflects life expectancy if there is benefit multiplied by the probability of benefit, together with life expectancy if there is harm multiplied by the probability of harm, and because life expectancy if there is harm equal to 0,

$$LE_{withguideline} = (1-P_h)\cdot\left(\frac{d}{\lambda_o} + \frac{(1-d)}{(\lambda_o - \lambda_b)}\right). \quad (A6)$$

We are interested in the situations in which the life expectancy with the guideline is less than the life expectancy without the guideline (because, in this situation, it would often be harmful to implement the guideline). Therefore, a guideline may harmful if

$$(1-P_h)\cdot\left(\frac{d}{\lambda_o} + \frac{(1-d)}{(\lambda_o - \lambda_b)}\right) < \frac{1}{\lambda_o}. \quad (A7)$$

Define ''proportional mortality reduction from benefits''

$$p_b \equiv \frac{\lambda_b}{\lambda_o} \quad (A8)$$

and substitute in Equation A7, which becomes

$$(1-P_h)\cdot\left(\frac{d}{\lambda_o} + \frac{(1-d)}{\lambda_o(1-p_b)}\right) < \frac{1}{\lambda_o}. \quad (A9)$$

This relationship can be reduced to

$$P_h > \frac{1-d}{\frac{1}{p_b} - d}. \quad (A10)$$

Substituting (A8) into (A10) yields

$$P_h > \frac{1-d}{\frac{\lambda_o}{\lambda_b} - d}. \quad (A11)$$

Note that the benefit attributable to a guideline will generally be a small proportional of overall mortality, particularly for highly comorbid patients with $\lambda_o \geq 0.1$ (Assumption A). Therefore, $\frac{\lambda_o}{\lambda_b}$ will generally be much larger than d (which by definition is <1) and Equation A11 can be approximated by the following equation:

$$P_h > \frac{1-d}{\frac{\lambda_o}{\lambda_b}}. \quad (A12)$$

This can be rewritten as

$$\left(\frac{P_h}{\lambda_b}\right)\cdot\left(\frac{1}{1-d}\right) > \frac{1}{\lambda_o}. \quad (A13)$$

Because d was defined to be equal to $(1-e^{-\lambda_o t_d})$ (the proportion of deaths before t_d in the absence of the guideline), we can substitute this into Equation A13 to yield

$$\left(\frac{P_h}{\lambda_b}\right)\cdot\left(\frac{1}{e^{-\lambda_o t_d}}\right) > \frac{1}{\lambda_o}. \quad (A14)$$

Note that this equation is analogous to Equation 6. The left side of the equation may be considered an adjustment to the payoff time for delayed benefit, composed of the unadjusted payoff time $\left(\frac{P_h}{\lambda_b}\right)$ multiplied by a ''payoff time adjustor'' $\left(e^{\lambda_o t_d}\right)$, which will increase the payoff time as time until benefit (t_d) increases. The right side of the equation remains the DEALE-estimated life expectancy. Therefore, if the payoff time adjusted for delayed benefit $\left[\left(\frac{P_h}{\lambda_b}\right)\cdot\left(e^{\lambda_o t_d}\right)\right]$ is greater than the life expectancy in the absence of the guideline, the guideline will decrease life expectancy.

QALY Is Outcome of Interest

From Equation 2, we are interested in the scenario when

$$P_h > \frac{(QALY_b - QALY_o)}{(QALY_b - QALY_h)}.$$

Because $QALY_o$ and $QALY_h$ are not affected by a delay in benefits, their formulas remain unchanged:

$$QALY_o = \frac{u_o}{\lambda_o} \quad (A15)$$

$$QALY_h = \frac{(u_o - u_h)}{\lambda_o} \quad (A16)$$

However, $QALY_b$ is affected by a delay in benefits. Consider now the scenario in which there is a delay (t_d) before guideline-associated benefits begin to accrue. The equation for $QALY_b$ will now have two functional forms, one before t_d and one after t_d:

$$QALY_b = \int_0^{t_d} u_o\cdot e^{(-\lambda_o t)}dt + \int_{t_d}^{\infty}\left[u_o\cdot e^{(-\lambda_o t)}\cdot e^{\left(-\lambda_b(t-t_d)\right)} + (u_o+u_b)\cdot e^{(-\lambda_o t)}\cdot\left(1-e^{\left(-\lambda_b(t-t_d)\right)}\right)\right]dt. \quad (A17)$$

Approximate $\left(1-e^{\left(-\lambda_b(t-t_d)\right)}\right)$ as $\lambda_b(t-t_d)$ and approximate $\left(e^{\left(-\lambda_b(t-t_d)\right)}\right)$ as $1-\lambda_b(t-t_d)$. Equation A17 reduces to

$$QALY_b = \int_0^{t_d} u_o \cdot e^{(-\lambda_o t)} dt + (u_o - u_b \lambda_b t_d) \cdot \int_{t_d}^{\infty} e^{(-\lambda_o t)} dt + u_b \lambda_b \cdot \int_{t_d}^{\infty} t \cdot e^{(-\lambda_o t)} dt. \quad \text{(A18)}$$

Solving these integrals,

$$QALY_b = \frac{u_o}{\lambda_o} + \frac{u_b \lambda_b}{\lambda_o^2} e^{(-\lambda_o t_d)}. \quad \text{(A19)}$$

The guideline should not be applied in situations in which

$$QALY_o > QALY_h \cdot P_h + QALY_b \cdot (1 - P_h).$$

Inserting terms from Equations A15, A16, and A19, the guideline should not be applied if

$$\frac{u_o}{\lambda_o} > P_h \cdot \frac{(u_o - u_h)}{\lambda_o} + (1 - P_h) \cdot \left[\frac{u_o}{\lambda_o} + \frac{u_b \lambda_b}{\lambda_o^2} e^{(-\lambda_o t_d)} \right]. \quad (20)$$

This reduces to

$$P_h u_h > (1 - P_h) \cdot \frac{u_b \lambda_b}{\lambda_o} e^{(-\lambda_o t_d)}. \quad (21)$$

Because $P_h \ll 1$ (Assumption I), this can be approximated as

$$\left(\frac{P_h}{\lambda_b}\right) \cdot \left(\frac{u_h}{u_b}\right) \cdot e^{\lambda_o t_d} > \frac{1}{\lambda_o}. \quad (22)$$

Note that the left side of the equation is the lower bound estimate for the QALY payoff time, and the right side of the equation is the life expectancy estimated using the DEALE, adapted for discounting.

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