CORE-MD

Coordinating Research and Evidence for Medical Devices

Scientific report on statistical methods for medical device trials

Deliverable 1.4

Deliverable factsheet

Source Activity:	Work package 1, Deliverable 1.4
Title:	Scientific report on statistical methods for medical device trials
Lead Beneficiary:	LUMC
Nature:	Report
Dissemination level:	Public
Editor:	Alan Fraser (European Society of Cardiology)
Authors:	Jasper van Egeraat, Bas Penning de Vries, Ewout Steyerberg
Status:	Final
Date:	30.09.2022
Contractual Delivery Date:	Month 18

Version Log

Issue Date	Version	Involved	Comments
30.09.2022	1.0	Jasper van Egeraat, Bas Penning de Vries, Ewout Steyerberg	Project developed by JvE and BPdV, supervised by ES. Report written by JvE and ES.
30.10.2022	2.0	Alan Fraser	Supporting text added, to describe next steps for evaluation of this deliverable by the CORE MD consortium.
29.11.2022	3.0	Ewout Steyerberg, Valentina Tageo	Drafting conclusions and final editing for submission

Acronyms and abbreviations

OPC	Objective Performance Criteria
FDA	Food and Drug Administration

Table of Contents

Index of figures

Index of tables

Executive Summary

Evidence for the safety and efficacy of new medical devices can come from randomized controlled trials, which are costly to perform. Instead, prospective single arm studies are often used. Due to the high-risk nature of many implantable devices, and to the absence of specific guidance about sample sizes or minimum cumulative follow-up required, limited sample sizes are common. This practice implies substantial uncertainty of the resulting risk estimates.

We aimed to provide a practical tool to give insight into the relation between sample size and the implications for the level of risk that is accepted. Given an event rate, the tool generates a graph displaying the relation between an upper bound to an n-year risk as function of the sample size. For example, for an event rate of 3%, an upper bound to the 5-year risk for varying hypothetical cumulative device experience with confidence of 95% can be generated with the calculator. In addition, the tool generates a nomogram for fixed sample size from which the upper bound can be read off, for different time periods and confidence levels.

We employed Bayesian reasoning to compute these figures. We define a prior gamma distribution, which may be informed by knowledge on the medical area where the device is proposed. This distribution is updated with knowledge on the total observed cumulative device experience and the amount of device failures, in an on-line calculator.

The calculator can currently be accessed via https://jwavanegeraat.shinyapps.io/RiskCalculator/. It can be used to understand the risks that are implicit in approving high-risk medical devices on the basis of cumulative experience (e.g., patient years) that is limited. The utility of insights provided by the calculator will now be tested by members of the CORE-MD consortium, so that the tool can be developed into a practical application.

1 Introduction

To assess the efficacy and safety of pharmaceutical products, randomized clinical trials are the gold standard. They are also required to gain market approval by regulatory bodies such as the FDA and EMA. In contrast, current regulatory guidance does not mandate that medical devices require a randomized clinical trial for approval. In the EU, single-arm studies are sometimes considered sufficient to provide evidence on complications and failure rates of a new device, by the Notified Body undertaking its conformity assessment.

A characteristic of device development is that incremental improvements are made upon previously developed devices. For drugs, one can modify the dosage but not change the structure of the active drug without having to demonstrate clinical efficacy once more. For medical devices, slightly changing the size, structure or material is relatively easy, and may improve their safety and/or efficacy.

2 Understanding risks of medical devices using a newly developed online calculator

2.1 Device regulations

Market access for high-risk medical devices in the EU is granted at EU-member level by designated organizations called notified bodies. The notified bodies assess the conformity of medical devices to applicable legal requirements. When a device is deemed safe and effective, it is given a certificate of conformity, which leads to CE-marking. Pre-defined specific clinical evidence requirements do not exist, other than generic high-level requirements that leave room for interpretation. A criticism is a lack of uniformity, transparency or adequacy of authorization procedures.

For some classes of devices such as prosthetic heart valves, objective performance criteria (OPC) may be used for market approval. Commonly, they are derived from experience of previously approved heart valves. For example, we can use the average complication rate of a certain type of device as a reference. New iterations of these devices are compared to the OPCs, and they can be approved for market access if the failure rate of the new device is at least equivalent to the OPC.

Demonstration that a new device meets the standard of a relevant OPC may be provided by a single-arm study, which avoids randomization and allows all patients to receive the device. This is statistically efficient, in the sense that single-arm trials require fewer patients than randomized trials.

2.2 Risk calculator

One of the current problems of using OPCs and single-arm studies for medical devices in general, is that the cumulative experience at the time of its regulatory approval is limited, despite the possible high-risk nature of devices. Thus, we aimed to provide regulators with an online tool that can help them to understand the sample size required to exclude an increased and/or unacceptable risk. One assumption is that the event rate observed from the single-arm study is equal to the true event rate of the medical device.

To achieve these goals, we used Bayesian reasoning. This provides a formal framework to estimate risks based on empirically observed data. The Bayesian reasoning is treated with its mathematical background in Section 3, but a brief overview is given here. We assume that the failure time of a device (time to event) is characterized by exponential distribution with rate λ. This parameter is unknown, but is essentially the esteemed which the single-arm study intends to measure. Before the study is done, researchers may have some information on the quantity, based on prior knowledge from other studies from this device or similar devices. This uncertain information is captured in a prior distribution for the parameter λ. The Bayesian framework entails updating this prior with the likelihood of the observed data to gain a posterior distribution for the unknown parameter, reflecting both the prior information and the new information from the data.

The online tool uses a prior Gamma distribution for the event rate, whose hyperparameters should be determined by experts in the corresponding device field. We use a weakly informative prior as a reference, as shown in Figure 7. The prior distribution is updated with the observed event rate and the cumulative device experience. From this updated distribution, the graph and nomogram are generated. For the exact procedure, please see the code and the mathematical proof.

We employed Bayesian reasoning to compute an upper bound to the risk after having observed the empirical event rate (observed number of events divided by the cumulative device experience). The user can decide at which time point the risk should be evaluated. The tool plots a graph of the upper bound to the n-year risk as a function of the hypothetical cumulative device experience in person-years. Additionally, a nomogram is drawn from which the user can read the event risk for different timepoints. In both figures, the assessor can review different confidence levels for the upper bound.

2.3 Examples

In the following section, we provide figures generated by the calculator from observed data in a single-arm study of a real-world medical device that has been approved using an OPC. The example is used for illustrative purposes here.

The Medtronic Avalus Bioprosthesis was granted both CE marking and FDA approval in 2017. The market approval is based on data from the single arm PERIGON Pivotal Trial. In the following, we use the FDA Summary of Safety and Effectiveness[1]. In Table 1 we summarize the number of occurrences of each event during 834 patient-years of observation.

Adverse event	Number of events	Event rate
Thromboembolism	14	0.017
Valve thrombosis	0	0
All hemorrhage	30	0.036
Major hemorrhage	21	0.025
All paravalvular leak	5	0.006
Major paravalvular leak	0	0
Endocarditis	11	0.013

Table 1. Adverse events for Medtronic Avalus Bioprosthesis

To showcase the use of the calculator, we generate the graphs corresponding to these results. In the following, we assume a prior Gamma distribution with hyperparameters $\alpha=1$ and $\beta=0$ (see Figure 7).

[1] https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170006B.pdf.

2.3.1 Thromboembolism risk

The following three graphs correspond to the risk of thromboembolism. Figures 1 and 2 show the lowest value (vertical axis) by which the risk of thromboembolism is upper bounded with y probability after having observed the event rate, as a function of the hypothetical cumulative device experience in person years (horizontal axis). The risk is evaluated after 1 year in Figure 1 and after 10 years in Figure 2.

In Figure 3, the nomogram is displayed for this situation. We have drawn an isopleth from the first axis at 90% to the last axis at 5 years. Thus, after observing the results from the single-arm study, there is a 90% probability that the risk, for an individual patient with this device, of thromboembolism after 5 years is not greater than approximately 0.11.

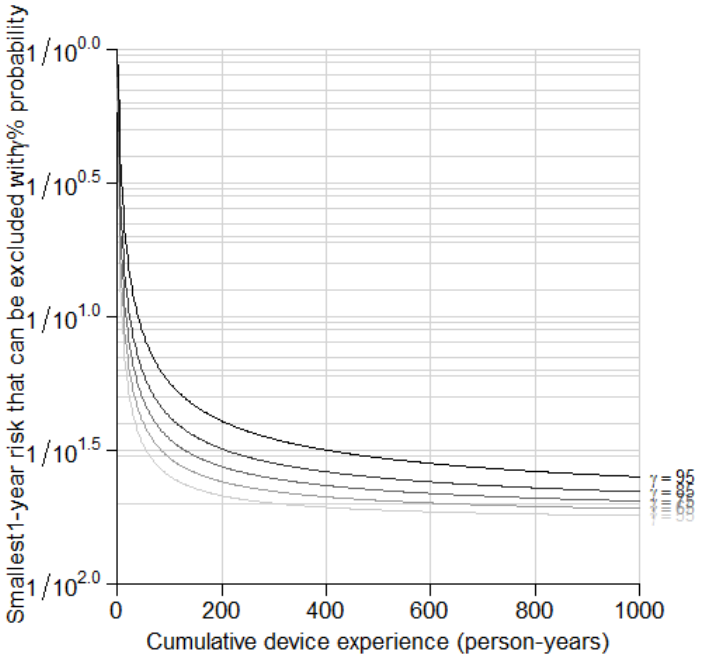

Figure 1. Upper bound to risk of thromboembolism after 1 year as function of cumulative device experience, after observing an event rate of 0.017 in 834.2 patient years.

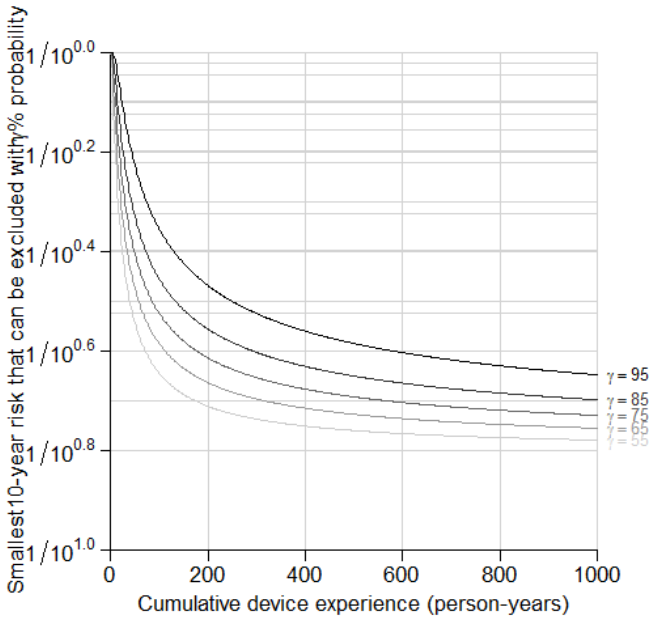

Figure 2. Upper bound to risk of thromboembolism after 10 years as function of cumulative device experience, after observing an event rate of 0.017 in 834.2 patient years.

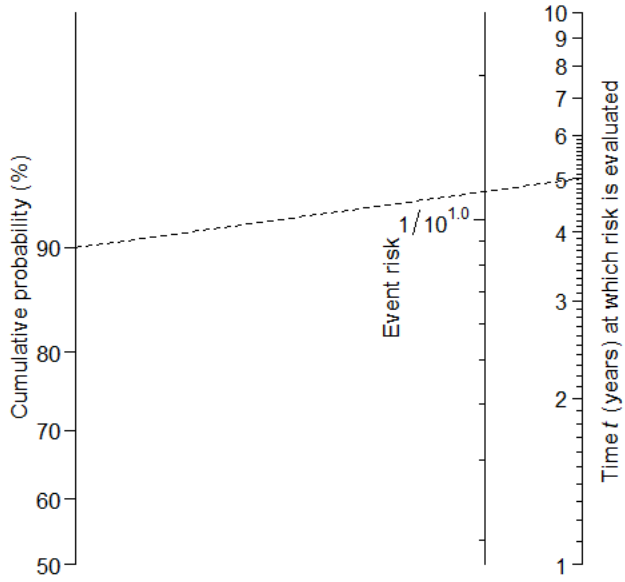

Figure 3. Nomogram for upper bound to risk of thromboembolism after observing an event rate of 0.017 in 834.2 patient years.

2.3.2 Hemorrhage risk

In this section, we generate graphs for all hemorrhage events. There were 30 cases of hemorrhage in 834 patient-years, resulting in an event rate of 3.6% (Table 1). In Figures 4 and 5 the upper bound to the risk after respectively 3 and 5 years is plotted as a function of hypothetical sample size. In Figure 6, the nomogram is displayed for this study. We have drawn an isopleth from the first axis at 50% to the last axis at 3 years. Thus, after observing the failure rate of 3.6% from 834 patient years, there is a 50% probability that the risk of any hemorrhage after 3 years for a new patient with this device is not greater than approximately 0.1.

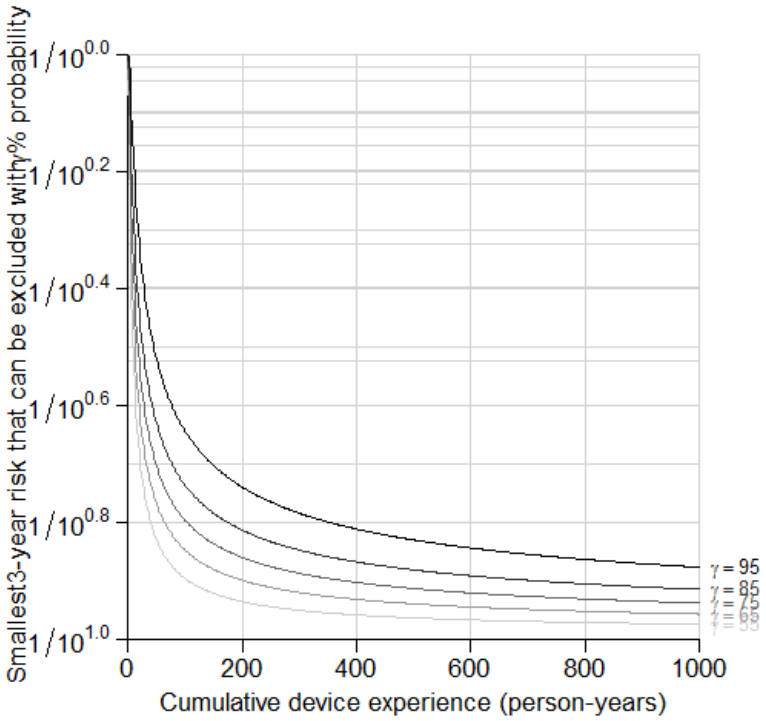

Figure 4. Upper bound to risk of hemorrhage after 3 years as function of cumulative device experience, after observing an event rate of 0.036 in 834.2 patient years.

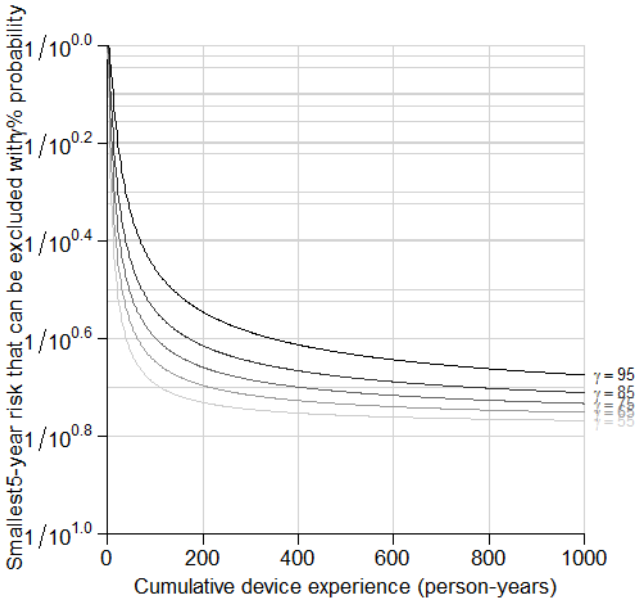

Figure 5. Upper bound to risk of hemorrhage after 5 years as a function of cumulative device experience, after observing an event rate of 0.036 in 834.2 patient-years.

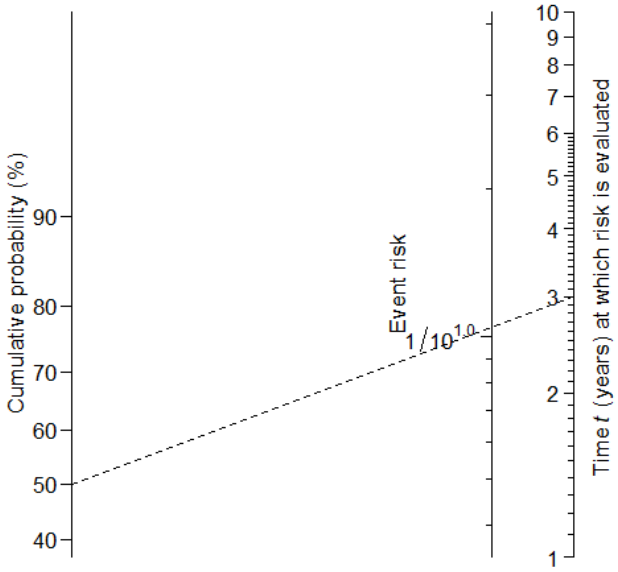

Figure 6. Nomogram for upper bound to risk of hemorrhage after observing an event rate of 0.036 in 834.2 patient-years.

2.4 Discussion

Market approval for medical devices is often based on small-scale single-arm studies. Pre-defined clinical evidence requirements do not exist or are generic requirements that leave room for interpretation by the notified bodies and other organizations in charge of assessing device quality.

We have used Bayesian reasoning to create an online tool to assist the notified bodies with understanding the risk that can be accepted when the cumulative device experience is limited.

Limitations of the calculator include the choice of parameters in the prior distribution. A Bayesian perspective is needed to allow for a proper interpretation of the probability that a device does not have risks above a certain number, for example a 3% annual risk. A challenge for such a perspective is the definition of a prior distribution: what is a plausible picture of the clinical setting; what risks are plausible, and what is an extreme risk that cannot be anticipated? A classic idea is to specify 'uninformative' priors, which contain limited information. This implies that as soon as real data are observed, the posterior estimate is very close to the observed estimate. In our examples we assumed a prior with parameters $\alpha = 1$ and $\beta = 0$, which we consider 'weakly informative'.

For further work, we envision that testing in concrete clinical use cases is necessary, in collaboration with relevant stakeholders, including policy makers, regulators and clinicians.

3 Mathematical Proof

In this section, we give a short overview on the Gamma distribution and a mathematical treatise of the calculator.

3.1 Gamma distribution

The Gamma distribution is characterized the shape parameter α and the rate parameter β. Its probability density function is given by

$$f(x) = \frac{\beta^{\alpha}}{\Gamma(\alpha)} x^{\alpha-1} e^{-\beta x}.$$

In figure 7, a Gamma distribution is displayed, with parameters α and β equal to 1.

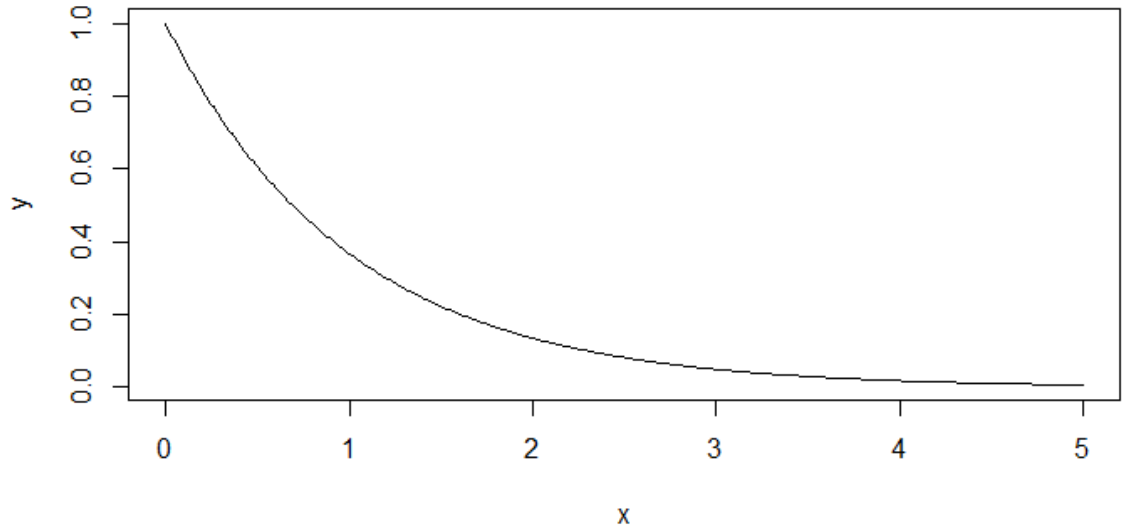

Figure 7. Gamma distribution with α =1, β = 0

3.2 Mathematical Proof of Calculator

Let $\boldsymbol{T}$ denote the failure time of interest and $\boldsymbol{S}$ the censoring time. Let

$$(\boldsymbol{T_1}, \boldsymbol{S_1}), \ldots, (\boldsymbol{T_n}, \boldsymbol{S_n})$$

be $\boldsymbol{n}$ independent and identically distributed pairs of variables such that $(\boldsymbol{T_i}, \boldsymbol{S_i})$ has the same distribution as $(\boldsymbol{T}, \boldsymbol{S})$ for all $\boldsymbol{i}$.

We assume $\boldsymbol{T}$ takes the exponential distribution with rate parameter $\boldsymbol{\lambda}$, i.e.,

$$\boldsymbol{P(T \leq t) = 1 - \exp(-\lambda t)}, \text{ for all } \boldsymbol{t \geq 0},$$

and we denote by $\boldsymbol{\theta}$ the parameter fully characterising the distribution of $\boldsymbol{S}$. We assume independent censoring, e.g. $(\boldsymbol{T}, \boldsymbol{\lambda}) \perp\!\!\!\perp (\boldsymbol{S}, \boldsymbol{\theta})$ for all $\boldsymbol{i}$.

Rather than observing $(\boldsymbol{T_i}, \boldsymbol{S_i})$, we observe $\boldsymbol{T_i^* = \min\{T_i, S_i\}}$ and $\boldsymbol{\delta_i = I(T_i \leq S_i)}$. We use boldface to denote vectors of variables, e.g. $\boldsymbol{T^* = (T_1^*, \ldots, T_n^*)}$. Further, define $\boldsymbol{X = (T^*, \delta)}$.

We will begin by showing the relation between the posterior and prior distributions for $\boldsymbol{\lambda}$.

$$\begin{aligned}
\boldsymbol{p_{\lambda|\mathbf{X}}(\lambda|x)} &= \int \boldsymbol{p_{(\lambda,\theta)|\mathbf{X}}(\lambda, \theta|x)}\, \mathbf{d\theta} \\
&\propto \int \boldsymbol{p_\lambda(\lambda) p_\theta(\theta) p_{\mathbf{X}|(\lambda,\theta)}(\mathbf{x}|\lambda, \theta)}\, \mathbf{d\theta}, && \text{since } \boldsymbol{\lambda \perp\!\!\!\perp \theta} \\
&= \int \boldsymbol{p_\lambda(\lambda) p_\theta(\theta)} \prod_{i=1}^{n} \boldsymbol{p_{(T^*,\delta)|(\lambda,\theta)}\,(t_i^*, d_i|\lambda, \theta)}\, \mathbf{d\theta}, && \text{by the i.i.d. assumption} \\
&= \int \boldsymbol{p_\lambda(\lambda) p_\theta(\theta)} \prod_{i=1}^{n} \left[\boldsymbol{p_{T|\lambda}(t_i^*|\lambda)} \mathbf{Pr}(\boldsymbol{S \geq t_i^*|\theta})\right]^{\boldsymbol{d_i}} \left[\mathbf{Pr}(\boldsymbol{T > t_i^*|\lambda}) \boldsymbol{p_{S|\theta}(t_i^*|\theta)}\right]^{\mathbf{1-}\boldsymbol{d_i}} \mathbf{d\theta}, \\
&\propto \boldsymbol{p_\lambda(\lambda)} \prod_{i=1}^{n} \left[\boldsymbol{p_{T|\lambda}(t_i^*|\lambda)}\right]^{\boldsymbol{d_i}} \left[\mathbf{Pr}(\boldsymbol{T > t_i^*|\lambda})\right]^{\mathbf{1-}\boldsymbol{d_i}} \\
&= \boldsymbol{p_\lambda(\lambda)} \prod_{i=1}^{n} \boldsymbol{\lambda^{d_i} \exp[-\lambda t_i^*]^{d_i} \exp[-\lambda t_i^*]^{1-d_i}} \\
&= \boldsymbol{p_\lambda(\lambda)} \prod_{i=1}^{n} \boldsymbol{\lambda^{d_i} \exp[-\lambda]^{t_i^*}} \\
&= \boldsymbol{p_\lambda(\lambda) \lambda^{\sum_{i=1}^n d_i} \exp[-\lambda]^{\sum_{i=1}^n t_i^*}}.
\end{aligned}$$

This shows that the posterior density of $\boldsymbol{\lambda}$ given $\boldsymbol{E} := \sum_{i=1}^{n} \boldsymbol{T_i^*}$ and $\boldsymbol{R} := \sum_{i=1}^{n} \boldsymbol{\delta_i}\, \boldsymbol{/E}$ is equal to

$$\boldsymbol{\pi(\lambda) \lambda^{RE} \exp[-\lambda]^E}$$

up to a proportionality constant, where $\boldsymbol{\pi}$ is the prior density function of $\boldsymbol{\lambda}$.

3.3 Posterior density of λ under Gamma (conjugate) prior distribution

Suppose our prior belief on $\boldsymbol{\lambda}$ is given by a Gamma distribution with parameters $\boldsymbol{\alpha > 0}$ (shape) and $\boldsymbol{\beta > 0}$ (rate):

$$\begin{aligned}
\boldsymbol{\pi(\lambda)} &= \frac{\boldsymbol{\beta^\alpha}}{\boldsymbol{\Gamma(\alpha)}} \boldsymbol{\lambda^{\alpha-1} \exp[-\lambda\beta]} \\
&\propto \boldsymbol{\lambda^{\alpha-1} \exp[-\lambda\beta]}.
\end{aligned}$$

Our posterior density then satisfies

$$\begin{aligned} p_{\lambda|(E,R)}(\lambda|e,r) &\propto \pi(\lambda)\lambda^{RE}\exp[-\lambda]^{E} \\ &\propto \lambda^{\alpha-1}\exp[-\lambda\beta]\lambda^{RE}\exp[-\lambda E] \\ &= \lambda^{(RE+\alpha)-1}\exp[-\lambda(E+\beta)], \end{aligned}$$

and so

$$\lambda|(E,R) \sim \mathbf{Gamma}(RE+\alpha, E+\beta).$$

3.4 Quantile function of t-year risk for fixed t and observed event rate

We will now demonstrate how the previous helps us to generate a graph as shown in Figures 1, 2, 4 and 5 in the main text.

Fix the time at which we wish to evaluate the risk at t, fix R at r and also fix hyperparameters α, β. We wish to depict for various levels e of E, the lowest value by which the risk $\mathbf{Risk}(\lambda) := \mathbf{Pr}(T \le t|\lambda) = 1 - \exp[-\lambda t]$ is upper bounded with $\gamma\%$ posterior probability. With $Q(\gamma, e)$ defined as $\min\{u: \mathbf{Pr}(\mathbf{Risk}(\lambda) \le u|R=r, E=e) \ge \gamma\%\}$, this means that we wish to depict the relationship between $Q(\gamma, e)$, γ and e.

Now, $\mathbf{Risk}(\lambda) = \mathbf{Pr}(T \le t|\lambda) = 1 - \exp[-\lambda t]$, so $\partial\mathbf{Risk}(\lambda)/\partial\lambda = t\exp[-\lambda t]$ and so $\mathbf{Risk}(\lambda)$ is strictly increasing over $\lambda \in (0, +\infty)$ if $t > 0$. Letting $\mathbf{Risk}^{-1}(u) = -\log[1-u]/t$ for all u, it follows that

$$\begin{aligned} Q(\gamma, e) &= \min\{u: \mathbf{Pr}(\mathbf{Risk}(\lambda) \le u|R=r, E=e) \ge \gamma\%\} \\ &= \min\{u: \mathbf{Pr}\left(\lambda \le \mathbf{Risk}^{-1}(u)|R=r, E=e\right) \ge \gamma\%\} \\ &= \min\{\mathbf{Risk}(v): \mathbf{Pr}\left(\lambda \le \mathbf{Risk}^{-1}\left(\mathbf{Risk}(v)\right)|R=r, E=e\right) \ge \gamma\%\} \\ &= \min\{\mathbf{Risk}(v): \mathbf{Pr}(\lambda \le v|R=r, E=e) \ge \gamma\%\} \\ &= \mathbf{Risk}(\min\{v: \mathbf{Pr}(\lambda \le v|R=r, E=e) \ge \gamma\%\}) \\ &= \mathbf{Risk}\left(Q^{*}(\gamma, e)\right), \end{aligned}$$

where $Q^{*}(\gamma, e) = \min\{v: \mathbf{Pr}(\lambda \le v|R=r, E=e) \ge \gamma\%\}$, the quantile function of the gamma distribution with parameters $re + \alpha$ and $e + \beta$. Thus,

$$Q(\gamma, e) = 1 - \exp[-Q^{*}(\gamma, e)t].$$

This can be plotted using statistical software such as R.

3.5 Quantile function of t-year risk for fixed observed event rate and cumulative person-time

In this section, we show that we are able to summarize the results in a nomogram, like in Figures 3 and 6 in the main text.

First, fix $\boldsymbol{R}$ at $\boldsymbol{r}$ and $\boldsymbol{E}$ at $\boldsymbol{e}$ and also fix hyperparameters $\boldsymbol{\alpha}, \boldsymbol{\beta}$. Using the arguments above, we can express, as a function of time horizon $\boldsymbol{t}$ and parameter $\boldsymbol{\gamma}$, the lowest value by which the risk $\mathbf{Risk}(\boldsymbol{\lambda}, \boldsymbol{t}) := \mathbf{Pr}(\boldsymbol{T} \leq \boldsymbol{t}|\boldsymbol{\lambda})$ is upper bounded with $\boldsymbol{\gamma}\%$ prior/posterior probability. To this end, redefine $\boldsymbol{Q}$ as a function of $\boldsymbol{\gamma}$ and $\boldsymbol{t}$ such that $\boldsymbol{Q}(\boldsymbol{\gamma}, \boldsymbol{t}) = \mathbf{min}\{\boldsymbol{u}: \mathbf{Pr}(\mathbf{Risk}(\boldsymbol{\lambda}, \boldsymbol{t}) \leq \boldsymbol{u}|\boldsymbol{R} = \boldsymbol{r}|\boldsymbol{E} = \boldsymbol{e}) \geq \boldsymbol{\gamma}\%\}$ and likewise redefine $\boldsymbol{Q}^*$ as function of $\boldsymbol{\gamma}$ such that $\boldsymbol{Q}^*(\boldsymbol{\gamma}) = \mathbf{min}\{\boldsymbol{v}: \mathbf{Pr}(\boldsymbol{\lambda} \leq \boldsymbol{v}|\boldsymbol{R} = \boldsymbol{r}, \boldsymbol{E} = \boldsymbol{e}) \geq \boldsymbol{\gamma}\%\}$. Then,

$$\begin{aligned} \boldsymbol{Q}(\boldsymbol{\gamma}, \boldsymbol{t}) &= \mathbf{1} - \mathbf{exp}[-\boldsymbol{Q}^*(\boldsymbol{\gamma})\boldsymbol{t}], \text{ i.e.,} \\ \mathbf{log}\{-\mathbf{log}[\mathbf{1} - \boldsymbol{Q}(\boldsymbol{\gamma}, \boldsymbol{t})]\} &= \mathbf{log}\big(\boldsymbol{Q}^*(\boldsymbol{\gamma})\big) + \mathbf{log}(\boldsymbol{t}), \text{ or} \\ \boldsymbol{h}\big(\boldsymbol{Q}(\boldsymbol{\gamma}, \boldsymbol{t})\big) &= \boldsymbol{f}(\boldsymbol{\gamma}) + \boldsymbol{g}(\boldsymbol{t}), \end{aligned}$$

where $\boldsymbol{h}(\boldsymbol{x}) = \mathbf{log}[-\mathbf{log}(\mathbf{1} - \boldsymbol{x})]$ for $\boldsymbol{x} \in (\mathbf{0}, \mathbf{1})$, $\boldsymbol{f}(\boldsymbol{x}) = \mathbf{log}\big(\boldsymbol{Q}^*(\boldsymbol{x})\big)$ for $\boldsymbol{x} \in (\mathbf{0}, \mathbf{100})$, and $\boldsymbol{g}(\boldsymbol{x}) = \mathbf{log}(\boldsymbol{x})$ for $\boldsymbol{x} > \mathbf{0}$.

In what follows we show that relationships of this form, i.e., $\boldsymbol{C} = \boldsymbol{A} + \boldsymbol{B}$, can be represented by a standard nomogram with three parallel scales. We embed the nomogram within a Cartesian coordinate system on a plane and stipulate (1) that each value $\boldsymbol{A}$ on the $\boldsymbol{A}$-scale (e.g., $\boldsymbol{A} = \boldsymbol{f}(\boldsymbol{\gamma})$) has coordinates $\big(\boldsymbol{x_1}(\boldsymbol{A}), \boldsymbol{y_1}(\boldsymbol{A})\big)$ with $\boldsymbol{x_1}(\boldsymbol{A}) = \mathbf{0}$ and $\boldsymbol{y_1}(\boldsymbol{A}) = (\boldsymbol{A} - \boldsymbol{l_A})/(\boldsymbol{u_A} - \boldsymbol{l_A})$ for fixed constants $\boldsymbol{l_A}, \boldsymbol{u_A}$; (2) that each value $\boldsymbol{C}$ on the $\boldsymbol{C}$-scale (e.g., $\boldsymbol{C} = \boldsymbol{h}\big(\boldsymbol{Q}(\boldsymbol{\gamma}, \boldsymbol{t})\big)$) has coordinates $\big(\boldsymbol{x_2}(\boldsymbol{C}), \boldsymbol{y_2}(\boldsymbol{C})\big)$; and (3) that each value $\boldsymbol{B}$ on the $\boldsymbol{B}$-scale (e.g., $\boldsymbol{B} = \boldsymbol{g}(\boldsymbol{t})$) has coordinates $\big(\boldsymbol{x_3}(\boldsymbol{B}), \boldsymbol{x_3}(\boldsymbol{B})\big)$ with $\boldsymbol{x_3}(\boldsymbol{B}) = \mathbf{1}$ and $\boldsymbol{y_3}(\boldsymbol{B}) = (\boldsymbol{B} - \boldsymbol{l_B})/(\boldsymbol{u_B} - \boldsymbol{l_B})$ for fixed constants $\boldsymbol{l_B}, \boldsymbol{u_B}$. We require that a straight line intersecting the $\boldsymbol{A}$- and $\boldsymbol{B}$-scales (the outer scales) at arbitrary points $\big(\boldsymbol{x_1}(\boldsymbol{A}), \boldsymbol{y_1}(\boldsymbol{A})\big)$ and $\big(\boldsymbol{x_3}(\boldsymbol{B}), \boldsymbol{y_3}(\boldsymbol{B})\big)$, respectively, intersects the $\boldsymbol{C}$-scale (the middle scale) at $\big(\boldsymbol{x_2}(\boldsymbol{C}), \boldsymbol{y_2}(\boldsymbol{C})\big)$, so that

$$\begin{aligned} & \tfrac{\boldsymbol{y_3}(\boldsymbol{B}) - \boldsymbol{y_2}(\boldsymbol{C})}{\boldsymbol{x_3}(\boldsymbol{B}) - \boldsymbol{x_2}(\boldsymbol{C})} = \tfrac{\boldsymbol{y_2}(\boldsymbol{C}) - \boldsymbol{y_1}(\boldsymbol{A})}{\boldsymbol{x_2}(\boldsymbol{C}) - \boldsymbol{x_1}(\boldsymbol{A})}, \\ \Leftrightarrow \quad & \boldsymbol{x_1}(\boldsymbol{A})\boldsymbol{y_2}(\boldsymbol{C}) + \boldsymbol{x_3}(\boldsymbol{B})\boldsymbol{y_1}(\boldsymbol{A}) + \boldsymbol{x_2}(\boldsymbol{C})\boldsymbol{y_3}(\boldsymbol{B}) - \boldsymbol{x_3}(\boldsymbol{B})\boldsymbol{y_2}(\boldsymbol{C}) - \boldsymbol{x_2}(\boldsymbol{C})\boldsymbol{y_1}(\boldsymbol{A}) - \boldsymbol{x_1}(\boldsymbol{A})\boldsymbol{y_3}(\boldsymbol{B}) = \mathbf{0}, \\ \Leftrightarrow \quad & \mathbf{det}\begin{bmatrix} \boldsymbol{x_1}(\boldsymbol{A}) & \boldsymbol{y_1}(\boldsymbol{A}) & \mathbf{1} \\ \boldsymbol{x_2}(\boldsymbol{C}) & \boldsymbol{y_2}(\boldsymbol{C}) & \mathbf{1} \\ \boldsymbol{x_3}(\boldsymbol{B}) & \boldsymbol{y_3}(\boldsymbol{B}) & \mathbf{1} \end{bmatrix} = \mathbf{0}. \end{aligned}$$

By stipulation, this requirement becomes

$$
\begin{aligned}
\mathbf{0} &= \det\begin{bmatrix} \mathbf{0} & \dfrac{\boldsymbol{A}-\boldsymbol{l_A}}{\boldsymbol{u_A}-\boldsymbol{l_A}} & \mathbf{1} \\ \boldsymbol{x_2(C)} & \boldsymbol{y_2(C)} & \mathbf{1} \\ \mathbf{1} & \dfrac{\boldsymbol{B}-\boldsymbol{l_B}}{\boldsymbol{u_B}-\boldsymbol{l_B}} & \mathbf{1} \end{bmatrix} \\
&= \big(\mathbf{1}-\boldsymbol{x_2(C)}\big)\frac{\boldsymbol{A}-\boldsymbol{l_A}}{\boldsymbol{u_A}-\boldsymbol{l_A}} + \boldsymbol{x_2(C)}\frac{\boldsymbol{B}-\boldsymbol{l_B}}{\boldsymbol{u_B}-\boldsymbol{l_B}} - \boldsymbol{y_2(C)}, \\
\boldsymbol{y_2(C)} &= \big(\mathbf{1}-\boldsymbol{x_2(C)}\big)\frac{\boldsymbol{A}-\boldsymbol{l_A}}{\boldsymbol{u_A}-\boldsymbol{l_A}} + \boldsymbol{x_2(C)}\frac{\boldsymbol{B}-\boldsymbol{l_B}}{\boldsymbol{u_B}-\boldsymbol{l_B}}.
\end{aligned}
$$

Letting $\boldsymbol{x_2(C)} = (\boldsymbol{u_B}-\boldsymbol{l_B})/[(\boldsymbol{u_A}-\boldsymbol{l_A})+(\boldsymbol{u_B}-\boldsymbol{l_B})]$, we have

$$
\begin{aligned}
\boldsymbol{y_2(C)} &= \frac{\boldsymbol{u_A}-\boldsymbol{l_A}}{(\boldsymbol{u_A}-\boldsymbol{l_A})+(\boldsymbol{u_B}-\boldsymbol{l_B})}\frac{\boldsymbol{A}-\boldsymbol{l_A}}{\boldsymbol{u_A}-\boldsymbol{l_A}} + \frac{\boldsymbol{u_B}-\boldsymbol{l_B}}{(\boldsymbol{u_A}-\boldsymbol{l_A})+(\boldsymbol{u_B}-\boldsymbol{l_B})}\frac{\boldsymbol{B}-\boldsymbol{l_B}}{\boldsymbol{u_B}-\boldsymbol{l_B}} \\
&= \frac{(\boldsymbol{A}+\boldsymbol{B})-(\boldsymbol{l_A}+\boldsymbol{l_B})}{(\boldsymbol{u_A}+\boldsymbol{u_B})-(\boldsymbol{l_A}+\boldsymbol{l_B})} \\
&= \frac{\boldsymbol{C}-(\boldsymbol{l_A}+\boldsymbol{l_B})}{(\boldsymbol{u_A}+\boldsymbol{u_B})-(\boldsymbol{l_A}+\boldsymbol{l_B})},
\end{aligned}
$$

as desired.

In summary, we have constructed a nomogram with parallel scales depicting the relationship between $\boldsymbol{Q}(\boldsymbol{\gamma},\boldsymbol{t})$, $\boldsymbol{\gamma}$ and $\boldsymbol{t}$. The scales have coordinates

$$
\begin{aligned}
\boldsymbol{x_1(A)} &= \mathbf{0}, \\
\boldsymbol{y_1(A)} &= \frac{\boldsymbol{A}-\boldsymbol{l_A}}{\boldsymbol{u_A}-\boldsymbol{l_A}}, \\
\boldsymbol{x_2(C)} &= \frac{\boldsymbol{u_B}-\boldsymbol{l_B}}{(\boldsymbol{u_A}-\boldsymbol{l_A})+(\boldsymbol{u_B}-\boldsymbol{l_B})}, \\
\boldsymbol{y_2(C)} &= \frac{\boldsymbol{C}-(\boldsymbol{l_A}+\boldsymbol{l_B})}{(\boldsymbol{u_A}+\boldsymbol{u_B})-(\boldsymbol{l_A}+\boldsymbol{l_B})}, \\
\boldsymbol{x_3(B)} &= \mathbf{1}, \\
\boldsymbol{y_3(B)} &= \frac{\boldsymbol{B}-\boldsymbol{l_B}}{\boldsymbol{u_B}-\boldsymbol{l_B}},
\end{aligned}
$$

where

$$
\begin{aligned}
\boldsymbol{A} &= \mathbf{log}\big(\boldsymbol{Q}^*(\boldsymbol{\gamma})\big), \\
\boldsymbol{B} &= \mathbf{log}(\boldsymbol{t}), \\
\boldsymbol{C} &= \mathbf{log}(-\mathbf{log}[\mathbf{1}-\boldsymbol{Q}(\boldsymbol{\gamma},\boldsymbol{t})]).
\end{aligned}
$$

4 Source Code Calculator

The calculator was programmed in R [1] with the Shiny app package[2]. Once compiled, the result is an interactive web app which can be published online and accessed by anyone with the link. The code for the calculator is given here.

4.1 R code

```
extra <- c(0,0)
pagewidth <- (100+2*extra[1])*scale # in mm
pageheight <- (100+2*extra[2])*scale
mm2inch <- function(mm) mm/25.4

plot1 <- function(alpha,beta,r,t,e,gamma){
 Risk <- function(lambda,t) 1-exp(-lambda*t)
 Qstar <- function(gamma,r,e) qgamma(gamma/100,shape=r*e+alpha,rate=e+beta)
 Q <- function(gamma,r,e,t) Risk(Qstar(gamma,r,e),t)

 cropMargin <- (c(3,3,3,3)+extra[c(2,1,2,1)])*scale # c(bottom,left,top,right)
 margin <- c(5,5,5,5)*scale # c(bottom,left,top,right)
 # derivatives
 framewidth <- pagewidth-sum(cropMargin[c(2L,4L)])
 frameheight <- pageheight-sum(cropMargin[c(1L,3L)])
 frame <- list(
  x=cropMargin[2L]+framewidth*c(0L,0L,1L,1L,0L),
  y=cropMargin[1L]+frameheight*c(0,1L,1L,0L,0L)
 )
 textframewidth <- pagewidth-sum(margin[c(2L,4L)])-sum(cropMargin[c(2L,4L)])
 textframeheight <- pageheight-sum(margin[c(1L,3L)])-sum(cropMargin[c(1L,3L)])
 textframe <- list(
  x=cropMargin[2L]+margin[2L]+textframewidth*c(0L,0L,1L,1L,0L),
  y=cropMargin[1L]+margin[1L]+textframeheight*c(0,1L,1L,0L,0L)
 )
 textheight <- diff(range(textframe$y))
 textwidth <- diff(range(textframe$x))
 tcl <- cropMargin[1L]/2
 vCropTicks <- data.frame(
  x0=cropMargin[2L]+(pagewidth-sum(cropMargin[c(2L,4L)]))*c(0,1,1,0),
  x1=cropMargin[2L]+(pagewidth-sum(cropMargin[c(2L,4L)]))*c(0,1,1,0),
  y0=c(0,pageheight-tcl)[c(1L,1L,2L,2L)],
  y1=c(0,pageheight-tcl)[c(1L,1L,2L,2L)]+tcl
 )
 hCropTicks <- data.frame(
  x0=c(0,pagewidth-tcl)[c(1L,1L,2L,2L)],
  x1=c(0,pagewidth-tcl)[c(1L,1L,2L,2L)]+tcl,
  y0=cropMargin[1L]+(pageheight-sum(cropMargin[c(1L,3L)]))*c(0,1,1,0),
  y1=cropMargin[1L]+(pageheight-sum(cropMargin[c(1L,3L)]))*c(0,1,1,0)
 )
 #lapply(vCropTicks,range)
 #lapply(hCropTicks,range)
```

[2] https://shiny.rstudio.com/reference/shiny/1.7.0/.

```
# plotting
#dev.new(width=mm2inch(pagewidth),height=mm2inch(pageheight))
par(mar=rep(0,4L))
#par(family="Palatino")
par(family="Times") # or download other fonts
plot(c(0,pagewidth),c(0,pageheight),type='n',axes=FALSE,xlab='',ylab='',bty='n',yaxs='i',xaxs='i')
if(FALSE){
 lines(frame,lty=2,lwd=.2)
 lines(textframe,lwd=.2)
 do.call(function(...) segments(...,lwd=.2),vCropTicks)
 do.call(function(...) segments(...,lwd=.2),hCropTicks)
}
dx <- diff(range(textframe$x))
dy <- diff(range(textframe$y))
targetframe <- list(x=min(textframe$x)+c(0.1,0.1,1,1,0.1)*dx,y=min(textframe$y)+c(.08*dx,dy,dy,.08*dx,.08*dx))
#lines(targetframe,lwd=.2)
convert <- function(x,y,current=list(x=c(0,0,1,1,0),y=c(0,1,1,0,0)),target=targetframe){
 ry <- (y-min(current$y))/diff(range(current$y))
 ny <- ry*diff(range(target$y))+min(target$y)
 rx <- (x-min(current$x))/diff(range(current$x))
 nx <- rx*diff(range(target$x))+min(target$x)
 return(data.frame(x=nx,y=ny))
}
f <- function(gamma) Q(gamma,r=r,e=e,t=t)
ylim <- c(10^floor(log(min(f(min(gamma))),10)),1)
xlim <- range(e)
current <- list(x=xlim[c(1,1,2,2,1)],y=log(ylim[c(1,2,2,1,1)],10))
pretty <- function(x){
        y <- base::pretty(x)
        y[y>=min(x)&y<=max(x)]
}
vGridLines <- data.frame(x0=pretty(xlim),y0=log(ylim[1],10),y1=log(ylim[2],10))
vGridLines[,1:2] <- with(vGridLines,convert(x0,y0,current))
vGridLines[,3] <- with(vGridLines,convert(x0,y1,current))$y
w <- which(abs(vGridLines$x0-min(targetframe$x))<1e-2)
if(length(w)) vGridLines <- vGridLines[-w,]
with(vGridLines,segments(x0=x0,y0=y0,y1=y1,col="lightgrey"))
hGridLines <- hGridLines0 <- data.frame(x0=xlim[1],x1=xlim[2],y0=pretty(log(ylim,10)))
hGridLines[,2:3] <- with(hGridLines,convert(x1,y0,current))
hGridLines[,1] <- with(hGridLines,convert(x0,y0,current))$x
w <- which(abs(hGridLines$y0-min(targetframe$y))<1e-2)
if(length(w)) hGridLines <- hGridLines[-w,]
with(hGridLines,segments(x0=x0,x1=x1,y0=y0,col="lightgrey"))
# secondary horizontal grid lines
y0 <- 10^hGridLines0$y0
y1 <- unlist(lapply(seq_along(y0[-1]),function(i)y0[i]*(2:9)))
y1 <- y1[y1>=ylim[1]&y1<=ylim[2]]
hGridLines2 <- data.frame(x0=xlim[1],x1=xlim[2],y0=log(y1,10))
hGridLines2[,2:3] <- with(hGridLines2,convert(x1,y0,current))
hGridLines2[,1] <- with(hGridLines2,convert(x0,y0,current))$x
with(hGridLines2,segments(x0=x0,x1=x1,y0=y0,col="lightgrey"))
#
xAxis <- convert(x=xlim,y=rep(log(min(ylim[1]),10),2),current)
lines(xAxis)
```

```
 yAxis <- convert(x=rep(xlim[1],2),y=log(ylim,10),current)
 lines(yAxis)
 ly <- diff(range(current$y))/50
 lx <- diff(range(current$x))/50
 vTicks <- data.frame(x0=pretty(xlim),y0=log(ylim[1],10),y1=log(ylim[1],10)-ly)
 vTicks[,1:2] <- with(vTicks,convert(x0,y0,current))
 vTicks[,3] <- with(vTicks,convert(x0,y1,current))$y
 with(vTicks,segments(x0=x0,y0=y0,y1=y1))
 hTicks <- data.frame(x0=xlim[1],x1=xlim[1]-lx,y0=pretty(log(ylim,10)))
 hTicks[,2:3] <- with(hTicks,convert(x1,y0,current))
 hTicks[,1] <- with(hTicks,convert(x0,y0,current))$x
 with(hTicks,segments(x0=x0,x1=x1,y0=y0))
 #txt <- paste0(formatC(pretty(ylim),format="f",digits=1))
 txt <- paste0("bquote(1/10^{\"",formatC(abs(pretty(log(ylim,10))),format="f",digits=1),"\"})")
 #with(convert(xlim[1]-1.5*lx,pretty(log(ylim,10)),current),text(x,y,"1",adj=c(1,.5),cex=.8))
 for(i in seq_along(txt)) with(convert(xlim[1]-1.5*lx,pretty(log(ylim,10)),current),
  text(x[i],y[i],eval(parse(text=txt[i])),adj=c(1,.5),cex=.8))
 txt <- pretty(xlim)
 with(convert(pretty(xlim),log(ylim[1],10)-1.5*ly,current),text(x,y,txt,adj=c(.5,1),cex=.8))
 with(convert(xlim[1]-9.5*lx,mean(log(ylim,10)),current),text(x-2,y,srt=90,bquote("Smallest "*.(t)*"-year risk that can be
excluded with "*gamma*"% probability"),adj=c(.5,1),cex=.8))
 with(convert(mean(xlim),log(ylim[1],10)-6*ly,current),text(x,y,srt=0,"Cumulative device experience (person-
years)",adj=c(.5,0),cex=.8))
 l <- length(gamma)+1
 cols <- rev(sapply(seq(0,1,length=l)[-l],function(x)rgb(x,x,x,maxColorValue=1)))
 for(i in seq_along(gamma)) lines(convert(e,log(f(gamma[i]),10),current),col=cols[i])
 txt <- paste0("bquote(gamma==",gamma,")")
 xy <- convert(rev(e)[1]+lx,log(sapply(gamma,function(x)rev(f(x))[1]),10),current)
 for(i in seq_along(txt)) with(xy,text(x[i],y[i],eval(parse(text=txt[i])),adj=c(0,.5),cex=.6,col=cols[i]))

}

plot2 <- function(alpha,beta,r,tt,e,gamma,isopleth, isoplethGamma, isoplethT){
 Risk <- function(lambda,t) 1-exp(-lambda*t)
 Qstar <- function(gamma,r,e) qgamma(gamma/100,shape=r*e+alpha,rate=e+beta)
 Q <- function(gamma,r,e,t) Risk(Qstar(gamma,r,e),t)
 pretty <- function(x){
          y <- base::pretty(x)
          y[y>=min(x)&y<=max(x)]
 }

 scale <- 1
 extra <- c(0,0)
 pagewidth <- (100+2*extra[1])*scale # in mm
 pageheight <- (100+2*extra[2])*scale
 cropMargin <- (c(3,3,3,3)+extra[c(2,1,2,1)])*scale # c(bottom,left,top,right)
 margin <- c(5,5,5,5)*scale # c(bottom,left,top,right)
 # derivatives
 framewidth <- pagewidth-sum(cropMargin[c(2L,4L)])
 frameheight <- pageheight-sum(cropMargin[c(1L,3L)])
 frame <- list(
  x=cropMargin[2L]+framewidth*c(0L,0L,1L,1L,0L),
  y=cropMargin[1L]+frameheight*c(0,1L,1L,0L,0L)
 )
```

```
textframewidth <- pagewidth-sum(margin[c(2L,4L)])-sum(cropMargin[c(2L,4L)])
textframeheight <- pageheight-sum(margin[c(1L,3L)])-sum(cropMargin[c(1L,3L)])
textframe <- list(
 x=cropMargin[2L]+margin[2L]+textframewidth*c(0L,0L,1L,1L,0L),
 y=cropMargin[1L]+margin[1L]+textframeheight*c(0,1L,1L,0L,0L)
)
textheight <- diff(range(textframe$y))
textwidth <- diff(range(textframe$x))
tcl <- cropMargin[1L]/2
vCropTicks <- data.frame(
 x0=cropMargin[2L]+(pagewidth-sum(cropMargin[c(2L,4L)]))*c(0,1,1,0),
 x1=cropMargin[2L]+(pagewidth-sum(cropMargin[c(2L,4L)]))*c(0,1,1,0),
 y0=c(0,pageheight-tcl)[c(1L,1L,2L,2L)],
 y1=c(0,pageheight-tcl)[c(1L,1L,2L,2L)]+tcl
)
hCropTicks <- data.frame(
 x0=c(0,pagewidth-tcl)[c(1L,1L,2L,2L)],
 x1=c(0,pagewidth-tcl)[c(1L,1L,2L,2L)]+tcl,
 y0=cropMargin[1L]+(pageheight- sum(cropMargin[c(1L,3L)]))*c(0,1,1,0),
 y1=cropMargin[1L]+(pageheight-sum(cropMargin[c(1L,3L)]))*c(0,1,1,0)
)
#lapply(vCropTicks,range)
#lapply(hCropTicks,range)
# plotting
#dev.new(width=mm2inch(pagewidth),height=mm2inch(pageheight))
par(mar=rep(0,4L))
#par(family="Palatino")
par(family="Times") # or download other fonts
plot(c(0,pagewidth),c(0,pageheight),type='n',axes=FALSE,xlab='',ylab='',bty='n',yaxs='i',xaxs='i')
if(FALSE){
 lines(frame,lty=2,lwd=.2)
 lines(textframe,lwd=.2)
 do.call(function(...) segments(...,lwd=.2),vCropTicks)
 do.call(function(...) segments(...,lwd=.2),hCropTicks)
}
targetframe <- list(x=min(textframe$x)+c(0.08,0.08,1,1,0.08)*diff(range(textframe$x)),y=textframe$y)
convert <- function(x,y,current=list(x=c(0,0,1,1,0),y=c(0,1,1,0,0)),target=targetframe){
 ry <- (y-min(current$y))/diff(range(current$y))
 ny <- ry*diff(range(target$y))+min(target$y)
 rx <- (x-min(current$x))/diff(range(current$x))
 nx <- rx*diff(range(target$x))+min(target$x)
 return(data.frame(x=nx,y=ny))
}
# settings
lgamma <- gamma[1]
ugamma <- gamma[2]
lA <- log(Qstar(lgamma,r,e),10); lA
log(Qstar(lgamma,r,e),10);lA #lA
uA <- log(Qstar(ugamma,r,e),10); uA
t_sq <- seq(tt[1],tt[2],by=1)#seq(1,10,by=1)
lB <- log(min(t_sq),10)
uB <- log(max(t_sq),10)
rr <- (uB-lB)/(uA-lA+uB-lB)
```

```
# functions
A <- function(gamma){
  log(Qstar(gamma,r,e),10)
}
B <- function(t) log(t,10)
C <- function(P) log(-log(1-P/100),10)
x1 <- function(lambda) rep(0,length(lambda))
y1 <- function(lambda) (log(lambda,10)-lA)/(uA-lA)
x3 <- function(t) rep(1,length(t))
y3 <- function(t) (B(t)-lB)/(uB-lB)
x2 <- function(Risk) rep(rr,length(Risk))
y2 <- function(Risk) (log(-log(1-Risk),10)-(lA+lB))/((uA+uB)-(lA+lB))

# check:
y1(Qstar(lgamma,r,e)) # 0 (correct)
y1(Qstar(ugamma,r,e)) # 1 (correct)
y3(min(t_sq)) # 0 (correct)
y3(max(t_sq)) # 1 (correct)
y2(Risk(Qstar(lgamma,r,e),min(t_sq))) # 0 (correct)
y2(Risk(Qstar(ugamma,r,e),max(t_sq))) # 1 (correct)

axis1 <- data.frame(x=c(0,0),y=c(0,1)) # lambda; level of 'confidence' (gamma)
axis3 <- data.frame(x=c(1,1),y=c(0,1))# event risk upper bound
axis2 <- data.frame(x=c(rr,rr),y=c(0,1)) # experience / number of years since baseline
with(with(axis1,convert(x,y)),segments(x0=x[1],y0=y[1],y1=y[2]))
with(with(axis2,convert(x,y)),segments(x0=x[1],y0=y[1],y1=y[2]))
with(with(axis3,convert(x,y)),segments(x0=x[1],y0=y[1],y1=y[2]))

# Time
xy <- convert(x3(t_sq),y3(t_sq))
with(xy,segments(x0=x,x1=convert(x3(t_sq)-1/50,NA)$x,y0=y))
with(convert(x3(t_sq)-1.5/50,y3(t_sq)),text(x,y,t_sq,adj=c(1,.5),cex=.8))
with(convert(x3(0)-4/50,.5),text(x+12,y,srt=90,bquote("Time "*italic(t)*" (years) at which risk is
evaluated"),adj=c(.5,0),cex=.8))

# secondary tick marks
tm <- t_sq
tm <- unlist(lapply(seq_along(tm[-1]),function(i)tm[i]+(1:9)/10))
xy <- convert(x3(tm),y3(tm))
#wh <- pmin(abs(y3(tm)-c(-Inf,y3(tm[-length(tm)]))),abs(y3(tm)-c(y3(tm[-1]),-Inf)))>=1e-2
wh <- 1:(9*5)
with(xy[wh,],segments(x0=x,x1=convert(x3(tm)-1/100,NA)$x,y0=y,lwd=1))

# Confidence
gamma_sq <- pretty(gamma)
lamb <- Qstar(gamma_sq,r,e)
log(Qstar(lgamma,r,e),10);lA #lA
xy <- convert(x1(lamb),y1(lamb))
with(xy,segments(x0=x,x1=convert(x1(lamb)-1/50,NA)$x,y0=y))
with(convert(x1(lamb)-1.5/50,y1(lamb)),text(x,y,paste0(gamma_sq,""),adj=c(1,.5),cex=.8))
with(convert(x1(0)-6.5/50,.5),text(x,y,srt=90,"Cumulative probability (%)",adj=c(.5,1),cex=.8))

# Risk
logR_l <- log(Risk(Qstar(lgamma,r,e),min(t_sq)),10)
```

```
 logR_u <- log(Risk(Qstar(ugamma,r,e),max(t_sq)),10)
 logR_lower <- ceiling(logR_l)
 logR_upper <- floor(logR_u)
 Risk_sq <- 10^(seq(logR_lower,logR_upper,by=1))
 xy <- convert(x2(Risk_sq),y2(Risk_sq))
 with(xy,segments(x0=x,x1=convert(x2(Risk_sq)-1/50,NA)$x,y0=y))
 txt <- paste0("bquote(1/10^{\"",formatC(-log(Risk_sq,10),format="f",digits=1),"\"})")
 for(i in seq_along(txt)) with(convert(x2(Risk_sq)-1.5/50,y2(Risk_sq)),
  text(x[i],y[i],eval(parse(text=txt[i])),adj=c(1,.5),cex=.8))
 with(convert(x2(0)-9/50,.5),text(x-2,y,srt=90,"Event risk",adj=c(.5,1),cex=.8))
 # secondary tick marks
 rsk <- 10^seq(floor(logR_l),ceiling(logR_u),by=1)
 rsk <- unlist(lapply(seq_along(rsk[-1]),function(i)rsk[i]*(2:9)))
 rsk <- rsk[log(rsk,10)>=logR_l&log(rsk,10)<=logR_u]
 xy <- convert(x2(rsk),y2(rsk))
 with(xy,segments(x0=x,x1=convert(x2(rsk)-1/100,NA)$x,y0=y,lwd=1))

 # Example isopleth
 if (isopleth && isoplethGamma >= lgamma && isoplethGamma <= ugamma &&
    isoplethT >= tt[1] && isoplethT <= tt[2]) {
  conf <- quantile(gamma,(isoplethGamma-lgamma)/(ugamma-lgamma))
  tm <- quantile(t_sq,(isoplethT-tt[1])/(tt[2]-tt[1]))
  lamb <- Qstar(conf,r,e)
  lines(convert(x=c(x1(lamb),x3(tm)),y=c(y1(lamb),y3(tm))),lty=2)
  #points(convert(x2(Risk(lamb,tm)),y2(Risk(lamb,tm))))
  Risk(lamb,tm)
 }
}


# ---------

library(shiny)

ui <- navbarPage(
 # Application title
 title = "Limited evidence and implicitly accepted risk",
 id="navbar",
 tabPanel(title="Figure 1",
  sidebarPanel(h3("General (layout) settings"),
  numericInput("Time","Time horizon (time in years at which risk is evaluated)",min=1,value=1,step=1)),
  sidebarPanel(h3("Observed data"),
  numericInput("EmpiricalEventRate","Empirical event rate (observed number of events / cumulative device
experience)",min=0,value=0,step=.001),
  numericInput("CumulativeExperience","Maximum cumulative device experience, in person-
years",min=0,value=3000,step=200)),
  sidebarPanel(h3("Prior distribution parameters"),
  numericInput("alpha","Alpha",min=0,value=1),
  numericInput("beta","Beta",min=0,value=0)),
  mainPanel(plotOutput("Plot"))
 ),
 tabPanel(title="Figure 2 (nomogram)",
  sidebarPanel(
   h3("General (layout) settings"),
```

```
    sliderInput("Gamma","Range of gamma",min=0,max=100,value=c(50,99),step=1),
    sliderInput("Time2","Range of times (in years) at which risk is evaluated",min=1,max=100,value=c(1,10),step=1),
    checkboxInput("isopleth", "Draw isopleth", value = TRUE),
    numericInput("isoplethGamma","Draw line from Gamma value",min=0,value=80,step=1),
    numericInput("isoplethT","to time value",min=1,value=5,step=1)

   ),
   sidebarPanel(h3("Observed data"),
    numericInput("EmpiricalEventRate2","Empirical event rate (observed number of events / cumulative device
experience)",min=0,value=0,step=.001),
    numericInput("CumulativeExperience2","Cumulative device experience, in person-years",min=0,value=800,step=200)
   ),
   sidebarPanel(
    h3("Prior distribution parameters"),
    numericInput("alpha2","Alpha",min=0,value=1),
    numericInput("beta2","Beta",min=0,value=0)
   ),
   mainPanel(plotOutput("Plot2"))
  ),
  tabPanel(title="Quit",value="stop",icon=icon("circle-o-notch"))
)

res <- 125
# Server logic
server <- function(input,output,session){
 observe({if(input$navbar=="stop") stopApp()})
 output$Plot <- renderPlot({
            alpha <- input$alpha
  beta <- input$beta
  tt <- input$Time
  e <- seq(0,input$CumulativeExperience,length=500)
  r <- input$EmpiricalEventRate
  gamma <- seq(55,95,by=10)
  plot1(alpha,beta,r,tt,e,gamma)
 },width=mm2inch(pagewidth)*res,height=mm2inch(pageheight)*res,res=res)
 output$Plot2 <- renderPlot({
            alpha <- input$alpha2
  beta <- input$beta2
  tt <- input$Time2
  e <- input$CumulativeExperience2
  r <- input$EmpiricalEventRate2
  gamma <- input$Gamma
  isopleth <- input$isopleth
  isoplethGamma <- input$isoplethGamma
  isoplethT <- input$isoplethT
  plot2(alpha,beta,r,tt,e,gamma,isopleth, isoplethGamma, isoplethT)
 },width=mm2inch(pagewidth)*res,height=mm2inch(pageheight)*res,res=res)
 session$onSessionEnded(function()stopApp())
}

app <- shinyApp(ui,server)
#runApp(app)
```

5 Summary and conclusions

Considering the limited resources available, the portion that could be allocated to this task was limited. In addition, an early change of personnel affected the task team composition. Though, task leaders have promptly notified the Coordinator and the Consortium and have put the appropriate mitigation actions as swiftly as they could.

In the present deliverable the LUMC team (led by Ewout Steyerberg and colleagues) has described an algorithm that can be used by manufacturers, notified body assessors and regulators to evaluate the implications for risk from studies of devices that may have limited sample sizes and/or statistical power.

The utility and usability of such tool will be tested and developed in further collaborations within the consortium during 2023. Although further contributions will not be funded by the CORE-MD grant, the investigators have also offered to advise on statistical questions raised by the systematic reviews performed in Task 1.1, after these have been completed.

A statistical review of methods for applying objective performance criteria is pending, thus an updated version of this deliverable will be provided during the second reporting period and submitted to the attention of the EC and the reviewers.

References

[1] R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.

CORE-MD

CORE-MD, Coordinating Research and Evidence for Medical Devices, aims to translate expert scientific and clinical evidence on study designs for evaluating high-risk medical devices into advice for EU regulators.

For more information, visit: www.core-md.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 965246.