– CASE STUDY – for the application of the
WHO RISK BASED DECISION SUPPORT TOOL FOR BLOOD SAFETY

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This case study is part of a series of documents intended for users of the "*WHO risk based decision support tool for blood safety*". The aim of this case study is to illustrate by going through a worked-out example how the tool may support the user in selecting among various safety interventions aiming to increase the safety of the blood supply.

For more information regarding multiple criteria decision making and the use of the tool, please refer to the ***User Guide*** which provides a general introduction on the risk based decision-making process and the role of the tool herein, and the ***User Manual*** which provides support on the actual operation of the Excel based tool.

A risk based decision-making assessment is comprised of different steps (Figure 1). In this manual, we will illustrate each of these steps by means of a modelled blood supply with various safety interventions that would be suitable to consider.

If you have any questions or suggestions concerning the tool or the approach presented here, please contact Mart Janssen, PhD, from Sanquin Blood Supply Foundation at m.janssen@sanquin.nl.

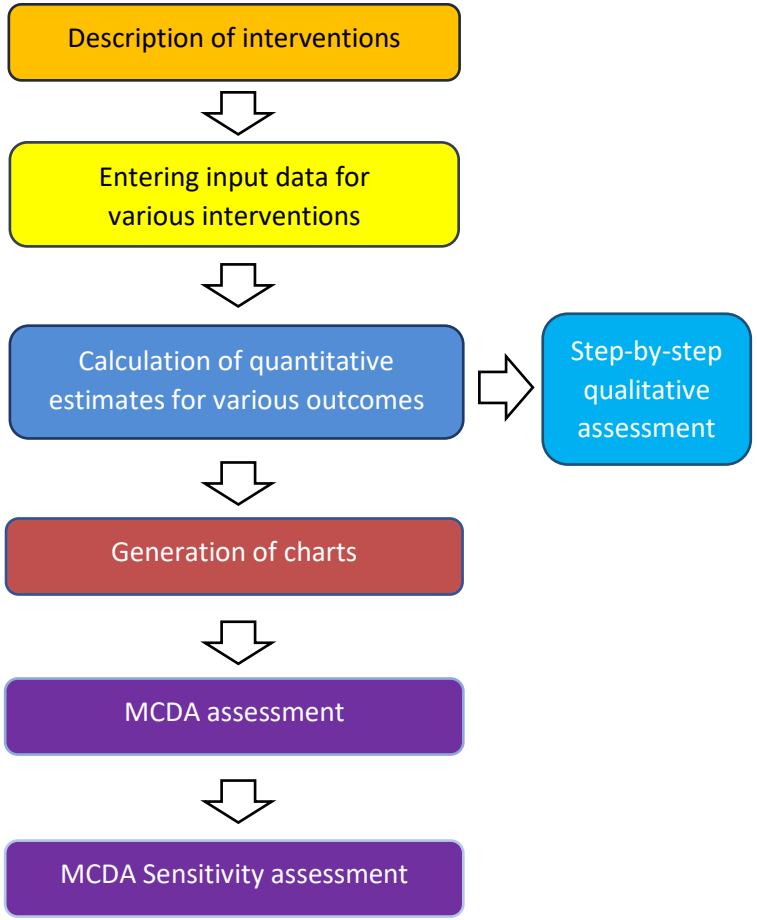


Figure 1 *Steps in a risk based decision-making assessment*

CASE STUDY: "WHICH SAFETY STRATEGY IS BEST FOR PREVENTING HIV TRANSMISSION BY BLOOD TRANSFUSION"?"

Description of the setting

We presume that a blood establishment which is supplying around 60,000 blood products per annum is considering the implementation of an intervention to reduce the risk of HIV transmission. The total budget that will be available for blood screening or processing is 100,000 US$ per year. Due to the narrow donor base, substantial amounts of products lost are considered unacceptable. The prevalence of HIV infections among donors is 2%, and about 10% of the transfusion recipients are already carriers of the HIV virus. Due to operational limitations, it will be possible to implement additional screening or processing of blood products for 50% of the blood supply only. The cost of treatment of an average HIV patient is 150 US$ and the excess mortality rate of HIV infected transfusion recipients is estimated at 17.5%.

Interventions that are being considered for implementation are:

1) Rapid serologic testing,
2) Conventional laboratory-based serological testing,
3) NAT testing, and
4) Pathogen Reduction Technology (PRT).

Decision at hand

The aim is to provide support for the decision as to which of the five risk management strategies (four risk reduction interventions, and in addition, the "do nothing" strategy) is best for the given setting. Note that the "do nothing" option is often forgotten or not considered a viable alternative, but in many cases may ultimately be shown to be the most favorable option.

We will assess various outcomes for each of the optional safety interventions using the Excel workbook. Next, following the process as indicated in Figure 1, we will perform an MCDA assessment as well as a qualitative (step-by-step) assessment. This case study will wrap up with a final conclusion concerning the most favorable intervention for the given setting and a comparison of the qualitative and quantitative approaches.

1. Description of interventions

On the worksheet “Description of interventions” a description of various safety interventions and associated outcomes are provided. The outcomes are defined in terms of total net costs, number of deaths under the option, annual cost of screening, the number of blood products lost, and technological complexity of the safety intervention considered. Note that the descriptions are rather generic, and for some combinations the descriptions are similar to those presented in the row above. In those cases, the word ‘Idem’ has been entered as a reference.

HIV screening of blood products

Optional Safety Interventions		**Total net costs [US$]**	**Annual number of deaths [-]**	**Annual cost of the intervention [US$]**	**Annual number of products lost**	**Technological complexity**	**Cost-effectiveness [US$ per death prevented]**
Option reference:	***Description:***	Total cost of the safety intervention + cost of treatment of infected patients	Total number of deaths given that the safety intervention indicated is implemented	Includes the total cost of the intervention (including costs of personnel, equipment training etcetera)	The proportion of blood products that are discarded/lost due to the safety intervention applied	The technological requirements considering education of personnel and availability of materials and support. These affect the overall effectiveness of the intervention	Total net cost per additional number of deaths prevented. This provides an indication of the "value for money" of the intervention relative to the baseline situation
No testing	Baseline situation where no testing is performed	The cost of treatment of patients due to lack of preventive measures	Number of deaths given the number of infected products transmitted to	No costs	No screening implies that no products are lost	Not applicable	Comparator intervention and therefore not applicable
Rapid serologic testing	Screening of all or part of all blood donations	Costs of screening plus costs of treatment of infected patients	Idem	Costs of screening	Loss of products is equal to the number of false positive donors	Rapid testing has been widely applied and has been shown effective if well applied	Total net costs divided by the decrease of the annual number of deaths relative to no screening
Laboratory serological testing	Screening of all or part of all blood donations	Idem	Idem	Idem	Idem	Serologic testing has been widely applied and has shown to be effective if well applied	Idem
NAT testing	Screening of all or part of all blood donations	Idem	Idem	Idem	Idem	Idem	Idem
Pathogen Reduction	Treatment of all or part of all blood donations with PR technology	Idem	Idem	Costs of treatement of blood components	Loss of products is equal to the prodution loss of the PR process	Novel not yet proven technology	Idem

2. Entering input data for various interventions

The second step of the assessment requires providing estimates for various parameters for each of the interventions as well as characteristics for the blood supply as a whole. Below an overview of all model parameters and point estimates for their respective values is provided. Note that setting a range of credible values is also required. This enables performing a sensitivity analysis for the preferred option at a later stage.

Model parameter	Best estimate		Minimum and maximum credible value	
Description	**Value**	**Units**	**Min Value**	**Max Value**
Number of donations	60,000	-	60,000	60,000
Prevalence among donors	2%	-	1%	20%
Proportion recipients not affected	10%	-	1%	20%
Coverage rate for the safety intervention	50%	-	50%	100%
Costs of treatment (per patient)	150.00	US$	100.00	200.00
Mortaility rate of infected patients	17.5%	-	10%	20%
Sensitivity of Rapid serologic testing	96.0%	-	65%	99.99%
Specificity of Rapid serologic testing	92.0%	-	80.0%	99.99%
Costs of Rapid serologic testing (per donation)	1.12	US$	0.50	2.50
Sensitivity of Laboratory serological testing	98.0%	-	75%	99.99%
Specificity of Laboratory serological testing	98.6%	-	98.0%	99.99%
Costs of Laboratory serological testing (per don.)	4.33	US$	3.25	5.40
Sensitivity of NAT testing	99.9%	-	99.4%	99.99%
Specificity of NAT testing	99.7%	-	99.6%	99.80%
Costs of NAT testing (per donation)	38.40	US$	24.90	59.50
Effectivity of Pathogen Reduction	90.0%	-	75%	99.99%
Costs of Pathogen Reduction (per donation)	20.00	US$	15.00	30.00
Production loss of Pathogen Reduction	5.0%	-	3%	7%

Note that the general blood supply characteristics are aligned with the case study description above. There is quite some uncertainty with respect to the prevalence of infection and the proportion of recipients not affected (both range between 1 to 20%). The costs for the tests include all overheads (so personnel, equipment, reagents, housing, training etc. etc.). These costs are likely to be dependent on the number of tests performed, and the number of tests one is able to perform may be uncertain to start with. In these cases, it might be desirable to perform multiple assessments in parallel in order to differentiate between various implementation scenarios.

Estimates for the sensitivity and specificity of tests foreseen and the effectiveness/production loss for Pathogen Reduction Technology (PRT) or other technologies applied can be obtained from manufacturer specifications or from the literature.

The parameter values used for the screening tests and PRT intervention in this example case study do not necessarily reflect representative values for these tests. Some of the values have been adapted to result in a more interesting case study (with conflicting outcomes) instead of reflecting realistic estimates for these parameters.

3. Quantitative estimates for various outcomes

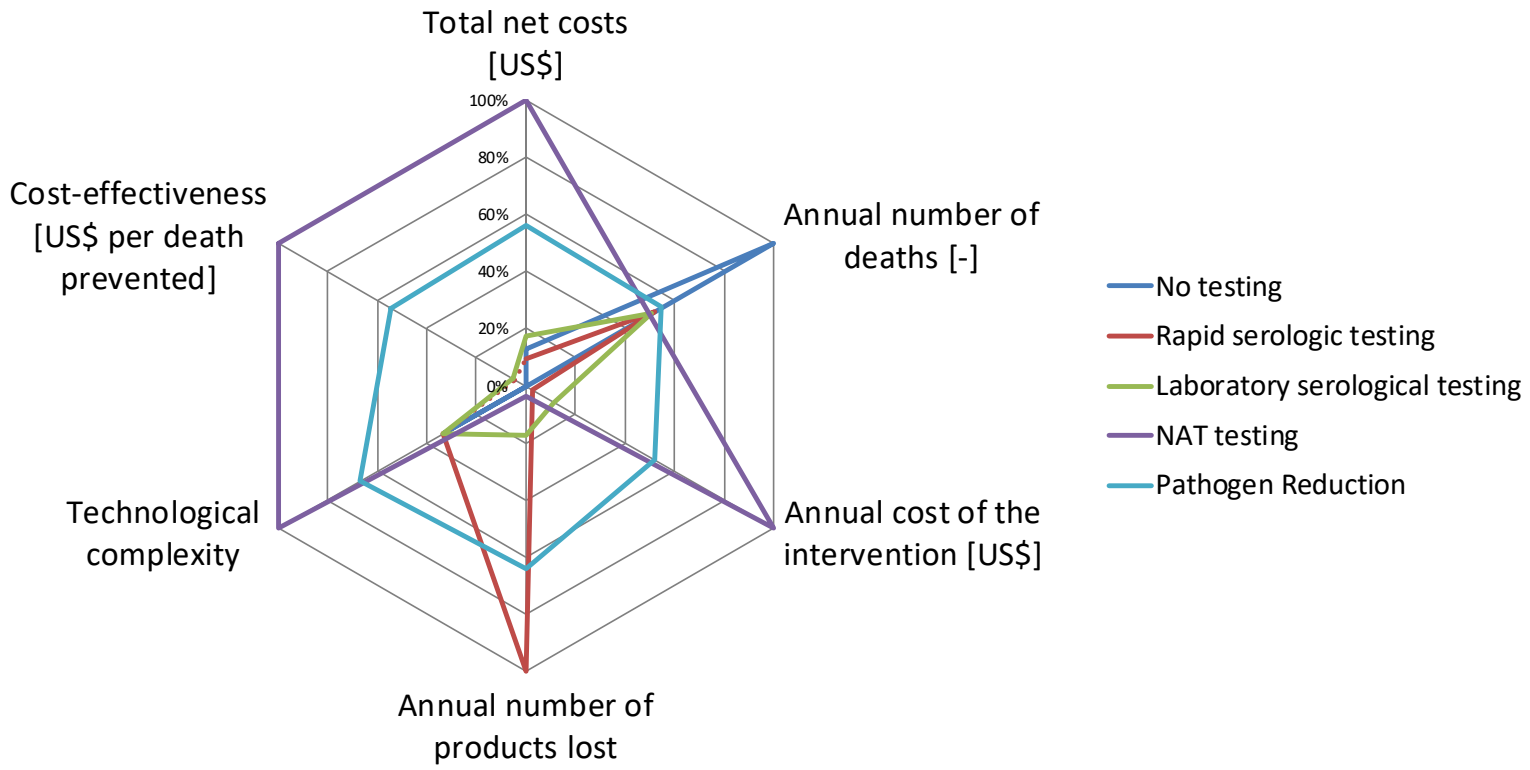
Based on the model parameters entered, the following estimates were calculated for the outcomes of various safety interventions:

Optional Safety Interventions		Total net costs [US$]	Annual number of deaths [-]	Annual cost of the intervention [US$]	Annual number of products lost	Technological complexity	Cost-effectiveness [US$ per death prevented]
No testing	Baseline situation where no testing is performed	162,000	189	0	0	Low	-
Rapid serologic testing	Screening of all or part of all blood donations	117,840	98	33,600	2,352	Low	-487
Laboratory serological testing	Screening of all or part of all blood donations	212,520	96	129,900	412	Low	546
NAT testing	Screening of all or part of all blood donations	1,233,081	95	1,152,000	88	High	11,346
Pathogen Reduction	Treatment of all or part of all blood donations with PR	689,100	104	600,000	1,500	Medium	6,198

It is clear that in this case study NAT testing is by far the most expensive intervention. On the other hand, the expected annual number of deaths prevented by each of the safety interventions is quite similar. This is around half the number of deaths estimated for 'no testing' and is the result of the limited coverage (50%). The total costs for the first three options are quite comparable (these are in the same order of magnitude). On the other hand, PRT and NAT testing are much more expensive. The number of products lost, however, is highest for Rapid serological testing. The number of products lost increases sequentially when changing from NAT to Laboratory serological testing, to pathogen reduction and to Rapid serological testing.

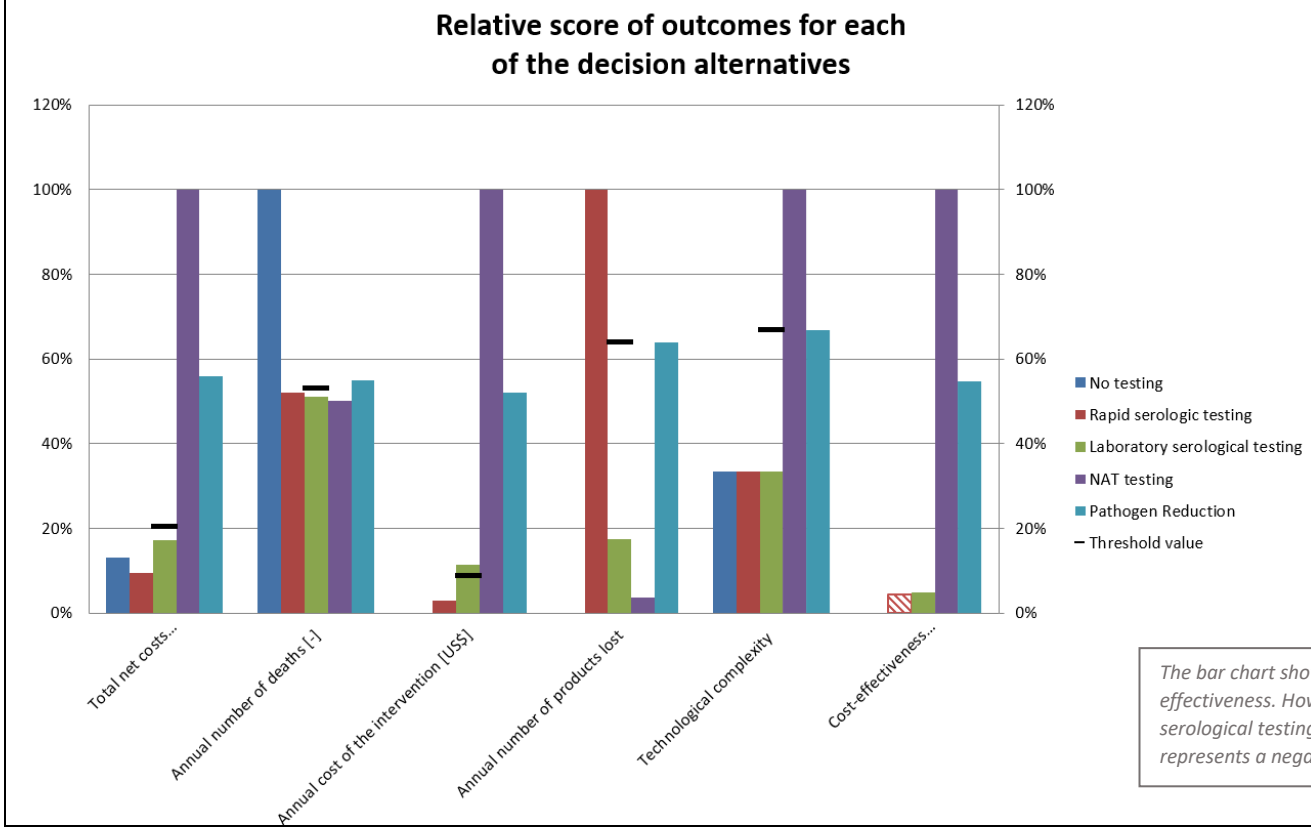
The level of technological complexity has to be entered for each option separately in the outcome table. One of the three levels (low, medium or high) needs to be assigned in this table. For NAT testing 'high' technological complexity is selected as it requires the most sensitive reagents, the most well-preserved operational environment and the highest technical skills from the personnel involved. For PRT, an advanced technology is applied, but it is a relatively robust process once implemented and up and running.

Various charts help to provide insight into the relative scores per safety intervention for each of the outcomes considered. In the spider graph below one can see that NAT testing scores highest (most adverse) on 4 out of 6 outcomes. The 'No testing' option scores highest on the annual number of deaths only and 'Rapid serological testing' has the highest annual number of products lost.



In the bar chart shown below the same information is presented as in the spider graph on the previous page. Unique to the bar chart is that applicable threshold values (limits determined as unacceptable to exceed) are shown as well. For this example, the following threshold values apply:

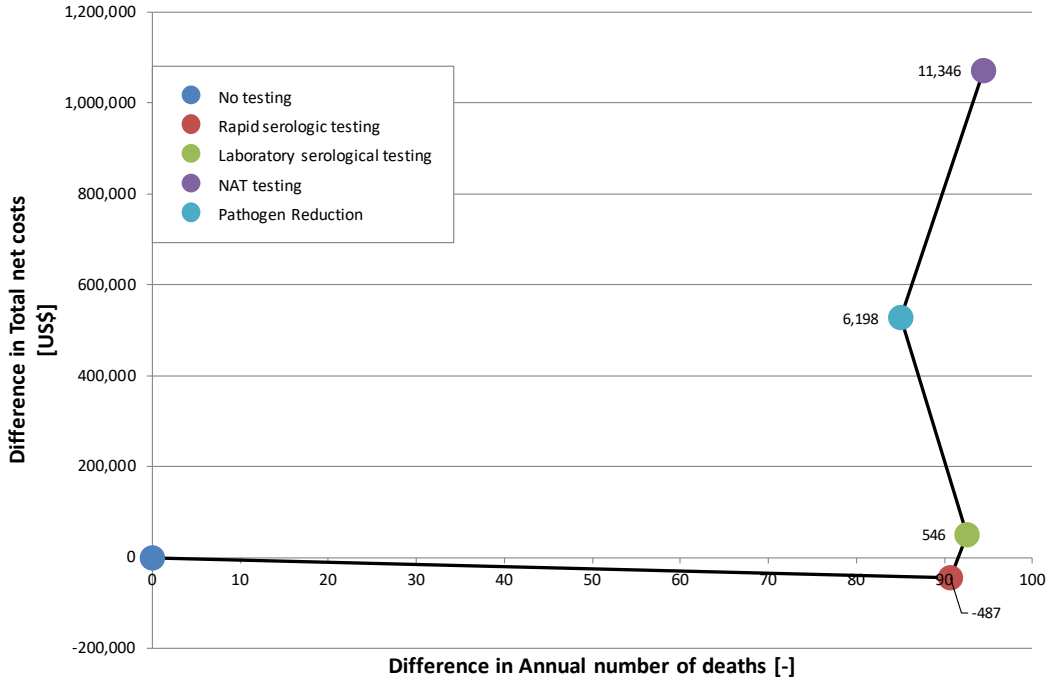
Total net costs [US$]	250,000
Annual number of deaths [-]	100
Annual cost of screening [US$]	100,000
Annual number of products lost	1,500
Technological complexity	Medium
Cost-effectiveness [US$ per death prevented]	150,000



The bar chart shows the relative absolute value of cost-effectiveness. However, as the cost-effectiveness of 'Rapid serological testing' is negative its bar is striped to indicate that it represents a negative value.

The cost-effectiveness of various options is calculated as the net total cost divided by the net health gain. It can therefore be seen as a measure of "value for money", as it represents the amount of money spent per unit of health change. In this case, the cost-effectiveness therefore represents the amount of money spent per death prevented. The cost-effectiveness is calculated as the total net costs of the option considered minus the total net costs of the no testing option divided by the number of deaths from the no testing option minus the number of deaths from the option considered. The cost-effectiveness of rapid serological testing is therefore calculated as (117,840-162,000) / (189.00-98.28) = -44,160/90.72 = -487.
The minus sign in this case reflects the fact that for rapid serological testing, the total net costs are negative while lives are being saved. This is the result of the fact that the cost of treatment of diseases prevented (roughly 50% of 162,000 US$) exceeds the cost of testing (33,600 US$).

In the graph below the increase in total net costs for all options and relatively small benefit from various options relative to the rapid serological testing option is clearly visible. This is a commonly seen feature when applying blood screening interventions: where the difference between applying an intervention and not applying an intervention is substantial, the actual effectiveness of the intervention that is applied becomes of secondary importance. Hence, in those cases the least expensive intervention will often also be the most cost-effective intervention.



5. MCDA assessment

The big question now is how to balance various outcomes. This type of problem is often referred to as a Multi-Criteria Decision-making Assessment (MCDA), as one has to compare and express a preference over various –often very different– outcomes. Ideally, one would have one single preference measure that would combine all relevant outcomes. This would then indicate which of the options considered would be most preferred, the one with the highest perceived benefits. One very simple way of achieving this is by assigning a linear weight to each of the individual outcomes. One could, for instance, make explicit for each of the outcomes how much money one would be willing to spend in order to prevent one additional unit (or case) of this outcome. By doing so, the preference is being made explicit, and an individual score per safety intervention can be calculated. However, this approach will often not reflect true preferences as one's preference may also be dependent on the magnitude of the outcome (so there is a non-linear association between preference and outcome), and on the combination of outcomes (the desire not to have a particular level of two outcomes). Nonetheless, if case outcomes do not differ too much, this approach of linear weighting might provide rational support for a specific risk management strategy.

The table below shows the weights and the MCDA assessment for each of the safety interventions from the HIV case example.

Optional Safety Interventions		**Total net costs [US$]**	**Annual number of deaths [US$]**	**Annual cost of the intervention [US$]**	**Annual number of products lost [US$]**	**Technological complexity [US$]**	**Overall MCDA score**	**Comments / Considerations**
No testing	Baseline situation where no testing is performed	162,000	27,972,000	0	0	0	**28,134,000**	
Rapid serologic testing	Screening of all or part of all blood donations	117,840	14,545,440	0	348,096	0	**15,011,376**	
Laboratory serological testing	Screening of all or part of all blood donations	212,520	14,265,720	0	60,917	0	**14,539,157**	
NAT testing	Screening of all or part of all blood donations	1,233,081	13,999,986	0	13,054	300,000	**15,546,121**	
Pathogen Reduction	Treatment of all or part of all blood donations with PR technology	689,100	15,384,600	0	222,000	100,000	**16,395,700**	
	Weights:	***1***	***148,000***	***0***	***148***	***100,000***		
						300,000		

Weights used

In this example the all outcomes are converted to US$. The weight for total net costs is set to 1, and the header of the column indicates US$ as the unit for this outcome. Comparing the values to the values shown in the previous table, one can see that these values are identical.

Next is the column of annual number of deaths. The annual number of deaths are weighted by 148,000 US$, indicating that the decision maker is willing to spend 148,000 US$ to prevent one additional death by HIV transmission by blood transfusion. This number is the Value of a Statistical Life (VSL) estimate by Viscusi *et al.* for Zimbabwe (as an example).[1]

The weight for the annual cost of screening has been set to zero as these costs are incorporated in the total net costs. For the production loss a value 148 US$ has been set, implying that for every 1000 products lost one additional death is expected. This number is difficult to estimate and should be based on expert knowledge on the local health care system and patient population. The more basic the setting the higher the impact of products not delivered will be. Technological complexity is also a weight that will be difficult to produce, as it will be dependent on an estimate of the impact complex technology will have on (medium to long-term) disruptions in the blood supply.

It is clear that in this case study the prevention of fatalities has the largest impact on the decision as this column provides by far the largest contributions to the overall score. The contributions from the other columns are more comparable for the different options, and ranges of contributions overlap for most outcomes. From the overall MCDA score column, it is clear that the 'No testing' option seems not to be a viable option. The benefits from any of the interventions seem worthwhile implementing irrespective of its cost.

Laboratory serological testing is preferred over Rapid serological testing despite the fact that its costs are higher (96,300 US$). The lower number of products lost (1940 x 148 = 287,179 US$) and the lower number of fatalities (1.9 x 148,000 = 279,720) outweigh these additional costs.

Laboratory serological testing is also preferred over NAT testing as the additional cost of NAT testing (1,022,100 US$) and the disadvantage of technological complexity (with a monetary equivalent of 300,000 US$) do not outweigh the benefits of the 1.8 fewer fatalities (with a monetary equivalent of 148,000 x 1.8 = 265,734 US$) and the 323 fewer products lost (with a monetary equivalent of 323 x 148 = 47,863 US$).

Despite the fact that the only clear conclusion is that it is worthwhile to implement a safety intervention, based on the weights selected (given that these can be further supported by expert opinion) a clear preference for one option (Laboratory serological testing) can be derived.

6. MCDA sensitivity assessment

One may wonder how robust the preference found is, considering various assumptions made and the uncertainty with respect to the model parameters applied. The simplest way to evaluate this is by analyzing whether the preferred option changes when one changes the value of an input parameter. In section 2 where the input of various model parameters was discussed, the provision of a credible range of values for each input parameter was mentioned. In the tool, 'changepoints' for each individual model parameter are determined. Changepoints for any model parameter are those values for which the preferred outcome changes. The list of model parameter, parameter ranges and changepoints is shown in the table below. The header of this table shows that the current preferred option is "Laboratory serological testing", From the changepoint column it becomes clear that there are many variables for which the preferred option does not change within the range of viable parameters (indicated as "Min Value" and "Max Value").

The first parameter for which a different point estimate would affect the preferred option is the prevalence of infection. The changepoint column indicates "At 10% a change from 3 to 4;", meaning that around a prevalence of 10% the preferred option changes from 'Laboratory serological testing' to 'NAT testing'. The interpretation of the numbers '3' and '4' can be found in the bottom left section of the table which contains a small legend for the safety interventions considered.
At a prevalence of 10% the number of transmissions is 5 times as high as in the reference situation, so the substantial benefit of 5x1.8=9.0 fewer fatalities, with a monetary equivalent of 148,000 x 9.0 = 1,332,000 US$ when applying NAT testing now does outweigh the additional cost of testing (1,022,100 US$) plus the disadvantage of technological complexity (with a monetary equivalent of 300,000 US$) compared to laboratory serological testing.

The next parameter for which a different point estimate would affect the preferred option is the sensitivity of rapid serological testing. When the sensitivity of this test would be higher than 99.4%, rapid serological testing would be preferred over laboratory serological testing. The same would hold when the sensitivity of Laboratory serological testing would drop below 94.6%.

The sensitivity of the MCDA weights show that 'No testing' would be preferred over 'Laboratory serological testing' if a fatality would be valued less than 1,203 US$. Also, for values above 708,830 US$ 'NAT testing' would be preferred over 'Laboratory serological testing'. In case the value of a product lost would exceed 3,262 US$, then again 'NAT testing' would be preferred over 'Laboratory serological testing'.

The most sensitive parameter affecting the decision for Laboratory serological testing to be preferred over rapid serological testing seems to be the sensitivity of Laboratory serological testing, which should be higher than 94.6%. If this is not the case, rapid serological testing would be preferred. Apart from that, given the fact that most values need to change substantially in order for the preference to change, one can conclude that in this setting (with the currently assigned weights) a fairly robust preference for the implementation of 'Laboratory serological testing' can be proposed.

Current preferred option: Laboratory serological testing

Model parameter description	Value	Units	Min Value	Max Value	Changepoints
Number of donations	60,000	-	60,000	60,000	
Prevalence among donors	2%	-	1%	20%	At 10% a change from 3 to 4;
Proportion recipients not affected	10%	-	1%	20%	
Coverage rate for the safety intervention	50%	-	50%	100%	
Costs of treatment (per patient)	150.00	US$	100.00	200.00	
Mortaility rate of infected patients	17.5%	-	10%	20%	
Sensitivity of Rapid serologic testing	96.0%	-	65%	99.99%	At 99,4% a change from 3 to 2;
Specificity of Rapid serologic testing	92.0%	-	80.0%	99.99%	
Costs of Rapid serologic testing (per donation)	1.12	US$	0.50	2.50	
Sensitivity of Laboratory serological testing	98.0%	-	75%	99.99%	At 94,6% a change from 2 to 3;
Specificity of Laboratory serological testing	98.6%	-	98.0%	99.99%	
Costs of Laboratory serological testing (per don.)	4.33	US$	3.25	5.40	
Sensitivity of NAT testing	99.9%	-	99.4%	99.99%	
Specificity of NAT testing	99.7%	-	99.6%	99.80%	
Costs of NAT testing (per donation)	38.40	US$	24.90	59.50	
Effectivity of Pathogen Reduction	90.0%	-	75%	99.99%	
Costs of Pathogen Reduction (per donation)	20.00	US$	15.00	30.00	
Production loss of Pathogen Reduction	5.0%	-	3%	7%	
MCDA weights					
Total net costs	1.00		1	1	
Annual number of deaths	148,000		0	1,500,000	At 1.203 a change from 1 to 3; At 708.830 a change from 3 to 4;
Annual cost of the intervention	0		0	0	
Annual number of products lost	148		0	5,000	At 3.262 a change from 3 to 4;
Medium Technological complexity	100,000		0	1,500,000	
High Technological complexity	300,000		0	1,500,000	

Risk management options considered:

1: No testing
2: Rapid serologic testing
3: Laboratory serological testing
4: NAT testing
5: Pathogen Reduction

The previous table shows a clear and fairly robust preference for Laboratory serological testing. However, in case the prevalence of infection would have been 9% instead, the preferred option would already change to NAT testing for a 1% increase in prevalence. The table blow shows that the preference would also change to NAT testing if there would be a smaller number of recipients not affected (because of already being infected), a slightly higher mortality rate, a higher coverage rate, a slightly smaller sensitivity for Laboratory serological testing, higher sensitivity of rapid testing or slightly lower cost of NAT testing. Changes in MCDA weights show that a slight increase of the weight for the number of deaths, an increase in weight for the number of products lost, or a reduction in the weight for technological complexity, would also lead to a preference for NAT testing. In addition, PRT would be preferred if its effectivity would be higher. Overall there is a far less profound preference for Laboratory serological testing.

Current preferred option: Laboratory serological testing

Model parameter description	Value	Units	Min Value	Max Value	Changepoints
Number of donations	60,000	-	60,000	60,000	
Prevalence among donors	9%	-	1%	20%	At 10% a change from 3 to 4;
Proportion recipients not affected	10%	-	1%	20%	At 4% a change from 4 to 3;
Coverage rate for the safety intervention	50%	-	50%	100%	At 67% a change from 3 to 4;
Costs of treatment (per patient)	150.00	US$	100.00	200.00	
Mortality rate of infected patients	17.5%	-	10%	20%	At 18,6% a change from 3 to 4;
Sensitivity of Rapid serologic testing	96.0%	-	65%	99.99%	At 98,3% a change from 3 to 2;
Specificity of Rapid serologic testing	92.0%	-	80.0%	99.99%	
Costs of Rapid serologic testing (per donation)	1.12	US$	0.50	2.50	
Sensitivity of Laboratory serological testing	98.0%	-	75%	99.99%	At 97,9% a change from 4 to 3;
Specificity of Laboratory serological testing	98.6%	-	98.0%	99.99%	
Costs of Laboratory serological testing (per don.)	4.33	US$	3.25	5.40	
Sensitivity of NAT testing	99.9%	-	99.4%	99.99%	
Specificity of NAT testing	99.7%	-	99.6%	99.80%	
Costs of NAT testing (per donation)	38.40	US$	24.90	59.50	At 35,90 a change from 4 to 3;
Effectivity of Pathogen Reduction	90.0%	-	75%	99.99%	At 99,2% a change from 3 to 5;
Costs of Pathogen Reduction (per donation)	20.00	US$	15.00	30.00	
Production loss of Pathogen Reduction	5.0%	-	3%	7%	
MCDA weights for					
Total net costs	1.00	-	1	1	
Annual number of deaths	148,000	US$/death	0	1,500,000	At 157.276 a change from 3 to 4;
Annual cost of the intervention	0	-	0	0	
Annual number of products lost	148	US$/product	0	5,000	At 398 a change from 3 to 4;
Medium Technological complexity	100,000	US$	0	1,500,000	
High Technological complexity	300,000	US$	0	1,500,000	At 225.071 a change from 4 to 3;

Risk management options considered:

1: No testing
2: Rapid serologic testing
3: Laboratory serological testing
4: NAT testing
5: Pathogen Reduction

6. Step-by-step qualitative assessment

There are many approaches to selecting the best option in a Multi-Criteria decision problem. There are various drawbacks to the linear weighting approach applied above. Next to the fact that the weights often vary according to the actual size of the outcome (so applying linear weights would in those cases not properly reflect the perceived balance of preferences), interactions between various outcomes may also affect perceived preferences.
A qualitative method, where the preferred option is selected on basis of the estimated outcomes directly and the supporting considerations discussed, may provide an alternative approach. However, considering all outcomes at once may be too complex a task. Therefore, a structured step-by-step approach is implemented in the tool. In this approach, first the perceived order of importance of the outcomes needs to be defined. Next, the analyst expresses his or her preference in a sequence of steps, where at each subsequent step one additional outcome is taken into consideration. By doing so, the thought process is structured in such a way that the decision problem grows from being relatively simple (with only two outcomes to consider) to finish with the complex multi-factorial decision problem at hand.
At each step the support for the preferred option is discussed and noted in terms of the considerations and argumentation leading to this preference. This allows for considering aspects that may apply but are not captured or reflected in the outcomes presented. Such a refinement may result in a more balanced and acceptable selection than one that is derived from a purely theoretical/quantitative analysis.

The step-by-step assessment requires setting the order of importance first. The order of importance is set by assigning a rank number to each of the outcomes (Rank 1 being the most important outcome).
For our case study, we defined the order of importance of outcomes to be:

1) Annual number of deaths
2) Annual cost of screening
3) Annual number of products lost
4) Technological complexity
5) Total net costs
6) Cost-effectiveness

Next in the assessment is the selection and discussion of the considerations leading to the preferred option based on an increasing number of outcomes (in a decreasing order importance defined).

In the table below the first step in the step-by-step qualitative assessment for our case study is shown. In this assessment only the annual number of deaths and the costs of screening are considered.

Optional Safety Interventions		**Annual number of deaths [-]**	**Annual cost of the intervention [US$]**	**Comments / Considerations**
Option reference:	***Description:***	Total number of deaths given that the safety intervention indicated is implemented	Includes the total cost of the intervention (including costs of personnel, equipment training etcetera)	***Rapid testing is the preferred option; costs are low and the difference in the remaining number of fatalities between this and other tests is acceptable***
No testing	Baseline situation where no testing is performed	189	0	Unacceptable number of fatalities
Rapid serologic testing	Screening of all or part of all blood donations	98	33,600	Preferred option, costs are low and the difference in the remaining number of fatalities between this and other tests is acceptable
Laboratory serological testing	Screening of all or part of all blood donations	96	129,900	Exceeds the budget available
NAT testing	Screening of all or part of all blood donations	95	1,152,000	Lowest number of fatalities but costs exceed the available budget by an order of magnitude
Pathogen Reduction	Treatment of all or part of all blood donations with PR technology	104	600,000	Not a viable option, performs worse than rapid and laboratory serological testing at higher cost

It is clear that given the limitations on outcomes provided (annual number of deaths < 100, and costs of screening < 100,000 US$) the only acceptable option is ‘Rapid serologic testing’.

In the table below, the second step in the step-by-step qualitative assessment for our case study is shown. In this assessment, in addition to the annual number of deaths and the costs of screening, the annual number of products lost is also considered.

Optional Safety Interventions		**Annual number of deaths [-]**	**Annual cost of the intervention [US$]**	**Annual number of products lost**	**Comments / Considerations**
Option reference:	***Description:***	Total number of deaths given that the safety intervention indicated is implemented	Includes the total cost of the intervention (including costs of personnel, equipment training etcetera)	The proportion of blood products that are discarded/lost due to the safety intervention applied	***Three 'hard' constraints are not met by any of the options (annual number of deaths less than 100, budget of 100,000 US$ and product loss less than 1500). This implies that one of these requirements needs to be relaxed. The budget for screening is most likely to be renegotiable. Too high a number of products lost might damage the reputation of the blood bank with a potentially unacceptable loss of donors. Laboratory serological testing is therefore the preferred option***
No testing	Baseline situation where no testing is performed	**189**	0	0	Unacceptable number of fatalities
Rapid serologic testing	Screening of all or part of all blood donations	98	33,600	**2,352**	Costs are low and the difference in the remaining number of fatalities between this and other tests is acceptable, but 4% loss of products (acceding the threshold by 57%) is unacceptable
Laboratory serological testing	Screening of all or part of all blood donations	96	**129,900**	412	Costs of testing exceed the budget available, but as the number of products lost with rapid testing is not acceptable, a reconsideration of the budget constraint seems appropriate
NAT testing	Screening of all or part of all blood donations	95	**1,152,000**	88	Lowest number of fatalities but costs exceed the available budget by an order of magnitude
Pathogen Reduction	Treatment of all or part of all blood donations with PR technology	**104**	**600,000**	1,500	Not a viable option, performs worse than laboratory serological testing at higher cost

With the inclusion of this outcome, it becomes clear that when considering the limitation of the number of products lost, in addition to the two previously mentioned restrictions, there is no option that fulfils all requirements. Therefore, one or more of the restrictions have to be relaxed: either the acceptable number of fatalities, the acceptable number of products lost, or the acceptable amount of money spent on screening. Either the threshold for the number of deaths or the number of products lost are exceeded substantially by the first and second options. As the threshold for the annual cost of screening is only exceeded by 30%, this limiting factor is presumed to be the threshold most easily adapted.

In the table below, the third step in the step-by-step qualitative assessment for our case study is shown. Note that including technological complexity as a new factor to consider does not affect the decision as this aspect does not change any of the previous considerations.

Optional Safety Interventions		**Annual number of deaths [-]**	**Annual cost of the intervention [US$]**	**Annual number of products lost**	**Technological complexity**	**Comments / Considerations**
Option reference:	***Description:***	Total number of deaths given that the safety intervention indicated is implemented	Includes the total cost of the intervention (including costs of personnel, equipment training etcetera)	The proportion of blood products that are discarded/lost due to the safety intervention applied	The technological requirements considering education of personnel and availability of materials and support. These affect the overall effectiveness of the intervention	***Laboratory serological testing seems to be the best achievable option, even though its costs exceed the available budget. Technological complexity does not at all affect the decision between the most suitable options.***
No testing	Baseline situation where no testing is performed	189	0	0	Low	Unacceptable number of fatalities
Rapid serologic testing	Screening of all or part of all blood donations	98	33,600	2,352	Low	Costs are low and the difference in the remaining number of fatalities between this and other tests is acceptable, but loss of products is unacceptable
Laboratory serological testing	Screening of all or part of all blood donations	96	129,900	412	Low	Costs of testing exceed the budget available, but as the number of products lost with rapid testing is not acceptable, a reconsideration of the budget constraint seems appropriate
NAT testing	Screening of all or part of all blood donations	95	1,152,000	88	High	Lowest number of fatalities but costs exceed the available budget by an order of magnitude. Also, technology is too complex to implement.
Pathogen Reduction	Treatment of all or part of all blood donations with PR technology	104	600,000	1,500	Medium	Not a viable option, performs worse than laboratory serological testing on all outcomes at higher cost

The fourth step in the step-by-step qualitative assessment is shown below. However, including the total net costs as an additional factor to consider does not shed any new light on the limitations and preference found earlier. The difference in total net costs between Rapid and Laboratory serological testing merely reflects the difference in the annual cost of screening for either option.

Optional Safety Interventions		**Annual number of deaths [-]**	**Annual cost of the intervention [US$]**	**Annual number of products lost**	**Technological complexity**	**Total net costs [US$]**	**Comments / Considerations**
Option reference:	***Description:***	Total number of deaths given that the safety intervention indicated is implemented	Includes the total cost of the intervention (including costs of personnel, equipment training etcetera)	The proportion of blood products that are discarded/lost due to the safety intervention applied	The technological requirements considering education of personnel and availability of materials and support. These affect the overall effectiveness of the intervention	Total cost of the safety intervention + cost of treatment of infected patients	***Laboratory serological testing seems to be the best achievable option, even though its costs exceed the available budget. Total net costs do not affect the decision between the two most suitable options. These costs merely reflect the difference in costs of testing.***
No testing	Baseline situation where no testing is performed	189	0	0	Low	162,000	Unacceptable number of fatalities
Rapid serologic testing	Screening of all or part of all blood donations	98	33,600	2,352	Low	117,840	Costs are low and the difference in the remaining number of fatalities between this and other tests is acceptable, but loss of products is unacceptable
Laboratory serological testing	Screening of all or part of all blood donations	96	129,900	412	Low	212,520	Costs of testing exceed the budget available, but as the number of products lost with rapid testing is not acceptable, a reconsideration of the budget constraint seems appropriate
NAT testing	Screening of all or part of all blood donations	95	1,152,000	88	High	1,233,081	Lowest number of fatalities but costs exceed the available budget by an order of magnitude. Also, technology is too complex to implement.
Pathogen Reduction	Treatment of all or part of all blood donations with PR technology	104	600,000	1,500	Medium	689,100	Not a viable option, performs worse than laboratory serological testing on all outcomes at higher cost

Finally, in the fifth step, adding the cost-effectiveness into the equation shows that the cost-effectiveness for each of the interventions seems favorable. For comparison, note that in the quantitative MCDA weight of 148,000 US$ per death prevented was used, which implies a cost-effectiveness ratio of 148,000 US$ per death prevented. The cost-effectiveness ratio for each of the interventions listed is well below this value.

Optional Safety Interventions		**Annual number of deaths [-]**	**Annual cost of the intervention [US$]**	**Annual number of products lost**	**Technological complexity**	**Total net costs [US$]**	**Cost-effectiveness [US$ per death prevented]**	**Comments / Considerations**
Option reference:	***Description:***	Total number of deaths given that the safety intervention indicated is implemented	Includes the total cost of the intervention (including costs of personnel, equipment training etcetera)	The proportion of blood products that are discarded/lost due to the safety intervention applied	The technological requirements considering education of personnel and availability of materials and support. These affect the overall effectiveness of the intervention	Total cost of the safety intervention + cost of treatment of infected patients	Total net cost per additional number of deaths prevented. This provides an indication of the "value for money" of the intervention relative to the baseline situation	***Laboratory serological testing seems to be the best achievable option, even though its costs exceed the available budget. On the other hand, rapid serologic testing exceeds the acceptable level of products lost but is cost saving: its cost-effectiveness is negative implying that the savings on health care exceed the cost of testing.***
No testing	Baseline situation where no testing is performed	189	0	0	Low	162,000	-	Unacceptable number of fatalities
Rapid serologic testing	Screening of all or part of all blood donations	98	33,600	2,352	Low	117,840	-487	Costs are low and the difference in the remaining number of fatalities between this and other tests is acceptable, but loss of products is unacceptable
Laboratory serological testing	Screening of all or part of all blood donations	96	129,900	412	Low	212,520	546	Costs of testing exceed the budget available, but as the number of products lost with rapid testing is not acceptable, a reconsideration of the budget constraint seems appropriate
NAT testing	Screening of all or part of all blood donations	95	1,152,000	88	High	1,233,081	11,346	Lowest number of fatalities but costs exceed the available budget by an order of magnitude. Also, technology is too complex to implement.
Pathogen Reduction	Treatment of all or part of all blood donations with PR technology	104	600,000	1,500	Medium	689,100	6,198	Not a viable option, performs worse than laboratory serological testing on all outcomes at higher cost

In conclusion
One can say that Rapid and Laboratory serological testing seem to be the most favorable alternatives. Both substantially reduce the number of fatalities, require funding within reach, and do not require complex technology. The drawback of rapid serological testing is that the number of products lost substantially exceeds a level that is considered acceptable. In case it is impossible to raise the budget, the discussion will focus on which of the two negative outcomes is more acceptable: the number of products lost with rapid serological testing or the expected number of fatalities without an additional intervention.

Comparing the quantitative and qualitative approaches
Comparing the quantitative and qualitative approaches is interesting in various ways. What is most striking, is that despite that the considerations applied in either method differ, the final conclusion and preference is the same in both cases. In the quantitative approach, the use of the weight for the number of deaths (the 148,000 US$ per death prevented) guides the decision toward Laboratory serological testing. Because of the high weight, its contribution is by far dominating the MCDA penalty, and therefore its outcome. The sensitivity assessment, however, shows that the preference is rather insensitive to the actual value (any value between 2,143 and 709,762 US$ would lead to the same preferred option). The disadvantage of this approach is that it does not (in its current form, at least) allow incorporation of the threshold values provided for this case study.
On the other hand, in the qualitative assessment, simply by looking at the cost and the change in fatalities for each test, the preference is pointed in the same direction. However, the fact that the threshold values threshold values as well as any other considerations can be easily incorporated, the qualitative assessment results in a more realistic and balanced argumentation to support this preference. A mathematical approach can never be expected to find a solution where formally there is none existing. This is exemplified in the case study presented, in which, as a result of various restrictions, for each of the optional safety interventions one or more of the outcomes exceeded one or more threshold values. However, in real life a balanced advice still has be provided. It is clear that this can only be obtained by adapting the rules of the game, which requires an interpretation of the context. In our case study, the conclusion is that the most viable way forward would be to try and extend the available budget to enable implementation of laboratory serological testing.

All in all, the conclusion should be that the quantitative and qualitative approaches are complementary with each having its own strengths and weaknesses. The quantitative approach allows for a straight-forward balance of outcomes. The fact that it does not allow incorporating any other aspects may reduce its usefulness in some cases. Further, the fact that it provides a purely mathematical “black box” best option may make it also less appealing. Conversely, the qualitative step-by-step approach does not have any restrictions in terms of what can be taken into consideration and how this is done, which can be considered both a strength and a weakness. The step-by-step approach as presented does help structure the thought process in a systematic manner and nicely supports the analyst in building-up a case for a preferred option with the right arguments.

With the decision-support tool it is also possible to compare the effectiveness of past interventions (already implemented to respond to certain “old” threats) with the effectiveness of potential new interventions to respond to “new” threats, e.g. emerging pathogens. This may result in a respective adaption of the potential intervention to past decisions, or a general reconsideration of interventions.

References

1. Viscusi WK, Masterman CJ. Income Elasticities and Global Values of a Statistical Life. Journal of Benefit-Cost Analysis 2017;**8**: 226-50.