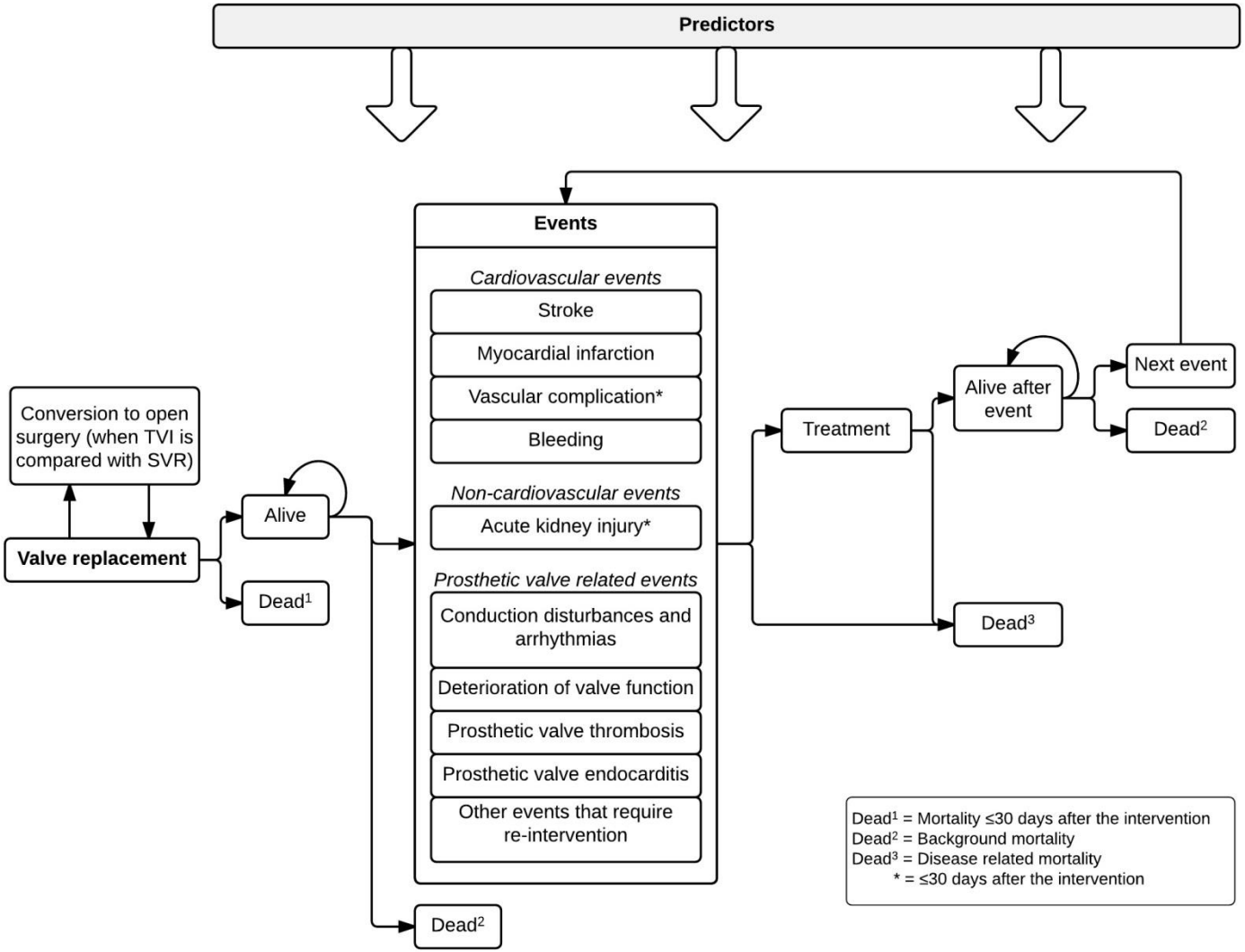
Online appendices 'A Conceptual Model for Early Health Technology Assessment of Tissue-Engineered Heart Valves'

Table of content:



Online Appendix Figure 1. Draft conceptual model for the early HTA of tissue-engineered heart valves as shown to the Delphi panel.

Online Appendix 1: Delphi panel questionnaires

Questionnaire 1

Introduction

Some time ago you participated in the first round of the Delphi panel to give advice on the development of a conceptual model to estimate the cost-effectiveness of current and future heart valve interventions. The Delphi panel consists of ten panelists with different expertises from different hospitals and universities: cardio-thoracic surgeons, cardiologists and a biomedical expert.

The conceptual model developed based on the advice of the Delphi panel will be the foundation of a microsimulation model. Using this microsimulation model, we want investigate the requirements for tissue-engineered heart valves to become cost-effective compared to current available surgical and transcatheter valve substitutes.

In this second round of the Delphi panel, I would like to ask a number of questions about the structure of the conceptual model trough this questionnaire. The purpose of this questionnaire is to reach consensus with the other panelists on the conceptual model.

The questionnaire contains 20 questions and you need about 15 minutes to complete the questionnaire. It is possible that the questionnaire contains several questions that I have already discussed with you, but not yet with the other panelists.

Reminder

The Figure of the conceptual model (see Appendix Figure 1) is shown below to refresh your memory about the conceptual model we have discussed. This figure will be shown at the top of each page in this questionnaire.

Several important characteristics of the model are:

- The focus is on valve substitutes in the **aortic and pulmonary position**.
- The interventions we will consider are **surgical valve replacement** with bioprostheses, homografts, the Ross procedure, mechanical or tissue-engineered heart valves and **transcatheter valve implantation** (transapical or transfemoral) with bioprostheses or tissue-engineered heart valves.
- To take into account differences in treatment options and outcomes between age groups, the study population will be divided over four age groups: **Children** (0-18 years), **Young adults** (18-60 years), **Middle-aged** (60-70 years), and **Elderly** (>70 years).

Below are some questions about the events in the model. The definitions of the events are displayed next to each question. The majority of the definitions are derived from the "Guidelines for Reporting Mortality and Morbidity After Cardiac Valve Interventions (Akins et al. 2008) or endpoint Updated standardized definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium2 Consensus document VARC-2 (Kappetein et al. 2012).

Before we start with the questions, I want to explain some changes in the model on which no questions are included in the questionnaire:

- The event ‘other events that require re-intervention’ is not included in the final model because it is unclear what events are covered in this category.

- The term ‘operated valve endocarditis’ caused confusion among some panelists, therefore we have changed it to 'prosthetic valve endocarditis.' This event can occur both after surgical and transcatheter valve replacement.

1. If you have comments about the introduction you can write them down here.

2. Do you feel that we should include transient ischemic attacks – in addition to strokes – in the model?

❑ Yes
❑ No

Explanation:

Vascular complications and acute kidney injury are procedure related events (predominantly after transcatheter valve implantation), therefore these events will only be included in the model during the first 30 days after the intervention. The other events will be considered during the patient’s lifetime.

3. Over which time period should myocardial infarction be considered in the model?

❑ Only peri-procedural myocardial infarction (<72 hours after the index procedures according to the VARC-2 guideline)
❑ Only myocardial infarctions within the first 30 days after the intervention.
❑ All myocardial infarctions after the intervention until the patients’ death.

Explanation:

N.B. If we only include myocardial infarction explicitly over a short time period (i.e. <72 hours or <30 days), then patients that die because of myocardial infarction later in life (>72 hours or >30 days) will be included in the ‘excess mortality’.

Explanation of excess mortality:
“The mortality of a patient after valve replacement is composed of mortality of the general population, operative mortality, valve-related mortality, and excess mortality. This excess mortality cannot be explained by valve-related events, but is due to mortality associated with underlying pathology, left ventricular function, increased occurrence of sudden unexplained cardiac death, and underreporting of valve-related events respectively.” (van Geldorp et al. 2007)

Bleedings can have different causes. In the early period after the intervention bleedings are predominantly post-operational bleedings (including cardiac tamponade). After the early period and during the rest of the patient’s life bleedings are predominantly related to anticoagulation medication use.

4. Do you agree to model post-interventional bleedings during the first 30 days after the intervention separately and afterwards (>30 days after the intervention) bleedings related to the use of anticoagulation medication?

❑ Yes
❑ No

Explanation:

Atrial fibrillation is a common complication after heart valve interventions in the post-intervention phase. On the long term atrial fibrillation is a common complication in the general elderly population (with or without valve problems) due to aging.

5. Do you agree that atrial fibrillation should only be included during the first 30 days after the intervention?

❑ Yes
❑ No

Explanation:

There are many other conduction disturbances and arrhythmias besides atrial fibrillation. A potential severe consequence of these conduction disturbances and arrhythmias is pacemaker implantation. Some panelists advised to only include conduction disturbances and arrhythmias that lead to pacemaker implantation. They reasoned that the model is too complex if we include all other conduction disturbances and arrhythmias that not lead to pacemaker implantation.

6. Do you feel it is sufficient to include conduction disturbances and arrhythmias (except for atrial fibrillation <30 days after the intervention) only when they lead to pacemaker implantation?

❑ Yes
❑ No

Explanation:

Some of the panelists noted that it is possible that after transcatheter valve implantation the function of the valve is not deteriorating, but the valve does not perform well from the beginning. Therefore we renamed this event to ‘prosthetic valve dysfunction’ rather than deterioration or valve function.
In line with the "Guidelines for Reporting Mortality and Morbidity After Cardiac Valve Interventions (Akins et al. 2008) and the VARC-2 guideline prosthetic valve dysfunction includes structural valve deterioration (SVD), nonstructural valve dysfunction (NSD, including paravalvular leakage) and valve malpositioning.

7. Do you agree that the causes of prosthetic valve dysfunction after the events in this category (SVD, NSD, valve malpositioning) may differ, but that the consequences for the patient (in terms of treatment and quality of life) are comparable?

❑ Yes
❑ No

Explanation:

The VARC-2 guideline (Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 Consensus Document) defines several other complications that can occur after TAVI. These complications are relatively rare. That is why we have discussed whether these complications should be included in the model or are already included in the model in a different way. The following questions concern several of these complications.

Conversion to open surgery

8. Do you agree that conversion of transcatheter valve implantation to open surgery (and therefore unscheduled use of cardiopulmonary bypass) is an important complication is that needs to be added to the model?

❑ Yes
❑ No

Explanation:

Conversion to transcatheter valve implantation

If we include conversion of transcatheter valve implantation to open surgery in the model, it might be interesting to include the flipside - conversion from open surgery to transcatheter valve implantation - to the model. This conversion will usually not be urgent, as is probably the case when conversion to open surgery is necessary. Therefore the transcatheter valve implantation can be planned later and the conversion probably does not affect the outcomes of the intervention. However, the organization of the original open surgery still comes with healthcare costs.

9. Do you agree that if we include conversion to open surgery, the flipside - conversion to transcatheter intervention – should also be included in the model?

❑ Yes
❑ No

Explanation:

Valve-in-valve implantation (in VARC2: TAV-in-TAV deployment)

Valve-in-valve implantation is not a complication, but a result of complications (such as regurgitation or valve malpositioning) already included in the model. Therefore valve-in-valve implantation will be one of the treatment options when re-intervention is necessary after a transcatheter valve implantation. However, valve-in-valve implantation can also take place during the index procedure.

10. Is it important to include valve-in-valve implantation at the index procedure as an event in the model?

❑ Yes
❑ No

Explanation:

Coronary obstruction

Several panelists have the opinion that coronary obstruction in most cases result in myocardial infarction or death. In such cases, the event is included in the model under myocardial infarction or mortality.

11. Do you agree that coronary obstruction should not be included in the model separately?

❑ Yes
❑ No

Explanation:

Ventricular septal perforation and mitral valve apparatus damage or dysfunction

'Ventricular septal perforation' and 'Mitral valve apparatus damage or dysfunction' are major complications, but occur rarely and are usually not reported in outcome studies.

12. Do you agree that 'ventricular septal perforation' can be excluded from the model?

❑ Yes
❑ No

Explanation:

13. Do you agree that 'mitral valve apparatus damage or dysfunction' can be excluded from the model?

❑ Yes
❑ No

Explanation:

Some panelists have made suggestions for events that were not included in the model. Below are some questions to determine whether the other panelists find it important to add these events to the model.

Heart failure

14. Do you agree that failure is an important event that should be added to the current model?

❑ Yes
❑ No

Explanation:

If we add heart failure to the model, than 'hospitalization for heart failure' will overlap with 'conservative treatment for prosthetic valve dysfunction'. Therefore, we might redefine the complication prosthetic valve dysfunction as 're-intervention for prosthetic valve dysfunction'

15. Do you agree that prosthetic valve dysfunction should be redefined as intervention for prosthetic valve dysfunction' when we decide to add heart failure as an event to the model?

❑ Yes
❑ No

Explanation:

Post-anesthesia problems and delirium

One of the panelists brought up that after surgery some patients suffer from confusion, balance problems and dizziness which might result in unemployment. This problem will occur more often after surgery compared to transcatheter valve implantation and is therefore one of the differences between these types of interventions. However, we are considering to not include these events in the model because (1) there is little information available about the occurrence of these problems after heart valve interventions, (2) the effect of these complications on the quality of life of the patient is difficult to estimate, and (3) it is difficult to estimate the cost of these complications.

16. Do you agree that we should not include post-anesthesia problems and delirium in the model?

❑ Yes
❑ No

Explanation:

17. This concludes my questions about the structure of the conceptual model.
If you have any other comments or suggestions for the conceptual model, you can write them down below.

References

- Akins CW, Miller DC, Turina MI, et al. Guidelines for Reporting Mortality and Morbidity After Cardiac Valve Interventions. European Journal of Cardio-Thoracic Surgery. 2008; 33: 523-28.
- Kappetein AP, Head SJ, Généreux P, et al. Updated Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation: The Valve Academic Research Consortium-2 Consensus Document†. Journal of the American College of Cardiology. 2012; 60: 1438-54.
- van Geldorp MWA, Jamieson WR, Kappetein AP, et al. Usefulness of microsimulation to translate valve performance into patient outcome: Patient prognosis after aortic valve replacement with the Carpentier–Edwards supra-annular valve. The Journal of thoracic and cardiovascular surgery. 2007; 134: 702-09. e1.

Questionnaire 2

Dear panelists,

Thank you for completing the first questionnaire. I have discussed your answers with Prof. Dr. Takkenberg. Based on your answers we have made some decisions about the structure of the model. This questionnaire will discuss our considerations and the adapted conceptual model is presented. Using this questionnaire I would like to ask you to look at the conceptual model again and give your remarks and some additional questions.

Thank you in advance.

Stroke and Transient Ischemic Attack (TIA)

The question in the previous questionnaire was: *Do you feel that we should include transient ischemic attacks – in addition to strokes – in the model?*

- Three panelists felt that TIAs should not be included in the model because it is hard to determine whether a patient suffered from a TIA and it does not have lasting consequences for the patient.
- Five panelists argued that TIAs should be included in the model because it is hard to distinguish TIAs from strokes.

There was no consensus, but the majority of the panelists wanted to include TIAs in the model. Therefore it was decided to include TIAs in the conceptual model for now. When it appears to be unfeasible to collect data about TIAs in addition to strokes, this decision can be reassessed. The event 'stroke' is now called 'cerebrovascular accident', including both strokes and TIAs.

1. If you have comments about the inclusion of TIAs in the model you can write them down here.

Myocardial infarction

The question in the previous questionnaire was: *Over which time period should myocardial infarction be considered in the model?*

- None of the panelists thought it was important to include myocardial infarction during the patient's lifetime.
- There was no consensus about the time period to take into account myocardial infarctions: within 72 hours or 30 days after the intervention.

Therefore it was decided to include myocardial infarctions during the first 30 days after the intervention. When possible (considering the available data) we can make a distinction between myocardial infarctions during the first 72 hours and 30 days after the intervention to determine how this would influence the model outcomes.

2. If you have comments about the time period over which myocardial infarctions are included in the model you can write them down here.

Atrial fibrillation

The question in the previous questionnaire was: *Do you agree that atrial fibrillation should only be included during the first 30 days after the intervention?*

- Five panelists agreed to only include atrial fibrillation during the first 30 days after the intervention.
- Three panelists did not agree but it was unclear whether they would include atrial fibrillation during the patient's lifetime or not at all.

These answers made us reconsider the inclusion of atrial fibrillation in the model. One option is to only include persistent atrial fibrillation (>7 days according to the ESC guideline 2010) within the first 30 days after the intervention in the model, because of increased mortality, stroke, heart failure and bleeding risks. This discussion resulted in the following question:

3. How should we include atrial fibrillation (AF) in the model?

❑ Not at all.
❑ Only during the first 30 days after the intervention, both transient and persistent AF.
❑ Only during the first 30 days after the intervention, only persistent AF.
❑ Lifetime, both transient and persistent AF.
❑ Lifetime, only persistent AF.

Explanation:

Pacemaker implantation

The question in the previous questionnaire was: *Do you feel that it is sufficient to include conduction disturbances and arrhythmias (except for atrial fibrillation <30 days after the intervention) only when they lead to pacemaker implantation?*

All panelists agreed that it is sufficient to include conduction disturbances and arrhythmias only when they result in pacemaker implantation. Therefore the event 'Conduction disturbances and arrhythmias' is changed into 'Pacemaker implantation'.

4. Over which time period should pacemaker implantation be included in the model?

❑ Only during the first 30 days after the intervention.
❑ Lifetime.

Prosthetic valve dysfunction

The question in the previous questionnaire was: *Do you agree that the causes of prosthetic valve dysfunction after the events in this category (structural valve deterioration, nonstructural valve dysfunction, and valve malpositioning) may differ, but that the consequences for the patient (in terms of treatment and quality of life) are comparable?*

- Five panelists agreed.
- Two panelists did not agree. One of these panelists felt that there are differences in the deterioration quality of life of patients between the events.
- One of the panelists did not have an opinion.

However, it is not feasible to incorporate the speed of deterioration of quality of life in the model because of limited available data. Therefore it was decided to model the different types of prosthetic valve dysfunction in the same way. We will remember this as a limitation of our model when interpreting the results.

5. If you have comments about the event 'Prosthetic valve dysfunction' you can write them down here.

Conversion to open surgery/transcatheter procedure

The question in the previous questionnaire was: *Do you agree that conversion to open surgery and the flipside (conversion to transcatheter intervention) should be included in the model?*

- Most panelists agreed that conversions from one approach to the other are important complications.
- Two panelists felt that both conversions were not important to take into account. One of these panelists argued that conversion from transcatheter valve implantation to open surgery is fatal for most patients.

However, because these conversions are accompanied with significant costs we decided to include them in the model.

6. If you have comments about the event 'Conversion to other approach' you can write them down here.

Coronary obstruction

The question in the previous questionnaire was: *Do you agree that coronary obstruction should not be included in the model separately, because the most common consequences (myocardial infarction and death) are already included in the model?*

- Five panelists agreed that coronary obstruction should not be included in the model.
- Three panelists felt that coronary obstruction should be included in the model. One of these panelists felt this way because coronary obstruction can lead to conversion to open surgery. However, in these cases the event will also be included in the 'conversion to open surgery' event. The other two panelists argued that coronary obstruction does not have to result in myocardial infarction or death when it is discovered in time.

Despite these arguments it was decided to exclude coronary obstruction from the model to prevent overlap with myocardial infarction. Furthermore, the occurrence rate of coronary obstruction after TAVI is relatively low (i.e. pooled estimate rate of 0.7% in meta-analysis of Genereux et al. 2012).

7. If you have comments about the event 'Conversion to other approach' you can write them down here.

Ventricular septal perforation and mitral valve apparatus damage or dysfunction

The questions in the previous questionnaire were: *Do you agree that 'ventricular septal perforation' and 'mitral valve apparatus damage or dysfunction' can be excluded from the model?*

- Five panelists agreed to exclude 'ventricular septal perforation' from the model and four panelists agreed to exclude 'mitral valve apparatus damage or dysfunction' from the model.
- The other panelists wanted to include these events in the model or combine them in an event group with 'other events'.

It is not possible to create a group with 'other events' without explicitly stating which events are included in this group. Otherwise it will not be possible to collect data on the incidence of these events and their accompanied costs and quality of life.

These events were considered for inclusion in the model because the VARC guideline discussed them under 'other TAVI-related events'. The events are not defined in the Guideline for reporting events after cardiac valve interventions (Akins et al. 2008; mostly used for surgical valve replacement) and therefore seem less relevant after surgical valve replacement. The intervention cardiologists in the Delphi panel that performed TAVI regularly agreed that these complications were not relevant for the model because of their low occurrence rate. In addition, Génereux et al. (2012) report a pooled estimate for 'ventricular septal perforation of 0.6% and no occurrence rate for 'mitral valve apparatus damage or dysfunction'.

8. If you have comments about the exclusion of the events 'ventricular septal perforation' and 'mitral valve apparatus damage or dysfunction' you can write them down here.

Heart failure

The question in the previous questionnaire was: *Do you agree that failure is an important event that should be added to the current model?*

- Five panelists argued that heart failure should not be included in the model when there is no association with the valve substitute.
- Three panelists felt that heart failure should be taken into account when it results in hospitalization of the patient.
- One panelist did not have an opinion.

We have decided that heart failure will not be included as an event in the model, because heart failure that is not caused by valve problems is not relevant for our decision problem. We assume that heart failure that is caused by valve problems is included in the model in the hospitalizations due to prosthetic valve dysfunction.

9. If you have comments about the exclusion of the 'heart failure' you can write them down here.

References

- Akins CW, Miller DC, Turina MI, et al. Guidelines for Reporting Mortality and Morbidity After Cardiac Valve Interventions. European Journal of Cardio-Thoracic Surgery. 2008; 33: 523-28.
- Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the Management of Atrial Fibrillation. European Heart Journal. 2010: ehq278.
- Généreux P, Head SJ, Van Mieghem NM, et al. Clinical Outcomes After Transcatheter Aortic Valve Replacement Using Valve Academic Research Consortium Definitions: A Weighted Meta-Analysis of 3,519 Patients From 16 Studies. Journal of the American College of Cardiology. 2012; 59: 2317-26.
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Online Appendix 2: Results of first input from experts and Delphi panel

First input from two clinical experts

After the discussion of the conceptual model with the clinical experts we reevaluated the draft conceptual model (**Error! Reference source not found.**). The following describes the most important changes that were made to obtain the new conceptual model.

First, the events are separated into cardiovascular events, non-cardiovascular events and prosthetic valve associated events to obtain a logic model structure.

Second, embolism is excluded from the model to avoid double counting of events. Instead two severe consequences of an embolism – stroke and myocardial infarction – are included.

Third, the experts agreed that the distinction between acute and progressive deterioration of the valve function was unrealistic and is not reflected in clinical guidelines. Therefore these events are combined into one event called: deterioration of valve function.

Fourth, the experts stated that events should not be divided in early and late events; instead timing of the events should be based on time-to-event rates. However, acute kidney injury and vascular complications are events that only occur as a consequence of the intervention within the first 30 days after the intervention. Therefore these events will only be included on the short-term as a discrete variable: the complication occurred within 30 days after the intervention or not. Time-to-event rates will be estimated for all other events.

Finally, the experts did not agree about the inclusion of the 'other TAVI-related complications' defined in the VARC guidelines.(24, 26) One panelist felt that these are technical complications that are not as relevant for the patient's quality of life compared to clinical complications, while the other panelist felt that these complications should be included in the model.

In the new model these complications will only be included when they require re-intervention. The inclusion of these events was further discussed with the experts in the Delphi panel. The first input from the two experts resulted in the model illustrated in Online Appendix Figure .

Delphi panel

The results of the interviews, first and second online questionnaire answered by the Delphi panel are described in detail per event in this appendix.

1. Cardiovascular events

1.1 Cerebrovascular accidents (CVA)

Interviews

In the draft conceptual model shown to the panelists only strokes were included. During the interviews several panelists suggested the inclusion of transient ischemic attacks (TIAs). Therefore this question was included in the first questionnaire to the panelists.

Questionnaire 1

Three panelists felt that TIAs should not be included in the model because it is hard to determine whether a patient suffered from a TIA and it does not have lasting consequences for the patient. In contrast, five panelists argued that TIAs should be included in the model because it is hard to distinguish TIAs from strokes. There was no consensus, but the majority of the panelists wanted to include TIAs in the model. Therefore it was decided to include TIAs in the conceptual model for now. When it appears to be unfeasible to collect data about TIAs in addition to strokes, this decision can be reassessed. The event 'stroke' is now called 'cerebrovascular accident (CVA)', including both strokes and TIAs.

Questionnaire 2

In the second questionnaire eight panelists did not have objections to this choice. Two panelists still felt that TIAs should not be included in the model because it is hard to determine whether a patient suffered from a TIA and the impact on quality of life is limited. Furthermore, large trials do not included TIA as an outcome. Since the majority of the Delphi panel is in favor of including TIAs, TIAs will be included in the base model.

1.2 Myocardial infarction

Interviews

During the interviews several panelists doubted whether a myocardial infarction can be considered as consequence of the heart valve intervention when they occur long after the intervention took place. In the questionnaire the panelists were asked whether myocardial infarction should be considered over a lifelong time horizon or only in a short post-procedure period.

Questionnaire 1

None of the panelists thought it was important to include myocardial infarction during the patient's lifetime. There was no consensus about the time period to take into account myocardial infarctions: within 72 hours or 30 days after the intervention. Therefore it was decided to include myocardial infarctions during the first 30 days after the intervention.

Questionnaire 2

In de second questionnaire nine panelists did not have objections to this choice. However, one (new) panelist would like to incorporate myocardial infarction longer than 30 days, preferably during the patients' lifetime. According to this panelist it is possible there will be differences in the occurrence of myocardial infarction between surgical valve replacement and transcatheter valve implantation. One other panelist agreed to include myocardial infarction only on the short term, but suggested to include myocardial infarction during the first three months because of the use of oral anticoagulants (for example with bioprostheses). However, lifetime myocardial infarctions are not included in the base model since the majority of the panelists advised to exclude myocardial infarctions after the first 30 days after the intervention.

1.3 Vascular complications

Interviews

Vascular complications are events that only occur as a consequence of transcatheter valve implantation within the first 30 days after the intervention. Therefore this event will only be included on the short term

as a discrete variable: the complication occurred within 30 days after the intervention or not. None of the panelists objected to this decision.

1.4 Bleeding

The event 'bleeding' includes postoperative bleedings (cardiac tamponades) and anti-coagulant related bleedings and will be considered over the patients' lifetime. None of the panelists had comments about this event.

1.5 Conduction disturbances and arrhythmias

Atrial fibrillation

Interviews

In the draft conceptual model all types of conduction disturbances and arrhythmias were included. During the interviews the panelists were asked whether they felt it was important to take into account all the types of conduction disturbances and arrhythmias. The majority of the panelists agreed that atrial fibrillation (AF) should be included in the model as a separate event because it is a common complication after heart valve intervention in the post-intervention phase.

Questionnaire 1

Although atrial fibrillation is a common complication after heart valve intervention in the post-intervention phase, on the long term atrial fibrillation is a common complication in the general elderly population (with or without valve problems) due to aging. Therefore the panelists were asked during what time period they thought atrial fibrillation should be included in the model.

Five panelists agreed to only include atrial fibrillation during the first 30 days after the intervention. The other three panelists did not agree but it was unclear whether they would include atrial fibrillation during the patient's lifetime or not at all. Therefore this question was included in the second questionnaire. Furthermore, we asked the panelists whether we should include both transient and persistent atrial fibrillation (>7 days according to the ESC guideline 2010) or only persistent atrial fibrillation.

Questionnaire 2

In the second questionnaire two panelists did not have an opinion about the inclusion of atrial fibrillation in the model. Six panelists would like to include both transient and persistent atrial fibrillation, but only during

the first 30 days to ensure there is a relationship between the intervention and occurrence of atrial fibrillation. One panelists agreed to include atrial fibrillation only during the first 30 days, but only persistent atrial fibrillation. In addition, this panelist argued that atrial fibrillation should not be arrayed under prosthetic valve events. Finally, one panelist argued that atrial fibrillation should not be included in the model at all because many patients experience transient atrial fibrillation within the first 30 days and most of these patients do not experience severe consequences, neither in terms of subsequent consequences nor reduced quality of life. The majority of the panelists chose to include atrial fibrillation (both transient and persistent) during the first 30 days. Therefore atrial fibrillation that occurs more than 30 days after the intervention will not be included in the model.

Pacemaker implantation

Interviews

The other types of conduction disturbances and arrhythmias were considered less relevant. However, one major consequence of these conduction disturbances and arrhythmias can be the implantation of a pacemaker. Therefore the panelists were asked if all other conduction disturbances and arrhythmias (besides AF) should be included in the model or only when it results in pacemaker implantation.

Questionnaire 1

All panelists agreed that it is sufficient to include conduction disturbances and arrhythmias only when they result in pacemaker implantation (PI). Therefore (with the exception of atrial fibrillation during the first 30 days after the intervention) conduction disturbances and arrhythmias without the need for pacemaker implantation will not be included in the model.

Questionnaire 2

In the second questionnaire the panelists were asked over what time period pacemaker implantation should be considered. There was no consensus about this subject in the Delphi panel. One panelist did not have an opinion. Six panelists agreed to include pacemaker implantation only during the first 30 days after the intervention because during that time period there is more certainty that the need for pacemaker implantation is a consequence of the intervention. However, three panelists felt pacemaker implantation

should be included during the patient's lifetime. Therefore it was decided to include pacemaker implantation during the first 30 days after the intervention in the base model.

2. Non-cardiovascular events

2.1 Acute kidney injury

Interviews

Acute kidney injury only occurs as a consequence of the heart valve intervention within the first 30 days after the intervention. Therefore this event will only be included on the short term as a discrete variable: the complication occurred within 30 days after the intervention or not. None of the panelists objected to this decision during the interviews.

3. Prosthetic valve related events

3.1 Prosthetic valve dysfunction

Interviews

In the draft conceptual model structural valve deterioration (SVD) and nonstructural valve dysfunction (NSD) were combined in the event 'deterioration of valve function'. Some of the panelists noted that after transcatheter valve implantation it is possible that the prosthetic valve does not function well from the beginning. The name 'deterioration of valve function' does not reflect this event. Therefore the name of this event was changed to 'prosthetic valve dysfunction'.

Questionnaire 1

In the questionnaire the panelists were asked whether the consequences in terms of treatment and quality of life of the events included in 'prosthetic valve dysfunction' can be considered comparable. Most panelists agreed that treatment of different types of prosthetic valve dysfunction is comparable; in most cases re-intervention. However, they felt that there are differences in the timing of re-intervention and the deterioration quality of life of patients with SVD (slowly deteriorating quality of life and need for re-intervention) or NSD (more rapidly deterioration in quality of life and need for re-intervention). However it is not feasible to incorporate the speed of deterioration of quality of life in the model because of limited

available data. Therefore it was decided to model the different types of prosthetic valve dysfunction in the same way.

Questionnaire 2

In the second questionnaire nine panelists did not have objections to this choice. However, one (new) panelist felt that the consequences of these events are not comparable. It was decided to model the different types of prosthetic valve dysfunction in the same way because the majority of the panelists agreed with this decision.

3.2 Prosthetic valve thrombosis and endocarditis

Interviews

The panelists did not have remarks about these events. Both prosthetic valve thrombosis and endocarditis will be considered over the patients' lifetime.

Other TAVI-related complications in the VARC-2 guideline

Interviews

In the "Updated Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation: the Valve Academic Research Consortium-2 Consensus Document"(26) several 'other TAVI-related complications' are defined in addition to the events described above: conversion to open surgery, unplanned use of cardiopulmonary bypass, coronary obstruction, ventricular septal perforation, mitral valve apparatus damage or dysfunction, cardiac tamponade, endocarditis, valve thrombosis, valve malpositioning, valve embolization, TAV-in-TAV deployment. The occurrence of these complications is relatively low.(33) Therefore the importance of including these events in the model was discussed with the panelists. Endocarditis and valve thrombosis are already included in the model and are therefore not discussed in this paragraph.

3.3 Conversion to open surgery and unplanned use of cardiopulmonary bypass

Interviews

According to the panelists the event 'conversion to open surgery' overlaps with 'unplanned use of cardiopulmonary bypass.' Therefore these events will be combined to one event. Some panelists

suggested that if we include ‘conversion to open surgery’ in the model, the flipside of this event (conversion to transcatheter valve implantation) should also be added to the model. This suggestion was added as a question to the questionnaire.

Questionnaire 1

Most panelists agreed that conversions from one approach to the other are important complications. Two panelists felt that both conversions were not important to take into account. One of these panelists argued that conversion from transcatheter valve implantation to open surgery is fatal for most patients. However, because these conversions are accompanied with significant costs it was decided to include them in the model (on the condition that relevant data is available or can be collected).

Questionnaire 2

In the second questionnaire none of the panelists had objections to this decision.

3.4 Coronary obstruction

Interviews

During the interviews some panelists argued that in most cases coronary obstruction results in a myocardial infarction or death. That means that those patients are already included in the model. Therefore the other panelists were asked in the questionnaire whether it is reasonable to exclude coronary obstruction as a separate event from the model.

Questionnaire 1

Five panelists agreed that coronary obstruction should not be included in the model because the most common consequences of coronary obstruction (i.e. myocardial infarction and death) are already included in the model. Three panelists felt that coronary obstruction should be included in the model. One of these panelists felt this way because coronary obstruction can lead to conversion to open surgery. However, in these cases the event will also be included in the ‘conversion to open surgery’ event. The other two panelists argued that coronary obstruction does not have to result in myocardial infarction or death when it is discovered in time. Despite these arguments it was decided to exclude coronary obstruction from the model to prevent overlap with MI. Furthermore, the occurrence rate of coronary obstruction after TAVI is relatively low (i.e. pooled estimate rate of 0.7% in meta-analysis of Genereux et al. 2012(33)).

Questionnaire 2

The panelists do not have objections to this decision. However, one panelist would like to know the percentage of myocardial infarctions caused by coronary obstruction.

3.5 Ventricular septal perforation and mitral valve apparatus damage or dysfunction

Interviews

Ventricular septal perforation and mitral valve apparatus damage or dysfunction are major complications that occur relatively rarely after heart valve interventions. The panelists did not reveal a clear opinion about the inclusion of these events in the model. Therefore the questions were added to the questionnaire.

Questionnaire 1

The panelists did not agree about the inclusion of ventricular septal perforation and mitral valve apparatus damage or dysfunction in the model. These events were considered for inclusion in the model because the VARC guideline discussed them under 'other TAVI-related events'. The events are not defined in the Guideline for reporting events after cardiac valve interventions(23) (mostly used for surgical valve replacement) and therefore seem less relevant after surgical valve replacement. The intervention cardiologists in the Delphi panel that performed TAVI regularly agreed that these complications were not relevant for the model because of their low occurrence rate. Furthermore, there is limited data available about the occurrence of these complications after transcatheter valve implantation or surgical valve replacement. To assure that we focus on the most relevant complications and to limit the model's complexity, it was decided to follow the intervention cardiologists' opinion and exclude ventricular septal perforation and mitral valve apparatus damage or dysfunction from the model.

Questionnaire 2

Seven panelists do not have objections to this choice. One panelist did not have an opinion. However, two panelists objected to the exclusion of these events. One of these panelists argued that these complications almost always occur after transcatheter valve implantation and not after surgical valve replacement and is therefore an important difference between these types of interventions. The other

panelist felt that excluding these events because of their rarity is not a valid reason. However, it was decided to exclude these events from the model, because the majority of the panelists agree with this decision and data about these events is limited.

3.6 Cardiac tamponade

Interviews

According to the panelists cardiac tamponade could be included in the (post-intervention) bleeding event.

3.7 Valve malpositioning

As described before the definition of ‘deterioration of valve function’ was changed to ‘prosthetic valve dysfunction’. Therefore valve malpositioning can be included in this event.

3.8 Valve embolization

Interviews

As described in the paper, embolism is excluded from the model as a separate event, because two severe consequences of an embolism (stroke and MI) are already included in the model. Including both the underlying mechanism and the resulting complications would lead to double counting of the events. However, because of this change in the model an embolism that not results in a stroke or myocardial infarction – like other noncerebral embolic events – are not included in the model.

3.9 TAV-in-TAV deployment

Interviews

TAV-in-TAV deployment (valve-in-valve implantation) can occur during or after the index procedure. If an additional valve needs to be included during the index procedure, this will be incorporated in the index procedure itself (by adding costs to the proportion of the valve implantations where a second valve is implanted). When valve-in-valve implantation occurs after the index procedure, it will be included as a treatment option. Therefore this complication will not be included as a separate event in the conceptual model.

4. Additional events

Interviews

After discussing the draft conceptual model, the Delphi panelists were asked if the draft conceptual model was complete or additional events needed to be added. Several panelists suggested additional events. The suggested events were considered within the small workgroup (SH, MR, JT). Three of the suggested events were not added to the model. (1) Respiratory and urinary tract infections were not included, because they are not specific to heart valve interventions. (2) Rheumatic fever is a potential event in developing countries. However, our conceptual model is based on the Dutch healthcare system and data from developed countries. Therefore rheumatic fever will not be added to the conceptual model. (3) Patients with less than optimal quality of life without experiencing any of the events included in the model will not be added explicitly in the conceptual model. The quality of life of these patients will be reflected in the average quality of life of patients that are alive after the intervention without experiencing any events included in the model. The other two suggested events (heart failure and post-surgery neurological problems) were included in the questionnaire for consideration by the other panelists.

4.1 Heart failure

Questionnaire 1

Five panelists argued that heart failure should not be included in the model when there is no association with the valve substitute. One of these panelists suggested incorporating cardiac hospital admissions instead. Three panelists felt that heart failure should be taken into account when it results in hospitalization of the patient.

It was decided that heart failure will not be incorporated as an event in the model, because heart failure that is not caused by valve problems is not relevant for our decision problem. It is assumed that heart failure that is caused by valve problems is included in the model in the hospitalizations due to prosthetic valve dysfunction.

Questionnaire 2

In the second questionnaire none of the panelists had objections to this decision.

4.2 Post-narcotic problems and delirium

Questionnaire 1

All panelists agreed it is not feasible to include post-narcotic problems and delirium in the model, because there is limited data available about the occurrence, impact on quality of life and costs of these events.

5. Summary

In summary, the input from the Delphi panel resulted in the following changes in the model.

- In addition to conversion from transcatheter valve implantation to open surgery, conversion from surgical valve replacement to transcatheter valve implantation is included in the model.
- Transient ischemic attacks (TIA) are added to the model. The event 'stroke' is redefined as 'cerebrovascular accident' and includes both strokes and TIAs.
- Myocardial infarction (MI) is only included during the first 30 days after the intervention and not during the patient's lifetime, because the majority of the panelists felt that myocardial infarctions that occur on the long term generally are not a direct consequence of the heart valve intervention.
- Except for atrial fibrillation (AF) during the first 30 days after the intervention, conduction disturbances and arrhythmias are excluded from the model, unless they result in pacemaker implantation (PI).
- Atrial fibrillation is only included during the first 30 days after the intervention instead of during the patient's lifetime because the majority of the panelists agreed that the occurrence of atrial fibrillation beyond the first post-interventional month is not necessarily a direct consequence of the heart valve intervention, but a common complication in the elderly population (with or without valve problems) due to aging..
- Atrial fibrillation (without pacemaker implantation) and pacemaker implantation are included in the category of cardiovascular events instead of prosthetic valve related events.
- Deterioration of valve function is now called prosthetic valve dysfunction including structural valve deterioration (SVD) and nonstructural valve dysfunction (NSD).

- ‘Other events that require re-intervention’ are excluded from the model. The following describes which events are included or excluded.
    - Conversion to open surgery is included separately.
    - Cardiac tamponade is included in ‘bleeding’.
    - Valve malpositioning is included in ‘prosthetic valve dysfunction’.
    - TAV-in-TAV deployment is a re-intervention and is therefore included in ‘treatment’.
    - Coronary obstruction is not included because the most common consequences (myocardial infarction and death) are included.
    - Ventricular septal perforation and mitral valve apparatus damage or dysfunction are not included because of relatively low occurrence rates of these events and limited data availability.