I. INTRODUCTION

Under the terms of a Settlement Agreement resolving Class Member claims in the *Bowling, et al. v. Pfizer Inc., et al.* heart valve litigation, financial benefits are made available to certain patients implanted with Bjork-Shiley Convexo-Concave (BSCC) heart valves, who undergo replacement surgery due to the risk of valve strut fracture. In accordance with the Settlement Agreement, an independent Supervisory Panel was appointed in May 1994 to develop and amend guidelines to be used to determine qualification for payment of benefits for qualifying valve replacement surgery.

In 1997, The Supervisory Panel adopted *Guidelines to Assess Patients with Bjork-Shiley Convexo-Concave Heart Valves for Elective Explantation*. These *Guidelines* were adopted after the Supervisory Panel had monitored a number of clinical studies, analyzed the worldwide database for BSCC valves, studied manufacturing records and undertaken extensive studies to understand the operative risk of elective explantation as it relates to age and cardiac functional ability. Expert cardiovascular surgeons, cardiologists, biostatisticians, epidemiologists and ethicists evaluated newly available data and formulated recommendations for the Supervisory Panel's *Guidelines*. The U.S. District Court approved these *Guidelines* in August 1997.

In 1999, based upon updated data from cohort studies and other updated data in the research database, the Supervisory Panel proposed amendments to the 1997 Guidelines, including adding gender as a risk factor. On March 8, 2000 the Supervisory Panel's proposed Amended Guidelines were adopted by the U.S. District Court (the 2000 Amended Guidelines).

The Supervisory Panel's research and work has continued and as a result, the Supervisory Panel has developed these *2003 Amended Guidelines* based on the best medical judgment of the Supervisory Panel.

Although these *2003 Amended Guidelines* will be used to establish qualification for compensation for elective replacement surgery, the *2003 Amended Guidelines* are not meant to imply that surgery is appropriate for individual patients. The final decision regarding explantation for a patient must be made by the patient in consultation with the managing cardiologist or cardiovascular surgeon, after careful examination and discussion of the individual patient's situation.

These *2003 Amended Guidelines* are based on the best estimates of the risks of fracture and reoperation from all data that are currently available. Standard statistical criteria were used to identify factors associated with increased risks of fracture and reoperative mortality. Each of the factors identified in these *2003 Amended Guidelines* have met those statistical criteria. However, because outlet strut fracture is a relatively rare event, and the worldwide data about reoperative mortality and morbidity for elective surgery are limited, there remains uncertainty in the risks of fracture and reoperative mortality. The *2003 Amended Guidelines* identify the subgroup of patients for whom on *average* reoperation will result in a gain in life expectancy. However, for some individual patients there can be a significant loss of life (if death results from reoperation) and for other patients there can be a significant gain (if a

strut fracture is avoided by a successful operation). For many other patients who undergo reoperation there may well be no change in life expectancy even if they survive the reoperation because they may not have had an outlet strut fracture if the valve had been left in place. Accordingly, in interpreting the *2003 Amended Guidelines*, it is important to emphasize that the recommendations are based on a biostatistical analysis of group data, and that the risk for an individual patient may differ from those of the group.

We emphasize that these *2003 Amended Guidelines* will be continuously reviewed by the Supervisory Panel as new data become available. They will be modified when appropriate in accord with the best epidemiological, clinical and other relevant information made available to the Supervisory Panel.

II. QUALIFICATION FOR VALVE REPLACEMENT SURGERY BENEFITS

Provided below are the procedures for determining the qualification for monetary benefits from the *Bowling* settlement when surgery for explantation of a BSCC heart valve takes place due to the risk of strut fracture. Qualification is dependent upon the elective replacement of a BSCC heart valve reasonably offering a meaningful extension of life expectancy, because of elimination of the risk of valve outlet strut fracture (OSF), assuming the reoperative risk of a patient in optimal health status. Qualification under these *2003 Amended Guidelines* does not mean that replacement surgery is appropriate for a particular patient because it assumes that the patient is in optimal health status and that the surgery would take place at a significantly experienced facility. Qualification only means that monetary benefits are available upon surgery for explantation due to the risk of strut fracture.

The determination of qualification for monetary benefits requires estimation of the risk from OSF of the individual patient's BSCC valve as well as the risk an optimal patient would experience from the reoperative surgery. In order to determine the OSF rate, the responsible physician managing the patient will need to communicate the valve serial number, along with the current age, gender and valve implant position of the patient, to the Claims Administrator. This may be

accomplished by telephone to 800-977-0779 in the United States or Canada or to 00-1-513-421-3517 internationally, by fax to 513-421-7696, or by mail to Claims Administrator, P.O. Box 3598, Cincinnati, Ohio 45201-3598, U.S.A.

From this information, the patient's estimated OSF rate may be calculated along with the determination as to whether an optimal patient with such an estimated OSF rate would be predicted to have a gain in life expectancy should explantation take place at a significantly experienced facility. If there is a predicted gain, the patient would qualify for monetary valve replacement surgery benefits.

"Optimal patient" means a patient whose health history and status present the optimal estimated risks of valve replacement surgery. See discussion on page 10 below.

The Supervisory Panel emphasizes that risk of valve fracture for the large majority of BSCC heart valve patients is not high enough to warrant explantation. Furthermore, not all patients who qualify for monetary benefits are in optimal health and good candidates for reoperation. Considerations which should be addressed by the patient and physician before deciding on the advisability of replacement surgery are provided in Part IV.

The procedures to be followed for determination of qualification to receive monetary valve replacement surgery benefits when surgery for explantation of a BSCC heart valve takes place due to the risk of strut fracture for three categories of patients with BSCC heart valves are summarized below.

1. Patients with single or multiple BSCC valves with known serial number(s).

Step One: The responsible physician managing the patient will communicate to the *Bowling* Claims Administrator the patient's age, gender, valve serial number and valve implant

position.

Step Two: The patient's estimated OSF rate (expressed as the per cent chance that the valve will fracture in the next year) will be calculated by the Claims Administrator using the formula and methods described in Part III. For patients with multiple valves, the patient's OSF rate will be calculated by summing the OSF rates for each valve.

Step Three: Determinations of life expectancy take into account both the estimated OSF rates and the estimated risks of death or serious morbidity from reoperation for replacement of BSCC valves for optimal patients. If the estimated OSF rate is greater than the threshold rate listed in Part V, Table 5 or Part V, Table 6 for single or multiple valve patients, respectively, then the patient would qualify for valve replacement surgery benefits.

2. Patients with BSCC mitral valves with unknown serial numbers.

Step One: The responsible physician managing the patient will communicate to the *Bowling* Claims Administrator the patient's age, gender, and documentation that the patient has a 29, 31 or 33 mm BSCC mitral valve implanted prior to April 1984. Proof of the characteristics of the valve may be made by x-ray, fluoroscopy or transesophageal echocardiography.

Step Two: If the patient is currently under age 35 and has a 29, 31 or 33 mm mitral BSCC valve implanted prior to April 1984, the patient would qualify for valve replacement surgery benefits.

3. Patients with documented single leg separation (SLS).

Step One: The responsible physician managing the patient will communicate to the Bowling Claims Administrator clear evidence of single leg separation of the patient's BSCC valve, as documented by x-ray images definitively showing offset of one of the valve's two outlet strut legs (equivalent to a class 5 designation in previously reported imaging studies).

Step Two: If SLS is documented, the patient would qualify for valve replacement surgery benefits.

In addition to the foregoing three qualification categories,

the Supervisory Panel determined that surgery to explant, due to the risk of strut fracture, a Class Member's BSCC heart valve that would comply with the 2000 Amended Guidelines would qualify the patient for the valve replacement surgery benefits. The Panel

concluded that it would be inappropriate to exclude those Class Members who may qualify under the 2000 Amended Guidelines but not under the *2003 Amended Guidelines*.

III. METHODS FOR DETERMINING QUALIFICATION FOR VALVE REPLACEMENT SURGERY BENEFITS

The Supervisory Panel developed the *2003 Amended Guidelines* from detailed reviews of the relevant clinical and epidemiologic data concerning risks of outlet strut fracture vs. risks from reoperations to replace BSCC heart valves. In all instances, the expert medical judgment of physicians, including those who are daily managing patients with complex cardiovascular conditions, was the final arbiter for these *2003 Amended Guidelines* as opposed to concerns about financial benefits provided to patients.

If the estimated risk from reoperation to replace the BSCC valve is such that a predicted gain in life expectancy in an optimal patient results, then the patient (regardless of his or her health status) qualifies for benefits when surgery for explantation takes place due to the risk of strut fracture. Methods used to determine estimated risks of valve fracture and estimated risks from reoperative surgery are described below.

A. METHODS FOR ESTIMATING OSF RISK

Information on the worldwide experience of OSF among BSCC heart valve patients was used to determine the characteristics of patients and their valves which are associated with increased rates of OSF. Data were obtained from a worldwide research database containing information on nearly 86,000 BSCC valves and from epidemiologic studies of nearly 20,000 BSCC patients in Europe and the United States specifically designed to measure rates of OSF according to valve size,

position, and other manufacturing characteristics and according to age, gender and other patient characteristics. Using the latest available worldwide data, statistical analyses were applied to determine which factors were significant predictors of increased risk of OSF and to estimate relative risk multipliers of OSF associated with each factor. The risk multipliers represent the extent to which the presence or level of the factor increases the risk of OSF.

Part V, Table 1 lists the factors, namely valve size, position, date of manufacture, welder, shoporder and rework status and patient age and sex, determined to significantly influence risk of fracture of BSCC 60 degree valves. From the information in Part V, Table 1 it is possible to calculate, for each individual with a known BSCC 60 degree valve serial number, the estimated rate (in per cent per year) of fracture for his or her valve. The Claims Administrator will use a formula, which applies the risk multipliers corresponding to the patient's valve characteristics and his or her gender and current age, to calculate the predicted probability (percent) that the valve will fracture within one year from the date of calculation. The constant factor (0.094) is the fracture rate (% per year) for a 35 year old patient all of whose

factors in Part V, Table 1 are equal to 1. This constant factor (0.094) has been adjusted for underreporting of fractures.

Part V, Table 2 illustrates the calculation of an OSF rate for a hypothetical 50 year old male patient with a size 29 mm BSCC 60 degree mitral valve implanted in the mitral position, welded in 1983 by Welder Group AB, in a shop order in which 3% of the other valves have fractured, and not reworked. In order to obtain the manufacturing data necessary to apply the calculations, the serial number for the valve must be known. The implanted valve position is also needed. As noted above, once this information is communicated to the Claims Administrator, this calculation will be made and transmitted in response to the physician managing the patient.

Part V, Table 3 presents the factors utilized in calculating potential OSF rates for 70 degree BSCC valves. The constant factor (0.79) is the fracture rate (% per year) for a 35 year old patient all of whose factors in Part V, Table 3 are equal to 1. This constant factor (0.79) has been adjusted for underreporting of fractures.

B. METHODS FOR ESTIMATING REOPERATIVE RISK

Part V, Table 4 provides estimates of the risk of mortality and serious morbidity from elective explantation among patients of various ages in optimal health status with single or multiple BSCC valves. The percentages in Part V, Table 4 represent the Supervisory Panel's best medical judgment of reoperative risks after review of clinical and epidemiologic studies of hospital mortality and serious morbidity following operations to replace prosthetic heart valves. Included in the review were surveys of reoperative risks in relatively large series of prosthetic heart valve patients of NYHA class I and II without cardiac co-morbidity, i.e., optimal or close to optimal patients. The collective data suggest the estimated operative risk (mortality and serious morbidity) of an optimal patient with a single BSCC valve at a significantly experienced facility averages approximately 6% at an approximate age of 58, with lower risks at younger and higher risks at older ages. The values in Part V, Table 4 were determined by setting the reoperative risk at age 58 at 6%, with the reoperative risks at younger and older ages estimated from the risk-age relationship observed in a large series of over 2,000 prosthetic heart valve reoperations in the United States.

The risk from reoperation was considered to consist of two components: risk of death and risk of serious morbidity such

as permanent neurologic deficit, renal failure or myocardial infarction. Based on the most recent data, the reoperative mortality for an optimal patient at a significantly experienced facility was estimated to be approximately 3% on the average at age 58. In addition, current data in the same patient studies indicate that serious permanent morbidity from reoperation approximately doubles the risk to an individual patient, so that the overall reoperative risk at age 58 is approximately 6%.

The Supervisory Panel noted that the observed rate of mortality only within 90 days of surgery among a group of 135 BSCC patients known to have undergone prophylactic replacement of their BSCC valves was 6.7% (with the rate varying with age from approximately 2% at ages below 50 to over 10% at ages above 70), but not all of these patients were optimal patients.

C. METHODS FOR COMPARING RISKS OF OSF AND REOPERATION: LIFE EXPECTANCY DETERMINATIONS

Qualification for receipt of valve replacement surgery monetary benefits is determined by comparison of predicted future life expectancies under scenarios where reoperation to replace the BSCC valve does or does not take place. Life expectancies can be calculated taking into account the patient's current OSF rate Part V, Tables 1-3, his or her future OSF rate (the annual OSF rate for successive years is 0.941 times the OSF rate in the preceding year), the reoperative risk for the optimal patient Part V, Table 4, and the patient's future underlying total mortality rate. Observed overall mortality rates during 1990-1997 from epidemiologic cohort studies of Dutch, British and American BSCC heart valve patients were used to predict future

underlying mortality according to age, sex and valve position.

Part V, Table 5 presents threshold values of estimated current OSF rates (in per cent per year) according to age, sex and valve position for persons with a single BSCC valve. If the patient's estimated OSF rate (as calculated in Part V, Tables 1-3) exceeds the threshold value for the patient's current age, then (if the patient were in optimal health) the reoperation would be predicted to result in a gain in life expectancy and the patient would qualify for monetary benefits when surgery for explantation takes place due to the risk of strut fracture. If the estimated OSF rate is below the threshold, then the reoperation would be predicted to result in a loss in life expectancy, and the patient would not qualify for valve replacement surgery benefits.

Part V, Table 6 presents threshold values for patients with both an aortic and a mitral valve. For these patients, if the sum of the estimated OSF rates for the patient's two valves exceeds the threshold value for the patient's current age (rounded to the nearest 5 years), there would be predicted to be a gain in life expectancy from reoperation (if the patient was an optimal patient) and the double-valve patient would qualify for monetary benefits when surgery for explantation takes place due to the risk of strut fracture. These thresholds are higher than for single valve patients because of the higher reoperative risks for double-valve patients. Note that this increased mortality pertains even if only one valve is to be replaced.

IV. ADDITIONAL INFORMATION REGARDING EXPLANTATION

Even if a patient qualifies for monetary valve replacement surgery benefits from the *Bowling* Settlement, the Supervisory Panel provides the following information about other considerations to be discussed between the patient and physician before undertaking reoperation to replace the BSCC valve. Some considerations to assist in these deliberations are outlined below, but in all cases it is the patient and his or her physician who must decide on the advisability of valve explantation.

Part II of these *2003 Amended Guidelines* describes the method for identifying patients who qualify for monetary valve replacement surgery benefits under the terms of the *Bowling* settlement. The criteria for qualification for monetary benefits are based on a comparison of the risk of valve fracture vs. the risk of reoperation. For the purposes of defining operative risk, the Supervisory Panel assumed that

surgery is to be performed on an “optimal” patient at a “significantly experienced” facility. Estimation of risk also assumed that the surgery is elective and the procedure only involves replacement of one or more BSCC valves. In practice one or more of these assumptions may often be violated with the result that the actual operative risk for an individual patient may exceed that used to calculate monetary benefits. In these cases surgery can result in a net *loss* of life expectancy and would not be medically indicated despite the fact that it would qualify for financial benefits.

The criteria used to establish risk based on each of these four assumptions (optimal patient, significantly experienced facility, elective surgery, and isolated explantation) and examples of situations in which these criteria may not be valid are listed below.

A. OPTIMAL PATIENT

In establishing reoperative risk the Supervisory Panel utilized the predicted risk for a patient in New York Heart association functional class I or class II, with no associated cardiovascular (coronary artery disease, depressed LV function, myopathy, significant arrythmia, or associated valvular or congenital heart disease), neurologic, pulmonary, renal, hepatic or other systemic disease likely to increase surgical mortality or morbidity. The risk for reoperation is greater for patients in non-optimal health as opposed to optimal health. While many factors need to be considered by the patient and physician in deciding whether to reoperate, the increased reoperative risk for some non-optimal patients may be such that a gain in life expectancy would be unlikely and therefore explantation not medically justified. Risk, for example, is more than double compared to the optimal patient

in cases with moderate left ventricular dysfunction (NYHA Class III), chronic renal failure and important tricuspid insufficiency.

There have been no reported fractures in BSCC valve conduits. The operative risk in these patients is 4.5 times higher than an optimal patient. Thus none of these patients qualify for valve replacement surgery benefits and should not undergo explantation.

B. SIGNIFICANTLY EXPERIENCED FACILITY

Although it is not possible to rank specific surgical facilities, a significantly experienced facility was considered to be one with a national or international reputation for cardiac surgery, a large surgical volume (>1000 cases per year) and

extensive experience in prosthetic valve explantation surgery. The Supervisory Panel strongly advises patients undergoing prophylactic valve removal to consult with their physicians to obtain advice on referral to centers with greater experience and overall excellence in reoperative valve procedures since such centers can be presumed to have the lowest surgical mortality.

C. ELECTIVE SURGERY

Risk estimates in Part II are based on elective surgery under ideal circumstances. Surgery in patients with infective endocarditis, hemodynamic instability, or prosthetic valve malfunction is not elective and is associated with higher surgical risk. Decisions in these cases must be based on medical necessity.

D. SURGERY IS PERFORMED FOR THE SOLE PURPOSE OF REMOVING ONE OR MORE BSCC PROSTHETIC VALVES

The surgical risk estimates described in Part II are based on data for elective explantation and replacement of a single or multiple prosthetic valves as an isolated procedure. In patients with multiple prior cardiac surgical procedures, those in whom additional valve surgery is anticipated in addition to replacement of their BSCC valve, and those with coexisting coronary artery disease requiring concomitant by-pass surgery the reoperative risk is increased by 40 to 80%.

Based on the above assumptions, data from literature suggests an operative mortality of approximately 3% for an optimal patient at an approximate age of 58, (See Part III). However, the actual mortality rate among a group of 135 BSCC patients known to have undergone prophylactic replacement of their BSCC valves was 6.7%. This suggests that not all patients were optimal patients.

The Supervisory Panel therefore advises that the decision reached by the patient and physician on whether to actually undergo replacement surgery (irrespective of qualification for monetary benefits) take into account the patient's actual health status (since many patients with prosthetic heart valves do not meet the criteria for optimal health) and the risk associated with the type of procedure to be performed.

E. GENERAL RECOMMENDATIONS FOR ALL BSCC PATIENTS

All patients with BSCC valves should regularly consult their physicians and should have a clear understanding of the symptoms which occur at the time of OSF. These should be made known to those relatives or friends in contact with the patient. These patients should also be made aware of the nearest center with significant experience in cardiovascular surgery, since early recognition and prompt surgical intervention may be lifesaving for the small percentage of BSCC valve recipients who actually experience OSF.

V. STATISTICAL TABLES

Table 1. Factors for Calculation of Rates of OSF (% per year) of BSCC 60 Degree Valves

Factor	Subgroup	Multiplier
Constant [1]	All	0.094
Size (mm)	21 or 25	1.00
	23 or 27	2.84
	29	3.99
	31	5.51
	33	9.60
Position	Aortic	1.00
	Mitral	2.51
Weld date	<1980, 7/82-3/84	1.00
	1980	0.48
	1/81-6/82	1.64
	> 4/84	0.00
Welder Group	AB	1.00
	C	1.51
Shop Order Rate [2]	<1.0%	1.00
	1.0-5.0%	1.88
	>5.0%	2.35
Current Age	<35	1.00
	>35	$(.941)^{(Age - 35)}$
Gender	Male	1.00
	Female	0.46
Rework	No crack or rework	1.00
	Crack, rework, missing	1.57

[1] Corresponds to the OSF rate for an individual whose factors are all equal to 1

[2] The percent of other valves in the same shop order which have fractured

Table 2.

Formula for and Example of Calculation of the Estimated OSF Rate (% per Year) for a Particular Patient with a BSCC 60° Valve

Estimated OSF Rate=Constant x Size x Position x Weld date x Welder group x Shop order rate x Current age x Gender x Rework status

Example for hypothetical 50 year old male with size 29 mm mitral valve implanted in the mitral position welded in 1983 by welder group AB in a shop order where the OSF rate of other valves is 3% and the valve has not been reworked:

Estimated OSF Rate =

Constant		0.094
Size	x	3.99
Position	x	2.51
Weld date	x	1.00
Welder group	x	1.00
Shop order rate	x	1.88
Current age	x	$(.941)^{50-35}$ =0.40
Gender	x	1.00
Rework	x	1.00
	=	0.70 % per year

Table 3. Factors for Calculation of Rates of OSF (% per year) of BSCC 70 Degree Valves

Factor	Subgroup	Risk Multiplier
Constant [1]	All	0.79
Size (mm)	21 or 25	1.00
	23 or 27	1.40
	29	2.13
	31 or 33	3.22
Position	Aortic	1.00
	Mitral	1.81
Welder Group	D	1.00
	E	2.29
Shop Order Rate [2]	<1.0%	1.00
	1.0-5.0%	2.46
	>5.0%	2.72
Current Age	<35	1.00
	>35	$(.941)^{(Age - 35)}$
Gender	Male	1.00
	Female	0.46
Rework	No Crack or Rework	1.00
	Crack, Rework or Missing	1.71

[1] Corresponds to the OSF rate for an individual whose factors are all equal to 1

[2] The percent of other valves in the same shop order which have fractured

Table 4. Estimated Risks of Death or Serious Morbidity from Reoperation for Replacement of BSCC valves for the Optimal Patient According to Age and Single and multiple valve status

	Reoperative Risk (%)	
Age	Single Valve	Multiple Valve
35	3.6	5.8
40	3.9	6.3
45	4.3	7.0
50	4.9	7.8
55	5.5	8.9
60	6.4	10.1
65	7.4	11.7
70	8.7	13.6
75	10.2	16.0
80	12.2	18.8

Table 5. Outlet strut fracture rates (per cent per year), by age, gender and valve position, above which the patient with a single BSCC valve will qualify for valve replacement surgery benefits

	Male		Female	
Age	Aortic	Mitral	Aortic	Mitral
30	0.26	0.27	0.25	0.26
35	0.37	0.39	0.36	0.38
40	0.43	0.46	0.42	0.44
45	0.51	0.54	0.49	0.52
50	0.61	0.66	0.58	0.62
55	0.75	0.81	0.71	0.76
60	0.94	1.02	0.89	0.96
65	1.20	1.31	1.12	1.22
70	1.57	1.72	1.45	1.59
75	2.08	2.30	1.92	2.11
80	2.81	3.14	2.59	2.87

Table 6. Outlet strut fracture rates (per cent per year), by age and gender, above which the patient with multiple BSCC valves will qualify for valve replacement surgery benefits

Age	Male	Female
30	0.45	0.43
35	0.65	0.62
40	0.75	0.72
45	0.89	0.85
50	1.08	1.02
55	1.33	1.25
60	1.68	1.57
65	2.15	2.00
70	2.81	2.60
75	3.75	3.44
80	5.10	4.65