Value Framework Net Health Benefit Worksheet:

Advanced Disease Setting

About This Worksheet

The American Society of Clinical Oncology (ASCO) Value Framework assesses the relative value of cancer therapies by calculating Net Health Benefit scores (NHBs) using measures of clinical benefits and toxicities, as demonstrated in randomized clinical trials.

ASCO has developed this "Value Framework Net Health Benefit Score Worksheet: Advanced Disease Setting," to provide step-by-step guidance for reliably calculating NHBs. ASCO acknowledges that trial interpretation is complex and that the accurate use of the framework requires a thorough understanding of its design and purpose. To assist users, the worksheet is heavily footnoted with guidance on resolving situations that may occur at extreme parameters within the framework and provides worked examples of calculations. The "Notes" field at the bottom of each page is intended to help users keep important information at-a-glance to assist with performing the framework's calculations.

This worksheet is divided into the following sections:

You may contact ASCO regarding this worksheet at valueframework@asco.org.

More information on ASCO's efforts to achieve high-quality, high-value care for all patients with cancer is available at www.asco.org/value.

General Notes

- There may be more than one relevant reference for the NHB calculation. For example, a later publication may provide quality of life data for which a QoL bonus may be given, or a later publication may provide more detailed toxicity data or overall survival data. List all publications that were used in calculating the NHB.
- The term "experimental/new treatment" is used for consistency throughout the NHB tool to refer to the treatment whose net health benefit is of interest. It may be neither experimental or new in context.
- The term "standard/control treatment" is used for consistency throughout the NHB tool to refer to the reference treatment against which the treatment of interest's health benefits are being compared. It may not be a standard treatment in context, and it may not be a treatment at all, per se (i.e. placebo, "usual care", "surveillance").

Step 1 – Clinical Benefit Scoring

Answer each question in Step 1 and follow the instructions depending on the answer.

1. A. Is a hazard ratio (HR) for overall survival reported AND was it statistically significant?

- If YES, continue with this section below the line.
- If NO, go to 1. B. NO means EITHER there was no HR of overall survival reported OR one was reported but it was not statistically significant.

Enter the Hazard Ratio for overall survival in box 1 (e.g. 0.84). The hazard ratio should be in such a form that a value less than 1 shows benefit for the experimental/new treatment for which a net health benefit is being calculated. If it is not in this form (e.g. a value greater than 1 shows benefit) put the reciprocal of the hazard ratio in box 1 (i.e. Box 1 = 1/HR).

BOX 1	Subtract the value in Box 1 from 1 and enter it in Box 2 (e.g. 1-0.84 = 0.16).
BOX 2	Multiply the value in Box 2 by 100 and enter it in the box labelled "HR Score (Death)" (e.g. 0.16 x 100 = 16)
HR Score (Death)	Copy this value to Step 4 into the box labeled "Clinical Benefit Score". Continue with the instructions in Step 2. Skip 1.B., 1.C., and 1.D.

Notes

1. B. Is the median overall survival (OS) reported for both arms of the trial AND is there a reported statistically significant difference between these values? A statistically significant difference will likely be reported as either a log-rank p-value or as an increase in overall survival with a confidence interval that does not include no difference (e.g. improved survival of 3 months (95% CI 1-6 months). If a statistically significant HR for overall survival is reported, go back to section 1.A.

- If YES, continue with this section below the line.
- IF NO, go to 1.C. NO means EITHER the median overall survival is not reported for one or both arms OR there is no reported statistically significant difference in median overall survival between the arms.

Enter the median overall survival for the experimental/new arm in the box labelled "Median New" and the value for the control/standard arm in the box labelled "Median Control" (e.g. Median New = 8.1 months, Median Control = 6.3 months). Ensure that the two values are in the same units (i.e. both months, both days).

Median New	Median Control	
		Subtract Median Control from Median New and enter the value in Box 1 (e.g 8.1-6.3 = 1.8)
BOX 1		Divide Box 1 by Median Control, and enter the value in Box 2 (e.g. 1.8/6.3 = 0.286)
BOX 2		Multiply Box 2 by 100 and enter the value into the box labelled "OS Score". (e.g. 0.286 x 100 = 28.6)
OS Score		Copy this value to Step 4 into the box labeled "Clinical Benefit Score". Continue with the instructions in Step 2. Skip 1.C. and 1.D.

Notes

1. C. Is a hazard ratio (HR) for progression-free survival reported AND was it statistically significant?
This hazard ratio may be reported as event-free survival or by similar names. The event definitions should be reviewed to ensure that the outcome is measuring progression. However, do not use: time to disease progression, time to disease-related death, or other measure that does not incorporate death from all causes as part of its definition. If a statistically significant hazard ratio for overall survival or statistically significant difference in median overall survival are reported, go back to section 1.A. and/or 1.B.

- If YES, continue with this section below the line.
- If NO, go to 1. D. NO means EITHER there was no HR for disease progression reported OR one was reported but it was not statistically significant.

Enter the Hazard Ratio for progression-free survival in box 1 (e.g. 0.84). The hazard ratio should be in such a form that a value less than 1 shows benefit for the experimental/new treatment for which a net health benefit is being calculated. If it is not in this form (e.g. a value greater than 1 shows benefit) put the reciprocal of the hazard ratio in box 1 (i.e. Box 1 = 1/HR).

BOX 1	Subtract the value in Box 1 from 1 and enter it in Box 2 (e.g. 1-0.84 = 0.16).
BOX 2	Multiply the value in Box 2 by 80 and enter it in the box labelled “HR Score (Progression)” (e.g. 0.16 x 80 = 12.8)
HR Score (Progression)	Copy this value to Step 4 into the box labeled “Clinical Benefit Score”. Continue with the instructions in Step 2. Skip 1.D.

Notes

1. D. Is the median progression-free survival reported for both arms of the trial AND is there a reported statistically significant difference between these values? A statistically significant difference will likely be reported as either a log-rank p-value or as an increase in progression-free survival with a confidence interval that does not include no difference (e.g. improved survival of 3 months (95% CI 1-6 months). Progression-free survival may be reported as event-free survival but the event definitions should be reviewed to ensure that the outcome is measuring progression. Do not use median time to progression, median time to cancer-related death, or similar measures that do not incorporate death from all causes as part of the definition. If a statistically significant HR for overall survival, median overall survival difference, or HR for progression-free survival is reported, go back to section 1.A., section 1.B. and/or section 1.C.

- If YES, continue with this section below the line.
- IF NO, then a Net Health Benefit cannot be calculated from this trial. NO means EITHER the median progression-free survival is not reported for one or both arms OR there is no reported statistically significant difference in median overall survival between the arms. While the JCO article upon which this worksheet is based references the potential use of objective response rate as a clinical benefit outcome, in practice using this outcome from non-comparative studies is impossible, as toxicity scores cannot be calculated for single-arm studies. Therefore, the use of objective response rate when it is the ONLY outcome reported is not covered by the worksheet.

Enter the median progression-free survival for the experimental/new arm in the box labelled "Median New" and the value for the control/standard arm in the box labelled "Median Control" (e.g. Median New = 8.1 months, Median Control = 6.3 months). Ensure that the two values are in the same units (i.e. both months, both days).

Median New	Median Control	Subtract Median Control from Median New and enter the value in Box 1 (e.g 8.1-6.3 = 1.8)
BOX 1		Divide Box 1 by Median Control, and enter the value in Box 2 (e.g. 1.8/6.3 = 0.286)
BOX 2		Multiply Box 2 by 80 and enter the value into the box labelled "PFS Score". (e.g. 0.286 x 80 = 22.9)
PFS Score		Copy this value to Step 4 into the box labeled "Clinical Benefit Score". Continue with the instructions in Step 2.

Notes

Step 2 – Toxicity Scoring

2. A. For each toxicity that was reported that is considered clinically relevant, determine the percentage of patients in each arm that experienced a Grade 1 or 2 toxicity (G1-2) and the percentage of patients that experienced a Grade 3 or 4 toxicity (G3-4) of that type. For this purpose, a clinically relevant toxicity is a toxicity that is experienced by the patient, as opposed to a laboratory value, physiological measurement, or similar. If toxicities are only reported in aggregate form, or if only a limited number of toxicities are reported separately, calculating a toxicity score, and therefore the overall net health benefit score, may not be possible. Also, these percentages may need to be calculated by the rater from the published information. For example, if the percentage of patients that experienced a G3-4 toxicity and the percentage that experienced toxicity of any grade are reported, the G1-2 toxicity may be calculated as the difference between those values (assuming no Grade 5 toxicity). Or, if toxicity is reported by Grade, the sum of the Grade 1 and 2 percentages is the G1-2 toxicity percentage, and the sum of the Grade 3 and 4 percentages is the G3-4 toxicity.

TABLE 1 – Experimental/New Treatment Toxicity

	Grade 1 and 2 percentage >=10%	Grade 1 and 2 percentage >0% and <10%	Grade 3 and 4 percentage >=5%	Grade 3 and 4 percentage >0% and <5%	
Toxicities (list out)					Total Experimental/New (Sum of Totals by Category)
Number of Toxicities					
Weight	1	0.5	2	1.5	
Total by Category (Number * Weight)					

TABLE 2 – Standard/Control Treatment Toxicity

	Grade 1 and 2 percentage >=10%	Grade 1 and 2 percentage >0% and <10%	Grade 3 and 4 percentage >=5%	Grade 3 and 4 percentage >0% and <5%	
Toxicities (list out)					Total Standard/Control (Sum of Totals by Category)
Number of Toxicities					
Weight	1	0.5	2	1.5	
Total by Category					

(Number * Weight)					

2.B. Continue below.

TOXIC NEW	TOXIC CONTROL	
		Divide TOXIC NEW by TOXIC CONTROL (e.g. 26.5/20 = 1.325) and write the result in Box 1
Box 1		Subtract Box 1 from 1, and write the value in Box 2. This value will be negative if the toxicity on the experimental/new arm was generally worse. (e.g. 1 – 1.325 = -0.325)
Box 2		Multiply the value in box 2 by 20 and enter the value into Box 3. (e.g. 20 * -0.325 = -6.5)
Box 3		If there are unresolved symptomatic treatment-related toxicities at 1 year after completion of treatment only on the experimental/new arm and not on the standard/control arm, subtract 5 from Box 3 and enter the result in Box 4. Otherwise, copy the value from Box 3 into Box 4. In what is expected to be the rare instance where there are unresolved treatment-related toxicities only on the standard/control arm at one year, 5 points may be added at this step.
Box 4		If Box 4 is greater than 20 or less than -20 then put “20” or “-20” into the box labelled “Toxicity Score”. Otherwise, copy the value from Box 4 into “Toxicity Score”.
Toxicity Score		Copy this value to the box labelled “Toxicity Score” in Step 4. This value should be between -20 and 20, and negative if the toxicity was generally worse on the experimental/new treatment.

Notes

Step 3 – Bonus Points

Step 3.A. – Tail of the Curve Bonus

If no Kaplan-Meier curves are reported for overall or progression-free survival, go on to Step 3.B.

Record the median overall survival, or the median progression free-survival if overall survival is not reported, for the standard/control arm in Box 1. (e.g. 12.3 months)

Box 1	Multiply the value in Box 1 by 2 and record in Box 2. (e.g. 12.3 months * 2 = 24.6 months)
Box 2	Locate the value in Box 2 on the time axis of the published Kaplan-Meier curve of overall (or progression-free, if appropriate) survival. Determine the OS or PFS at this time point for the standard/control arm and enter in Box 3. If this value is less than or equal to 20%, stop the calculation; no Tail of the Curve Bonus should awarded. This process should be done either using paper and ruler or in imaging editing software unless the tail of the curve bonus is self-evidently applicable. See the worked example.
Box 3	Determine the OS or PFS for the experimental/new arm at the same time point and enter in Box 4.
Box 4	If Box 4 is >= 1.5 times the value of Box 3, then enter 20 (if overall survival is being used) or 16 (if PFS is being used) in the box labelled “Tail of Curve Bonus”.
Tail of Curve Bonus	Copy this value to the box labelled “Tail of Curve Bonus” in Step 3.B.

Notes

Step 3. B. Final Bonus Point Calculation

Tail of the Curve Bonus	Tail of the Curve Bonus was calculated in Step 3.A.
Trmt-Free Interval Bonus	Treatment-Free Interval Bonus. If a statistically significant improvement in treatment-free interval is reported, multiply the percentage improvement in treatment-free interval by 20 and add points. (e.g. 20% improvement gives 20%*20 = 4 points)
Palliation Bonus	If a statistically significant improvement in any cancer-related symptom is reported only for the experimental/new arm, enter a 10 into the box labelled "Palliation Bonus", otherwise enter a 0. If any improvement in a cancer-related symptom is reported for the experimental/new arm, the bonus should be awarded. However, if both arms show a mixed picture of cancer-related symptom improvements (e.g. cognitive impairment is significantly improved on the experimental/new arm, but dyspnea is improved on the standard/control arm) no bonus should be awarded.
QoL Bonus	If a statistically significant improvement in quality of life is reported only for the experimental/new arm, enter a 10 into the box labelled "QoL Bonus", otherwise enter a 0. If any improvements in quality of life are identified, the bonus should be awarded. This would include both overall quality of life (e.g. full FACT-G) but also any single sub-domain (e.g. FACT-G Physical Well-Being). However, if both arms show a mixed picture of quality of life improvements (e.g. Physical Well-Being improved for experimental/new arm, Functional Well-Being improved for standard/control arm) no bonus should be awarded.
Total Bonus Points	Add together all four bonuses above (Tail of the Curve, Trmt Free Interval, Palliation, QoL) and enter the result into the box labelled "Total Bonus Points". Copy this value to the box labelled "Bonus Points" in Step 4.

Notes

Step 4. Final Net Health Benefit.

Clinical Benefit Score	The Clinical Benefit Score was calculated in steps 1.A., 1.B., 1.C., 1.D. or 1.E.
Toxicity Score	The Toxicity score was calculated in step 2. It will be negative if the experimental/new treatment is generally more toxic than the standard/control treatment and will be positive if it is generally less toxic.
Bonus Points	The Bonus points were calculated in step 3 and reflect the "tail of the curve", palliation, QoL, and treatment-free interval bonuses.
	Add the Clinical Benefit Score, Toxicity Score, and Bonus Points together and put the result into the box labelled "Net Health Benefit"
Net Health Benefit	This is the Net Health Benefit (NHB) of the experimental/new treatment compared to the standard/control treatment.

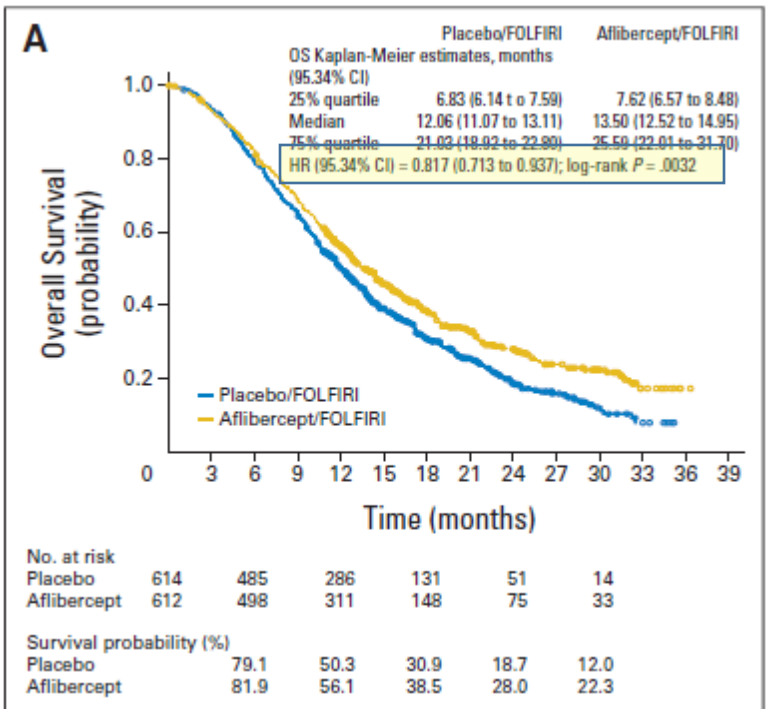
Notes

WORKED EXAMPLE

This example uses the report by Van Cutsem et al of a randomized trial of aflibercept versus placebo in patients with metastatic colorectal cancer who are receiving fluorouracil, leucovorin, and irinotecan (FOLFIRIT) and who had previously received an oxaliplatin containing regimen[A].

STEP 1.

The following figure can be found in the Van Cutsem et al study report.



The noted hazard ratio 0.817 (95.34% CI, 0.713-0.937) is also found in the text. This study used methods that corrected for interim analyses, thus the 95.34% confidence interval. As this is a statistically significant improvement in overall survival, this study should receive points in Step 1.A. The worksheet would be as follows:

Step 1 – Clinical Benefit Scoring

Answer each question in Step 1 and follow the instructions depending on the answer.

1. A. Is a hazard ratio (HR) of overall survival reported AND was it statistically significant?

- If YES, continue with this section below the line.
- If NO, go to 1. B. NO means EITHER there was no HR of overall survival reported OR one was reported but it was not statistically significant.

Enter the Hazard Ratio for overall survival in box 1:

BOX 1	Subtract the value in Box 1 from 1 and enter it in Box 2.
0.817	

[A] J Clin Oncol 2012;30:3499-3506.

BOX 2 **0.183**	Multiply the value in Box 2 by 100 and enter it in the box labelled "HR Score (Death)"
HR Score (Death) **18.3**	Copy this value to Step 4 into the box labeled "Clinical Benefit Score". Continue with the instructions in Step 2. Skip 1.B., 1.C., 1.D., and 1.E.

As noted above, you would now skip to step 2, all the points that should be awarded in Step 1 have been awarded.

STEP 2

In the report by Van Cutsem et al the following table is found:

Table 3. Summary of the Most Frequent Adverse Events (incidence ≥ 20% or ≥ 5% higher in aflibercept arm), Other Anti-VEGF–Associated Events, and Most Frequent Biologic Abnormalities: Safety Population

	Placebo/FOLFIRI (n = 605)			Aflibercept/FOLFIRI (n = 611)		
Adverse Event*	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Any	97.9	45.1	17.4	99.2	62.0	21.4
Diarrhea (PT)	56.5	7.6	0.2	69.2	19.0	0.3
Asthenic conditions (HLT)	50.2	10.4	0.2	60.4	16.0	0.8
Stomatitis and ulceration (HLT)	34.9	5.0	—	54.8	13.6	0.2
Nausea (PT)	54	3.0	—	53.4	1.8	—
Infections and infestations (SOC)	32.7	6.1	0.8	46.2	11.0	1.3
Hypertension	10.7	1.5	—	41.4	19.1	0.2
Hemorrhage	19	1.7	—	37.8	2.8	0.2
Epistaxis	7.4	—	—	27.7	0.2	—
GI and abdominal pains (HLT)	29.1	3.1	0.2	34	5.1	0.3
Vomiting (PT)	33.4	3.5	—	32.9	2.6	0.2
Decreased appetite (PT)	23.8	1.7	0.2	31.9	3.4	—
Weight decreased	14.4	0.8	—	31.9	2.6	—
Alopecia (PT)	30.1	—	—	26.8	—	—
Dysphonia (PT)	3.3	—	—	25.4	0.5	—
Constipation (PT)	24.6	1.0	—	22.4	0.8	—
Headache (PT)	8.8	0.3	—	22.3	1.6	—
Palmar-plantar erythrodysesthesia syndrome	4.3	0.5	—	11.0	2.8	—
Other anti-VEGF–associated events						
Arterial thromboembolic event	1.5	0.5	—	2.6	0.8	1.0
Venous thromboembolic event	7.3	2.6	3.6	9.3	3.1	4.7
Fistula from GI origin	0.3	0.2	—	1.1	0.3	—
Fistula from other than GI origin	0.2	—	—	0.3	—	—
GI perforation	0.5	0.2	0.2	0.5	0.2	0.3
Biologic abnormalities						
Hematologic						
Anemia	91.1	3.5	0.8	82.3	3.3	0.5
Neutropenia	56.3	19.1	10.4	67.8	23.1	13.6
Neutropenic complications	3.0	1.7	1.2	6.5	4.4	1.3
Thrombocytopenia	33.8	0.8	0.8	47.4	1.7	1.7
Nonhematologic						
Proteinuria	40.7	1.2	—	62.2	7.5	0.3
ALT increased	37.1	2.2	—	47.3	2.5	0.2

Abbreviations: FOLFIRI, infusional fluorouracil, leucovorin, and irinotecan; HLT, high-level term; PT, preferred term; SOC, system organ class; VEGF, vascular endothelial growth factor.
*Grades were determined according to National Cancer Institute Common Terminology Criteria of Adverse Events, version 3.0.

In this case, we see that the grade 3 and grade 4 toxicities are reported separately, and there is no separate reporting of grade 1 and 2 toxicity. Therefore, some extra processing is necessary to calculate the toxicity score. The grade 3 and 4 need to be added together to determine the overall percentage,

and then this value must be subtracted from the all grade percentage to determine the grade 1 and 2 percentage. For example, diarrhea is listed as: All Grades 69.2%, Grade 3 19.0%, Grade 4 0.3%. Therefore, the diarrhea grade 3 and 4 percentage is 19.0% + 0.3% = 19.3%, and the grade 1 and 2 percentage is 69.2% - 19.3% = 49.9%. This must be done for all of the relevant toxicities.

This leads to the following tables in the worksheet. The experimental/new arm is aflibercept, the standard/control arm is placebo.

Step 2 – Toxicity Scoring

2. A. For each toxicity that has been identified, determine the percentage of patients in each arm that experienced a Grade 1 or 2 toxicity (G1-2) and the percentage of patients that experienced a Grade 3 or 4 toxicity (G3-4) of that type.

TABLE 1 – Experimental/New Treatment Toxicity

	Grade 1 and 2 percentage >=10%	Grade 1 and 2 percentage >0% and <10%	Grade 3 and 4 percentage >=5%	Grade 3 and 4 percentage >0% and <5%	
Toxicities (list out)	Diarrhea, Asthenic Conditions, Stomatitis, Nausea, Infections, Hypertension, Hemorrhage, Epistaxis, GI Pain, Vomiting, Decreased Appetite, Weight Decrease, Alopecia, Dysphonia, Constipation, Headache	Palmar-plantar Erhy. Syndrome, Arterial thromboembolic event, Venous thromboembolic event, Fistula from GI origin, Fistula from other than GI origin GI Perforation	Diarrhea, Asthenic conditions, Stomatitis, Infections, Hypertension, GI Pain, Venous thromboembolic event,	Nausea, Hemorrhage, Epistaxis, Vomiting, Decreased appetite, Weight decreased, Dysphonia, Constipation, Headache, Palmar-plantar erhy. Syndrome, Arterial thromboembolic event, Fistula from GI origin, GI Perforation	Total Experimental/New (Sum of Totals by Category)
Number of Toxicities	15	6	7	13	
Weight	1	0.5	2	1.5	
Total by Category (Number * Weight)	15	3	14	19.5	51.5

TABLE 2 – Standard/Control Treatment Toxicity

	Grade 1 and 2 percentage >=10%	Grade 1 and 2 percentage >0% and <10%	Grade 3 and 4 percentage >=5%	Grade 3 and 4 percentage >0% and <5%	
Toxicities (list out)	Diarrhea, Asthenic conditions, Stomatitis, Nausea,	Hypertension, Epistaxis, Dysphonia, Headache, Palmar-	Diarrhea, Asthenic Conditions,	Nausea, Hypertension, Hemorrhage, GI	Total Standard/Control (Sum of Totals by Category)

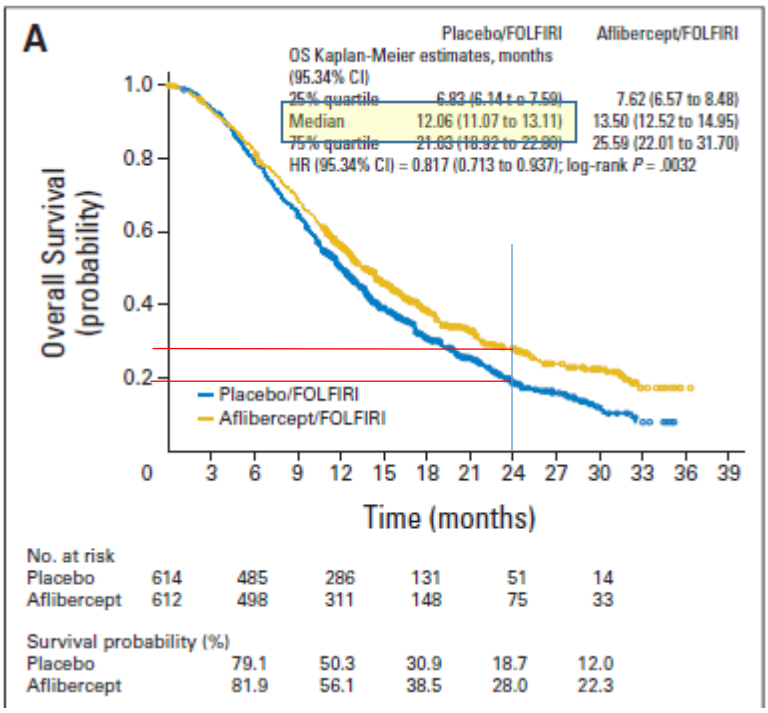
	Infections, Hemorrhage, GI pain, Vomiting, Decreased appetite, Weight decrease, Alopecia, Constipation	plantar eryth. Syndrome, Arterial thromboembolic event, Venous thromboembolic event, Fistula from GI origin, Fistula from other than GI origin, GI perforation	Stomatitis, Infections	pain, Vomiting, Decreased appetite, Weight decrease, Constipation, Headache, Palmar-plantar eryth. Syndrome, Arterial thromboembolic event, Venous thromboembolic event, Fistula from GI origin, GI perforation	
Number of Toxicities	12	10	4	14	
Weight	1	0.5	2	1.5	
Total by Category (Number * Weight)	12	5	8	21	46

2.C. Continue below.

TOXIC NEW	TOXIC CONTROL	
51.5	**46**	Divide TOXIC NEW by TOXIC CONTROL and write the result in Box 1
Box 1 **1.1196**		Subtract Box 1 from 1, and write the value in Box 2. This value will be negative if the toxicity on the experimental/new arm was generally worse.
Box 2 **-0.1196**		Multiply the value in box 2 by 20 and enter the value into Box 3.
Box 3 **-2.391**		If there are unresolved symptomatic treatment-related toxicities at 1 year after completion of treatment only on the experimental/new arm and not on the standard/control arm, subtract 5 from Box 3 and enter the result in Box 4. Otherwise, copy the value from Box 3 into Box 4.
Box 4 **-2.391**		If Box 4 is greater than 20 or less than -20 then put “20” or “-20” into the box labelled “Toxicity Score”. Otherwise, copy the value from Box 4 into “Toxicity Score”.
Toxicity Score **-2.391**		Copy this value to the box labelled “Toxicity Score” in Step 4. This value should be between -20 and 20, and negative if the toxicity was generally worse on the experimental/new treatment.

STEP 3

Returning to the diagram show in Step 1…



we see that the median overall survival in the control arm was 12.06 months. We know from the worked example for Step 1.A. that there was a significant difference in overall survival.

On this figure, a blue line has been drawn at at 24.12, twice the standard/control arm median overall survival. The red lines show the % remaining at those time points in each arm; ~19% on the standard/control arm and approximately ~27% Therefore the worksheet looks like this:

Step 3 – Bonus Points

Step 3.A. – Tail of the Curve Bonus

If no Kaplan-Meier curves are reported for overall or progression-free survival, go on to Step 3.B.

Record the median overall survival, or the median progression free-survival if overall survival is not reported, for the standard/control arm in Box 1.

Box 1 **12.06 months**	Multiple the value in Box 1 by 2 and record in Box 2.
Box 2 **24.12 months**	Locate the value in Box 2 on the time axis of the published Kaplan-Meier curve of overall (or progression-free, if appropriate) survival. Determine the OS or PFS at this time point for the standard/control arm and enter in Box 3. If this value is less than or equal to 20%, stop the calculation; no Tail of the Curve Bonus should awarded.
Box 3 **~19%**	Determine the OS or PFS for the standard/control arm at the same time point and enter in Box 4.
Box 4 **~27%**	If Box 4 is >= 1.5 times the value of Box 3, then enter 20 (if overall survival is being used) or 16 (if PFS is being used) in the box labelled “Tail of Curve Bonus”.

Tail of Curve Bonus **0**	Copy this value to the box labelled "Tail of Curve Bonus" in Step 3.B.

No treatment-free interval, quality of life, or long term symptom data are reported. Therefore, the rest of the Step 3 worksheet looks like this (transferring the tail of the curve bonus from above):

Step 3. B. Final Bonus Point Calcuation

Tail of the Curve Bonus **0**	Tail of the Curve Bonus was calculated in Step 3.A.
Trmt-Free Interval Bonus **0**	Treatment-Free Interval Bonus. If a statistically significant improvement in treatment-free interval is reported, multiply the percentage improvement in treatment-free interval by 20 and add points.
Palliation Bonus **0**	If a statistically significant improvement in any cancer-related symptom is reported only for the experimental/new arm, enter a 10 into the box labelled "Palliation Bonus", otherwise enter a 0.
QoL Bonus **0**	If a statistically significant improvement in quality of life is reported only for the experimental/new arm, enter a 10 into the box labelled "QoL Bonus", otherwise enter a 0.
Total Bonus Points **0**	Add together all four bonuses above (Tail of the Curve, Trmt Free Interval, Palliation, QoL) and enter the result into the box labelled "Total Bonus Points". Copy this value to the box labelled "Bonus Points" in Step 4.

STEP 4

Putting together all the information from the previous worked examples from the AFFIRM study, we have:

Step 4. Final Net Health Benefit.

Clinical Benefit Score **18.3**	The Clinical Benefit Score was calculated in steps 1.A., 1.B., 1.C., 1.D. or 1.E.

Toxicity Score **-2.391**	The Toxicity score was calculated in step 2. It will be negative if the experimental/new treatment is generally more toxic than the standard/control treatment, and will be positive if it is generally less toxic.
Bonus Points **0**	The Bonus points were calculated in step 3 and reflect the "tail of the curve", palliation, QoL, and treatment-free interval bonuses.
	Add the Clinical Benefit Score, Toxicity Score, and Bonus Points together and put the result into the box labelled "Net Health Benefit"
Net Health Benefit **15.909**	This is the Net Health Benefit (NHB) of the experimental/new treatment compared to the standard/control treatment.

The Net Health Benefit score for the Van Cutsem et al 2012 trial comparing aflibercept to placebo is 16, rounding to the nearest whole number.