**Appendix 3**

Grades of recommendation – Grading of Recommendations Assessment, Development and Evaluation System

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| Grade of Recommendation | Clarity of risk/benefit | Quality of supporting evidence | Implications |
| 1A.  Strong recommendation, high quality evidence | Benefits clearly outweigh risk and burdens, or vice versa. | Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. | Strong recommendations, can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present. |
| 1B.  Strong recommendation, moderate quality evidence | Benefits clearly outweigh risk and burdens, or vice versa. | Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate. | Strong recommendation and applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present. |
| 1C.  Strong recommendation, low quality evidence | Benefits appear to outweigh risk and burdens, or vice versa. | Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain. | Strong recommendation, and applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality. |
| 2A.  Weak recommendation, high quality evidence | Benefits closely balanced with risks and burdens. | Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. | Weak recommendation, best action may differ depending on circumstances or patients or societal values. |
| 2B.  Weak recommendation, moderate quality evidence | Benefits closely balanced with risks and burdens, some uncertainly in the estimates of benefits, risks and burdens. | Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate. | Weak recommendation, alternative approaches likely to be better for some patients under some circumstances. |
| 2C.  Weak recommendation, low quality evidence | Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens. | Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain. | Very weak recommendation; other alternatives may be equally reasonable. |