Appendix: Algebraic derivation of the models

Legend:

Target = target outcome that the treatment can prevent

Harm = any increase of an adverse outcome due to the treatment

CID = clinically important difference

ARR = absolute risk reduction

ARI = absolute risk increase

V = value

RV = relative value

1. Derivation of the simple model (one benefit, one harm)

The CID corresponds to the ARR for the target benefit sufficiently large to exactly offset the treatment harm. Allowing for a different value assigned to the target outcome prevented by the treatment and to the harm caused by the treatment (V_{target} and V_{harm}, respectively), the condition at the CID can be expressed algebraically as:

$$\mathbf{ARR_{target} * V_{target} = ARI_{harm} * V_{harm}} \qquad \mathbf{(1)}$$

1.1. Algebraic solution for the required $ARR_{benefit}$ to offset the treatment harm

Dividing each side of the equation (1) by V_{target}

$ARR_{target} = ARI_{harm} * V_{harm} / V_{target} \rightarrow$

$$\textit{required}\ \mathbf{ARR_{target} = ARI_{harm} * RV_{harm/target}} \qquad \mathbf{(2)}$$

1.2. Algebraic solution for the maximum ARI_{harm} above which treatment would not be justified

Dividing each side of the equation (1) by V_{harm}

$ARR_{target} * V_{target} / V_{harm} = ARI_{harm} \rightarrow$

$ARR_{target} * RV_{target/harm} = ARI_{harm} \rightarrow$

maximum $ARI_{harm} = ARR_{target} * RV_{target/harm}$

or, expressed in terms of $RV_{harm/target}$

maximum $\mathbf{ARI_{harm} = ARR_{target} / RV_{harm/target}}$ **(3)**

1.3. Algebraic solution for the maximum $RV_{harm/target}$ above which treatment would not be justified

$ARR_{target} = ARI_{harm} * V_{harm} / V_{target} \rightarrow$

$ARR_{target} = ARI_{harm} * RV_{harm/target}$

dividing each side of equation by ARI_{harm}

$ARR_{target} / ARI_{harm} = RV_{harm/target} \rightarrow$

maximum $\mathbf{RV_{harm/target} = ARR_{target} / ARI_{harm}}$ **(4)**

2. Derivation of the complex model (multiple benefits, multiple harms)

Legend:

Benefit = any reduction of an adverse outcome additional to the target outcome

At the CID, the sum of treatment benefits offsets the sum of treatment harms. Allowing for different values for every outcome prevented or caused by treatment, this can be expressed algebraically as:

$$\mathbf{ARR_{target}*V_{target} + ARR_{benefit(2)}*V_{benefit(2)} +\ldots+ ARR_{benefit(m)}*V_{benefit(m)} = ARI_{harm(1)}*V_{harm(1)} + \ldots+ ARI_{harm(k)} * V_{harm(k)}} \quad \mathbf{(5)}$$

where m is the total number of treatment benefits, the benefit(2) to benefit(m) are the benefits other than the target one, and k is the number of treatment harms. Or, likewise:

$$\mathbf{ARR_{target}*V_{target} + \sum_{(for\ j=2\ to\ m)} ARR_{benefit(j)}*V_{benefit(j)} = \sum_{(for\ j=1\ to\ k)} ARI_{harm(j)}*V_{harm(j)}} \quad \mathbf{(6)}$$

Subtracting $\sum_{(for\ j=1\ to\ m)} ARR_{benefit(j)}*V_{benefit(j)}$ from both sides and dividing both sides for V_{target}, we can obtain the required ARR_{target} such that the total treatment benefits offset the total treatment harms:

$$\mathbf{required\ ARR_{target} = \sum_{(for\ j=1\ to\ k)} ARI_{harm(j)}*RV_{harm(j)/target} - \sum_{(for\ j=2\ to\ m)} ARR_{benefit(j)}*RV_{benefit(j)/target}} \quad \mathbf{(7)}$$

where every RV is expressed as the value of that outcome, prevented or caused by the treatment, compared with the value assigned to the target outcome.