Chart, radar chart

Description automatically generated

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CALCULATING OVERTREATMENT DALYs:

This applies to the overtreatment branches: branches B & C (WHO) and branches K and L (NIRUDAK)

PART 1, YLL: **Deaths due to overtreatment** are now included

* The incidence is calculated using the 50/50 death/seizure split from the developing societies section of Figure 5 of the Fonseca et al. meta-analysis as discussed in the meeting (i.e., the incidence is now 0.02)

YLL = incidence of death x life expectancy at given age

= (0.02) (average life expectancy at patient age for that branch)

Branch B (WHO severe, actual some):

=(0.02)(42.13) = 0.8426

Branch C (WHO severe, actual no):

=(0.02)(31.82) = 0.6364

Branch K (NIRUDAK severe, actual some):

=(0.02)(49.65) = 0.993

Branch L (NIRUDAK severe, actual no):

=(0.02)(45.98) = 0.9196

PART 2, YLD: I incorrectly calculated the probability of **seizures** in two ways:

* Firstly, the incidence was wrongly calculated using the Sharifi et al. paper (I was using an incidence of 25% based a hypernatremic subset of the sample)
* Secondly, the DALY was multiplied by the number of people in the branch
* Both errors are corrected in this revised version
  + Seizure incidence values now calculated using the 50/50 death/seizure split from the developing societies section of Figure 5 of the Fonseca et al. meta-analysis as discussed in the meeting (we are using a 50/50 death/seizure split since the Fonseca article does not parse out death vs. seizure in its reporting of adverse events)
    - Incidence is now 7/419 or 0.02

YLD (Years Lived with Disability) = incidence x length of illness x disability weight

= (0.02)(0.003)(0.263)

= 0.000013

PART 3, SUMMATION:

DALYs = YLL + YLD

Branch B (WHO severe, actual some):

DALY = 0.8426 + 0.000013 = 0.842613

Branch C (WHO severe, actual no):

DALY = 0.6364 + 0.000013 = 0.636413

Branch K (NIRUDAK severe, actual some):

DALY = 0.993 + 0.000013 = 0.993013

Branch L (NIRUDAK severe, actual no):

DALY = 0.9196 + 0.000013 = 0.919613

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Therefore, the new ICER is:

negative sign preserves ICER interpretation (switches calculation from incremental DALYs to incremental DALYS averted)

Interpretation: using NIRUDAK over WHO means spending an extra $0.05 per DALY averted

More notes about calculation can be found in the Excel file attached to this email titled nirudak\_cea\_tree\_calculations.xlsx

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During a follow-up call, Jonah and I checked the total probability of overtreatment vs. undertreatment in the two models. NIRUDAK tends to overtreat while WHO tends to undertreat

* Undertreatment: WHO 0.061 > NIRUDAK 0.027
* Overtreatment: NIRUDAK 0.322 > WHO 0.274

Clinical question: which is worse? Overtreatment or undertreatment?

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Prior to this meeting, we had considered the alternative of using the average years of life lost based on Japanese life expectancy tables.

Per discussion in the meeting, we are keeping the Years of Life Lost (YLL) calculation (part of the DALY calculation) as is, since the NIRUDAK model takes age into account — we are not using average YLL based on Japanese life expectancy tables

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During a follow-up call, Jonah and I checked the ages of people in the undertreatment groups to make sure the DALYs weren’t being driven by age differences between the group of people who were undertreated by WHO and the group people who were undertreated by NIRUDAK. Per my recollection, these differences were either fine or Jonah planned to statistically account for the differences.

Undertreatment WHO:

Chart, histogram

Description automatically generated

Undertreatment NIRUDAK:

Chart, histogram

Description automatically generated