Safeguarding public health

Quantitative Assessment of Benefit – Risk across the Product Lifecycle

Andrew Thomson
17th May 2011

The views expressed are very much personal views of the presenter and do not necessarily reflect those of the MHRA / EMA

A little about me and why I think this is important

How statisticians could (and whether they should) get involved)

Implementing and evaluating benefit – risk models at the point of licensing

Interpreting models in light of new safety data

Statistical Assessor for 5 years at MHRA

Took part in pilot Decision Conference for a product

Now head the team of regulatory epidemiologists / statisticians in the post-licensing division

Benefit-Risk of medication is *the* #1 Topic of Conversation

- Example: Drugs given to patient after MI
- Side effects are clear and tolerated (just)
- No apparent benefit other than ‘being not dead’
- So why is the benefit-risk balance positive?
- *These decisions really matter to ordinary people*

Risk-Benefit is key, and will remain key, to making regulatory decisions, and the balance can (and does) change over time

Big drive to ‘use’ quantitative models

How, why and when they might be useful

No specific favouring of one method over others – important that this is being evaluated by independent experts.

(Personal Specific strong dislike of NNT / NNH)

Formally, MCDA not statistically complex. What value does the *statistician* add?

Is the statistician the best person to get involved? (in general, not ‘regulatory statistician’)

We have a good understanding of ‘numbers’

Model may be complex to clinical / other colleagues

Lots of experience at explaining things which are ‘simple’ to us to those to whom it is more ‘complex’

-trusting relationship is essential for effective decision conference

From a personal perspective, we see products across all indications work with every medical assessor

Understanding why you hold the views you do

Understanding where you sit on the benefit-risk spectrum (on the fence is not allowed!)

Linked to the above, how likely you might be to change your position

Understand what data at the point of licensing is, and potentially what data might make you change your mind

Facilitate internal (within Agency) communication

Facilitate between Agency communication – may be beneficial if many countries have differing views

Facilitate communication with Industry. Is it clearer than just saying ‘the risks outweighed the benefits’? By how much?

Facilitate communication with the outside world – is this a pipe dream?

Anything without weights lacks scientific rigour – anything with weights is subjective

Pick weights to ensure you get the answer you want

Could we define these *a prioiri*?

Efficacy – yes. Safety? We don't know what we're going to see, that's one of the problems / purposes of clinical research

What do we do if we see a common but 'not serious' AE we were not expecting?

Who does it? (Whatever the model / framework used)

Industry?

Regulators?

When? At submission for industry? First Report for regulators? As part of a discussion at Day 150?

Have we *truly* progressed if an argument about whether the risks outweigh the benefits is replaced by whether a weight of 0.8 or 0.75 is appropriate?

Allows the communication of why one is positive or negative *and* strength of that position

Include all relevant risks and benefits

Include (safety) data generated post licensing. Allows an ongoing risk : benefit decision to be made

Excellent ‘what if’ potential. What happens if we see rare but serious events post licensing – is our model robust?

It ‘seems’ intuitive for medical assessors

Easy to pick up, although time taken to do so may vary.

Whether how to do it is forgotten between products is unclear!

Comparison between products is possible. Comparative efficacy key for marketing departments / HTAs but not always for regulation

Requires communicatee to understand MCDA

Weights to fit the decision arbitrary (not unique to MCDA)

To do it properly may require facilitation and a lot of time – a precious regulatory commodity

When do you do it? If every country is clearly positive do we need this exercise at licensing – emerging signals?

Swing weight definition – key variable

Do we need to do it? – Abiraterone Case Study

	Abiraterone	Placebo
Patients randomised	797	398
Death	333 (41.8%)	219 (55.0%)
Censored	464 (58.2%)	179 (45.0%)
Overall Survival (days)		
Median (95% CI)	450 (430, 470)	332 (310, 366)
Log-rank p-value (stratified)	< 0.0001	
Hazard ratio (95% CI)	0.646 (0.543, 0.768)	

The overall efficacy results of the study are considered clearly positive. The primary endpoint is very relevant to the patient and the magnitude of the observed effect (HR=0.646 interim analysis; HR=0.740 updated analysis) is considered clinically significant. In addition, all the other efficacy endpoints show very consistent results

Abiraterone - Safety

	Placebo COU-AA-301 (N=394)	AA COU-AA-301 (N=791)
Treatment-Emergent Adverse Events (TEAEs)[a]	390 (99.0%)	782 (98.9%)
Drug-related[b]	303 (76.9%)	604 (76.4%)
Grade 3-4 TEAEs	230 (58.4%)	431 (54.5%)
Drug-related[b]	74 (18.8%)	161 (20.4%)
Serious TEAEs[a]	163 (41.4%)	297 (37.5%)
Drug-related[b]	39 (9.9%)	70 (8.8%)
Grade 3-4	139 (35.3%)	254 (32.1%)
Drug-related Grade 3-4[b]	31 (7.9%)	60 (7.6%)
TEAEs Leading to Abiraterone Acetate/Placebo Discontinuation	88 (22.3%)	148 (18.7%)
Drug-related[b]	23 (5.8%)	38 (4.8%)
TEAEs Leading to Death	58 (14.7%)	92 (11.6%)
Drug-related[b]	10 (2.5%)	4 (0.5%)

The safety profile of abiraterone acetate is considered acceptable and generally manageable with basic medical interventions. Toxicities were generally mild, and resulted in infrequent dose reductions, dose interruptions, or discontinuations.

Allows a conversation

May not always be necessary

Difficult to see how one can make it optional without overcoming pre-specification issues

Model might be useful to consider emerging safety

Uncertainty about risks often still quite great

Rare Events

Post-Authorisation Commitments

Spontaneous Reports

Well known that the effectiveness in the market is not the same as efficacy in trials. What about Safety?

Integrating Efficacy and Effectiveness data

When measuring the same endpoint
When measuring different endpoints (e.g. long term efficacy)

Longer term data may not be available for all treatments, and may not be controlled

Incorporating new emergent signals

MCDA should do this easily

Defining the weight is always *post hoc*. Is this acceptable?

Incorporating updated safety information, e.g. long term safety

What weights to use?

How do we account for data *quality*?

Personal opinion: Not sufficient to just put wider uncertainty bounds around the data

Weight for ‘cardiac events’ was 0.6 at time of license

New data from observational data suggests slightly higher risk than before.

Create 2 outcomes with weights that total 0.6, so say weigh the trial data as 0.5, observational data as 0.1

Sensitivity analyses on these combined weights to see effect on decision

What about the lack of placebo / active control?

Case Control Studies produce relative risks

Regulatory Decision making is often (usually?) about absolute risks

Underlying rate of outcome may be:

- unknown
- uncertain
- variable depending on baseline characteristics

How do we reliably turn that in to risk difference measures with appropriate uncertainty?

More nuanced regulatory decisions

At Licensing, SmPC is agreed. Licensing is binary decision

Pot-Licensing Regulatory action may not be. i.e. adding in a warning to ensure ‘appropriate use’

Aim is to minimise adverse event profile

What values do we use in our model?

Benefit-Risk decision making is changing

It can and does help – although can be resource intensive

Targeted Assessment – Targeted Inspections – Targeted Risk : Benefit analyses? At the cost of pre-specification?

Unclear whether statisticians are the best people to *facilitate* it, but we may end up doing it nevertheless

Lots more work needs to be done, especially post-licensing (and is being done!)

Thanks

Any Questions?