Safeguarding public health

What would convince me?
That we may not need a TQT study

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The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to the organisations I work with..(MHRA/CHMP).

First, let us look at what is needed?

Mechanism

Magnitude of effect

Applicability

Confidence

What are we looking for?!

Mechanistic information

- hERG & /or Ion channel
- hERG trafficking
- Margin to clinical dosing

Magnitude of effect

- is it proportional ?
- does extrapolation work?

Early phase studies;

- C-QT relation (yes/ no)
- Concentrations clinically seen
- number of doses tested..

Metabolism/ metabolites

- Pathways--interactions
- do metabolites contribute

Hysteresis

Do we know the mechanism

Others;

If C-QT-R is not shown....what and where is the maximum effect.

Assay sensitivity

Pilot analysis (of Sci Adv)

	2006	2007	2009	2010
TQT Qs	18	50	34	38
TQT need Identified	4	6	4	4
TQT or data inadequate	7	5	2	2
Exemptions sought	6	10	6	8

Experience with MAAs

- ~55 MAAs reviewed by the QT subgroup (since 2010)
- Between 2006-2008
- Relation between Non-clin and Clin data is limited
  - Many reasons
  - Mainly because study aims were disparate

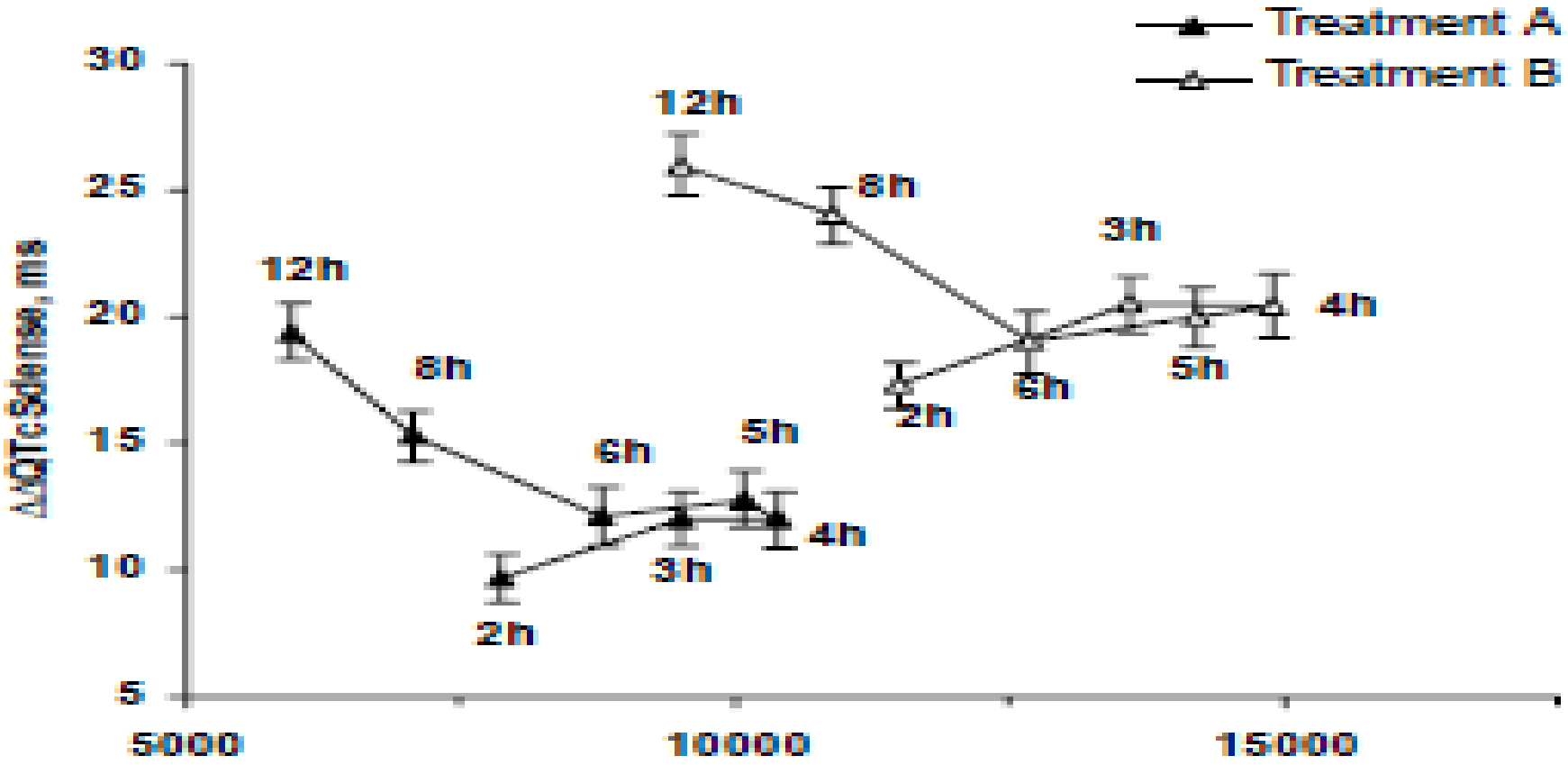
Lessons/Notes from this analysis

- approach to the issue & tQT **varies**
- In some, poor choice of dose for tQT

  E.g., relation of dose chosen to IC50,
- External influences not investigated

  autonomic tone, metabolic disturbances
- HR correction methods vary but improving
- Few have investigated effect on hERG channel traffic
- Little detail on other homologous channels

Challenge
Defining Hysteresis adequately



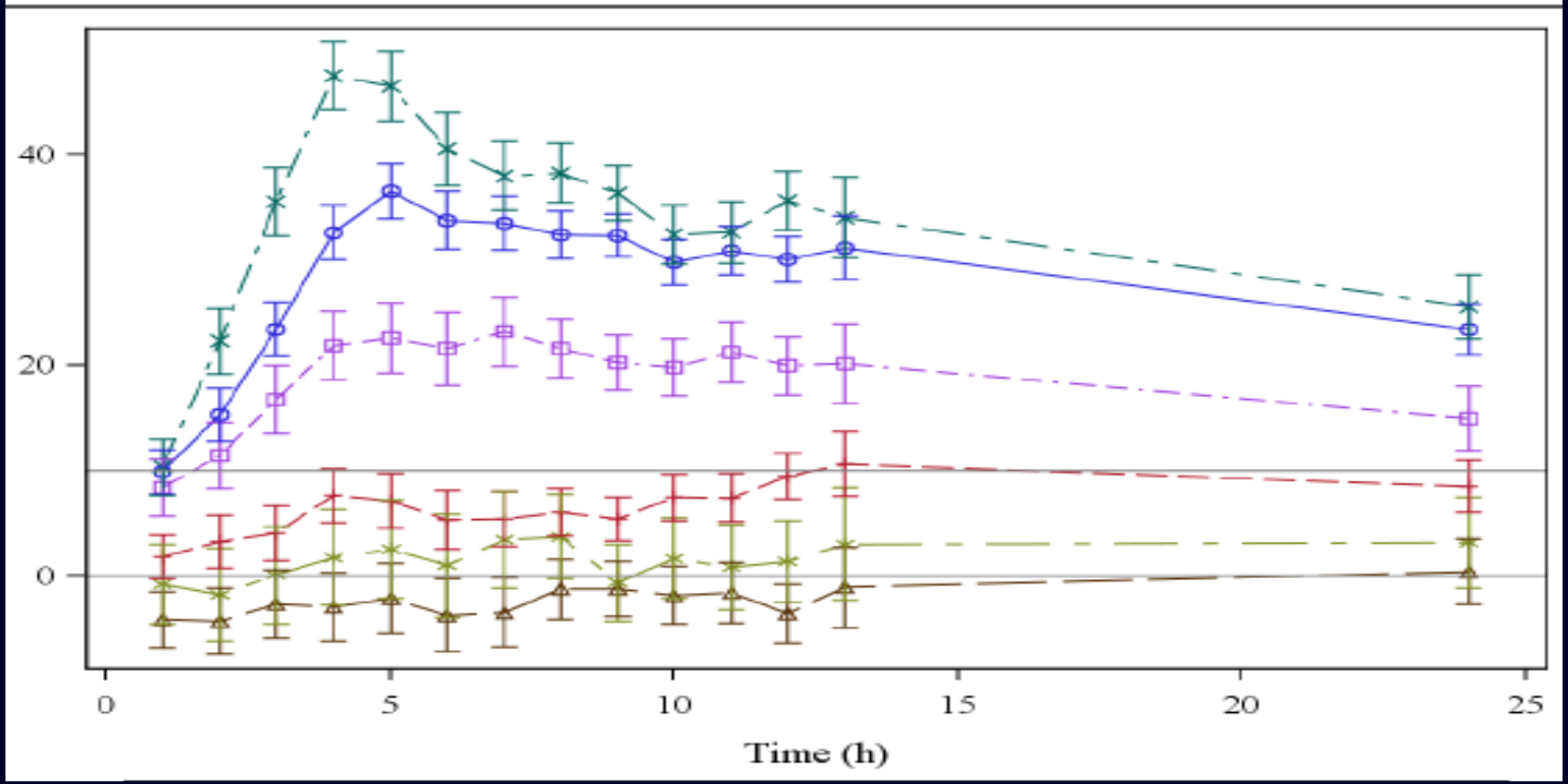
- Clear time delay between C max and Max QT effect

Reasons ???

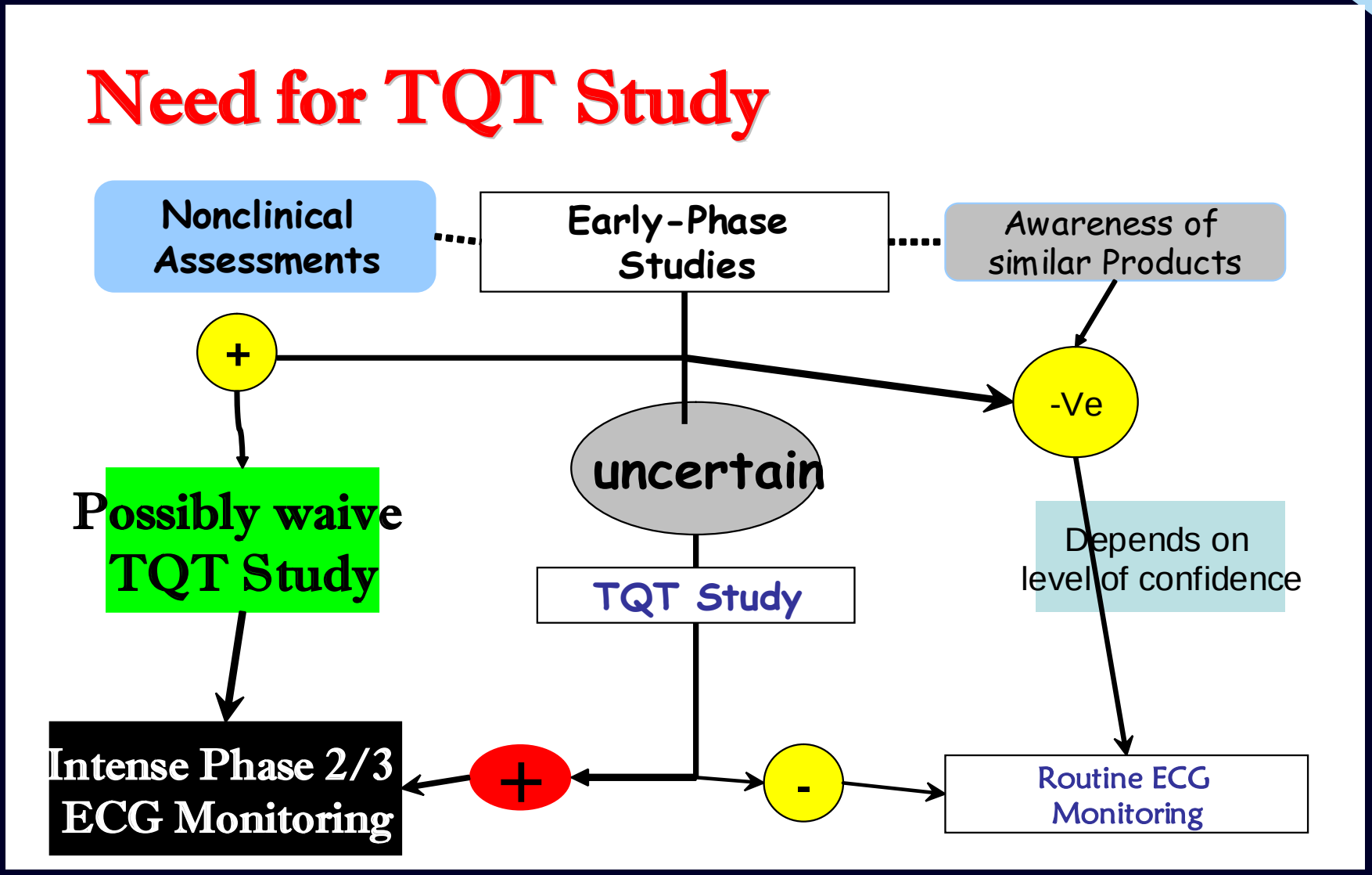
Challenge -2

Defining the effect adequately (food effect?!)

.1 - 2 Estimate of treatments effect over time on time-matched changes in QTcF
licate ECG analysis set



Decision tree;



Finally: Summarising,

Tell me a consistent, flowing story..
I will leave the specifics to the authors...

Thank you..

Another personal but common view

I consider the non-clinical data important, because there is no convincing evidence of a clinical QT prolongation when preclinical data have excluded the mechanistic aspects. If this preclinical absence of an effect is confirmed by ECG monitoring in the phase I studies, I would be convinced that a TQT study is not warranted.

On the other hand, if a clear QT-prolongation is present in these studies, at least in therapeutic dosages, and a mechanism is confirmed by preclinical data, I would focus on the clinical phase III data and a TQT study would not really contribute.

So only in case of doubts preclinically or when the quantification of the clinical effect is unclear, in particular in relation to the dose that will be applied in the phase III studies, a TQT study would contribute to the B/R assessment.

Categorical analysis of maximum time-matched actual values and maximum time-matched changes from baseline for QTcF

QTcF (ms)	Comb-C low-Kcal (-60)	Comb- R (N-60)	PBO (Grp 3) (N-40)	Combi-C high-Kcal (N-400)	Combi-C fasting (N-40)	PBO (Grp 6) (N-20)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Actual values						
›450 ms	12 (18.8)	2 (3.1)	0 (0.0)	9 (22.5)	4 (10.0)	0 (0.0)
›480 ms	3 (4.7)	0 (0.0)	0 (0.0)	3 (7.5)	0 (0.0)	0 (0.0)
›500 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Changes from baseline						
›30 ms	47 (73.4)	5 (7.8)	0 (0.0)	24 (60.0)	26 (65.0)	0 (0.0)
›60 ms	10 (15.6)	0 (0.0)	0 (0.0)	14 (35.0)	0 (0.0)	0 (0.0)