Improving trial methodology: Examples from epilepsy

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This talk

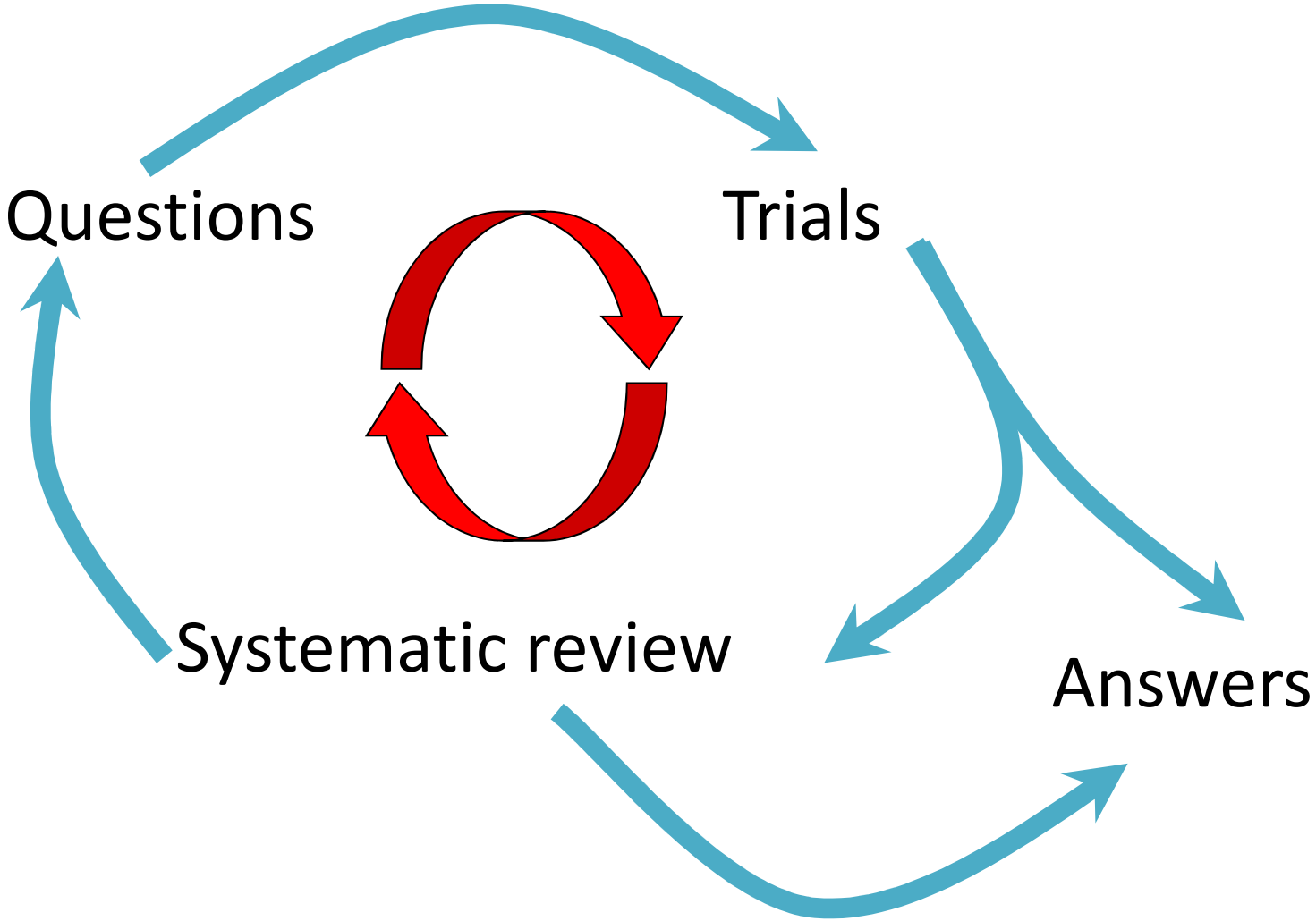
- Examples of trial methodology research
- Focus on epilepsy…… but
- Examples are relevant to any field

Epilepsy

- Manifests with spontaneous epileptic seizures
- Chronic condition
- Heterogeneous
  - Multiple differing seizure types
  - Multiple epilepsy syndromes
  - Aetiology
    - Genetic  symptomatic
  - Outcome
    - Good  bad
    - Numerous outcomes to consider

Example 1.
Network meta-analysis

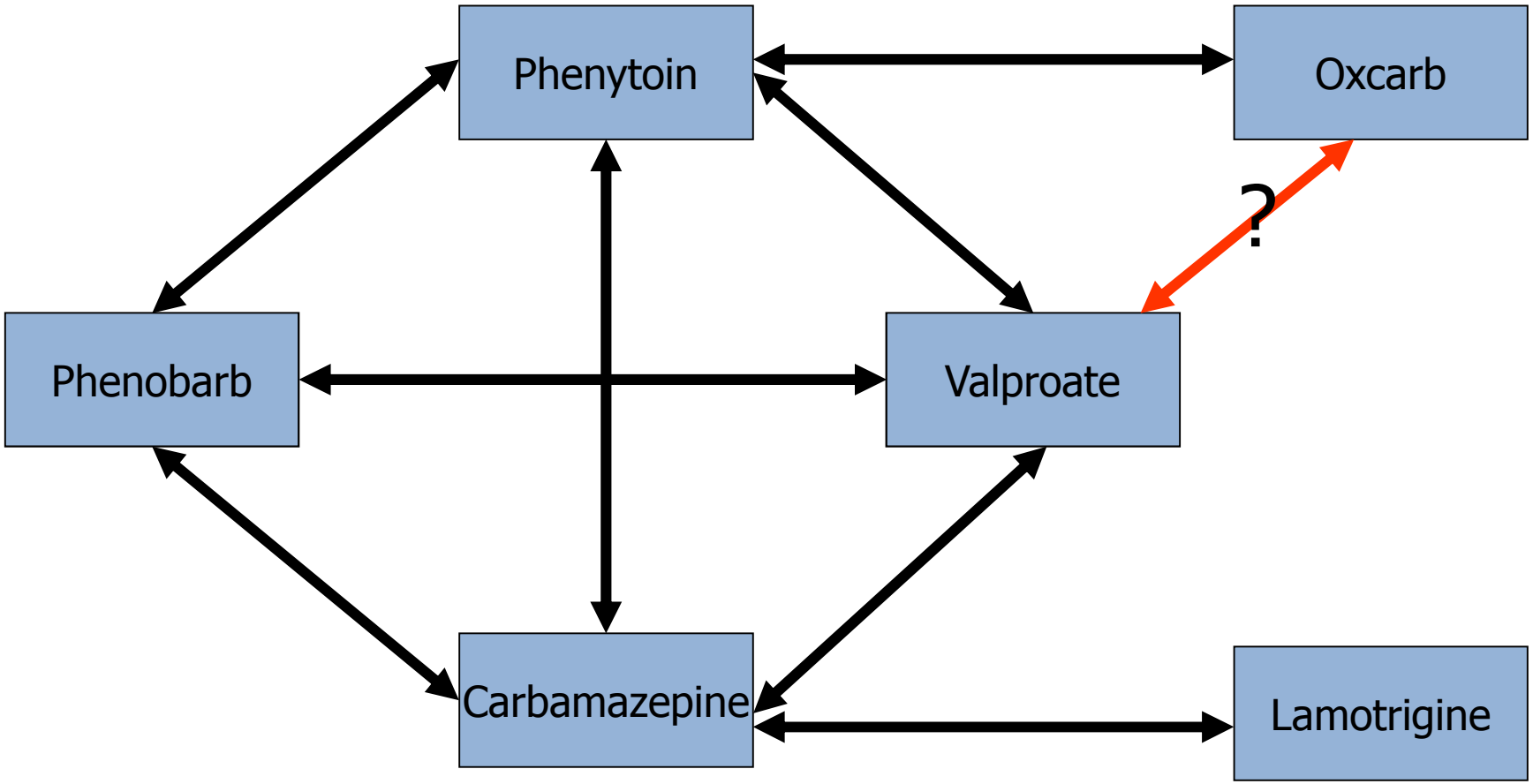
The Systematic Review / trial Cycle



Network meta-analysis

- We need a summary of evidence about the effects of available treatment options to inform
  - Questions and trial design
  - Treatment policies
- For epilepsy monotherapy (first line therapy)
  - Multiple treatment alternatives
    - Not all alternatives have been compared head to head
  - Time to event outcomes - e.g. time to 12 month remission, time to treatment failure
    - Meta-analysis requires individual patient data approach.

Network of 18 RCTs, 4500 patients



Trials

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Multiple treatment comparisons in epilepsy monotherapy trials

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Time to treatment failure

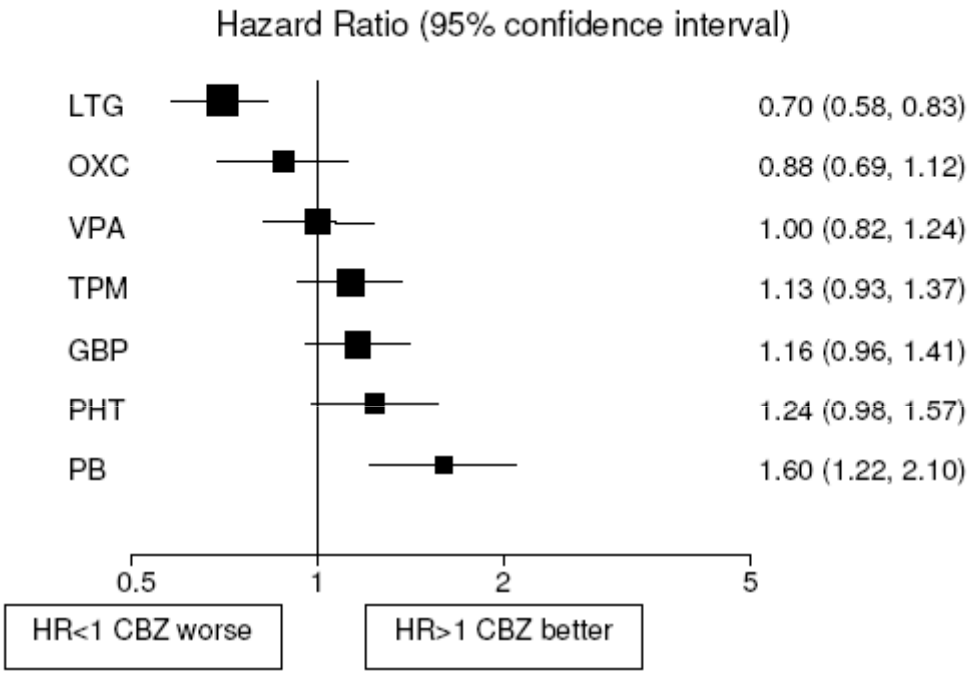


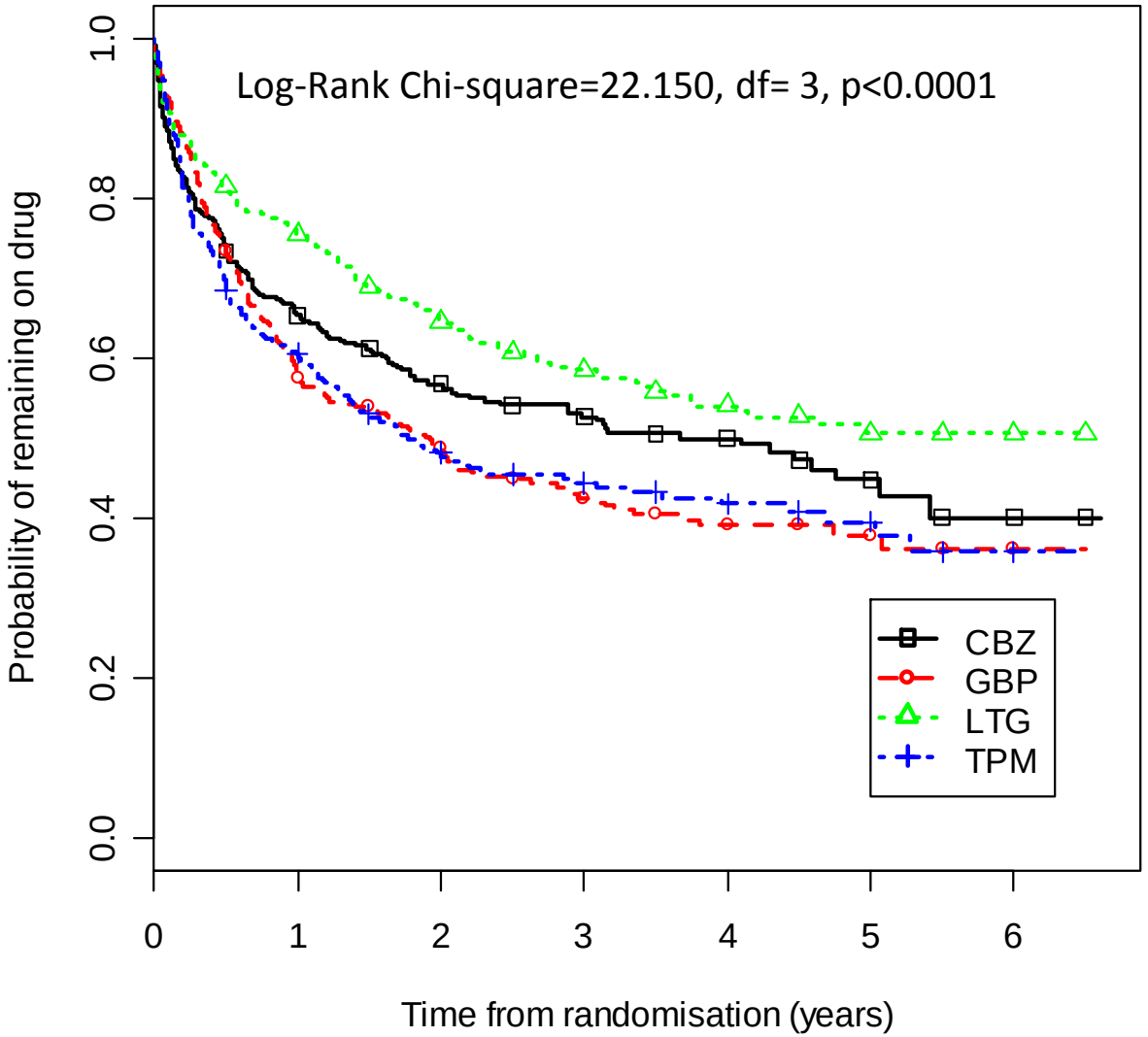
Figure 1
Time to treatment failure for partial onset seizures (Hazard Ratio for each AED compared to standard CBZ). **CBZ**: Carbamazepine, **VPA**: Sodium Valproate, **PHT**: Phenytoin, **PB**: Phenobarbitone, **LTG**: Lamotrigine, **OXC**: Oxcarbazepine, **GBP**: Gabapentine, **TPM**: Topiramate

Example 2.
Competing risks for treatment failure

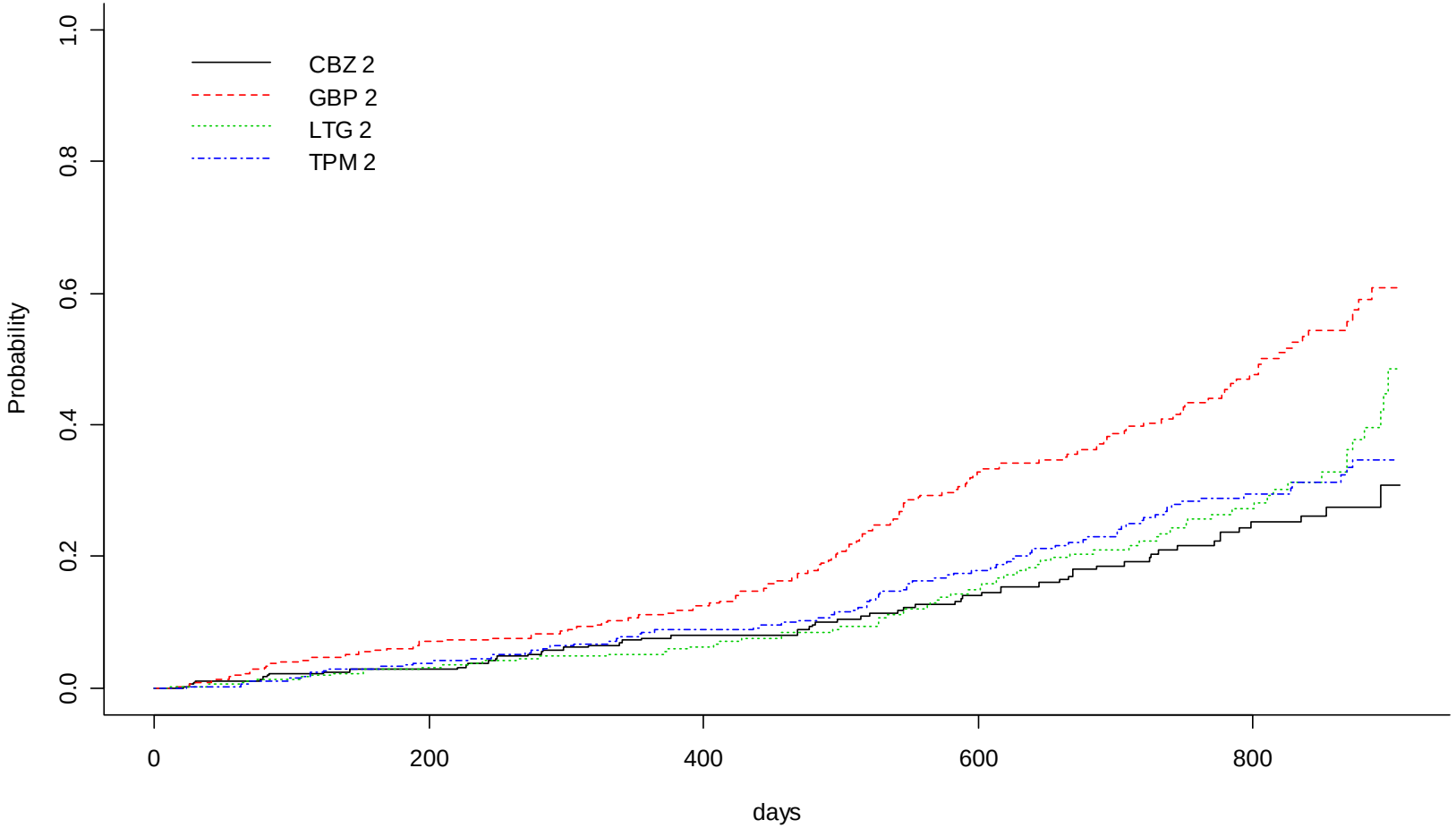
Time to treatment failure

- Primary outcome for antiepileptic drug monotherapy studies recommended by ILAE
- Treatment fails due to
  - Lack of efficacy
  - Adverse effects
- Provides overall measure of a treatments effectiveness
- Analysis of time to treatment failure for any reason can use traditional survival methods – eg Cox
- Estimating risk of failure for a specific reason (eg lack of efficacy) needs to take competing risks of failure into account
  - Can’t just censor patient with failure for alternative reason
  - Develop competing risk approach

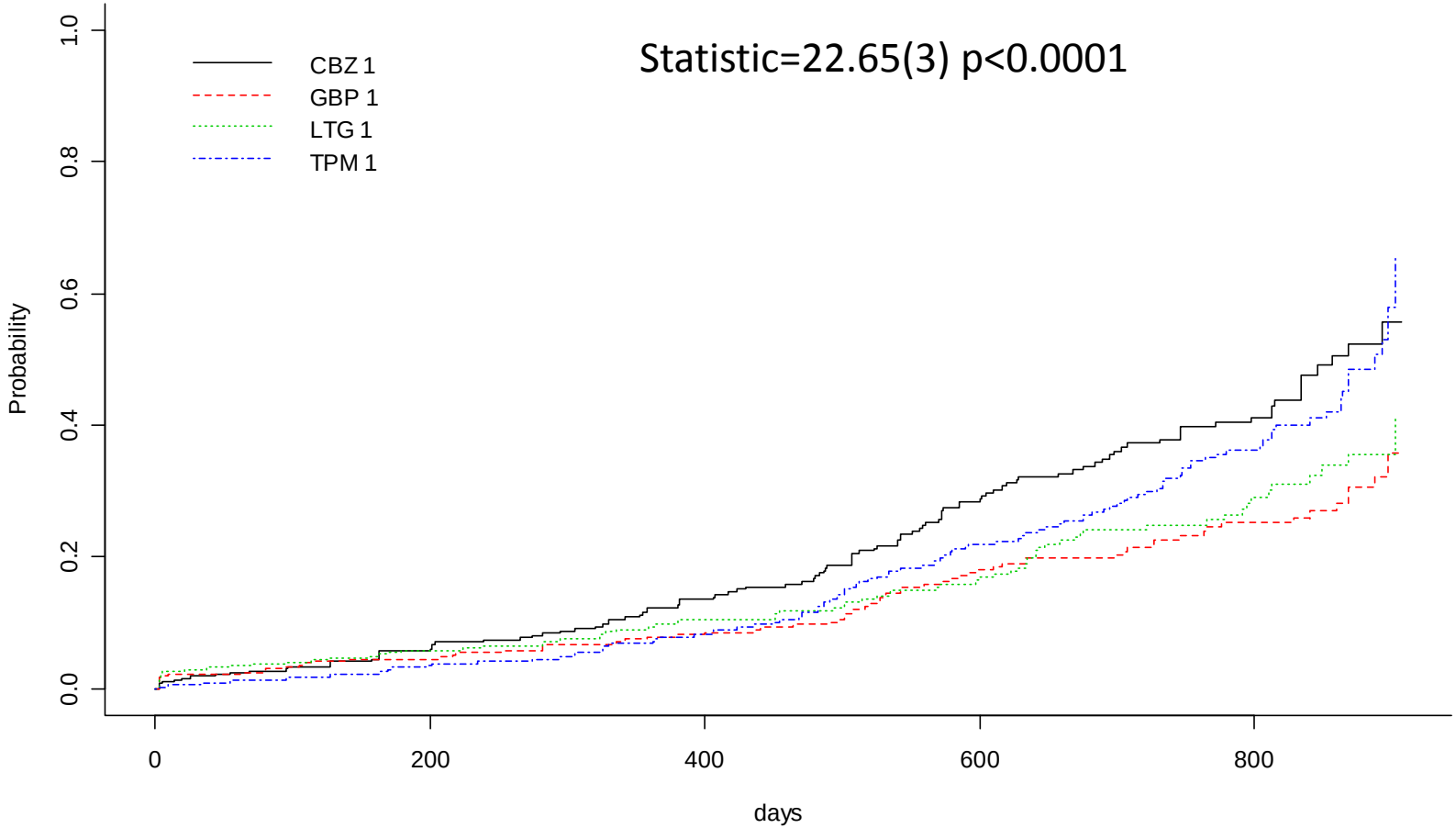
Time to treatment failure
Intention to treat



Time to treatment failure for inadequate seizures control

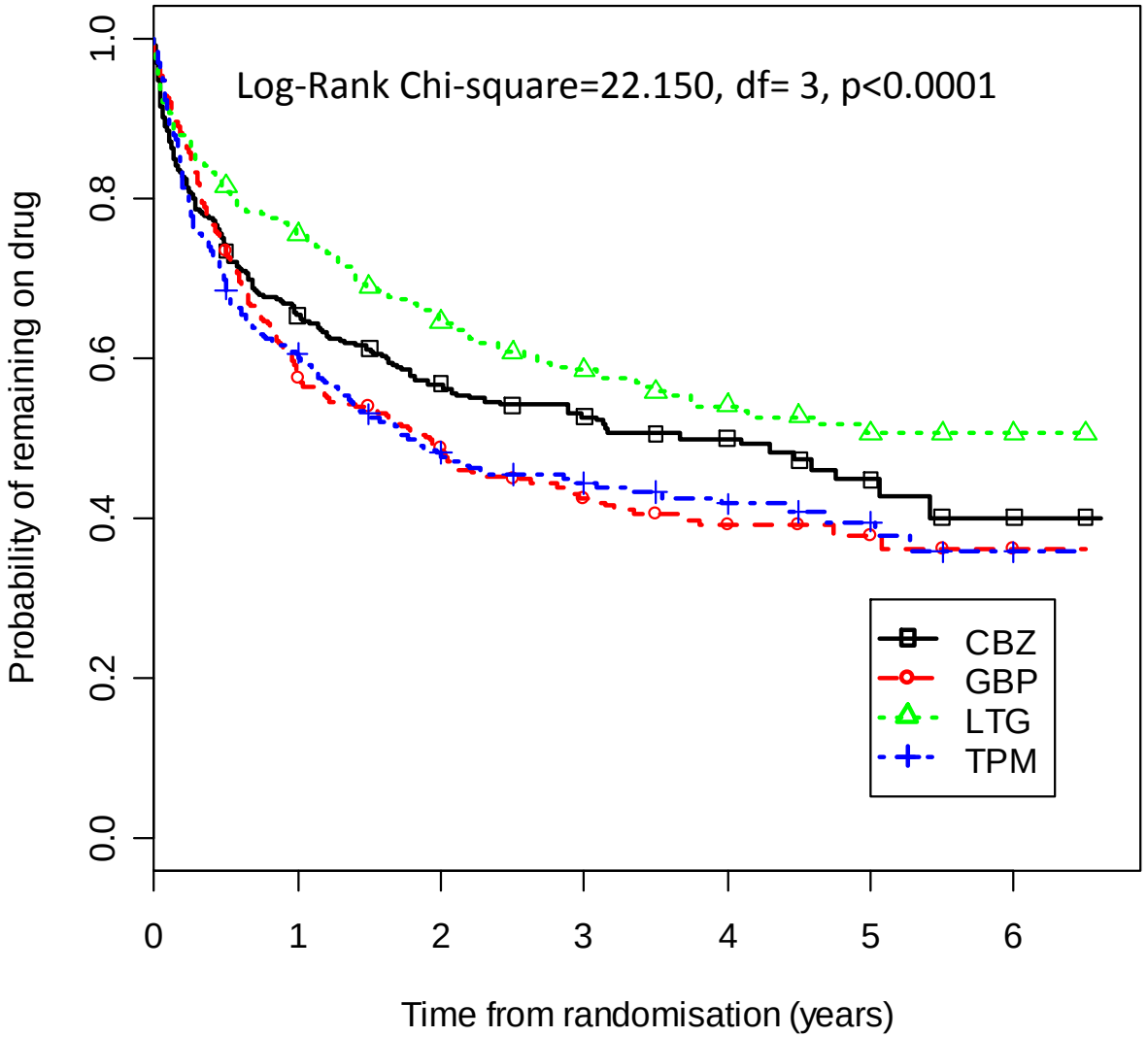


Time to treatment failure for unacceptable adverse events



Example 3.
Joint modelling

Time to treatment failure
Intention to treat



Time to treatment failure

- Drugs have differing titration rates
  - Carbamazepine 4 weeks
  - Lamotrigine 6-8 weeks
- Initial maintenance doses might not be equivalent
- Has this biased results in favour of lamotrigine?
- Explore using joint modelling approach

Joint modelling

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Joint modelling of longitudinal and competing risks data

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- Analysis calibrated for dose
- Lamotrigine still preferred – probably more so

Joint modelling

- See Ruwanthi Kolamunnage-Dona's poster

Example 4.
Predictive modelling

The epilepsies are heterogeneous

- Can we identify patient characteristics that influence overall treatment outcome?
- Can we identify patient characteristics that influence outcome with specific treatments?

- For patients with a generalised epilepsy, SANAD shows that valproate is superior for seizure control compared to lamotrigine or topiramate.
- Are these results consistent across epilepsy types?
  - Absence epilepsies
  - Juvenile myoclonic epilepsy
  - Etc
- Answers
  - Overall outcome differs among epilepsy syndromes
  - Valproate remains the preferred treatment

Predictive modelling

- Informs
  - Prognostication
  - Treatment policy
  - Trials design
    - Lumping versus splitting
  - Regulatory decisions
    - Assay sensitivity and the FDA / EMEA
- See Laura Bonnett’s poster

Example 5
Understanding and defining equivalence

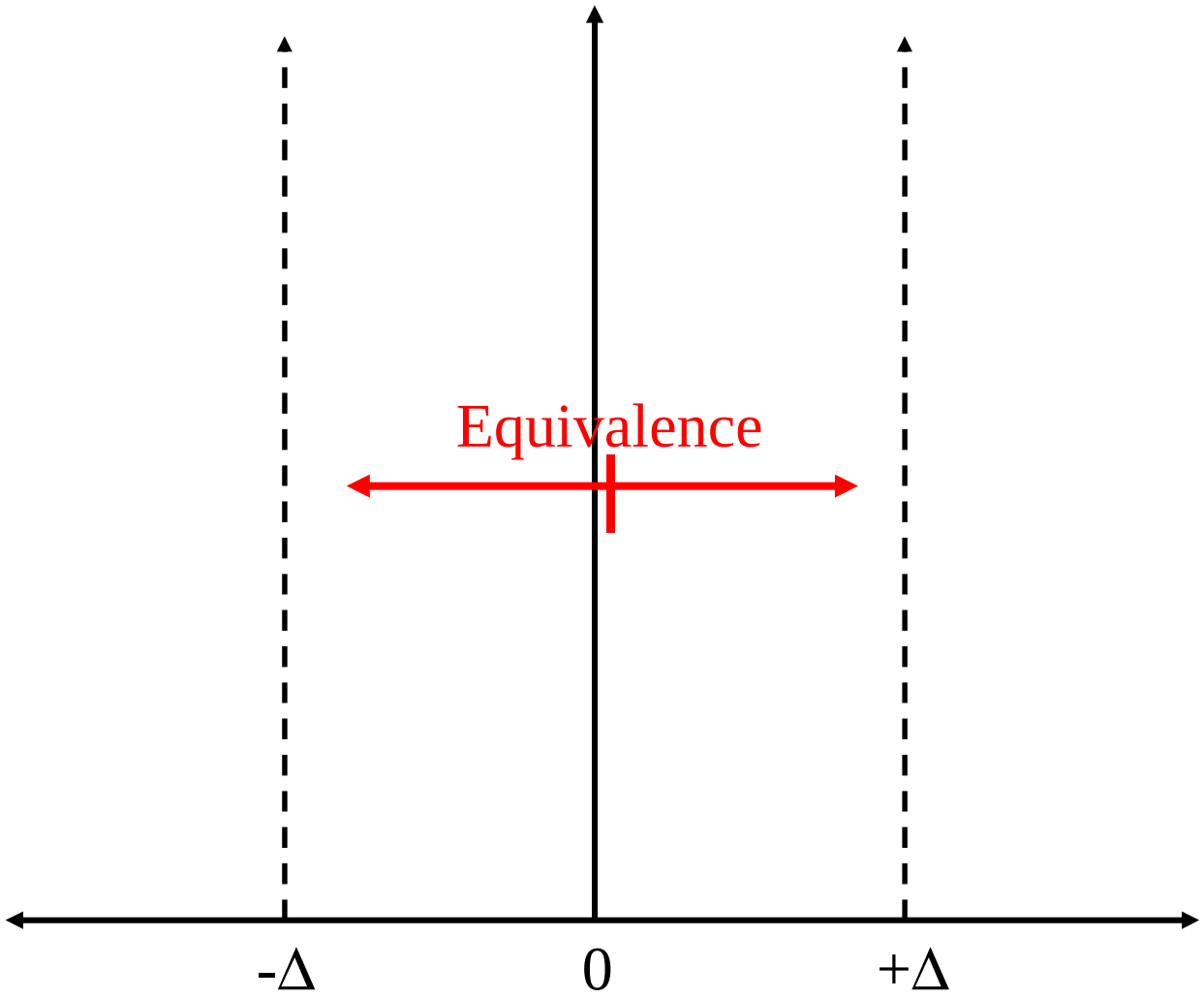
Equivalence and antiepileptic drugs

- A new drug might be useful if it is
- Equivalent to a standard drug for seizure control
- And
- Better tolerated than a standard drug

Equivalence for seizure control

- Time to 12 month remission is the recommended outcome
- To infer equivalence we need to exclude the possibility of an important difference between treatments
- ILAE has a definition for equivalence assuming smallest important difference is 10% absolute difference

Equivalence



Choice of Δ

- Is the ILAEs choice of Δ reasonable?
- Is this definition acceptable to
  - Patients?
  - Clinicians?
  - Other stakeholders?
- Assess in discrete choice experiments
  - Identify reasonable value of Δ
  - Assess trade offs between benefit and harm

Example 6
Estimating quality adjusted life years

SANAD identified lamotrigine as likely to be cost effective compared to carbamazepine

Costs per QALY	Gabapentin	Lamotrigine	Topiramate	Oxcarbazepine*
£10,000	0·04	0·42	0·20	0·69
£30,000	0·31	0·82	0·47	0.86
£50,000	0·41	0·89	0·54	0.89

- QALY's estimated with EQ-5D

EQ-5D

- Generic tool
- Can be used across health fields
- Generic tools do not have face validity or sensitivity for every disease area

EQ-5D?

Mobility
I have no problems in walking about
I have some problems in walking about
I am confined to bed

Self-care
I have no problems with self-care
I have some problems washing or dressing myself
I am unable to wash or dress myself

Usual activities (e.g. work, study, housework, family or leisure activities)
I have no problems with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities

Pain/Discomfort
I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort

Anxiety/Depression
I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed

Developing an epilepsy QALY tool

- Collaboration with John Brazier, Sheffield
- Utilising Liverpool Quality of life battery
- Use psychometric methods to identify questions for tool
- Interview general public to assign utilities to health states
- Interview people with epilepsy also
- Tool can then be used in health economic analyses

Conclusion

- Methodological research can improve the design, analysis, delivery and implementation of trials

- Examples in this talk were from epilepsy, but the issues are generic and relevant to all health fields