Making progress in rare tumours

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Background

- Typical Phase III trial
  - Years of investment
  - Intellectual, practical, financial
  - 5 to 10 years from idea to result

- But high chance of new treatment not better
  - 30-40% success rate
  - True for academia and industry

- Takes many decades to make progress

Context

- Whatever study you do you are likely to spend many, many years of your life doing it

- Maximise the chance of making progress

- Concentrate on superiority trials
  - Improve major outcomes

- Randomise

How are you most likely to improve outcomes?

- Patient population
  - E.g. early rather than advanced disease?

- Do not do a study comparing tweddledee vs. tweedledum
  - Make research and control arms as different as possible

- Given that phase III trials in oncology have a ~40% ‘success’ rate, consider more than one research arm

How should we approach trial size?

- What is the largest study that can be done in a reasonable timeframe?
  - Few 10s
  - ~100
  - Few 100s
  - Many 100s
  - 1000s

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- Three parameters you can ‘play’ with
  - Targeted treatment effect
  - Power
  - Type I error/significance level

- One of these has to ‘give’

Targeted Treatment effect

- Don’t expect too much
- For many cancers a hazard ratio of around 0.75 is the best we can expect
  - Except perhaps when we are dealing with advanced disease
- Don’t compromise on this!

Power

- If a new treatment is truly effective then we want to a good chance of detecting that difference

- Don’t compromise on power (80% or 90%)

Significance level

- Typically set at 5%
- However, there may be arguments for relaxing this in specific situations
  - particularly, if there is external evidence
- Need to think through the consequences of doing this…

Relaxing the type I error

- Increase the chance of saying there is a difference when in truth there is no difference
  - 5%- 20%

- This can be justified when
  - Limited numbers of patients can be entered
  - Insisting on 5% means that the trial is just not possible
  - Secondary outcome measures support the primary outcome measure
  - External evidence

- Need to consider the consequences
  - Is the toxicity sufficiently worrisome to be more concerned about making a type I error
  - Will routine use of the new therapy mean that testing further therapies will be particularly challenging

Relaxing the significance level

- Depends on the # of patients and # of events

- One possible approach

Sample Size	Possible type I error
10s	20%
100	15%-20%
Few 100s	10%-15%
Many 100s	5%-10%
1000+	5%

How ambitious can you be?

- Example: Osteosarcoma

- We have not made progress in this disease since introduction of chemotherapy more than 40 years ago…

Large-scale rare disease randomised trials are feasible: EURAMOS-1

Osteosarcoma = rare disease

:: <5/10,000 cases/yr

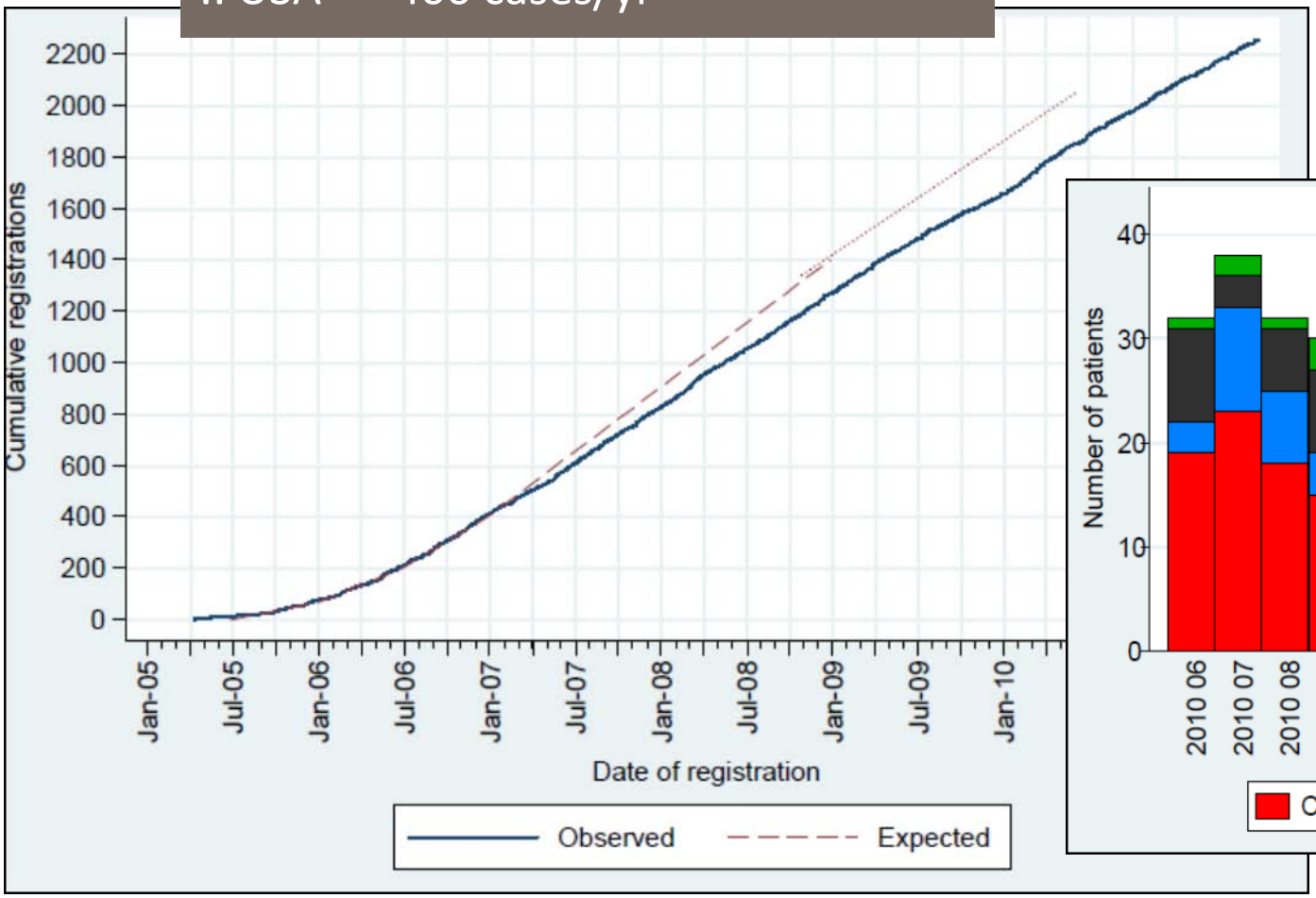
:: UK = ~150 to 200 cases/yr

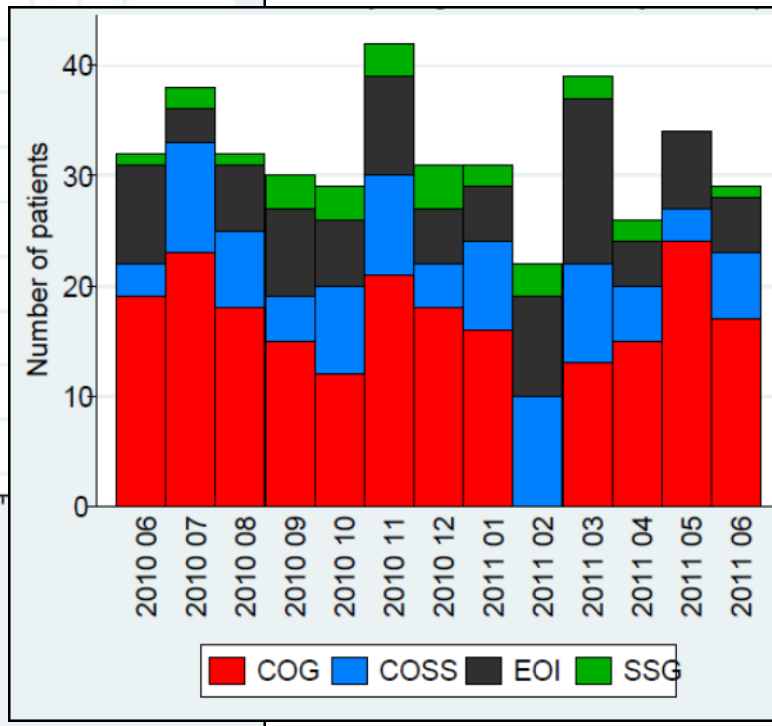
:: USA = ~400 cases/yr

2260 patients

~6 years

>300 hospitals



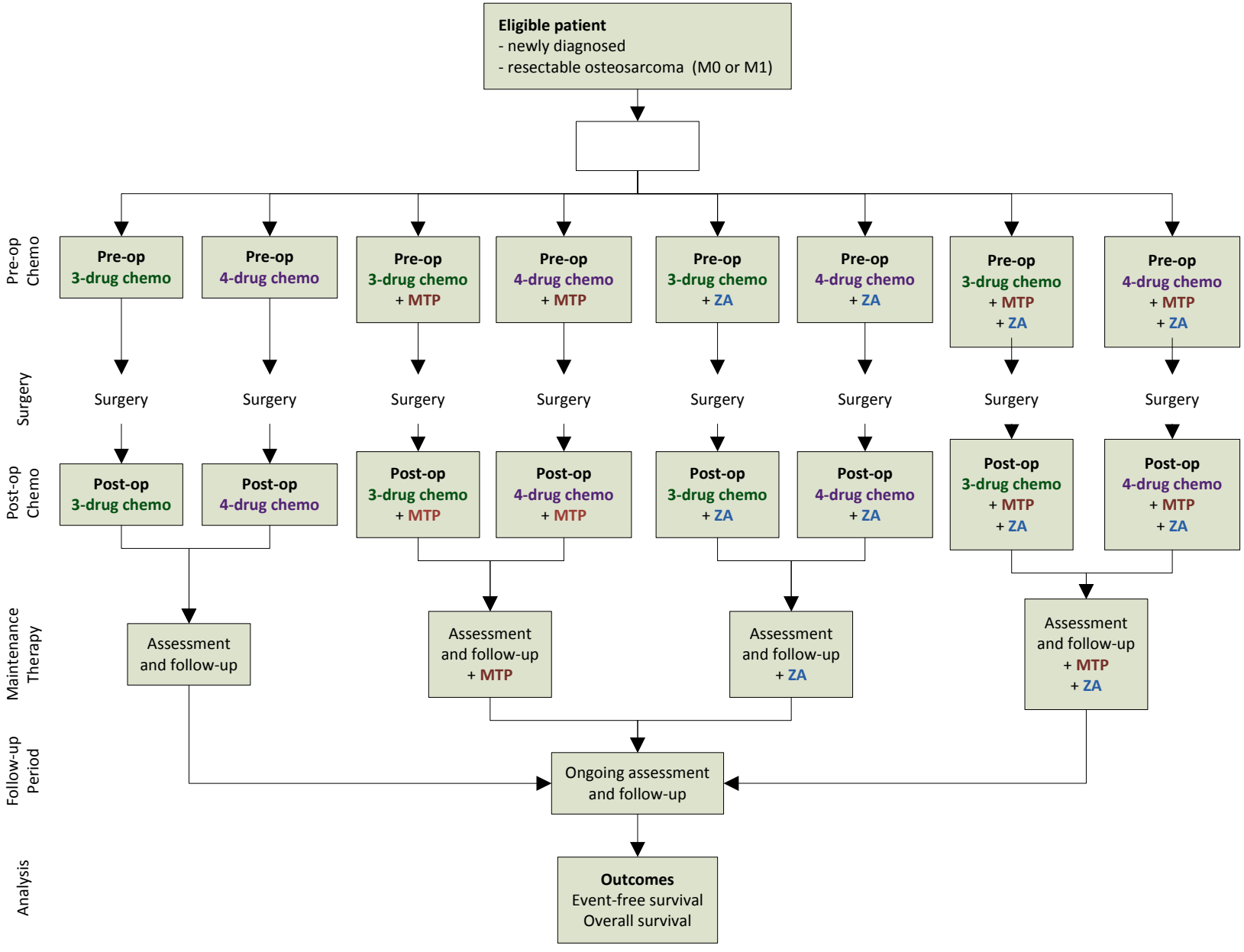


EURAMOS Strategy Group Meeting

- Set priorities for next trial
  1. Mifamurtide (MTP)
  2. Zoledronic acid
  3. Chemotherapy backbone (3 or 4 drugs)

- Other points
  - Continue and expand collaboration
  - Explore innovative approaches to trial methods

Multi-arm, Multi-stage design for potential trial



Multi-arm, multi-stage design for potential trial

- Assess important questions on 3 drugs
  - Including combinations

- ~2,000 patients required → just like EURAMOS-1
  - Even if all research arms better than control
  - 400 pts/yr accrual
  - 5.0 yr accrual

- Results on Event-Free Survival in 6.5 yr
  - 1.5 yr follow-up

- It is hoped that this trial (or a similar) one will be agreed by all groups soon

Conclusions: Trials in rare tumours

- Have to be driven by what is feasible
- Should not use this as an excuse to limit ambition
  - Consider a multi-arm, multi-stage trial
- However, in situations where only limited sized trials are possible
  - Use a relaxed significance level

Summary – 2

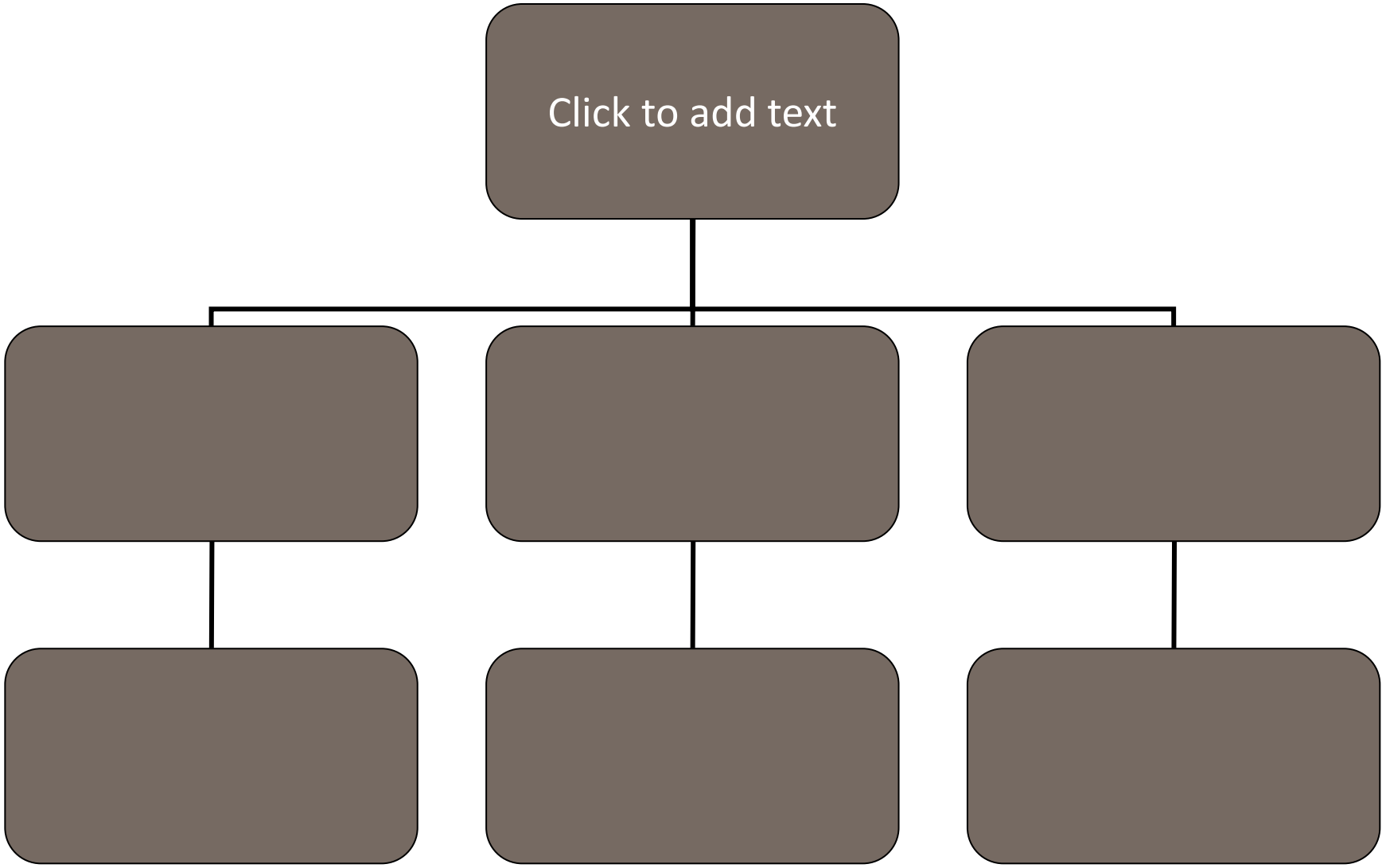
- MAMS trials speed evaluations
  - Test many treatments at the same time
  - Use lack of benefit analyses

- MAMS trials suitable in many instances
  - Common diseases
  - Rare diseases

- MAMS trials are
  - Feasible in practice
  - Efficient
  - Supported by those that have engaged including:

    → Clinicians, patients, industry, funders, regulators, etc

Example organisational chart



Example Table

Test							
1							
2							
3							
4							

Example graph