Identifying appropriate phase II trial designs

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Overview

- Introduction to phase II trials
  - Phase II trials in the drug development pathway
  - Aims of phase II trials
  - Phase IIa or IIb?
- Current issues
  - Which design?
  - Ever changing treatment
- Solutions
  - *Identifying* designs
  - Thought process
- Challenges
  - *Choosing* a design
  - Simulation
  - Speed vs. reliability
  - Software
- Summary

Introduction to phase II trials

Phase II trials in the drug development pathway

- Phase II trials act as an intermediate step between:
  - Phase I - very few patients; establish initial safety; and
  - Phase III - large number of patients; confirm efficacy
- The transition from phase II to III involves the highest risk compared to transition between other phases
  - Phase II to III transition rate = 44% (1)
  - Need to be more sure that moving to phase III is the correct decision
- Increasing pressure to improve efficiency in the drug development process
  - Ever-changing environment, and pressure to speed up the drug development process
- Need to balance speed with making more informed decisions

Refs: 1) Walker and Newell, 2009

Aims of phase II trials

- To act as a screening tool for phase III
- To determine dose response and select an ‘optimal’ dose, assuming phase I trials have identified ‘acceptable doses’, rather than a single recommended dose
- To assess short-term efficacy, or activity
- To further confirm safety
- To decide whether or not to proceed to phase III

- How can we do all of this in one trial?

Phase IIa or IIb?

- Phase IIa
  - Proof of concept
  - Obtain initial estimates of activity, only safety data available to date
- Phase IIb
  - Decision making regarding phase III
  - May incorporate randomised control arm

- Example: new treatment - A; only prior safety data available; good historical data to compare to;

  How should we proceed if:
  - A is a single agent?
  - A is a combination treatment?

Current issues in designing phase II trials

Which design?

- Over 120 different phase II trial designs published to Jan 2010 (2)

Q: How do we distinguish between them?

- By endpoint?
- By randomisation?
- ...

A: Qualitatively: define trial-specific design criteria

Q: How do we choose between designs that fit our trial-specific criteria?

- Personal experience?
- Practicalities?
- ...

A: ???

Refs 2) Brown et al, 2011

Ever-changing treatments

- The way in which treatments work differs both across and within different disease areas
- Need to understand how the treatment under investigation works to allow informed decisions regarding patient populations, endpoints, randomisation, ...
- More new therapies are combinations of standard treatments + a new agent. Need to:
  - understand how these work in combination
  - ensure any increased activity is due to new agent, and not patient population
- Biomarker development may impact patient selection, choice of endpoints, or use of randomisation. Need to use well defined biomarkers

Solutions

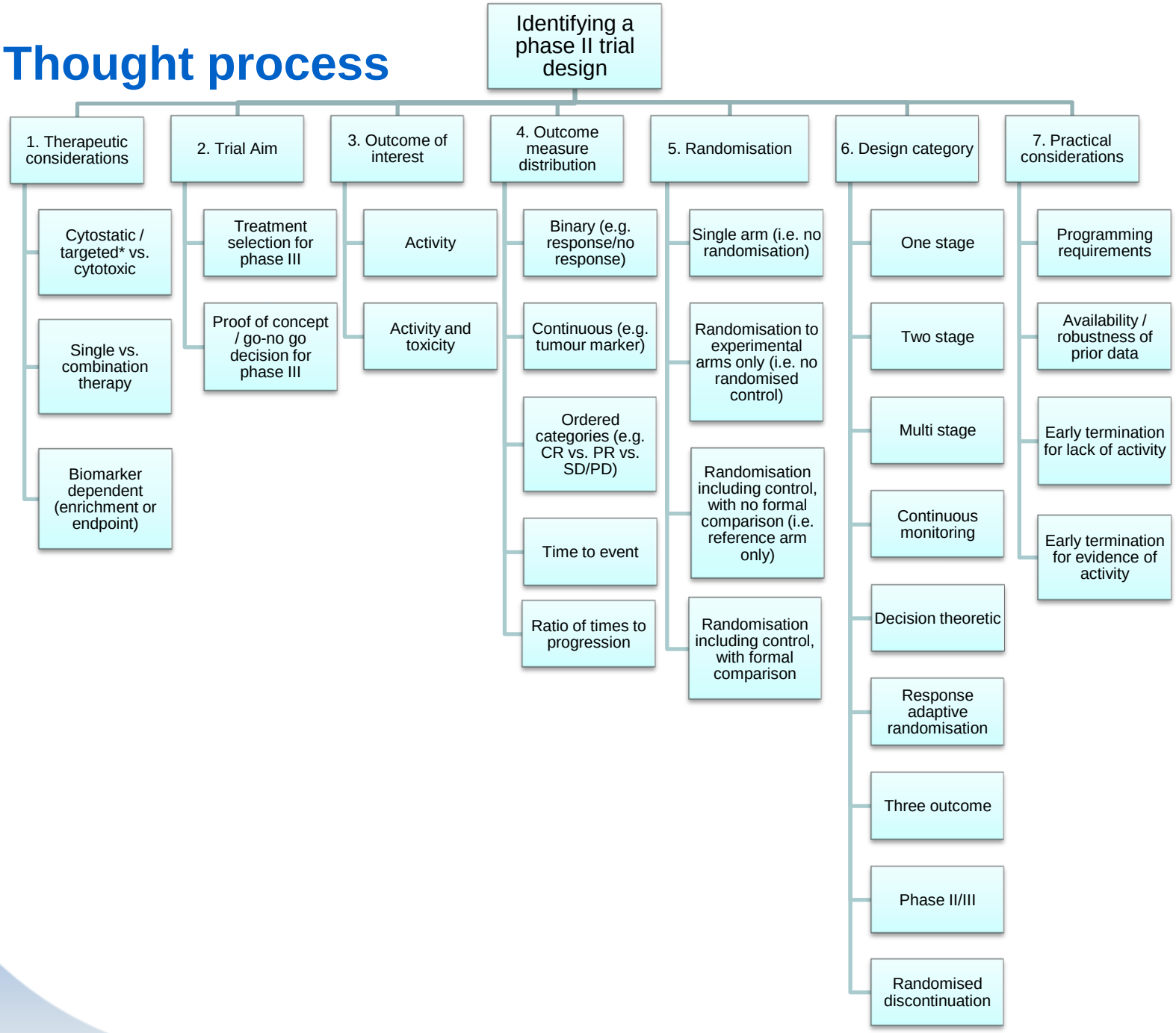
How do we IDENTIFY appropriate phase II designs?

- Thought process & guidance document developed to aid researchers in identifying phase II designs
  - Key points to consider when designing a phase II trial
  - Library of available phase II designs
  - Based on results of systematic literature review of phase II trial design methodology (2)

- Grouped designs into 9 categories based on practical identification and implementation, reflecting trial *design* rather than trial *analysis*

- Close collaboration between clinician and statistician is key

Thought process



Key points for consideration

- 1. Therapeutic considerations
  - Cytostatic / targeted vs. cytotoxic
  - Single vs. combination therapy
  - Biomarker dependent (enrichment of endpoint)
- 2. Trial aim
  - Treatment selection for phase III
  - Proof of concept / go-no go decision for phase III
- 3. Outcome of interest
  - Activity
  - Activity and toxicity

Points for consideration contd.

- 4. Outcome measure distribution
  - Binary; Continuous; Ordered categories; Time to event; Ratio of times to progression
- 5. Randomisation
  - Single arm
  - Randomisation to experimental arms only
  - Randomisation including control, no formal comparison
  - Randomisation including control, formal comparison
- 6. Design category
- 7. Practical considerations
  - Programming requirements
  - Availability of data
  - Early termination

Worked example

- Scenario:
  - A new agent (drug A) is hypothesised to improve the efficacy of current standard treatment for patients with intermediate head and neck squamous cell carcinoma (HNSCC), when given in combination
  - The patient population is relatively small, and there is minimal historical control data available for the current standard treatment in this population (radiotherapy alone)
  - Drug A has an acceptable toxicity profile from use in other disease areas
  - A phase II trial of drug A in combination with current standard treatment is proposed to determine whether a larger phase III trial is worthwhile

Worked example – following the thought process

- 1 – Therapeutic considerations:
  - Monoclonal antibody; multiple mechanisms of action; acts synergistically with radiotherapy
  - Given in combination with radiotherapy
  - No known biomarkers associated with drug A or disease

- 2 - Trial aim: to make a go / no-go decision for further testing in phase III

- 3 – Outcome of interest: Activity
  - toxicity profile acceptable based on studies in other disease areas

Worked example – following the thought process

- 4 – Outcome measure distribution: Binary (disease control rate at 6 months)
  - Patients have curative disease – primary focus therefore cure, or ‘disease control’
  - Drug A acts as a radiosensitiser, targeting disease elimination
  - Shorter-term than, e.g. event-free survival

- 5 – Randomisation: randomisation to a control with formal comparison
  - Very little historical control data available
  - Available data from overlapping populations with more advanced disease
  - Combination treatment

Worked example – following the thought process

- 6 – Design category: one stage, phase II/III
  - Key: very small population of patients, difficult to recruit
  - Interim assessments not required in phase II
  - Data obtained in phase II to be used in phase III

- At this point, use the library of designs to identify potential designs available that fit the criteria specified to date
  - One stage: Thall et al, 1990; Stone et al, 2007
  - Phase II/III: Storer, 1990; Lachin et al, 2007

- 7 – Practical considerations:
  - Software available to implement?
  - Robust against misspecification ?
  - No early termination requirements in phase II

Challenges

How do we CHOOSE between designs?

- Consider practical elements such as program availability and early termination requirements
- Incorporate past experience – easy to go with what we know, but could a new design be more efficient?
- Simulation
  - Phase I trials often designed incorporating simulations to consider different designs and dose-toxicity relationships (3,4)
  - In phase II, investigate differing scenarios and how each design might perform (5,6,7) .
  - Newer designs may be less used therefore need to work out how they perform to become more familiar with them
  - Need software/programs available to simulate different trial designs

3) Ahn, 1998; 4) Miller, 2005; 5) Holford et al, 2000; 6) Pond et al, 2011; 7) Tang et al, 2009;

Simulation

- **Example**: Pond and Abbasi (6) investigated the use of randomisation in phase II, specifically comparing two designs
- Compared two-stage single arm phase II (Simon, 1989) with two-stage randomised phase II (Jung, 2008) under various scenarios:
  - Assumed fixed number of patients available;
  - Varied: $p_{0,}$ $p_{1,}$ variability in response rates, treatment effects and historical control rate;
  - Incorporated historical bias and proportion of trials using truly active agents
- Evaluated the proportion of phase III trials conducted using truly active agents, via each design
- Concluded both designs appear warranted in certain situations
- Apply similar methods to investigate performance of different designs, considering scenarios most relevant to your trial

Speed vs. reliability

- Investigators often need a trial design NOW, limiting the time available to thoroughly put into practice the thought processes and simulations needed to explore all options
- Taking time to design the trial appropriately ensures more informed decisions can be made regarding moving to phase III
- Highlights the need for clinician and statistician interaction as early in the trial concept process as possible
- Phase II trials may need to be larger (and therefore longer) to allow better-informed decisions to be made

Software

- Many designs identified via the systematic review did not detail software to implement the design being described
- Designs that are used more often tend to be those for which software is readily available
- It is vital that when new designs are published, corresponding software be made available to allow researchers to use these designs

Summary

- Phase II trials continue to pose challenges in their design, with ever changing drug mechanisms, new designs, and time pressures
- It is vital that we balance the pressure to speed up the design and implementation of phase II trials, with the need for better-informed decisions on moving to phase III
- A structured thought process allows key points for consideration to be incorporated when designing phase II trials, aiding appropriate trial design
- Detailed guidance provides discussion on key points and a library of trial designs available
- Accessible software needed to allow timely implementation and simulation of designs
- Where a number of designs already exist for specific trial scenarios, need to focus on comparing the designs already available to us rather than developing new designs

Collaborators

- Prof Julia Brown
- Prof Walter Gregory
- Prof Chris Twelves
- Prof Marc Buyse
- Prof Mahesh Parmar
- Prof Matt Seymour

References

1) Walker and Newell. Nat Rev Drug Discov, 2009; 8:15-16

2) Brown et al. BJC, 2011; 105: 194-199

3) Ahn. SIM, 1998; 17: 1537-1549

4) Miller. J Pharmacokinet Pharm, 2005; 32: 185-197

5) Holford et al. 2000; Annu Rev Pharmacol Toxicol; 40: 209-234

6) Pond and Abbasi. 2011; Clin Trials; 8: 260-269

7) Tang et al. JCO, 2009; 27: 15s, Abstract 6512

8) Simon. Control Clin Trials, 1989; 10: 1-10

9) Jung. SIM, 2008; 27: 568-83

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Guidance document: http://ctru.leeds.ac.uk/phaseII