EARLY PHASE TRIALS IN RARE DISEASES AND ATIMPS

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Background

- Early phase: phases I-II (or seamless I/II)
- Safety/tolerability, dose-finding, signal of efficacy
- Model-based approach (e.g. CRM) preferable to A+B designs in **dose-finding**:
  - Statistical vs rule-based escalation (de-escalation)
  - Good operating characteristics
  - Precision around estimated 'MTD'

Question?

- Are model-based methods **always** appropriate?
  - Require ‘priors’
  - Operating characteristics/precision depend on **sample size**

ATIMPs (1)

- New treatments such as gene therapy or cell/tissue engineering are emerging
- Rare genetic conditions targeted by such treatments mean **small populations**
- Typically small numbers <10 due to availability of material/participants
- Added complexity: virus vector-based gene therapy treatments cannot be repeated in individuals due to build-up of antibodies

“one shot treatments”

ATIMPs (2)

- Want to treat as quickly as possible at a 'biologically optimum dose' whilst taking account of safety and tolerability
- 'Toxicity' approach (oncology) not necessarily right one
- How should '*dose limiting events*' be defined/treated?
- Novel (ground-breaking) treatment approaches mean **no strong 'priors'**

More questions?

- What are appropriate trial designs for ATIMPs in rare diseases?
  - Ad-hoc ‘rule-based’ approaches accepted by regulators but considered ‘old-hat’
  - Reviewers question lack of model-based design in funding applications?
- Can a model-based approach be right comparing 2/3 doses with only 10 subjects say?

An early phase framework for rare diseases?

- For mainstream phase III studies, Bogaerts et al [2015] and Parmar et al [2016] outlined design approaches for rare diseases
- A reduction in power, increased type I error, and one-sided testing were suggested as ways to mitigate the lack of availability of patients within a realistic timeframe
- There is no such framework for early phase designs (I/II)

Task

- Discuss in groups the following scenarios based on real-life trials
  - What would you suggest as an appropriate trial design?
  - How would you decide on an ‘optimal biological dose’?
  - What stopping rules might you impose?

Scenario 1

AAV vector gene therapy treatment for OTCD in children

Urea Cycle Defects (UCDs) share high rates of mortality and neurodisability. Ornithine Transcarbamylase Deficiency (OTCD) is the most common UCD, accounting for 60% of all such cases (estimated at 1:56,500 live births). An X-linked inherited disorder, males are more severely affected with presentation in the newborn period resulting in coma or death if untreated. Liver transplantation cures UCDs but with a risk of mortality and morbidity, including lifelong immunosuppression. An Adeno-associated viral vector targeting OTCD is being investigated as a possible alternative to transplantation, and has shown great promise in pre-clinical studies. A first in man/patient study is the next stage balancing the need to demonstrate safety in a small population, and evaluate efficacy whilst limiting the number of children exposed to sub-therapeutic doses.

Scenario 2

CAR Donor T-Cells

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered the cornerstone in treatment of haematological malignancies. However, relapse of the haematological disease after allo-HSCT remains a challenge and is associated with poor long-term survival. Chimeric Antigen Receptor (CAR) Donor T-cells are a novel immunotherapy under investigation for treating haematological malignancies. T-cells are removed from a suitable donor and modified so that they express receptors specific to the patient's particular cancer. The modified T cells, which can then recognize and kill the cancer cells, are transplanted into the patient. A trial is proposed of CAR Donor T-cells in patients who express the B-lymphocyte antigen CD19, and have leukaemias or lymphomas that have relapsed after receiving allo-HSCT.