Key factors in trial design

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…..with thanks to Dr Wendy Baird and Prof Will Steward
Maximising Chance of Success

• Ensure questions meaningful
  – if not, trial will have little/no value
  – Drives interest of investigators/patients

• Think through the questions to be answered
  – Formulate specific aims/trial objectives
  – Integrate potential investigators/teams in the development of questions/objectives

• Decide on biological endpoints and their value early during development of trial
  – Integrated, integral or correlative?
Understand the Setting

• The key questions
  • how much, how safe, how active, how effective?
  • vary depending on the phase of development
  • Understand which questions are appropriate for each stage of development
  • Recognize that some questions bridge stages

• Tailor the design of the trial to the therapy
  • The standard approach is not the only approach
  • Design a trial that incorporates – or is even built around - measurements best suited to capture the effect of that therapy
Impact

Research Question
1. Impact

- **Low risk strategy** (incremental advance) e.g. Combining existing therapies
  
  If it is too modest (low-risk):
  - Will anyone be interested?
  - Does it justify use of resources?

- **High risk strategy** (breakthrough, paradigm changing advance) e.g. replacing standard therapy with new agent (imatinib in CML or GIST)

  If it is too innovative (high-risk):
  - Will anyone understand and want to participate?
  - Put yourself in the place of a colleague who knows nothing about the background of the trial:
    - Would you participate?
    - If so, with what level of enthusiasm?
2. Study design

- **Research approach** (qualitative, quantitative or mixed methods)
- **Study population** (define, inclusion/exclusion criteria, sub-groups)
- **Intervention** (define intervention and comparator)
- **Data collection** (volume of data and collection methods)
- **Data analysis** (meta-analysis, homogeneous, type of study, presentation of results)
- **Appropriate primary endpoint** (PFS, OS)
3. Ethical Considerations

- NHS patients, data or premises
- Vulnerable participants
- Highly sensitive topics
- Highly sensitive methods
- Patient burden
- Human Tissue Act
4. Is the study feasible?

• **Scientifically?**
  – Are the clinical and biological endpoints valid, reliable, and appropriate?

• **Pragmatically?**
  – Is it reasonable to expect that the RR will double or that the relapse rate will be reduced to zero?
  – A question that is relevant today may not remain relevant if the study takes 10 years to complete
  – Do you have access to an adequate number of patients to complete the trial in a reasonable period of time?
  – Do you have the time to devote to all aspects of study development, recruitment and completion?

• **Financially?**
  – Who will pay for extra tests, data collection, and follow-up?

• **Ethically?**
  – Are you asking patients to forego “effective” treatment to participate in your trial?
5. A literature review will help…

- Establish how good the pre-clinical data is
- Demonstrate a research need/gap
- Find similar study designs approaches to help demonstrate feasibility/expected outcomes
- Further develop the research question
6. Research team and collaborations

• Integrate potential investigators/teams in the development of questions and study objectives
• Ensure centres have experience and track record of quality
• Seek support from other departments early:
  – Surgery
  – Radiology
  – Research nurses
  – Statisticians
  – Data managers
  – Pathology
  – Laboratories or Clinicians
6. Research team

In your Grant application you should highlight:

– Relevant skills and experience of the team that make them well placed to carry out the work

– ensure all components of the project have an appropriate person listed to complete the work

– ‘sell’ previous experience, such as working on other research projects

– if you have limited experience of running research then emphasise links with organisations that will guide you through – R&D, CTU, NIHR networks
7. Involvement of patients and public

In your Grant application you should highlight where patients and public have been involved with:

– Design of the research
– management of the research (e.g. steering group membership)
– developing participant information resources
– undertaking/analysing the research (e.g. member of the research team)
– contributing to the drafting of the study report
– dissemination of the research
Ethical considerations
Study Design
Feasibility
Research Question
Impact
Literature
Research team & collaborations
Involvement of patients and public
Safety and responsibility
8. Safety and responsibility

- Don’t underestimate adverse event reporting
- Ensure training of teams for data processing
- Inform the patient
- Establish a process to report toxicity
- Ensure data timeliness

**Sponsor’s responsibilities**
- Submission of SAEs as reported by the investigator
- Assessment of expectedness (SUSAR)
- Reporting SUSARs to Authorities
- Annual safety reports

**Investigator’s responsibilities**
- Causality of AEs
- Reporting all adverse events in the source documents and CRFs
- Reporting SAEs within time period specified in the protocol
- Notifying Ethics committee
Research Question

- Ethical considerations
- Feasibility
- Literature
- Involvement of patients and public
- Research team & collaborations
- Study Design
- Safety and responsibility
- Appropriate funding stream
- Impact

Figure courtesy of Dr Wendy Baird – NIHR Research Design Service - 2013
9. Appropriate funding streams

• Ensure your research question is within scope of the funding stream you are applying to

• If you are unsure ask *before* submitting an application
How to find our way through the biomarker maze?
Categories of Biomarkers

• Intended Use in the Trial
  – Integral
  – Integrated
  – Correlative
  – See definitions at http://biqsfp.cancer.gov/

• EU Commision


Hall JA, Brown R, 2013, Developing translational research infrastructure and capabilities associated with cancer clinical trials, Expert Reviews in Molecular Medicine, Vol:15, ISSN:1462-3994
Why do biomarker proposals not reach funding cut-off (a personal perspective)?

- No or flawed scientific hypothesis
- Stamp collecting
- Kitchen sink science
- Statistically underpowered
- Samples not fit for purpose
- Assay not fit for purpose
- Analysis not fit for purpose
- Committee didn’t understand the proposal and they are all a bunch of idiots
NCRI Biomarkers and Imaging CSG

• To promote high quality translational (correlative) science within the NCRN portfolio of clinical trials in cancer through the following activities

  • **Identifying and monitoring strengths, weaknesses, opportunities and barriers**

  • **Methodology harmonisation, design of generic protocols and education**

  • **Interactions with tumour specific Clinical Studies Groups**
BICSG Work-Streams

- Imaging integration and harmonisation (Fiona Gilbert)
- Biomarker technologies and applications (Craig Robson)
- Bioinformatics and biostatistics in biomarker study design (Expert Working Group)
- Education in biomarkers and personalised medicines