Key factors in trial design

Professor Robert Brown
Imperial College London

…..with thanks to Dr Wendy Baird and Prof Will Steward

The Experimental Cancer Medicine Centre Initiative is jointly funded by Cancer Research UK, the National Institute for Health Research in England and the Health Departments for Scotland, Wales and Northern Ireland

Maximising Chance of Success

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

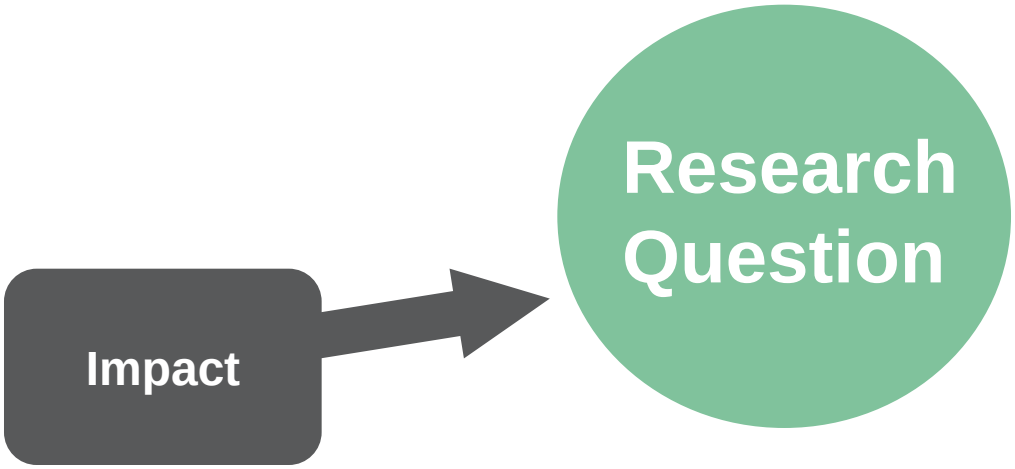
- **Think through the questions to be answered**
  - **Formulate specific aims/trial objectives**
  - **Integrate potential investigators/teams in the development of questions/objectives**

- **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**


Research Question
Impact

1. Impact

- **Low risk strategy** (incremental advance) e.g. Combining existing therapies

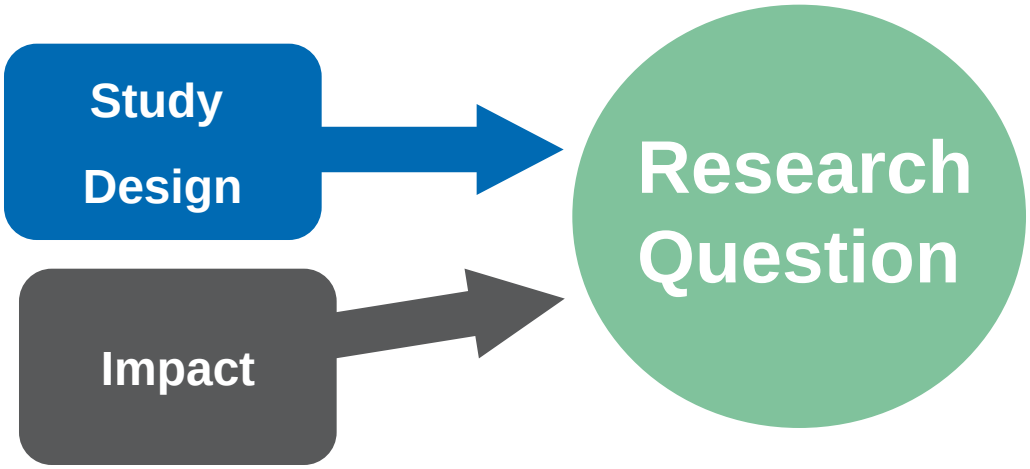
  If it is too modest (low-risk):

  – 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)

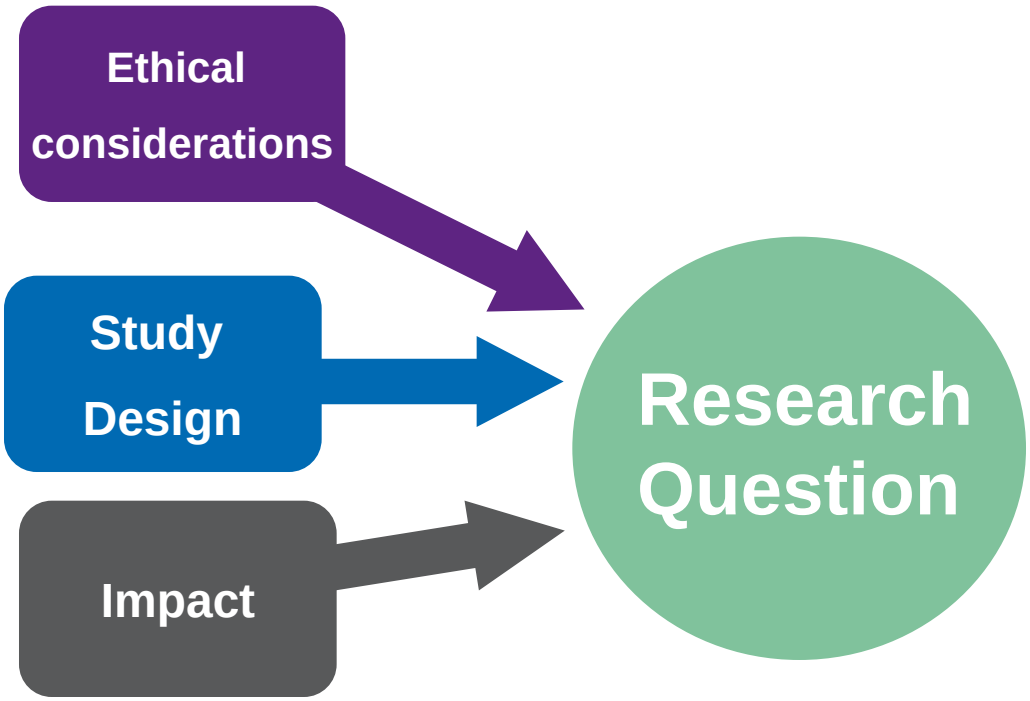
  If it is too innovative (high-risk):

  – 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?


Study
Design
Impact
Research
Question

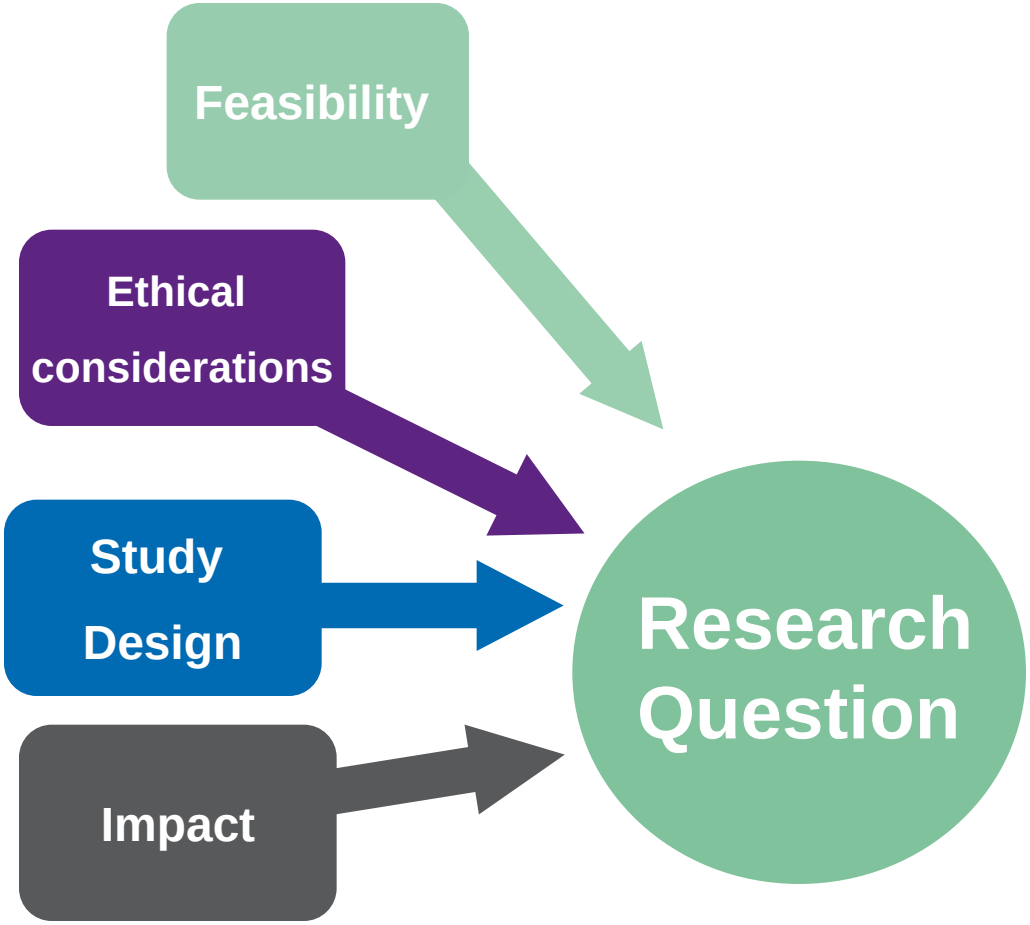
2. Study design

- **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)


Ethical considerations
Study Design
Impact
Research Question

3. Ethical Considerations

- NHS patients, data or premises
- Vulnerable participants
- Highly sensitive topics
- Highly sensitive methods
- Patient burden
- Human Tissue Act


Feasibility
Ethical considerations
Study Design
Impact
Research Question

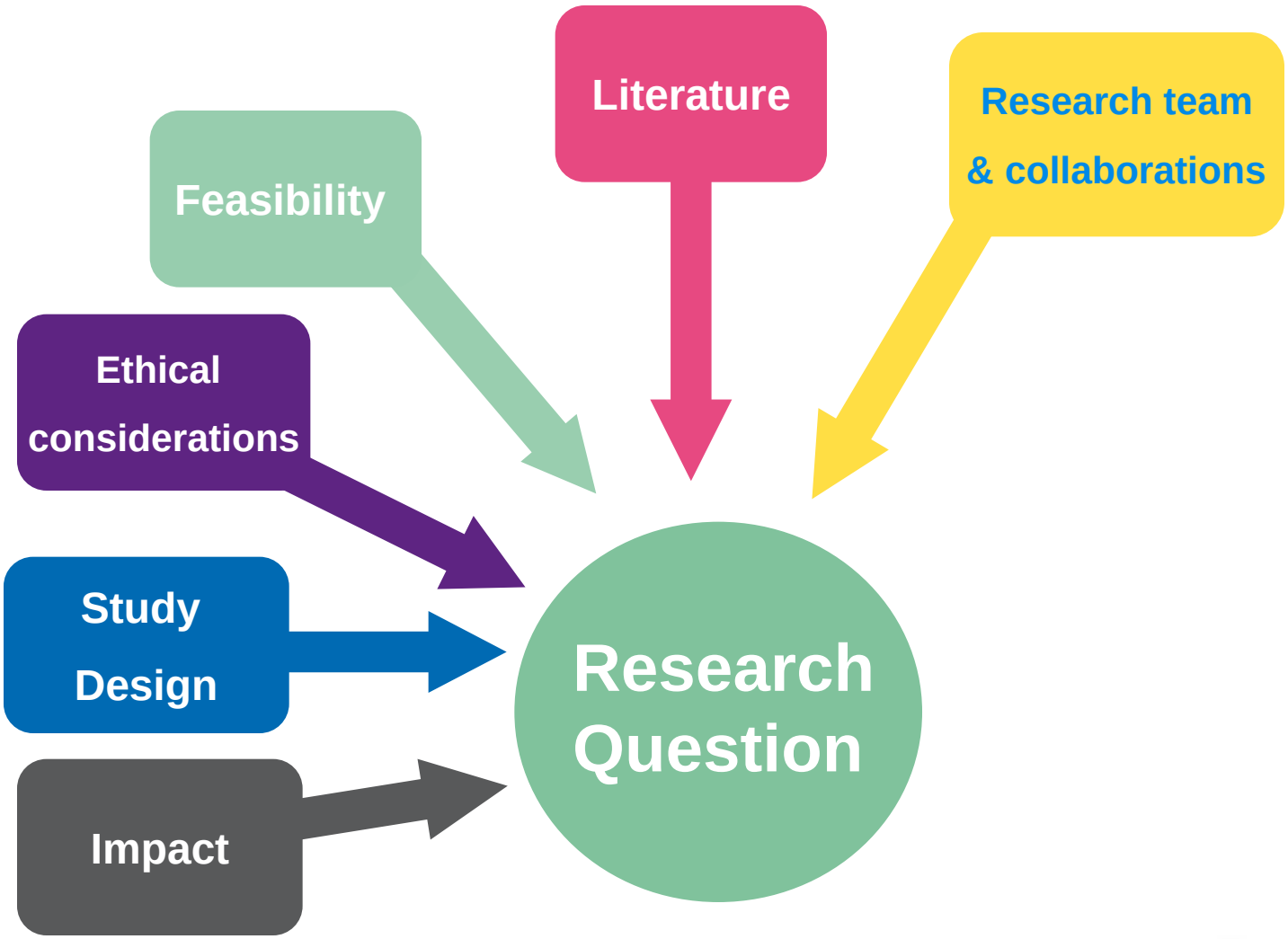
4. Is the study feasible?

- **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?


Literature
Feasibility
Ethical considerations
Study Design
Impact
Research Question

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


Literature
Research team & collaborations
Feasibility
Ethical considerations
Study Design
Impact
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

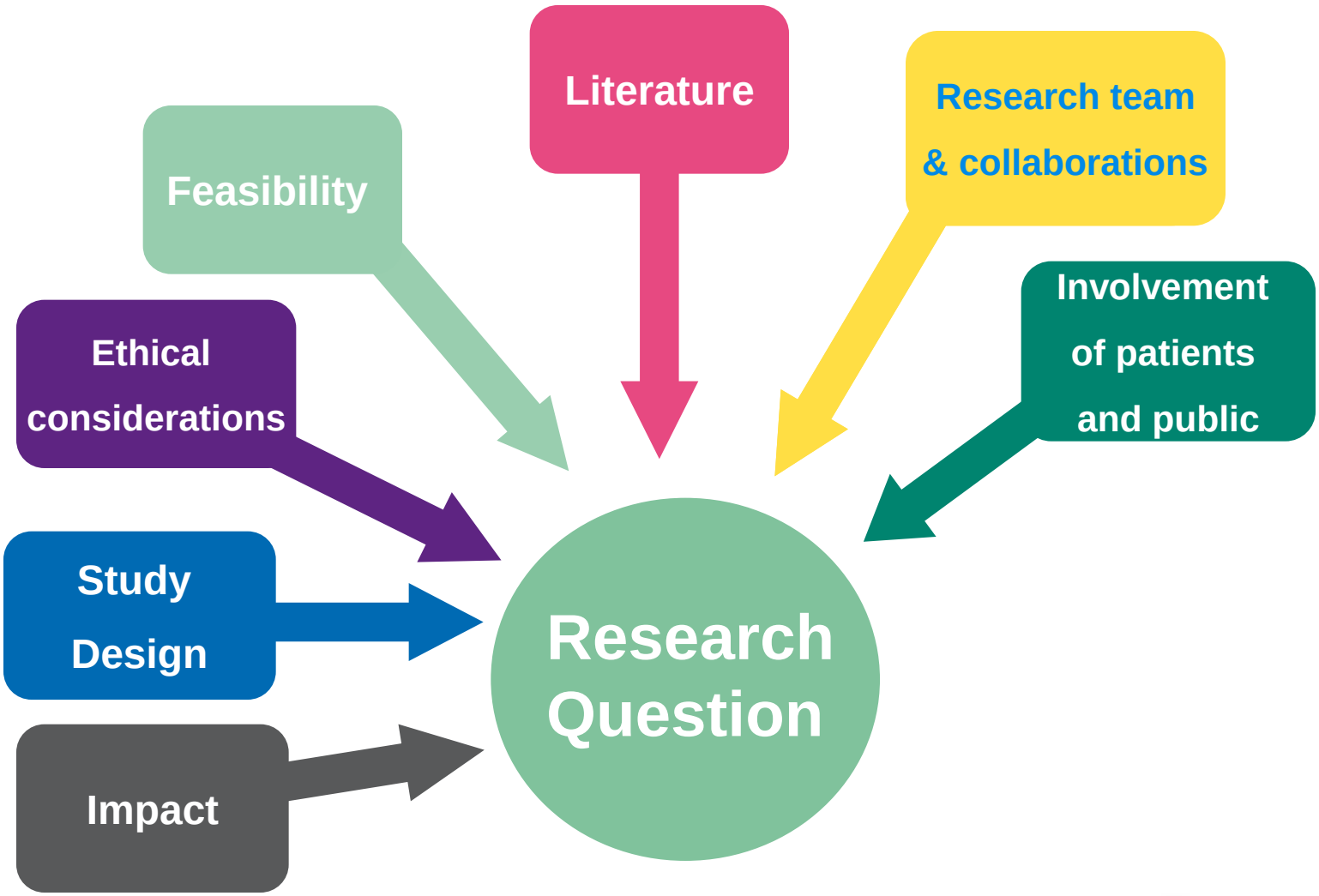
In your Grant application you should highlight:

– 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

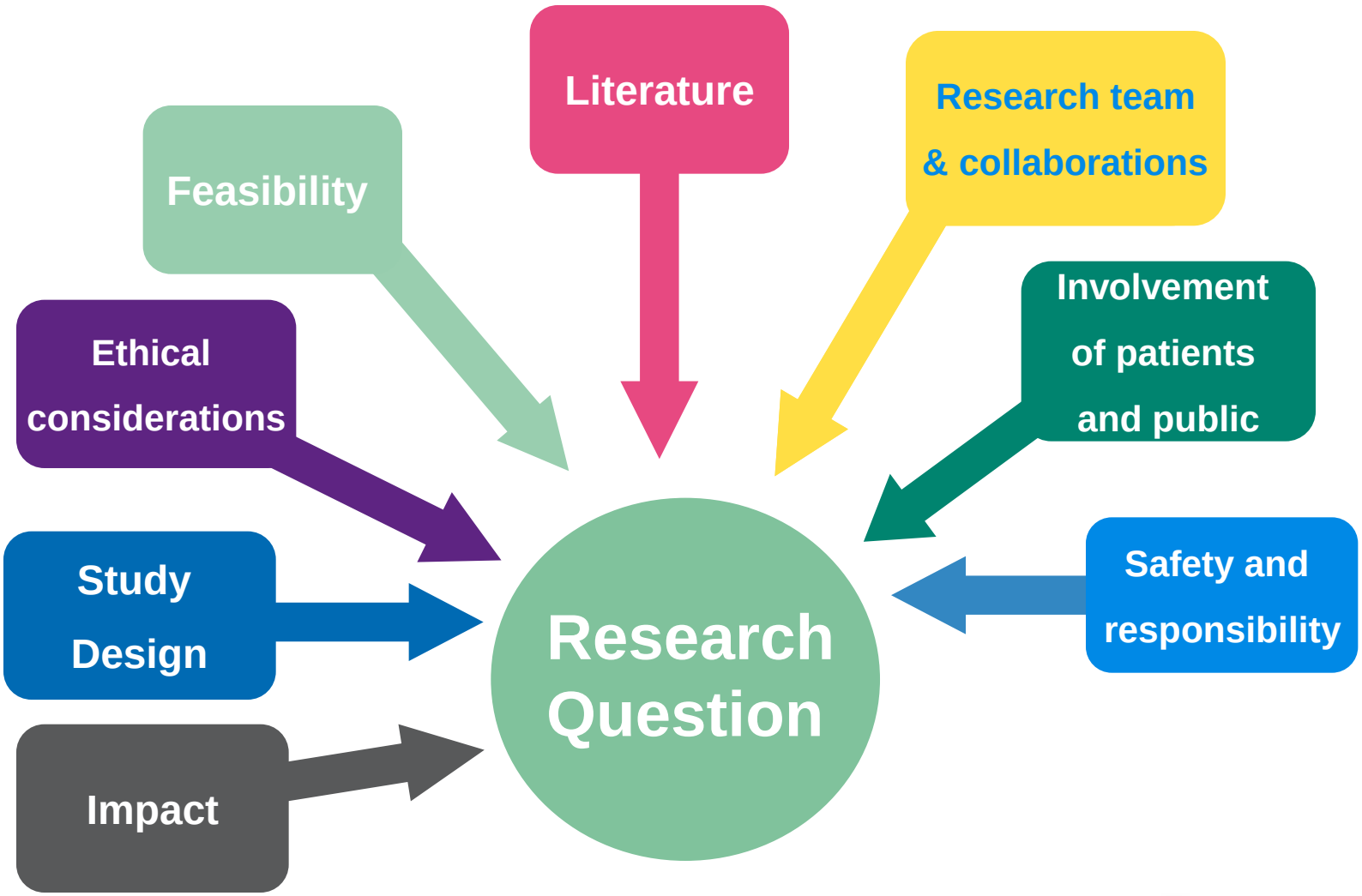
– if you have limited experience of running research then emphasise links with organisations that will guide you through – R&D, CTU, NIHR networks


Literature
Feasibility
Research team & collaborations
Ethical considerations
Involvement of patients and public
Study Design
Research Question
Impact

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**


Literature
Feasibility
Research team & collaborations
Ethical considerations
Involvement of patients and public
Study Design
Research Question
Safety and responsibility
Impact

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

ECMC

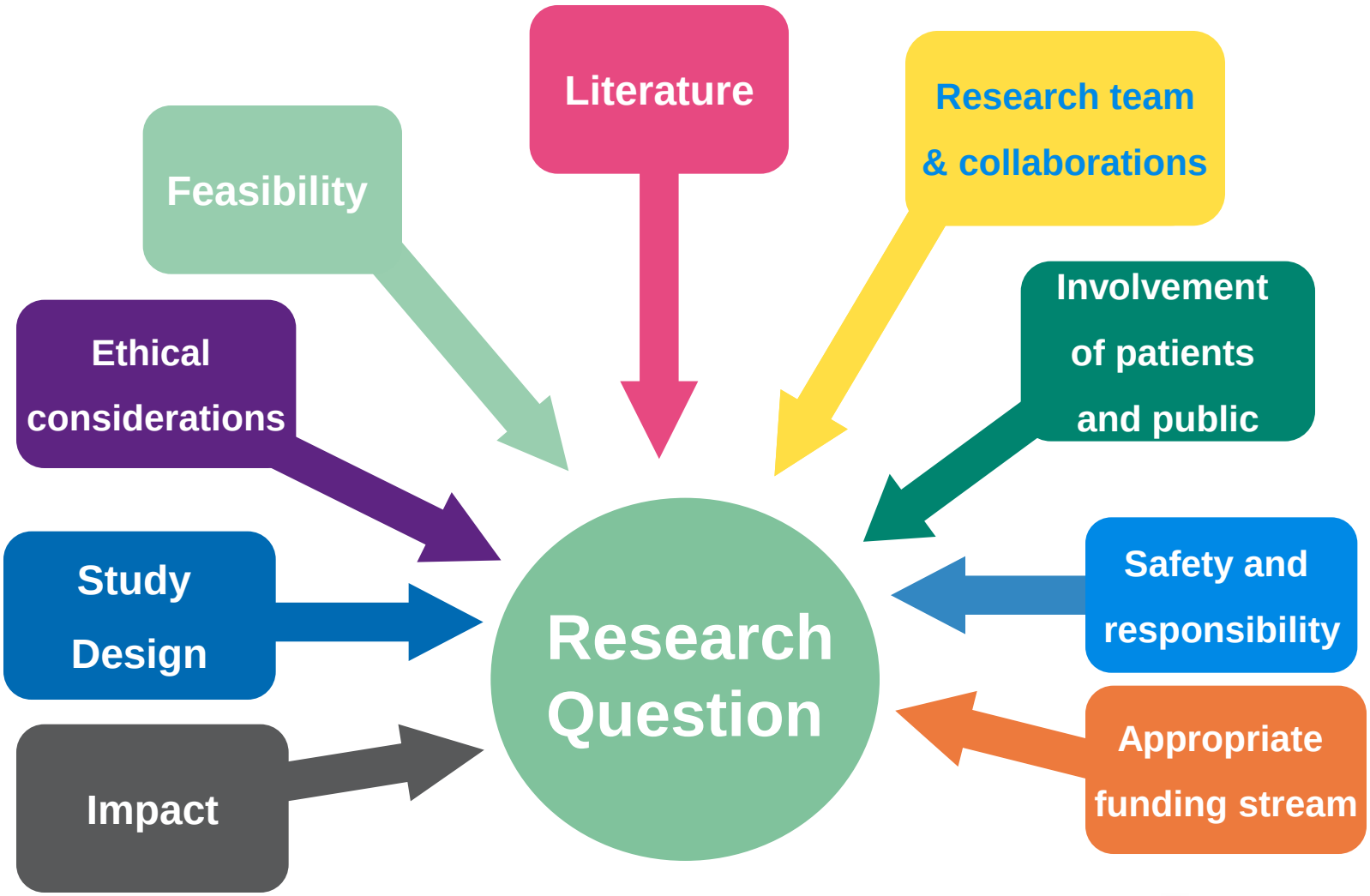


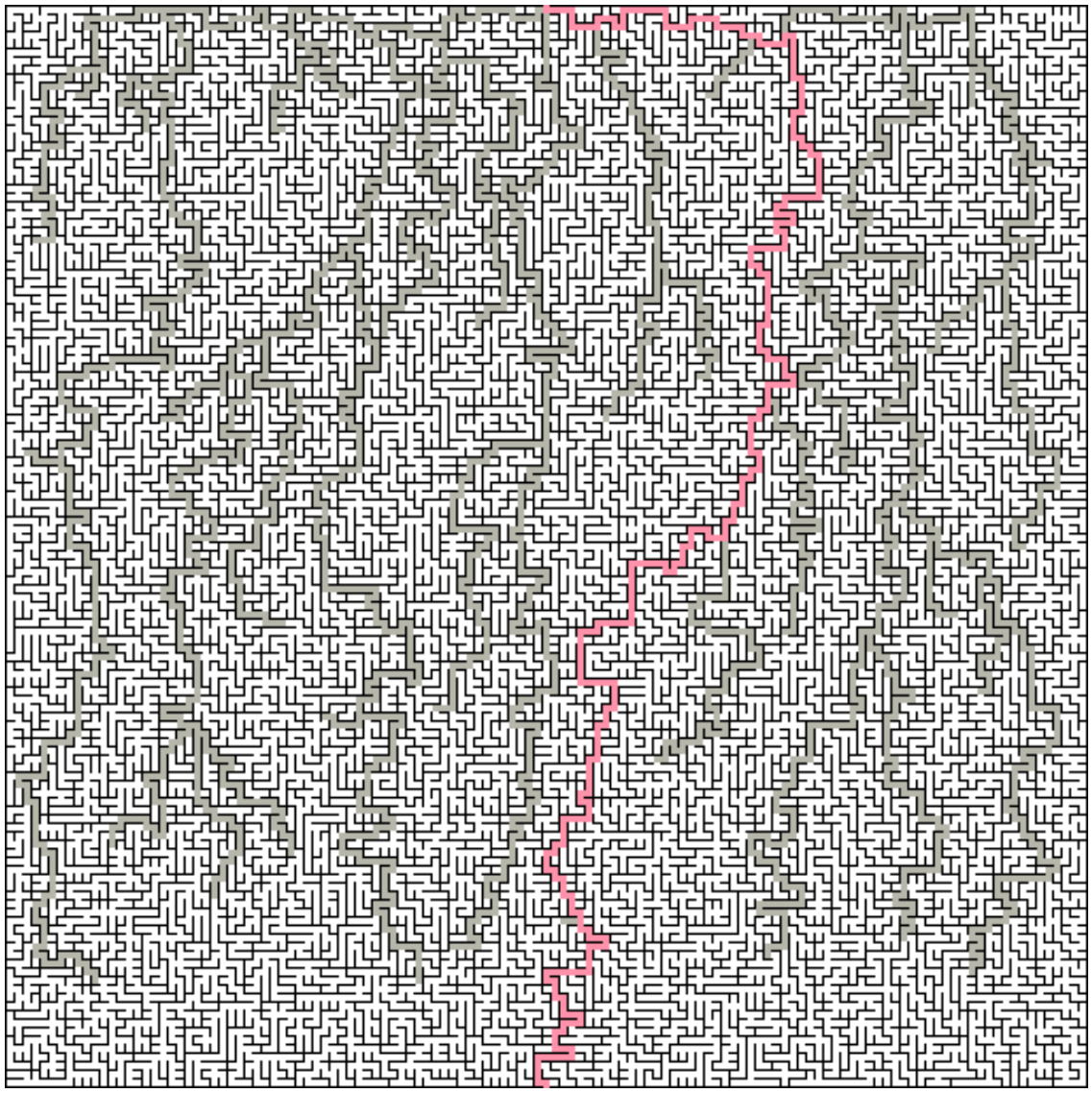
Figure courtesy of Dr Wendy Baird – NIHR Research Design Service - 2013

ECMC

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**
- **Seek advice and support:**
  - **Internal review**
  - **NCRI Clinical Studies Groups**
  - **Biomarker and Imaging Advisory Group**
  - **Speak to funders (e.g. CDD)**

How to find our way through the biomarker maze?



NCRI National Cancer Research Institute

NCRN

NHS National Institute for Health Research

Cancer Research Network

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***

NCRI National Cancer Research Institute

NCRN

NHS National Institute for Health Research

Cancer Research Network

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**

Categories of Biomarkers

- **Intended Use in the Trial**
  - **Integral**
  - **Integrated**
  - **Correlative**
  - **See definitions at http://biqsfp.cancer.gov/**
- EU Commision

http://ec.europa.eu/health/medical-devices/documents/revision/index_en.htm

REporting recommendations for tumor MARKer prognostic studies (REMARK). Breast Cancer Res Treat. 2006 Nov;100(2):229-35.

McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM; Statistics Subcommittee of NCI-EORTC Working Group on Cancer Diagnostics

Cancer Research UK Biomarker Roadmaps: http://www.cancerresearchuk.org/science/funding/funding-committees/science-committee/biomarker-research/

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
- Not cool and sexy
- Ignoring the literature
- Stamp collecting (no clear hypothesis)
- Kitchen sink science (over ambitious)
- Statistically underpowered (involve a statistician)
- Samples not fit for purpose (preliminary data)
- Assay not fit for purpose (SOPs)
- Analysis not fit for purpose (over interpretation)
- Committee didn't understand the proposal and they are all a bunch of idiots

ECMC