Rare Cancers: Statisticians Perspective

Methodology to Influence Clinical Practice in Rare Cancers

Lucinda (Cindy) Billingham
Professor of Biostatistics and Director of Statistics
Cancer Research UK Clinical Trials Unit
University of Birmingham

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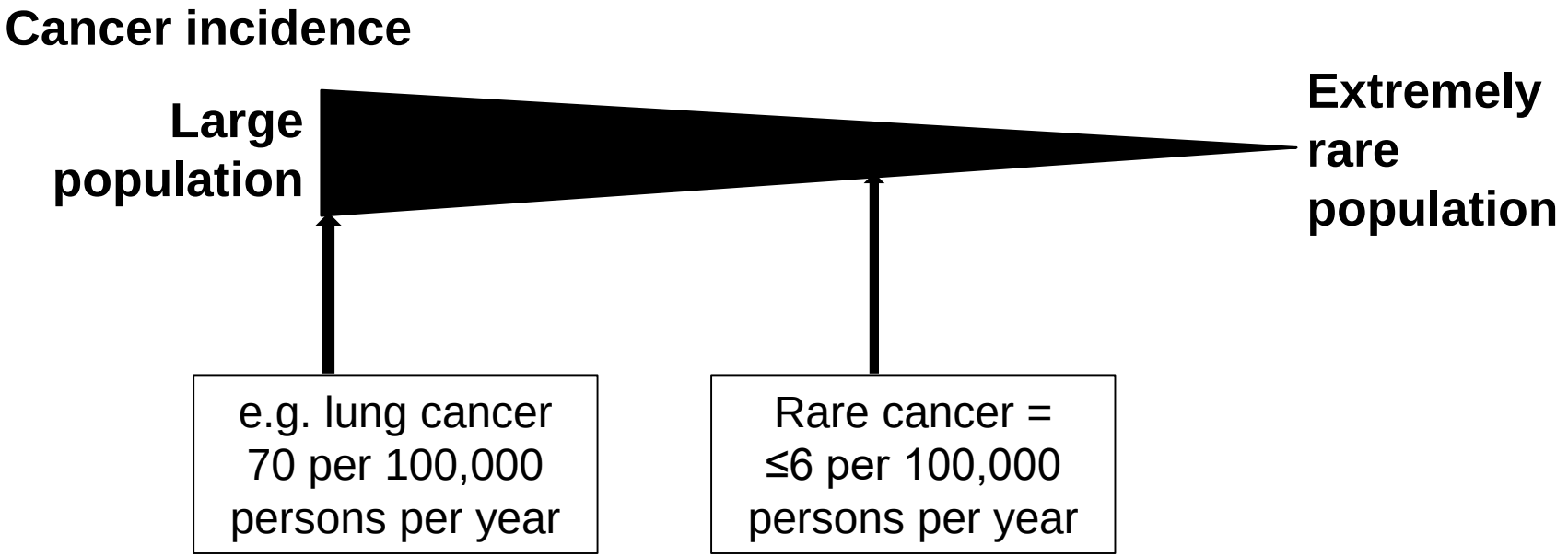
Disclosures

I have received honorarium from:
Eli Lilly, Pfizer, Roche, Celgene, Astra Zeneca

Importance of evidence-based treatments for rare cancers



- Collectively rare cancers affect > 20% of all patients diagnosed with cancer
- Ethically patients with a rare cancer have as much entitlement to evidence-based health care as those with more common cancers
- Growing phenomenon through molecular reclassification of cancers

So how can we evaluate the effectiveness of treatments in rare cancers?
Need to think differently about clinical trial methodology

International Rare Cancers Initiative (IRCI)

- Established in 2011 to facilitate development of trials in rare cancers
- Joint initiative between
  - National Institute for Health Research Cancer Research Network
  - Cancer Research UK
  - USA National Cancer Institute
  - European Organisation for Research and Treatment of Cancer
- Rare = <2 per 100,000 (not molecularly defined subtypes)
- Encourages use of innovative trial designs

Salivary gland cancer
Anaplastic thyroid cancer
Small bowel adenocarcinoma
Gynaecological sarcoma
Fibrolamellar hepatocellular carcinoma
Penile cancer
Thymoma
Ocular melanoma
Relapsed or metastatic anal cancer

Commentary by Nicola Keat, Kate Law, Matthew Seymour, Jack Welch, Ted Trimble, Denis Lascombe, Anastassia Negrouk; Lancet Oncology Vol 14 Feb 2013

Expression of Interest Call 2018 for new rare cancer working groups

European Journal of Cancer (2015) 51, 271–281

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

Clinical trial designs for rare diseases: Studies developed and discussed by the International Rare Cancers Initiative

Jan Bogaerts [a,1,*], Matthew R. Sydes [b,1], Nicola Keat [c], Andrea McConnell [c], Al Benson [z],

THE LANCET Oncology

Research methods to change clinical practice for patients with rare cancers

Lucinda Billingham, Kinga Malottki, Neil Steven

Lancet Oncol 2016; 17: e70–80

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CCR Perspectives in Drug Approval

Clinical Cancer Research

Rare Cancer Trial Design: Lessons from FDA Approvals

Himabindu Gaddipati[1], Ke Liu[2], Anne Pariser[3], and Richard Pazdur[2]

Annals of Oncology 26: 300–306, 2015
doi:10.1093/annonc/mdu459
Published online 1 October 2014

Rare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper

P. G. Casali[1]*, P. Bruzzi[2], J. Bogaerts[3] & J.-Y. Blay[4] on behalf of the Rare Cancers Europe (RCE) Consensus Panel

Parmar *et al. BMC Medicine* (2016) 14:183
DOI 10.1186/s12916-016-0722-3

BMC Medicine

CORRESPONDENCE Open Access

How do you design randomised trials for smaller populations? A framework

Mahesh K. B. Parmar[1], Matthew R. Sydes[1] and Tim P. Morris[1,2*]

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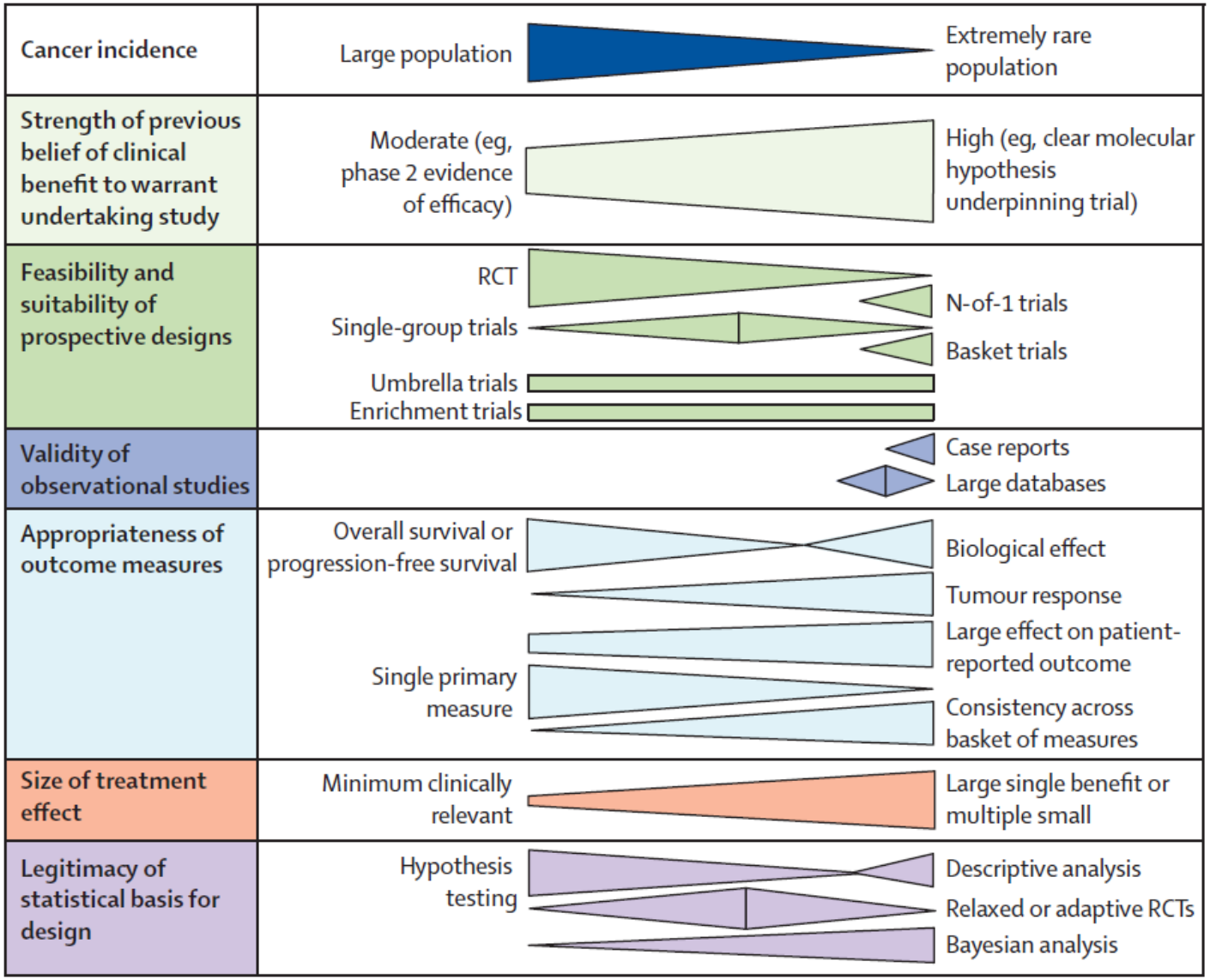
Methodology in relation to sliding scale of rarity

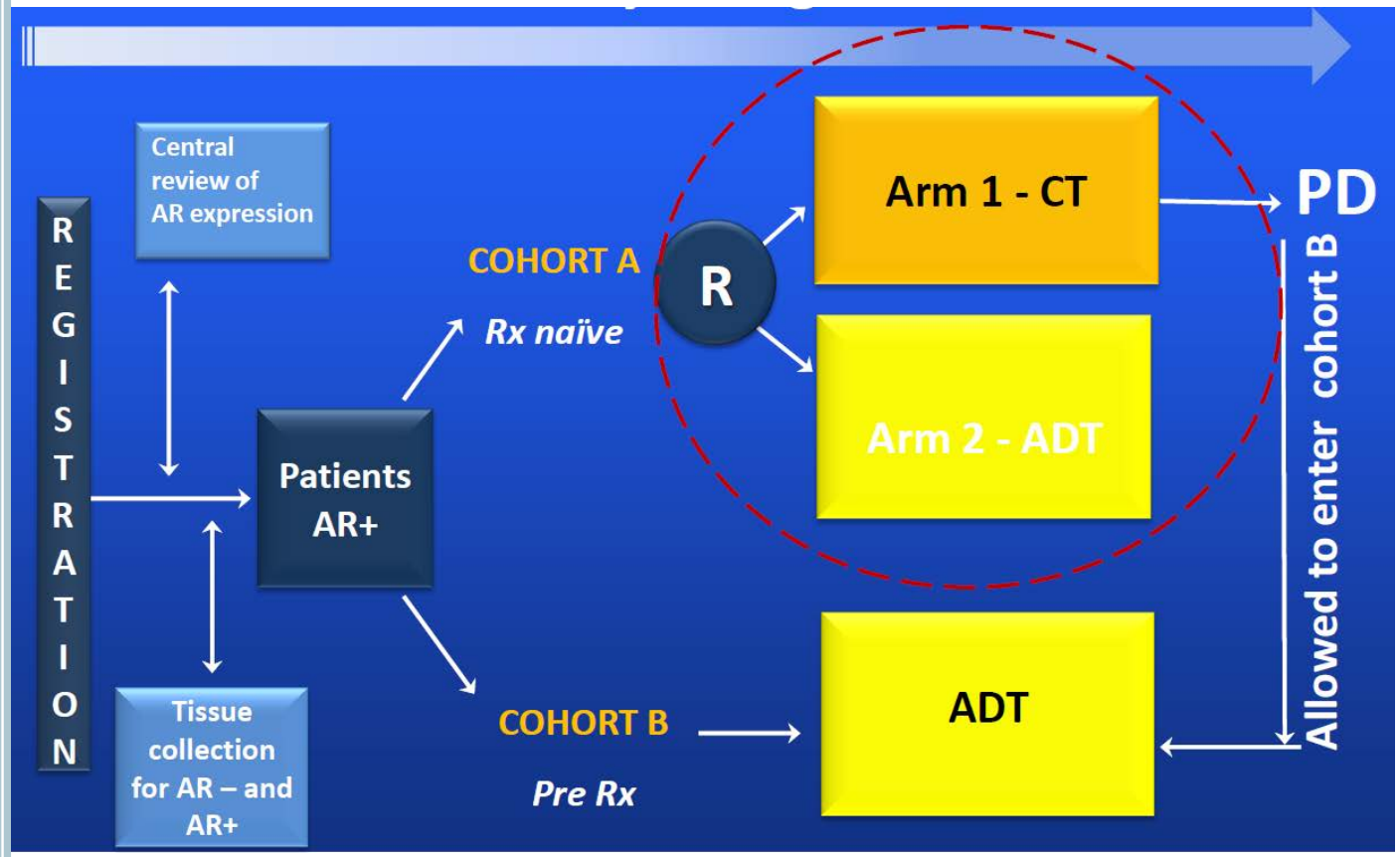


Overview of methodological options (1)

Strategies that enable the application of conventional clinical trial designs to rare cancer populations

- Maximising recruitment
- Minimising sample size
  - Selecting population and treatment to maximise treatment effect
  - Compromising on phase III trial convention
  - Simple designs to minimise sample size
  - External rather than internal controls
  - Selection of outcome measurements
- Maximise utility of the evidence
  - Complex designs
  - Selection of outcome measurements
  - Minimising noise

Relaxing the phase III conventions: Example IRCI007 in recurrent/metastatic salivary gland cancer



- Patient selection maximises treatment effect and minimises sample size
- PFS analysis minimises sample size
- Substudy maximises utility
- Bayesian sensitivity analysis

80% power to detect HR=0.56 with one-sided 10% significance level gives N=76

Is it really Phase II?

Example: Single arm phase III trial

(The 111 Trial - Michael Cullen, Emma Hall)

Patient with newly diagnosed stage 1, high risk (i.e. with vascular invasion) non-seminomatous or mixed germ cell tumours of the testis

↓

Patient deemed fit to receive chemotherapy as definitive treatment

↓

REGISTRATION INTO TRIAL

↓

Experimental treatment arm
Patient receives 1 course of BEP chemotherapy
Day 1: Bleomycin 30,000IU iv infusion
Etoposide 165mg/m^2 iv infusion
Cisplatin 50mg/m^2 iv infusion
Day 2: Etoposide 165mg/m^2 iv infusion
Cisplatin 50mg/m^2 iv infusion
Day 3: Etoposide 165mg/m^2 iv infusion

↓

Follow-up at: 2, 3, 4, 5, 6, 8, 10, 12, 15,18, 24, 28, 32, 36, 42, 48, 54, 60 months

↓

Primary outcome measure:
2-year recurrence-free rate (RFR2)
Secondary outcome measures:
immediate and delayed toxicity, contralateral second primary testicular germ cell malignancy, relapse-free survival time, overall survival time

Standard treatment: 2 cycles RFR2=98%

Use single arm single stage phase II design by Ahern

α=5%; β=20%

Minimum acceptable level for experimental treatment = 95%

N=236

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Adaptive designs improve efficiency but not necessarily feasibility

- Use information from interim analysis to make adaptations to trial design whilst in progress
- E.g. adaptive randomisation, stopping rules, multi-arm multi-stage (MAMS)
- Mentioned in most reviews of methodology for rare diseases
- More efficient in long run but no guarantee in single trial being planned that sample size will be smaller than fixed
- Multiple arms may result in infeasible sample size
- Unknown sample size problematic

Overview of methodological options (2)

Alternative designs that address specific challenges of rare cancers with aim to potentially influence clinical practice

- Bayesian methodology: extracting more meaning from underpowered trials
- Observational studies: capturing retrospective data on rare cancer populations
- Singletons, baskets and umbrellas: capturing the patient with a rare cancer in prospective research

Lilford's Proposal

Lilford R, Thornton JG, Braunholtz D Clinical trials and rare diseases: a way out of a conundrum BMJ 1995

Ethics of small clinical trials

- Small well designed study better than no study
- Contribute to a pool of knowledge

Proposes an alternative view to clinical trials

- Carry out a trial NOT to gain a definitive answer but to change the level of uncertainty

Make use of all prior knowledge

<u>Bayesian perspective</u> is useful in these circumstances

Bayesian gives:
p (treatment effect lies in a particular range | data, prior)

Frequentist hypothesis testing gives:
p-value = p (data | no treatment effect)

What is a Bayesian Approach to Statistical Analysis?

- **Alternative method of statistical analysis to the classical / frequentist approach**
  - 'The explicit quantitative use of external evidence in the design, monitoring, analysis, interpretation of a health-care evaluation' Spiegelhalter et al 2004
- **Based on theorem devised by Reverend Thomas Bayes (1702-1761)**

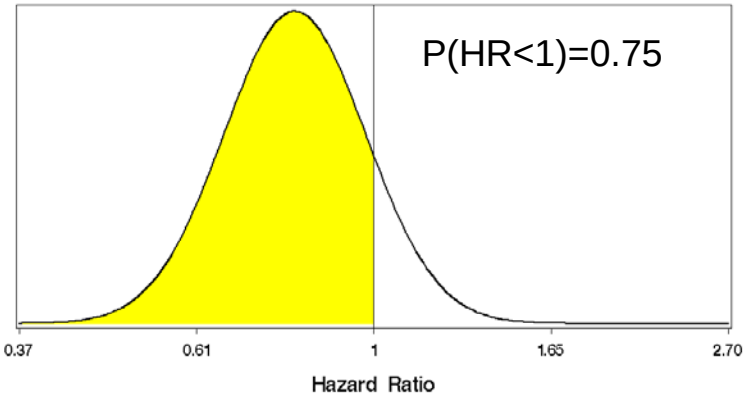
Bayes Theorem:

$$p(B/A) = \frac{p(A/B) \times p(B)}{p(A)}$$

- **Basic maths:**

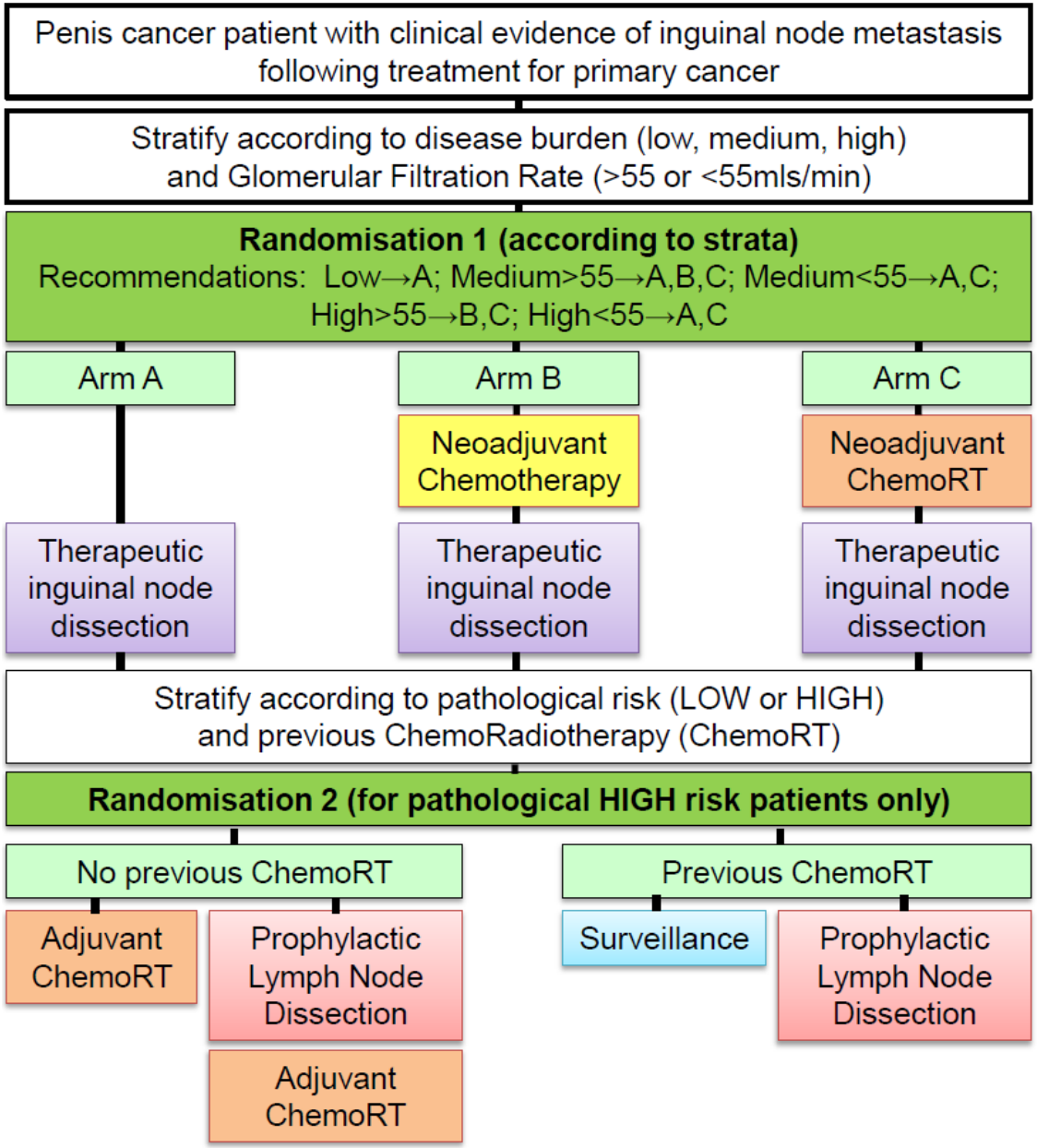
Prior x Data → Posterior

Posterior probability distribution



Example (IRCI004): The InPACT Trial

(Steve Nicholson, Emma Hall, Lucinda Billingham)



- International
- Strata-specific randomisations to allow all patients
- Multiple randomisations to ask different questions in pathway
- Bayesian analysis of overall survival time
- N=400 over 5 years justified using reverse philosophy concept

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Bayesian Approach with Reverse Philosophy

Usual approach

Detectable difference in trial
Decide the minimum clinically relevant difference for the trial to detect in terms of survival on experimental arm compared to that expected on the control arm

Number of events
Calculate the number of events needed to test null hypothesis of no difference with 5% significance level and 90% power

Number of patients
Estimate the number of patients the trial needs to recruit to observe the number of events in r years recruitment and f years follow-up

Reverse Philosophy

Detectable difference in trial
For the given number of events:
(i) Can the trial provide helpful information for future decision-making
(ii) What are the error rates for pre-specified decision criteria

Number of events
Calculate the expected number of events that will be observed given r years recruitment and f years follow-up

Number of patients
Estimate the feasible number of patients that the trial can recruit in r years

InPACT: would 400 patients give worthwhile information?

- 3 research questions: (i) Neoadjuvant: Yes or No; (ii) Neoadjuvant: Chemo vs ChemoRT; (iii) PLND for high risk: Yes or No
- 400 patients gives 88, 84,181 events for each question
- If OBSERVED HR=0.8 then p(True HR<1) = 86% (averaged across different questions and different priors)
- Decision from posterior distribution: if p(HR<1.0) > 60% then ACCEPT treatment for future use, otherwise remain uncertain
  - 81% chance of true positive conclusion (average)
  - 8% chance of false positive conclusion (average)

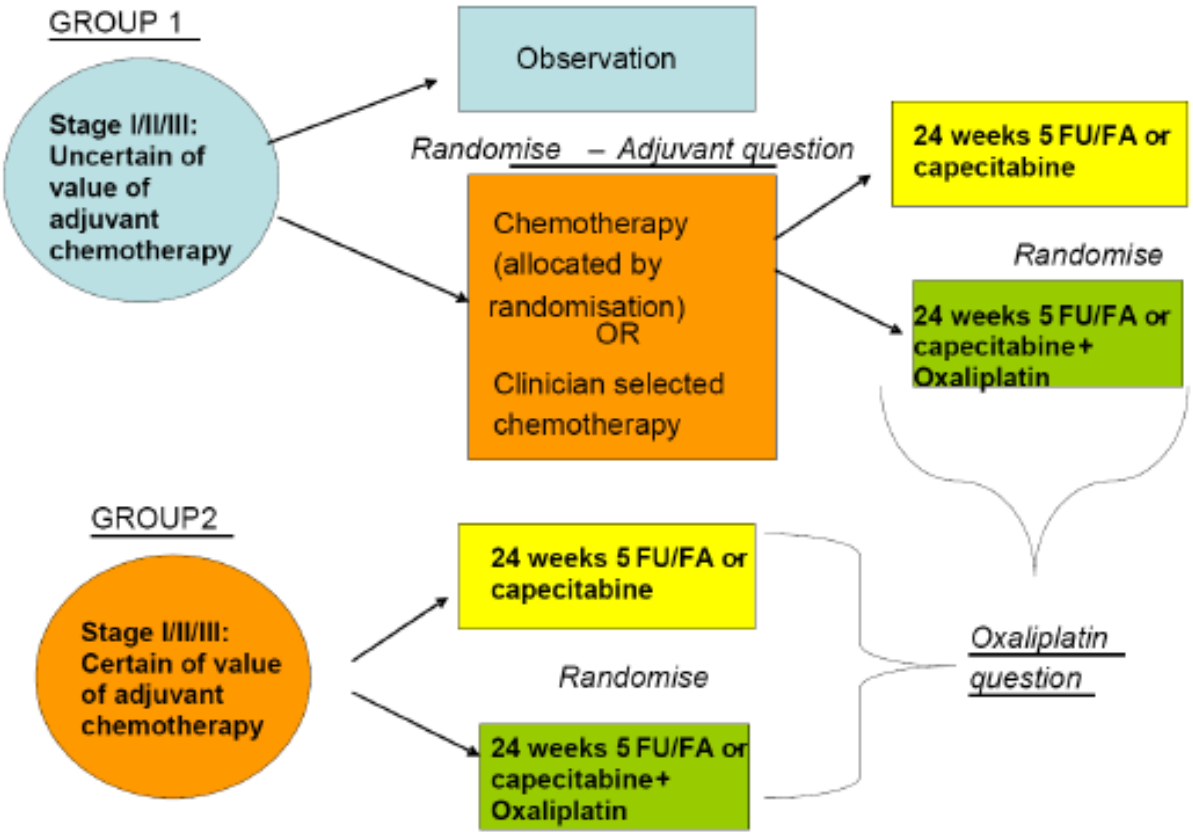
What about Incorporating Existing Evidence as a Prior Distribution?

Tan S-B, Dear KBG, Bruzzi P, Machin D; Strategy for randomised clinical trials in rare cancers BMJ 2003

- Aim: Combine all current evidence into a single prior probability distribution for the treatment effect
- Use systematic review of literature to identify relevant studies
  - Include all types of evidence: randomised trials, single arm trials, retrospective series, single case studies
  - Maximise broadness of search strategy
- Obtain log HR from each study
- Weight the different studies according to:
  - Pertinence: how close is the information to that we wish to obtain
  - Validity: quality of the study
  - Precision: depends on number of events
- Combine the log HR and weights

BALLAD Trial (IRCI002) : Resected Stage I-III Small Bowel Adenocarcinoma (N>545)

(Richard Wilson, Jim Paul)



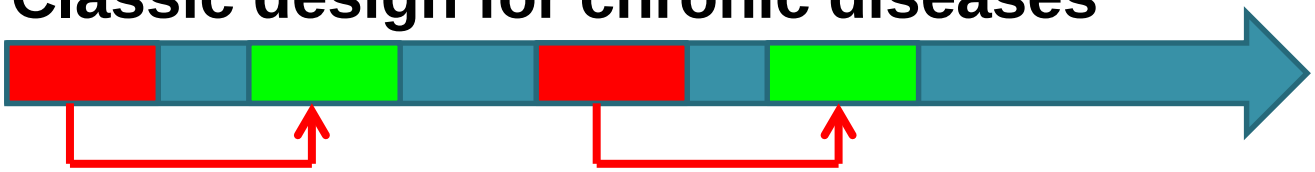
- Pragmatic design to maximise recruitment
- Use surrogate DFS rather than survival
- Use relaxed error rates: 80% power for HR=0.75 with 20% 1-sided significance level
- Futility stopping rule
- If statistically significant then use Bayesian analysis to combine trial results with elicited clinician prior to give final posterior probability distribution for HR

N-of-1 trials

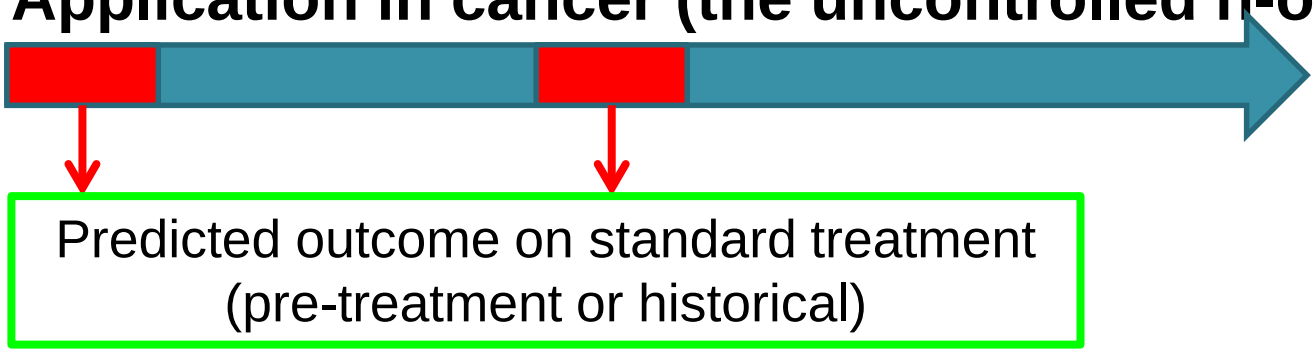
Investigational treatment

Control treatment (standard / placebo)

Classic design for chronic diseases



Application in cancer (the uncontrolled n-of-1 trial)



Prospective protocol-defined study
Serial n-of-1 trials
Aggregate using meta-analysis type methods

Summary

- Need to think differently when designing, running and interpreting trials in rare diseases
- Strive for good quality designs that minimise bias
- Be prepared to compromise on quantity of evidence i.e. accept more uncertainty than normal
- Choose methodology appropriate to the level of rarity
- Bayesian is proving to be a useful approach
- Serial uncontrolled n-of-1 trials may be a good approach at the extreme end of the scale
- Multiple strategies is a common approach
- If objective is to potentially change clinical practice then call it phase III