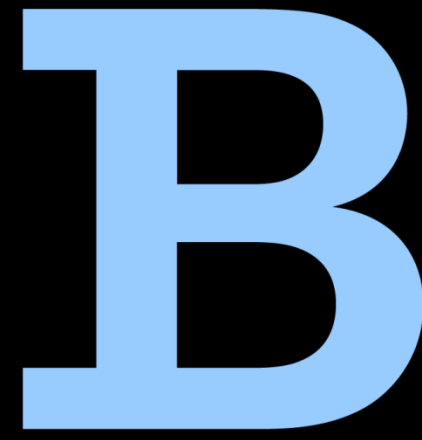




**Introduction to  
clinical trial  
methodology**



**Keith Wheatley  
University of Birmingham**

# Outline

- **Randomisation**
- **Design**
- **Eligibility**
- **End points**
- **Sample size**
- **Compliance and follow-up**
- **Analysis**
- **Evidence-based medicine**

# SAB – a promising new treatment for AML in the elderly?

Treatment	Number of pts	CR rate
DAT	167	47%
SAB	284	61%

p-values: p=0.006 (unadjusted)  
p=0.0006 (adjusted)

# SAB – a promising new treatment for AML in the elderly?

Treatment	Number of pts	CR rate	Induction deaths	Resistant disease
DAT	167	47%	30%	23%
SAB	284	61%	15%	24%

$p=0.00007$

# SAB – Conclusion?

**SAB is a better treatment for AML in the elderly than DAT, because it is as effective against the disease but is much less toxic**

# What is SAB?

**Answer:**

S = same

A = as

B = before

# SAB – Reason for difference

- Cannot be certain
- Most likely improved supportive care

# DAT v. MAC in AML9 and AML11

Treatment	Trial	Period	CR rate
DAT	AML9	1984-90	47%
DAT	AML11	1990-98	61%
MAC	AML11	1990-98	55%

MAC v. DAT (AML9):

p=0.01

MAC v. DAT (AML11):

p=0.04

# Problems with historical comparisons

- **Cannot eliminate confounding – other things change over time**
- **Concomitant therapy improves – e.g. medical therapy, surgery, radiotherapy and/or supportive care change**
- **Time shift bias – even if earlier diagnosis does not improve outcome, patients will appear to live longer**
- **Stage migration (Will Rogers phenomenon) – modification of staging systems frequent**
- **Cannot adequately adjust for these**

# Trial design

- Important to consider in detail at the beginning

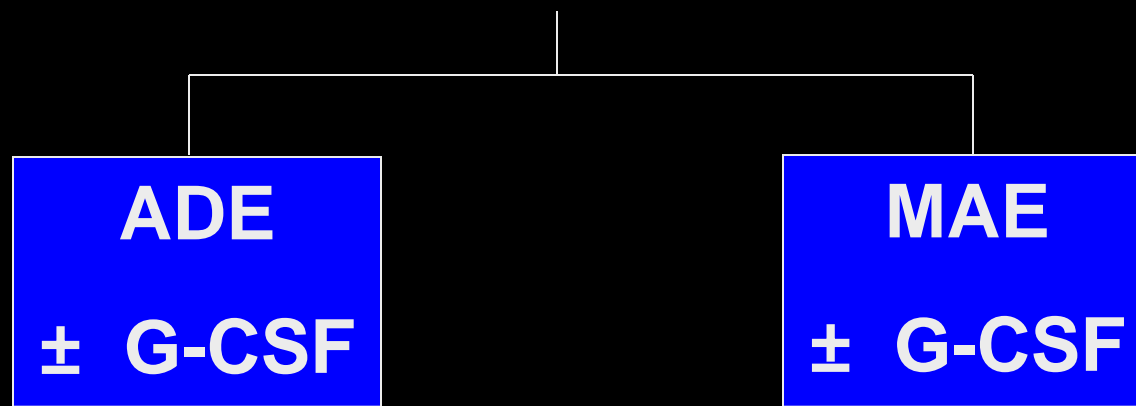
# Blinding and placebo control

- When should blinding be considered?  
Subjective endpoints – e.g. QoL
- Who to blind – patient, treater, assessor?
- PD REHAB – why no placebo?
  - What would be placebo?
  - Logistics – adds to cost

# Factorial design – AML12

Induction:

Randomise



Consolidation:

Randomise



# Factorial designs – PD REHAB?

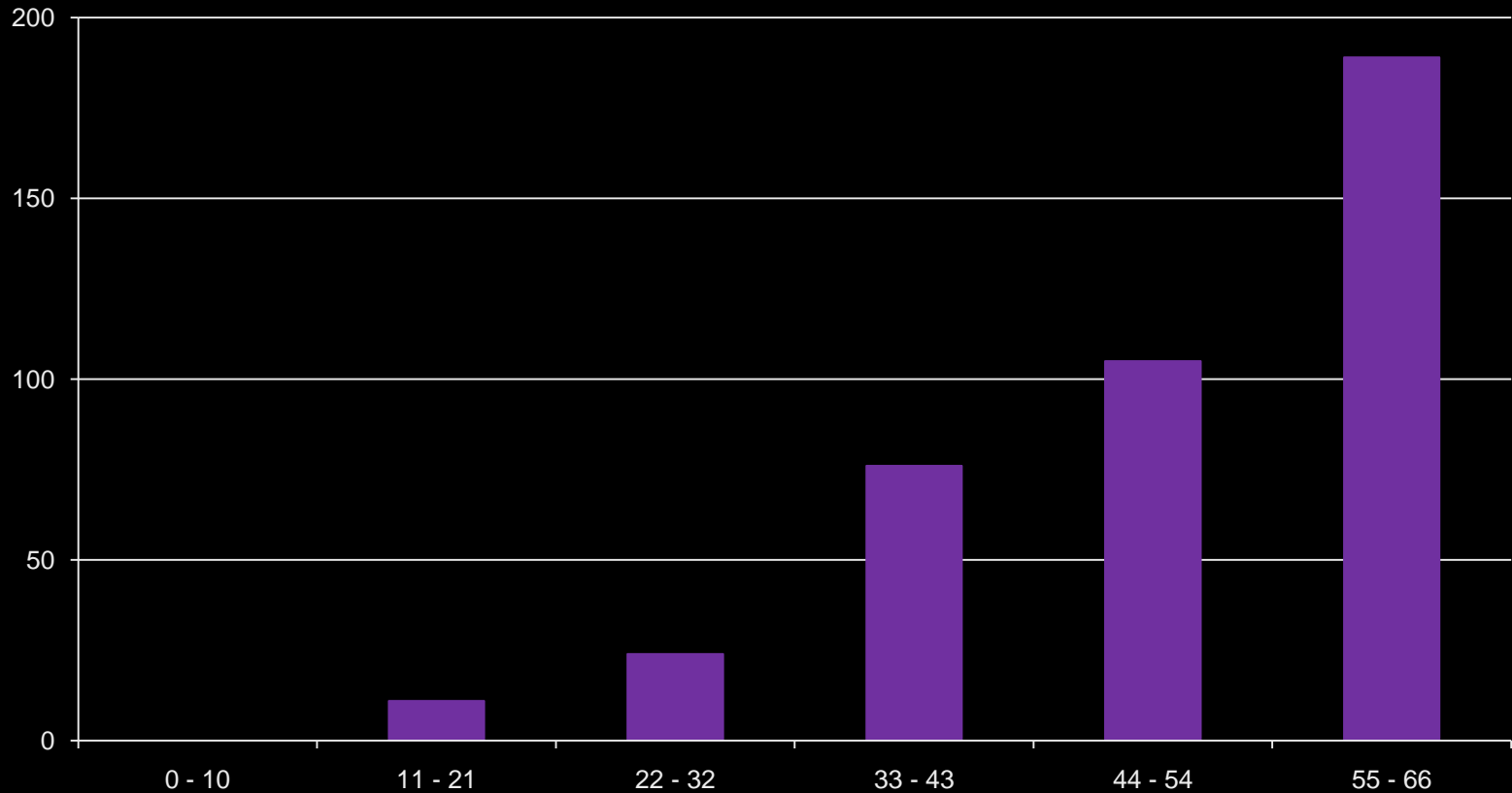
- If PD REHAB shows a benefit, how do we know if it's due to both PT and OT or just one or the other?
- Original design submitted to HTA had factorial design with 4 arms
- HTA wanted 2 arm trial
- Probably the correct decision as can't separate PT and OT in practice

# Eligibility

- **Want to recruit patient population representative of those who would receive the therapy in routine clinical practice**
- **Need broad eligibility in order to recruit a heterogeneous set of patients**
- **Base eligibility on the “uncertainty principle”**

# PD REHAB – baseline NEADL

NEADL Score at Baseline



# Endpoints

- **Need to be clinically relevant – i.e. important to patients**
- **Treatments should be used if they improve the quantity and/or quality of life of patients**
- **PD REHAB – proposed both NEADL and PDQ-39 as primary endpoints, but HTA wanted single primary endpoint**
- **Will improvement in NEADL with PT/OT be meaningful to patients – i.e. improve QoL?**

# Endpoints

- In progressive diseases, need long-term outcomes
- Primary time point for analysis of PD REHAB is 3 months – i.e. immediately after treatment in PT/OT arm
- But, is any benefit maintained? PT/OT will be more useful (and cost-effective) if it is
- Hence, also analyse at 9 and 15 months

# Sample size

- Calculation involves guesswork
- Dichotomous or time-to-event variables

Control	Experimental	Power	No. patients
20%	40%	80%	150
20%	30%	80%	500
20%	30%	90%	680
40%	50%	90%	1000
40%	45%	90%	3900

# Sample size

- Continuous variables
- Require fewer patients than dichotomous
- PD REHAB
  - clinically meaningful difference in NEADL = 2.5 points
  - SD from PD OT = 10.1
  - $2p = 0.05$ , power = 90%
  - 680 patients needed (750 with drop outs)

# Sample size

- **PD REHAB**
  - clinically meaningful difference in PDQ-39 SI = 3.5 points
  - SD from PD OT = 13.5
  - $2p = 0.05$ , power = 90%
  - 620 patients needed

# Compliance

- **Important to minimise crossovers since need to do intention-to-treat (ITT) analysis**
- **Crossovers will dilute treatment effect (if treatment is effective)**

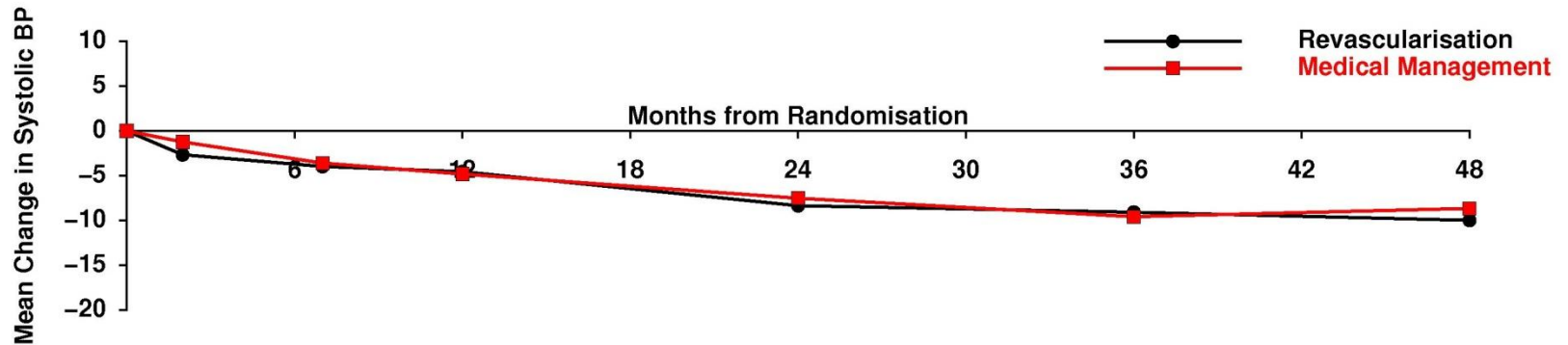
# Analysis

- **Comparing proportions – Chi-squared test**
- **Comparing survival times – logrank test**
- **Comparing continuous variables – t-test or Wilcoxon test**
- **Multivariate methods, e.g. Cox regression**
- **Repeated measures analysis**
  
- **Keep it simple**

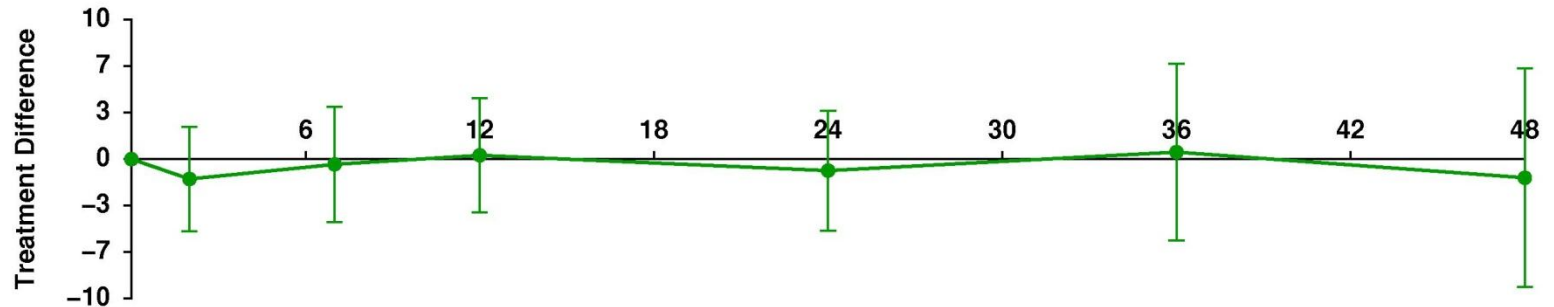
# Analysis

- **Intention-to-treat (ITT) principle – analyse all patients in the group to which allocated irrespective of compliance, ineligibility, etc**
- **Subgroup analyses – want to know whether some types of patients benefit more than others, but dangerous and can lead to misleading results**

# Repeated measures - ASTRAL



Revascularisation:	384	337	330	312	252	189	118
Medical:	388	355	345	327	258	171	116



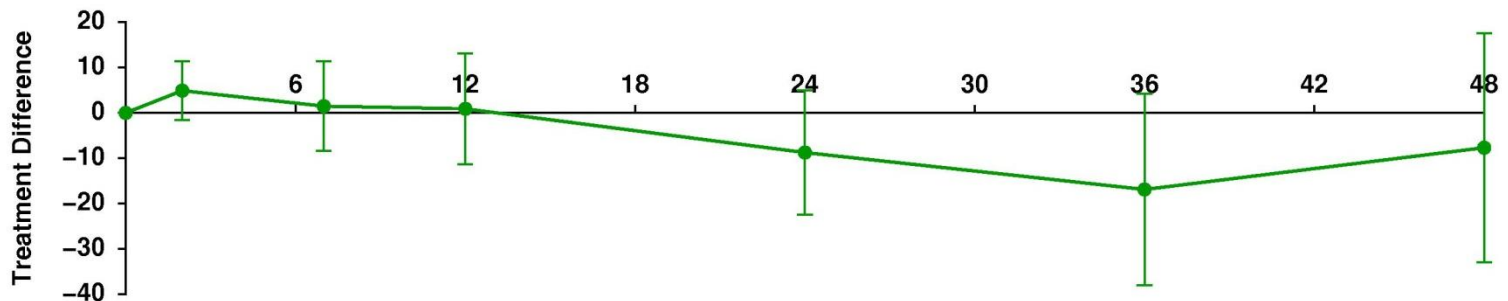
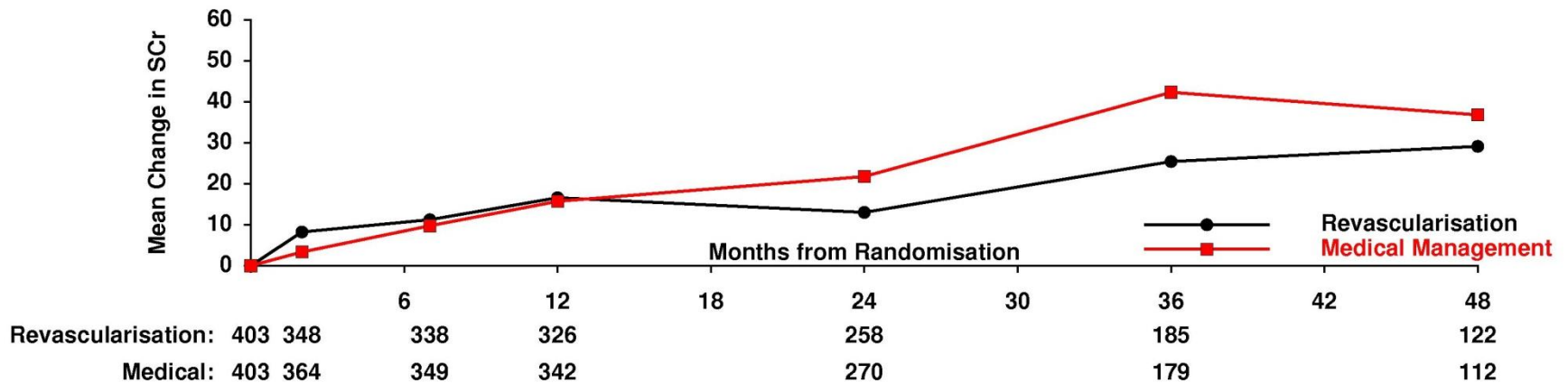
Repeated Measures analysis:  $p=1.0$

# ASTRAL trial

- Renal artery stenosis (RAS) is a relatively common condition
- Annual mortality rate of about 15%
- Commonly associated with both chronic kidney disease (CKD) and hypertension
- Treatment has traditionally focussed on correcting the stenosis by revascularisation using balloon angioplasty and stent insertion
- Widely used procedure, but not without risks

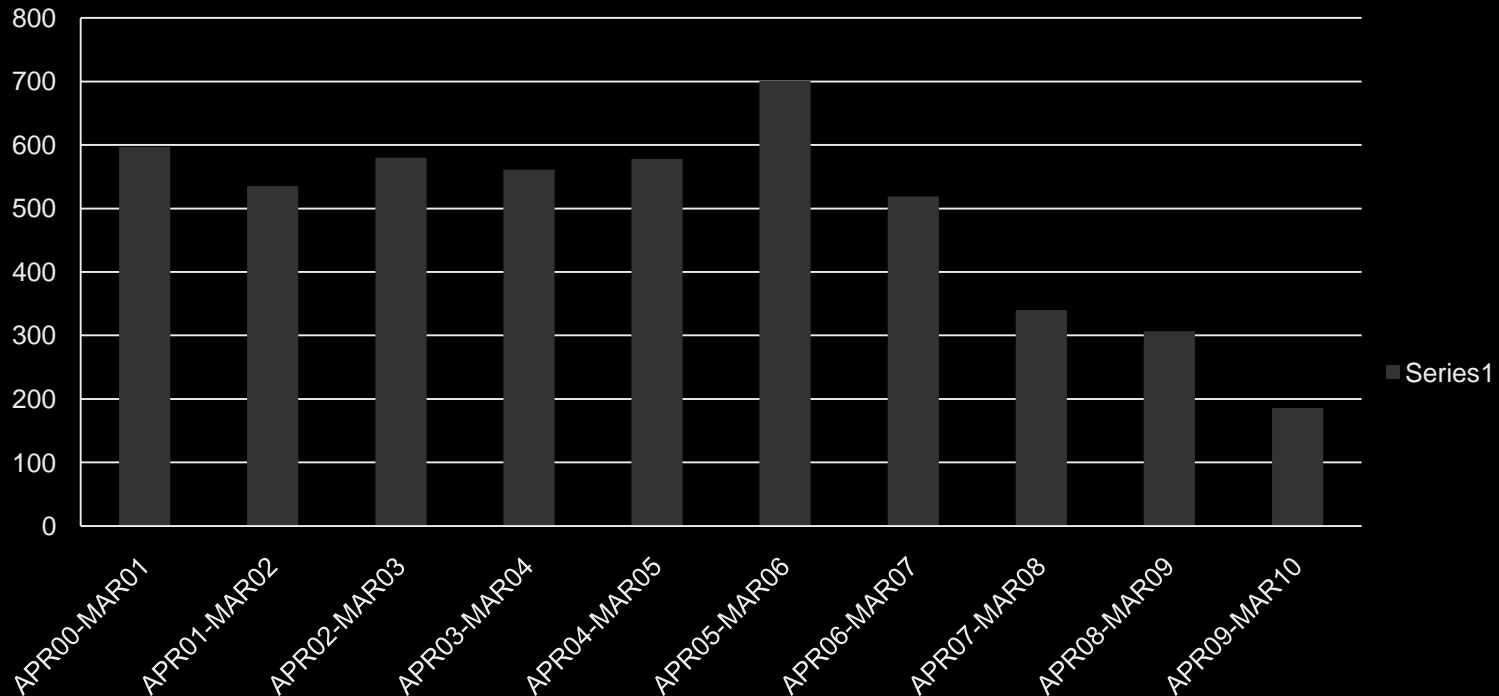
# ASTRAL: Results

- No benefit for revascularisation on any endpoint
- Primary endpoint – serum creatinine,  $p=0.6$



# ASTRAL – Practice changing

## NON- ASTRAL HES DATA



# CRASH trial

- Intravenous corticosteroids widely used for treatment of severe head injury – in 64% of trauma centres in USA
- CRASH randomised 10,008 patients to steroid versus placebo
- Result – risk of death within 2 weeks:
  - 21% v. 18%,  $p=0.0001$
- Conclusion – a harmful treatment had been used for many years on the basis of belief, not evidence

# Evidence-based medicine

- Treatments used should be based on **reliable** evidence that they are effective
- Effective = makes the patient live longer and/or feel better
- Increasingly, cost-effectiveness is coming into the equation

# Summary

- **Randomised controlled trials are the gold standard for evaluating therapy (meta-analysis is the platinum standard!)**
- **Good design is important for generating reliable (and believable) results**
- **Negative trials are as informative as positive ones – can prevent limited resources being wasted on ineffective therapies and can allow them to be diverted to effective ones**

# Want to learn more?

- Courses available
- BCTU 3-day course on Research Methods for Clinical Trials
- Shorter courses being developed

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