PRACTICAL ISSUES OF IMPLEMENTING A MULTI-ARM MULTI-STAGE TRIAL: NEGOTIATIONS, APPROVALS, INTERACTIONS WITH COMMITTEES AND OPINIONS OF PATIENTS

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1. MAMS trials

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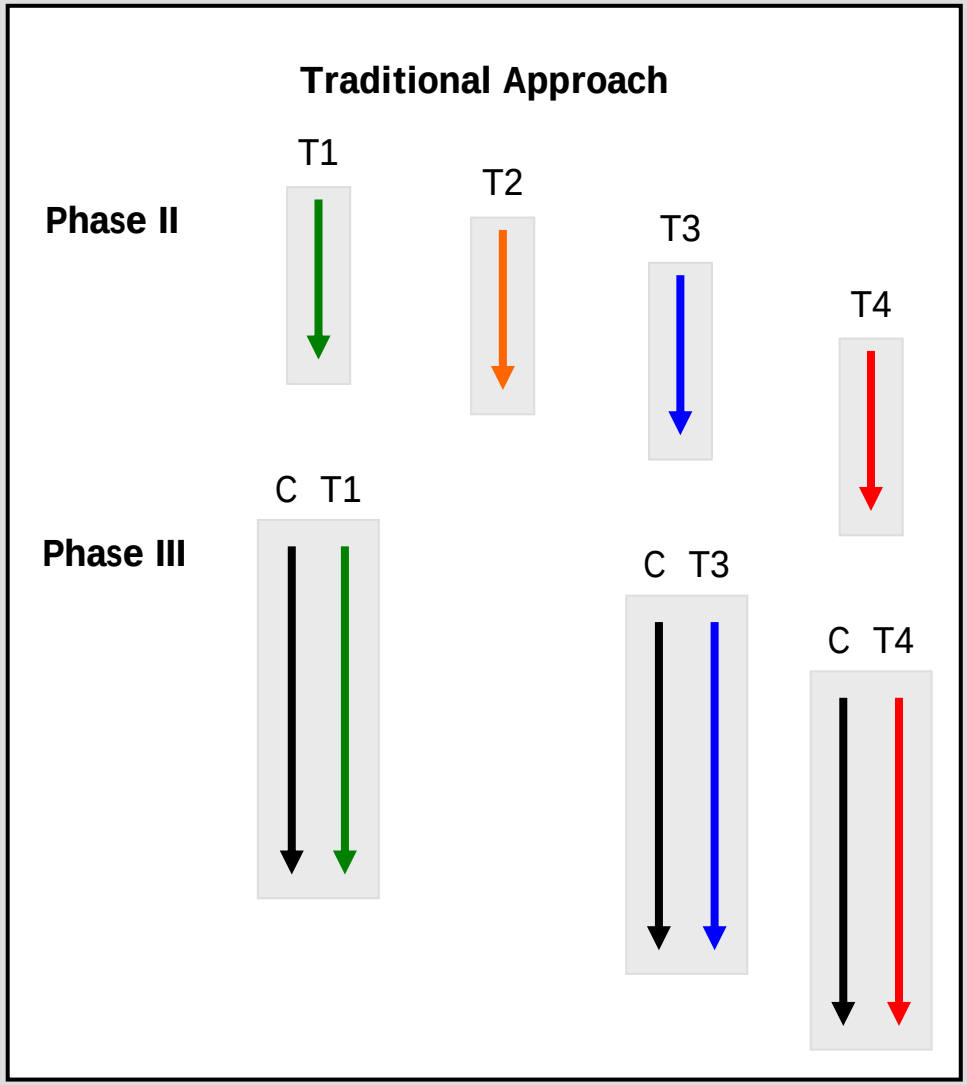
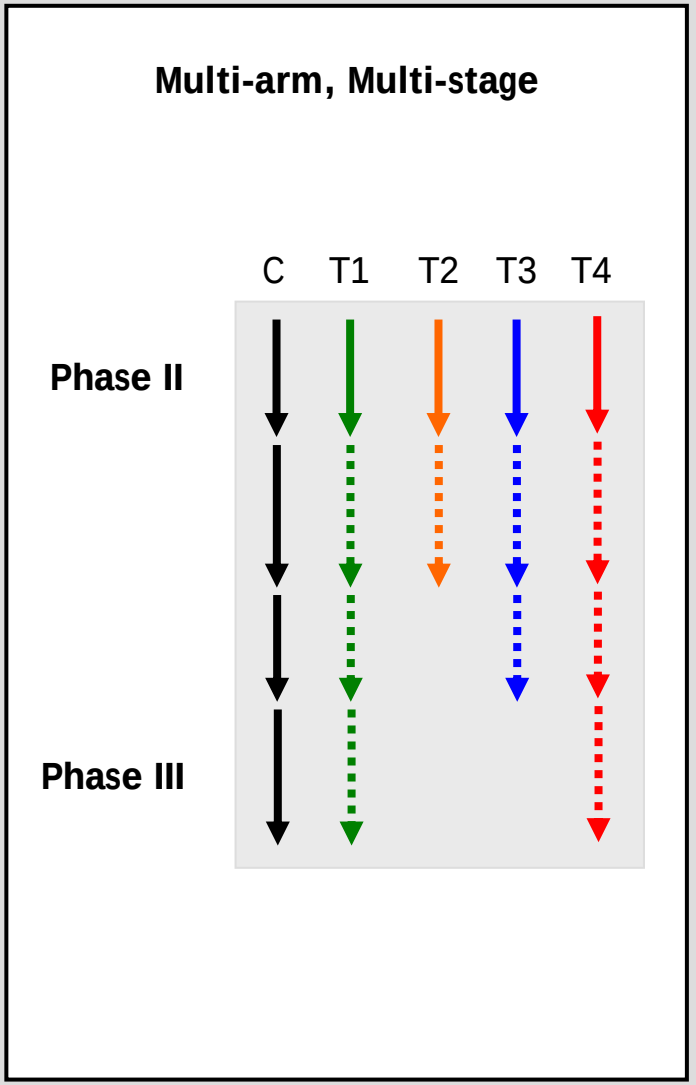
2. Application in trial design and conduct
3. Issues in analysis
4. Conclusions

Multi-Arm Multi-Stage trials

- New is not better than current
- Phase III trials require huge time and effort
  - High chance new treatment not superior (60-70%)
- Need better mechanism to select treatments for phase III trials
- Start by testing many promising treatments
- Start to randomise as quickly as possible
- Potential to discontinue unpromising arms
  - Use intermediate outcome measures
  - Lack-of-benefit testing on intermediate OM

MAMS vs traditional





Advantages of MAMS trials

1. Fewer patients	Randomised from the start
2. Less overall time	Concurrent assessment of agents (not sequential assessment) No delay between phase II and III Fewer applic^{n}s: finance, approvals
3. Increased flexibility	Adapts to intermediate results Focus on more promising arms
4. Reduced costs	Limited resources for trials Must use fairly and efficiently Provide value

Statistical issues not considered here
(Time-to-event workshop on 14-Feb, London)

2. Issues in trial design and conduct

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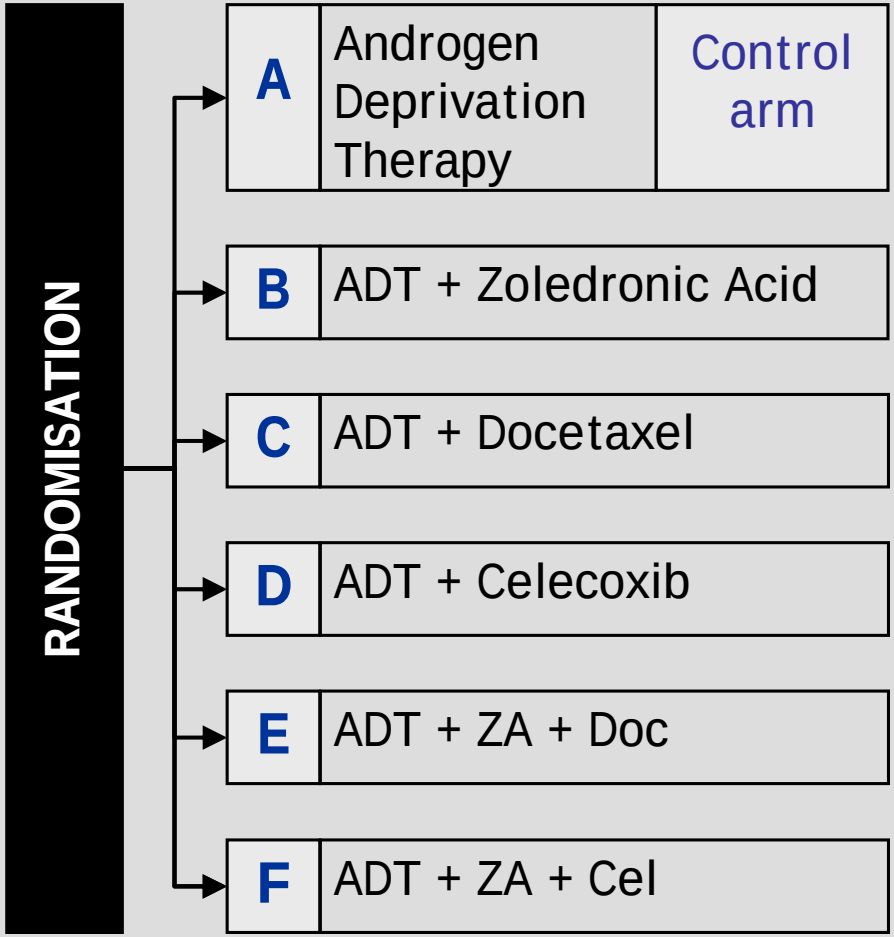
Need in prostate cancer

- 900,000 new prostate cancer in 2008
- Many high risk
  - Standard treatment = hormone therapy
  - Median survival: ~ 4 to 5 years
  - Median failure-free survival: ~2 years
- No new therapies improving survival for this group of men for many years
  - Urgent need to improve outcomes for these men

Design rationale

- Many interesting agents
  - Different classes and modes of action
  - Many used in later stages of disease
  - Others new
- No clear reason to choose a particular one
  - Many choices
  - Don’t want to choose arbitrarily
  - Want to assess all interesting agents
- Quicker and efficient to use MAMS design
  - Test many

STAMPEDE trial design



Treatment detail

Androgen Deprivation Therapy
:: Standard hormones
:: Given for >3 year

Zoledronic Acid
:: 3rd generation bisphosphonate
:: IV for 2 years every 3 to 4 weeks

Docetaxel
:: Taxane chemotherapy
:: IV for 6 cycles over 18 weeks

Celecoxib
:: Cox-2 inhibitor
:: Oral for 1 year

Groups to convince: industry

- Industry partners
  - Zoledronic acid — Novartis
  - Docetaxel — Sanofi-Aventis
  - Celecoxib — Pfizer
  - (Hormones therapy) — (as standard care)
- Free/discounted drug plus educational grant
- All keen on design because...
  - Efficient design
  - Early “get-out” if agent not so beneficial

Groups to convince: industry

- Engage companies with appropriate agents
  - Obtained three from priority list of agents
  - Some other companies not cooperative
  - Could have taken others but less scientifically interesting
- More companies = more negotiations
  - = More contracts = more time = more delays…?
  - But not unique to this design
  - Also true for many two arm trials

Groups to convince: clinicians

- Medical community
  - Patient group mostly seen by urological surgeons
  - Oncologists need to give some trial treatments
  - Help to work on relationships and streamlining
- Would it appear complex?
  - Discussions with peers in MDT meetings
  - Discussions with patients in clinics
  - Needed broad buy-in from across UK

Groups to convince: clinicians

- Previous multi-arm trials
  - Excellent recruitment to:
  - FOCUS – colorectal cancer – 5 arms
  - ICON5 – ovarian cancer – 5 arms
- Amendments
  - Tried to keep trial as simple as possible
  - Further simplifications to follow-up data
- Oncologist and urologists supportive

Groups to convince: clinicians

- Survey of sites – summer 2010 (n=29/90)
  - Site recruitment:
    - **19%** better than expected
    - **65%** as expected
    - **12%** less than expected
  - Ease of accrual:
    - **17%** easier than other trials
    - **54%** same as other trials
    - **28%** more difficult
  - Trial workload:
    - **21%** less than other trials
    - **58%** same as other trials
    - **21%** more than other trials

Groups to convince: patients

- Involved patient groups throughout
  - **Design:** One patient involved from initial design meeting
  - **Conduct:** Two patients on Trial Management Group
- Patients asked:
  - “Why wouldn’t you do this type of trial?”
- TMG has very positive opinions
  - Identified through NCRI Prostate CSG
  - Patient involvement good for trial

Groups to convince: patients

- Two-part PIS
  - Developed prior to current NRES guidance

1. General information sheet
   - Given prior to randomisation

2. Arm-specific information sheets
   - All given prior to randomisation OR
   - Allocation-relevant sheet given afterwards
   - Information need driven by patient choice

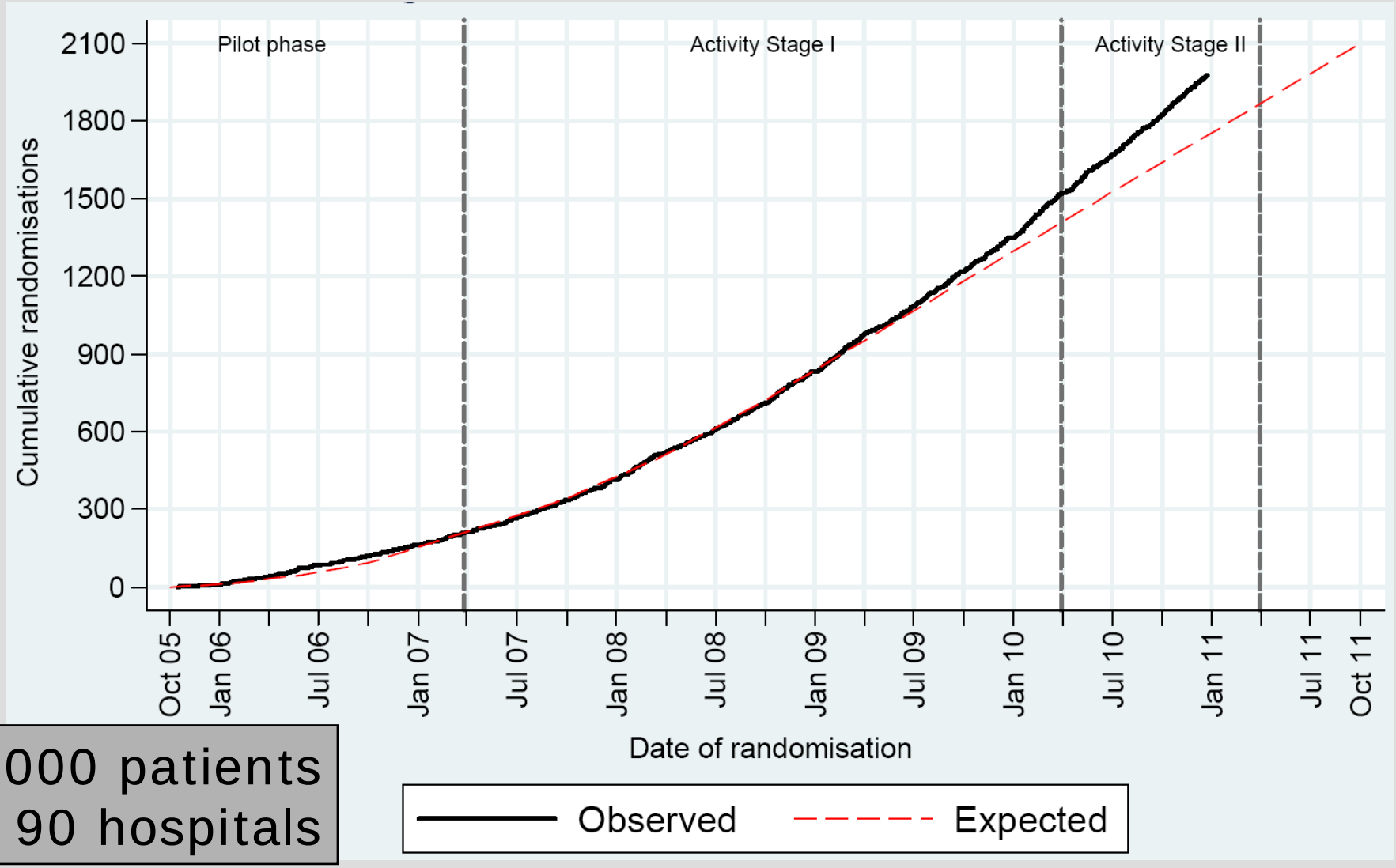
Groups to convince: funders

- Funding bodies
  - Cancer Research UK
  - (And industry partners)
- Potential for conservative reviews
  - No prior precedent for such approaches
- Approved
  - After much discussion

Groups to convince: others

- Regulatory approval
  - MHRA
- Ethics committees
  - 2-part PIS
- Hospital governance committees
  - Many!
- Approved
  - UK and Switzerland

Current accrual



>2000 patients
90 hospitals

Trial Design Stages

Stage	Outcome Measures	
	Primary	**Secondary**
Pilot	**Safety**	Feasibility
Activity I-III (phase II)	**Failure-free survival** (PSA-driven)	Overall survival Toxicity (safety) Skeletal-related events
Efficacy IV (phase III)	**Overall survival**	Failure-free survival Toxicity (safety) Skeletal-related events Quality of life

Target: Improvement OS at 4-yr 50% - 60% (HR = 0.75)

Trial plans

Stage	Type	1^0 OM	1-s sig	Power	HR_A	Critical HR	Events (Arm A)
I	Activity	FFS	0.50	95%	0.75	**1.00**	114
II	Activity	FFS	0.25	95%	0.75	**0.92**	215
III	Activity	FFS	0.10	95%	0.75	**0.89**	334
IV	Efficacy	OS	0.025	90%	0.75	-	400

- Target sample size depends on:
  - Traditional factors eg recruitment and event rates
  - MAMS factors eg arms, power, alpha at *each* stage

3. Issues in analysis

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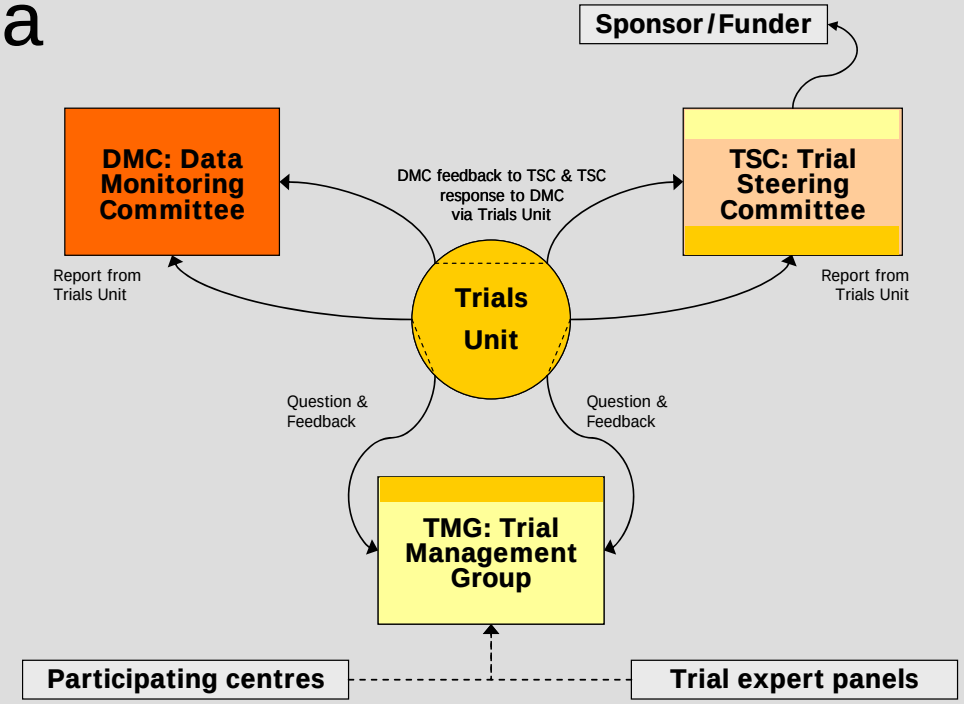
Comparisons

- Pairwise comparisons
  - Each research arm separately against control
- Research arms directly compared only if
  - Both are better than control
  - Accept limited power for comparison

Moving through stages

- IDMC review accumulating data
  - Make recommendations to TSC and TMG

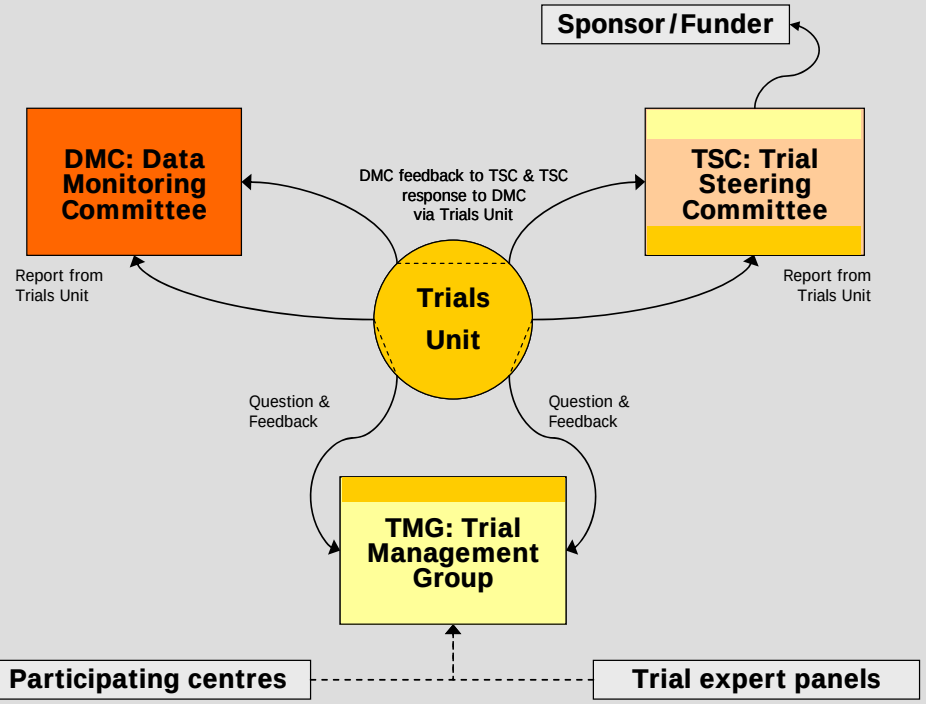
- Assess totality of data
  - Activity
    - Guided by critical HR
    - Increasingly stringent
  - Safety
  - External data



Moving through stages

- IDMC review interim data
  - Make recommendations to TSC and TMG

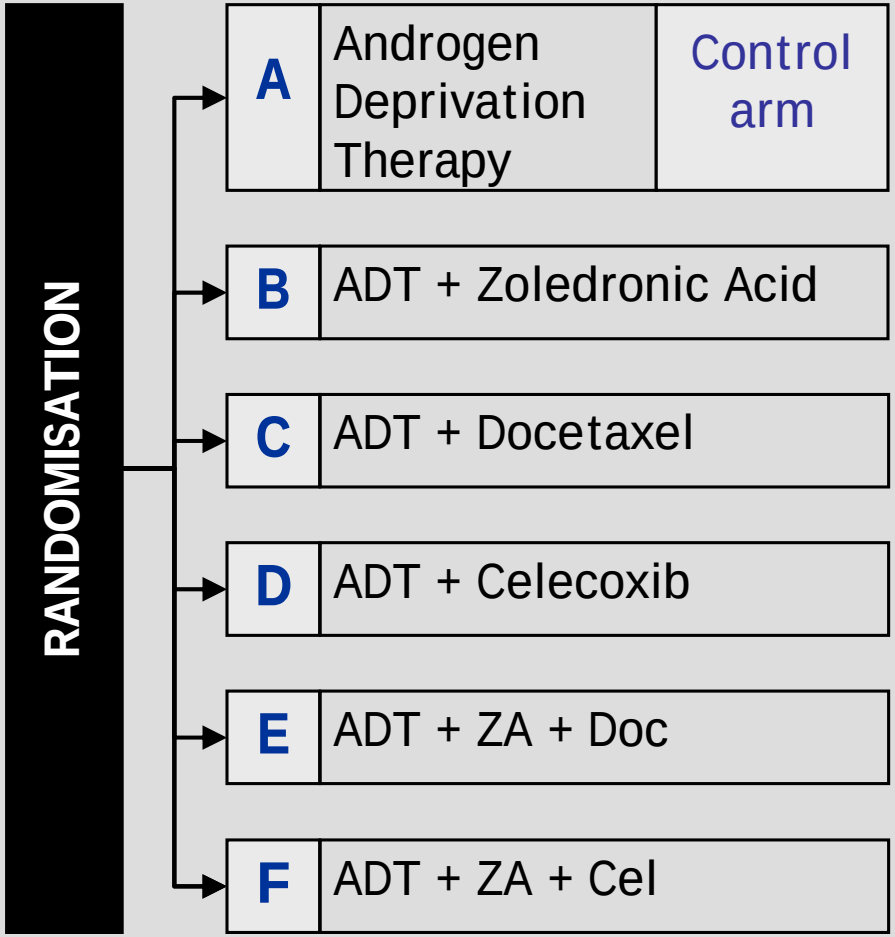
- Education & training
  - For all committees
  - Trust in relationships
  - Hypothetical examples



Possible recommendations

- May stop recruitment to arms
  - None, some or all
- May also stop treatment on these arms
  - Depends on data presented
- Follow-up will always continue

Trial design



- Drugs appear in multiple arms
  - ZA in 3 arms
  - Doc in 2 arms
  - Cel in 2 arms

Dropping arms or agents

- If combination arm stopped for lack of sufficient effect
  - Should “single” agent arm stop too?
- If single agent arm stopped for lack of sufficient effect
  - Should combination arm stop too?
- Training and discussion
  - Totality of evidence
  - Treat as if external data from another trial

Intermediate analyses

- Activity Stage I analysis
  - March 2010
  - 1469 patients overall
  - 129 FFS events on control arm
- Outcome
  - IDMC recommended **all** arms continue accrual
  - TSC agreed to recommendation

When arms continue…

- Intermediate assessments require only modest evidence to continue accrual
  - Primarily consider activity rather than efficacy
  - Emphasized to investigators
- Intermediate results reinforce need to continue randomisation
  - Gain stronger evidence!
  - Researchers not taken out of equipoise by implicit intermediate information

If arms stop…

- Recruitment continues seamlessly
- Randomisation to “stopping arms” turned off
  - Sites notified immediately
  - Sites tell new pts which parts of PIS irrelevant
- Processes agreed by MHRA and REC
  - Fundamental part of trial design
  - Will be notified by amendment
- Tailored information to patients if trt stopped
- PIS, CF and protocol revised asap
  - Quickly but not immediately

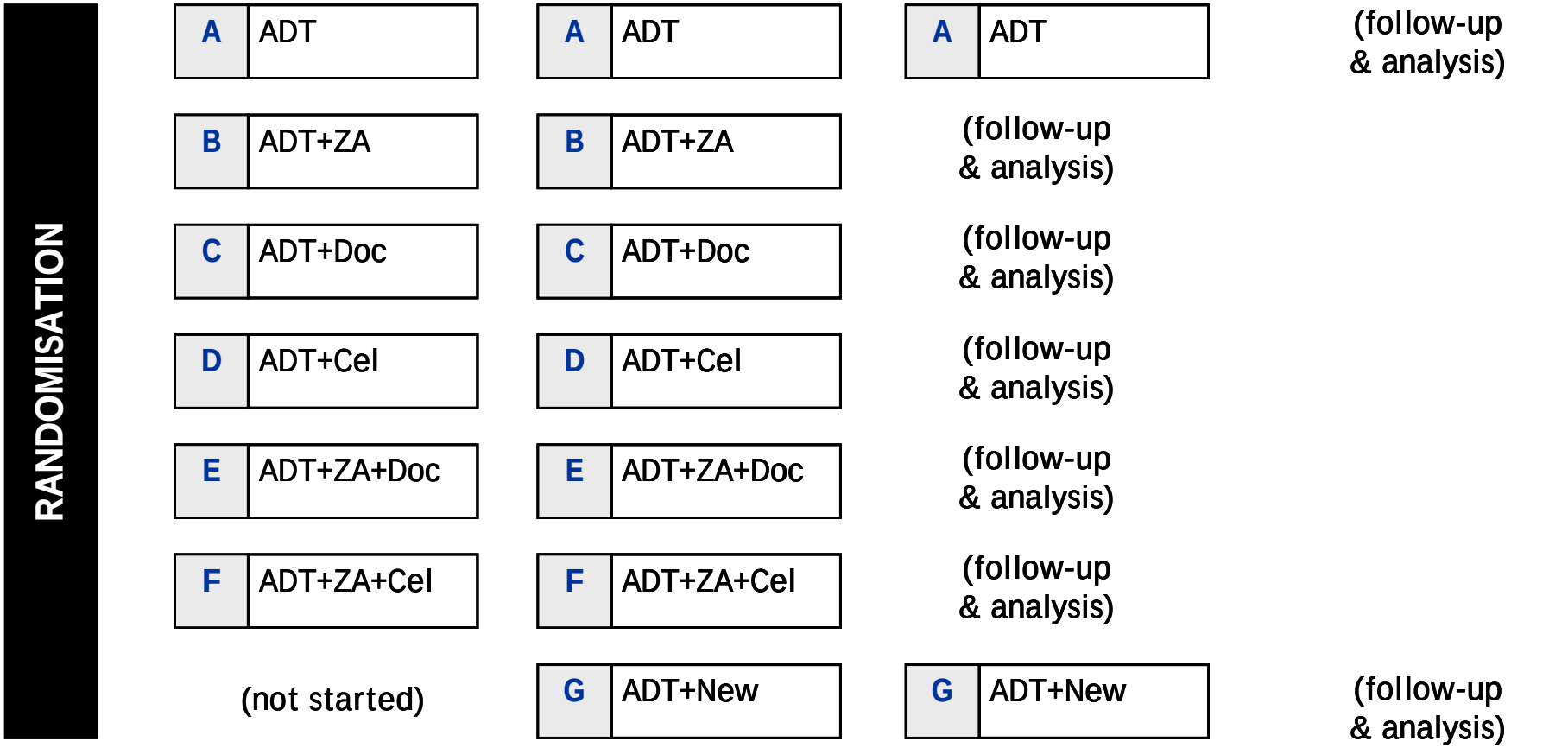
Intermediate analyses

- Activity Stage I
  - March 2010
- Activity Stage II
  - March 2011
  - >2000 patients
  - ~220 FFS events on control arm
  - Bar raised for activity (critical HR)

Flexibility and extension

- "Dropping" arms?
  - Adding arms?!
- Design adapts to include further agents
  - Add new research arms during trial
- New agents subjected to same hurdles
  - Apply same design parameters to new arms
  - New arm matures after original research arms
- Only compare to contemporaneous controls

Flexibility and extension



Flexibility and extension

- Can start recruiting quickly
  - Protocol amendment = simple
  - Scientific review = as amendment
  - Drug & funding = discussions
- Discussions ongoing to do this
  - Advanced discussions with one company
  - Discussions starting with others
  - Scientific review for first new drug = completed
- New agents must be selected for right reasons!

4. Conclusions

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Key points – 1

- Many diseases have many potential new treatments
- Most likely to prove no more effective than control
- MAMS trials speed evaluation of new treatments by testing many treatments at the same time and using lack-of-benefit analyses

Key points – 2

- MAMS trials can be implemented successfully
- Engagement from all communities required
  - Clinicians, patients, funders, industry, others
- Flexible design may allow further savings of time and effort in the future

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Software

- Free software available
  - Design MAMS trials
  - Available from MRC CTU
  - Implemented in Stata

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