Flexible trial design in practice – dropping and adding arms in STAMPEDE: a multi-arm multi-stage randomised controlled trial (MRC PR08, CRUK/06/019)

Matthew Sydes

MRC Clinical Trials Unit, London, UK

ND James, MD Mason, NW Clarke, C Amos, J Anderson, J de Bono, DP Dearnaley, J Dwyer, G Jovic, ASW Ritchie, JM Russell, K Sanders, G Thalmann, MKB Parmar

on behalf of the STAMPEDE investigators

STRUCTURE

1. Rationale for multi-arm, multi-stage (MAMS) RCTs

2. Overview of STAMPEDE

3. Stopping recruitment early to some trial arms
   - Methodological and practical issues
   - Following an intermediate analysis

4. Addition of new research arms during the trial
   - Methodological and practical issues

STRUCTURE

1. Rationale for multi-arm, multi-stage (MAMS) RCTs

2. Overview of STAMPEDE

3. Stopping recruitment early to some trial arms
   - Methodological and practical issues
   - Following an intermediate analysis

4. Addition of new research arms during the trial
   - Methodological and practical issues

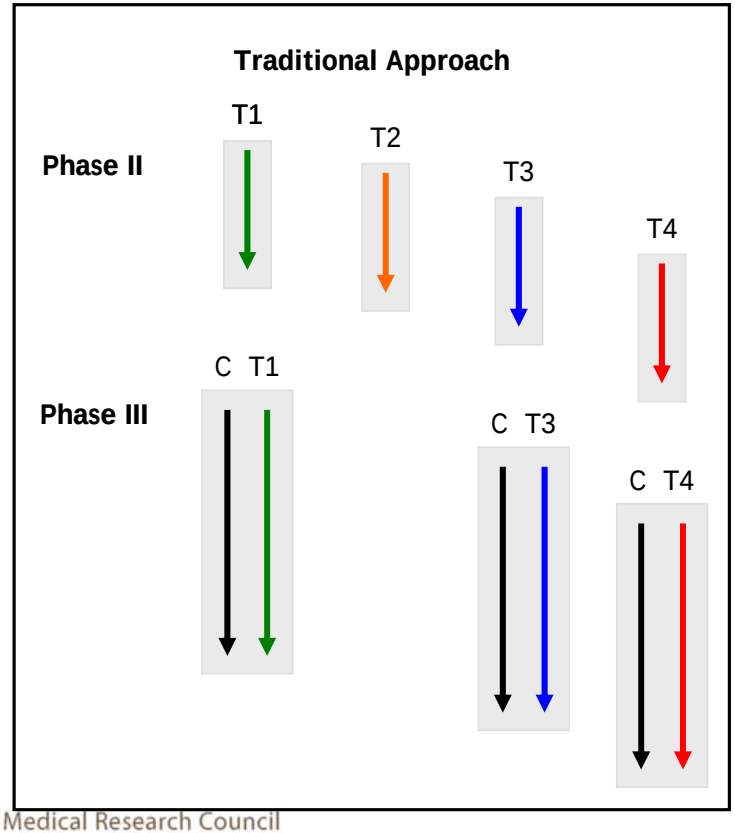
Research environment

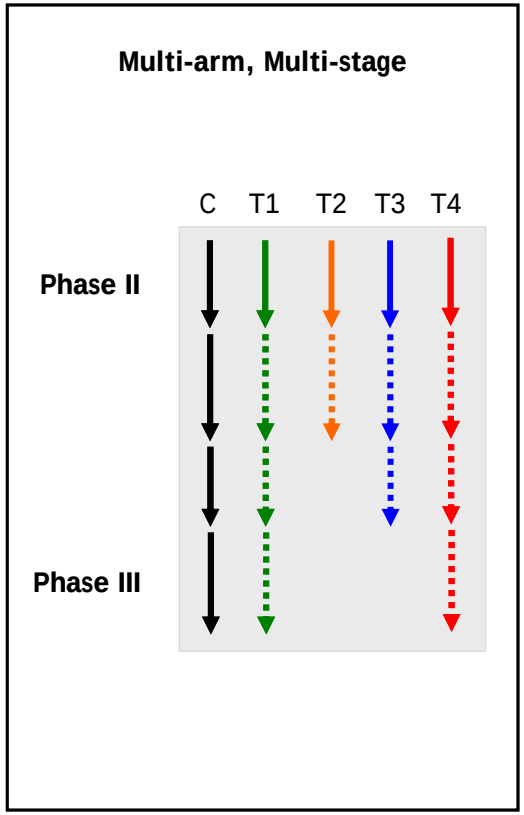
- New treatments usually not better than current
  - About 30 to 40% are positive
  - Both academia and industry
- Phase III trials require huge time, effort and cost
  - High chance new treatment not superior in given trial
- Must be a better way to select treatments for efficacy assessments

Advantages of MAMS trials

1. Fewer patients
2. Less overall time

- Concurrent assessment of agents
- Start randomising from the start
- One seamless trial
- Fewer applic^{n}s: finance, approvals



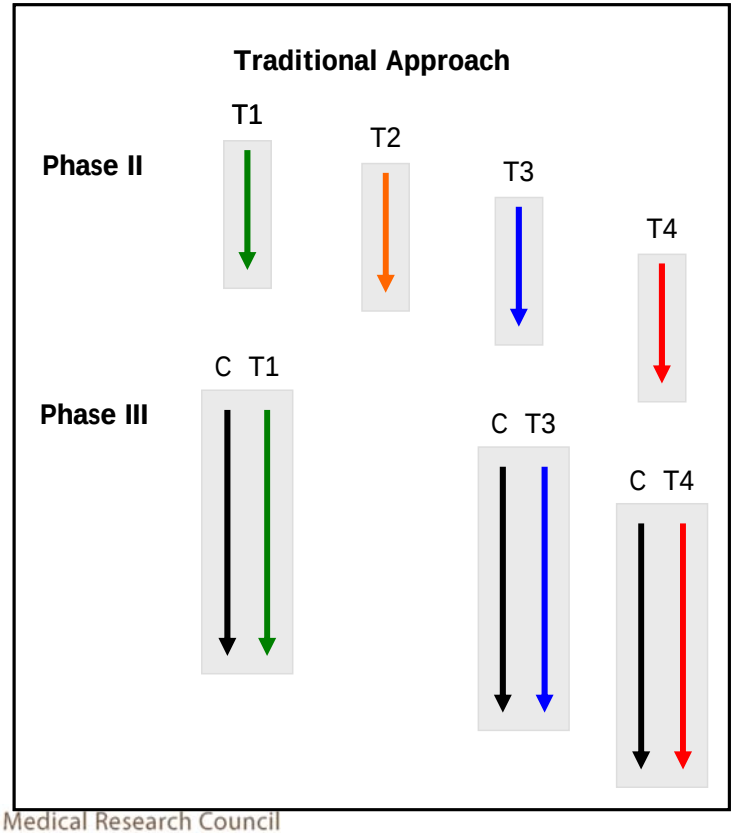


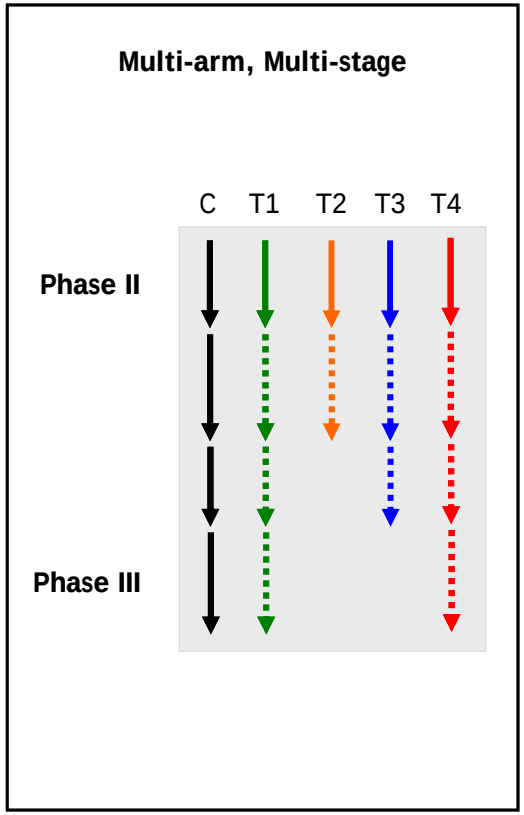
Advantages of MAMS trials

MRC Clinical Trials Unit

3. Increased flexibility

- Adapts to intermediate results
- Focus on more promising arms

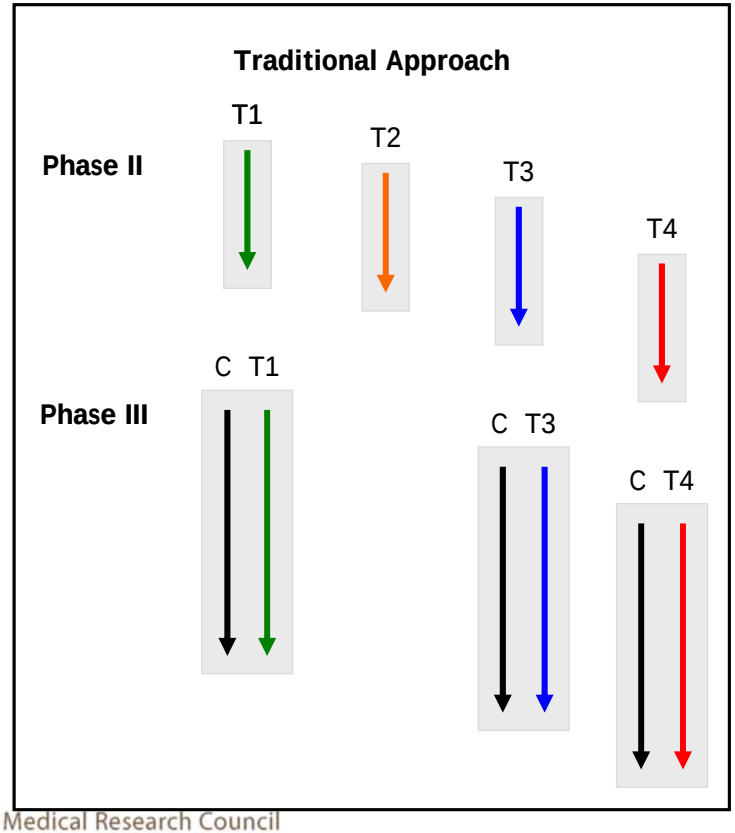


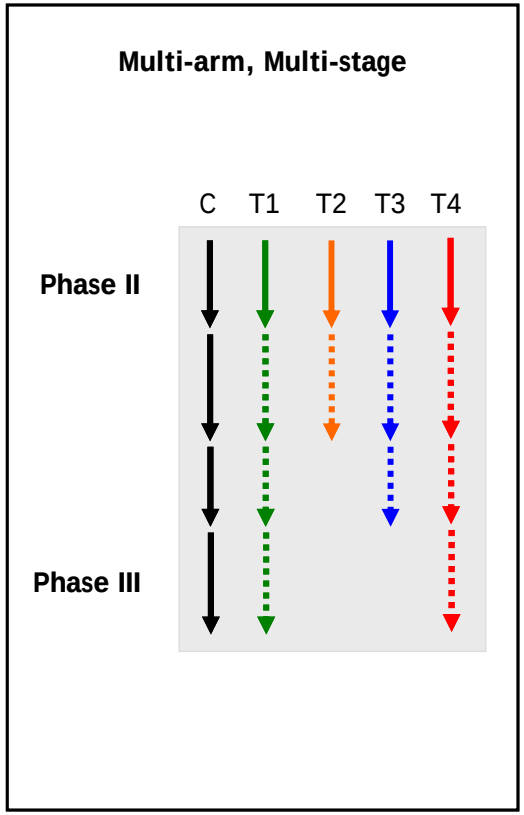


Advantages of MAMS trials

4. Reduced costs

- Limited resources for trials
- Must use fairly and efficiently
- Provide value





STRUCTURE

1. Rationale for multi-arm, multi-stage (MAMS) RCTs

2. Overview of STAMPEDE

3. Stopping recruitment early to some trial arms
   - Methodological and practical issues
   - Following an intermediate analysis

4. Addition of new research arms during the trial
   - Methodological and practical issues

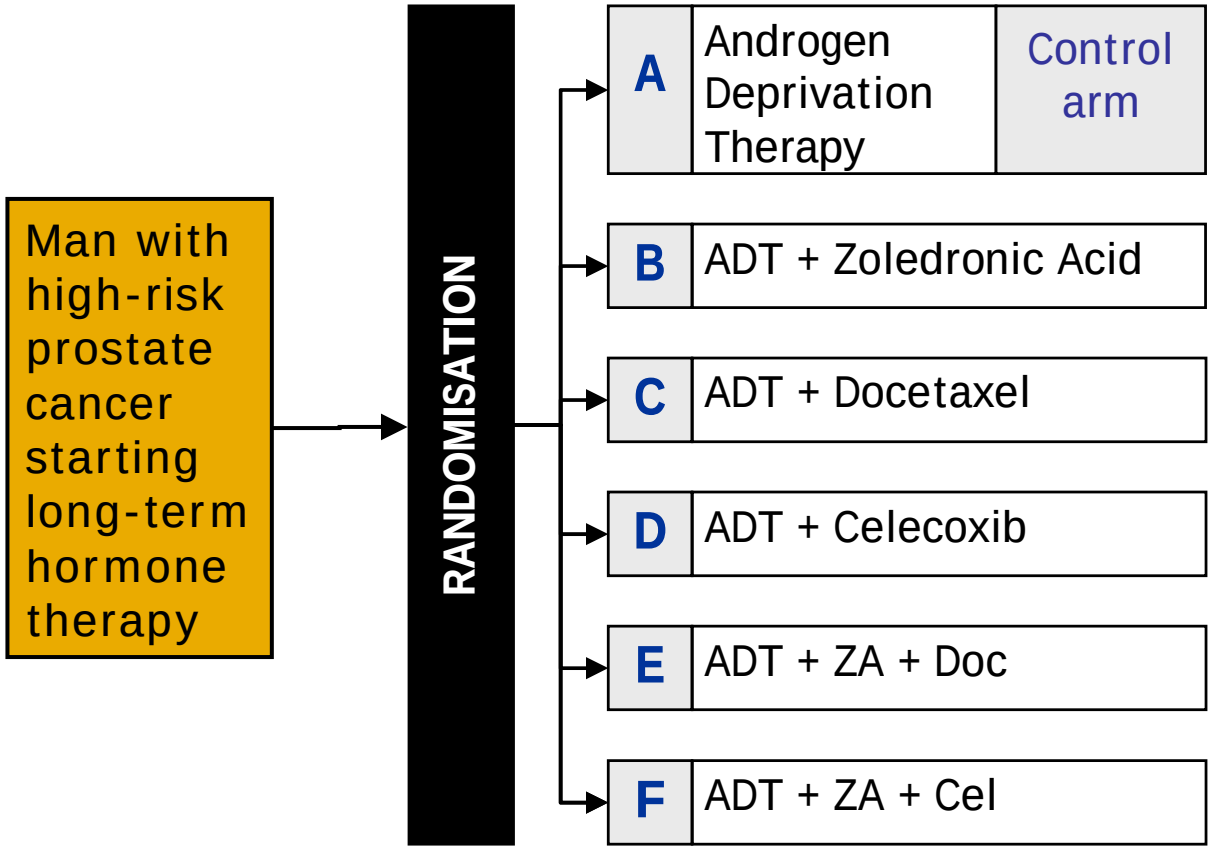
Need in prostate cancer

- 900,000 new prostate cancers in 2008
- Large proportion locally advanced or metastatic
  - Median survival: ~5 years
  - Median failure-free survival: ~2 years
- Standard treatment = hormone therapy (HT or ADT)
- No new therapies demonstrating improved survival for this whole group of men for many years

Design rationale

- Many interesting agents to assess
  - Different classes, different modes of action
- No clear reason to choose a particular one to study
- Quicker and efficient to use MAMS design
  - Start to test many agents
  - Focus towards more active agents using LOB analyses

STAMPEDE original design



MRC PR08 – CRUK/06/019 ISRCTN78818544 -- NCT00268476

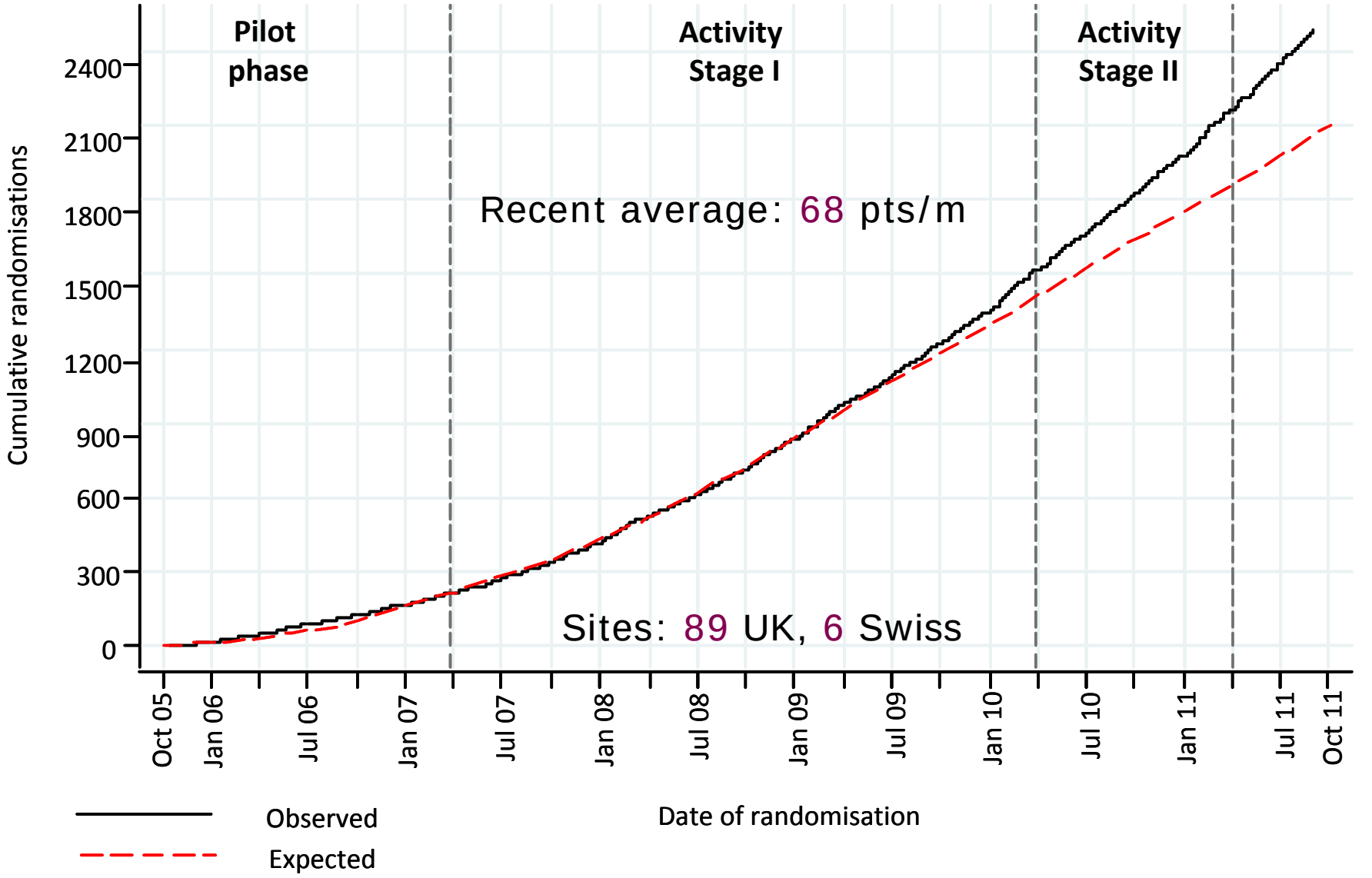
Trial plans

Stage	Type	1^0 OM	HR_A	Power	1s sig	Critical HR	Control Events
1	Activity	FFS	0.75	95%	0.500	1.00	114
2	Activity	FFS	0.75	95%	0.250	0.92	215
3	Activity	FFS	0.75	95%	0.100	0.89	334
4	Efficacy	OS	0.75	90%	0.025	-	400

OM=outcome measure, FFS=failure-free survival, OS=overall survival

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

STAMPEDE accrual



STRUCTURE

1. Rationale for multi-arm, multi-stage (MAMS) RCTs

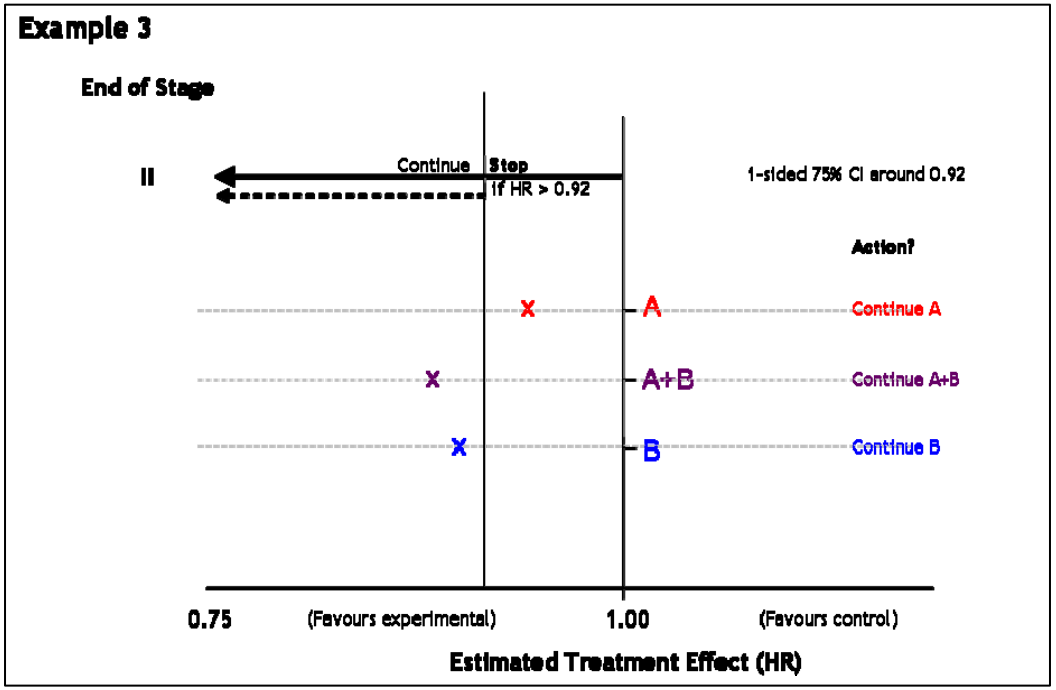
2. Overview of STAMPEDE

3. Stopping recruitment early to some trial arms
   - Methodological and practical issues
   - Following an intermediate analysis

4. Addition of new research arms during the trial
   - Methodological and practical issues

Preparations: training IDMC, TSC

- Joint meeting of IDMC and TSC
- Reinforce trial design
- Discuss hypothetical data
- Consider possible recommendations from IDMC
- Totality of evidence
- Treat data from other comparisons as if from another trial



Preparations: internal planning

- Many discussions re actions and communications
  - Start some months before IDMC meeting

- What if …
  - Arm(s) stopped for safety?
  - Arm(s) stopped for lack-of-benefit?
  - Both
  - Neither

Prep: what if stop for safety?

Time	Action
Day -28	Notify sites in writing of IDMC meeting date to pre-warn
Day -28	Circulate prior MHRA letter confirming that stopping early for LOB is **not** a substantial amendment, but part of trial design
Day -7	IDMC meeting
(<1 wk)	IDMC notes and recommendations finalised
Day 0	TSC meeting: stop / continue decision for each research arm
< 24 h	Turn off randomisation to arms stopping early for safety
< 24 h	Notify centres by email; pts to ignore irrelevant parts of PIS
< 24 h	Notify relevant industry partners
< 24 h	Notify TMG members
< 24 h	Alert CTU staff to potential queries

Prep: what if stop for safety?

Time	Action
Day -28	Notify sites in writing of IDMC meeting date to pre-warn
Day -28	Circulate prior MHRA letter confirming that stopping early for LOB is **not** a substantial amendment, but part of trial design
Day -7	IDMC meeting
(<1 wk)	IDMC notes and recommendations finalised
Day 0	TSC meeting: stop / continue decision for each research arm
< 24 h	Turn off randomisation to arms stopping early for safety
< 24 h	Notify centres by email; pts to ignore irrelevant parts of PIS
< 24 h	Notify relevant industry partners
< 24 h	Notify TMG members
< 24 h	Alert CTU staff to potential queries

Prep: what if stop for safety?

Time	Action
Day -28	Notify sites in writing of IDMC meeting date to pre-warn
Day -28	Circulate prior MHRA letter confirming that stopping early for LOB is **not** a substantial amendment, but part of trial design
Day -7	IDMC meeting
(<1 wk)	IDMC notes and recommendations finalised
Day 0	TSC meeting: stop / continue decision for each research arm
< 24 h	Turn off randomisation to arms stopping early for safety
< 24 h	Notify centres by email; pts to ignore irrelevant parts of PIS
< 24 h	Notify relevant industry partners
< 24 h	Notify TMG members
< 24 h	Alert CTU staff to potential queries

Prep: what if stop for safety?

Time	Action
Day -28	Notify sites in writing of IDMC meeting date to pre-warn
Day -28	Circulate prior MHRA letter confirming that stopping early for LOB is **not** a substantial amendment, but part of trial design
Day -7	IDMC meeting
(<1 wk)	IDMC notes and recommendations finalised
Day 0	TSC meeting: stop / continue decision for each research arm
< 24 h	Turn off randomisation to arms stopping early for safety
< 24 h	Notify centres by email; pts to ignore irrelevant parts of PIS
< 24 h	Notify relevant industry partners
< 24 h	Notify TMG members
< 24 h	Alert CTU staff to potential queries

Prep: what if stop for safety?

Time	Action
Day -28	Notify sites in writing of IDMC meeting date to pre-warn
Day -28	Circulate prior MHRA letter confirming that stopping early for LOB is **not** a substantial amendment, but part of trial design
Day -7	IDMC meeting
(<1 wk)	IDMC notes and recommendations finalised
Day 0	TSC meeting: stop / continue decision for each research arm
< 24 h	Turn off randomisation to arms stopping early for safety
< 24 h	Notify centres by email; pts to ignore irrelevant parts of PIS
< 24 h	Notify relevant industry partners
< 24 h	Notify TMG members
< 24 h	Alert CTU staff to potential queries

Prep: what if stop for safety?

Time	Action
< 1 wk	Phone all site PIs. Instructed to hand-amend PIS and CF. Updated documentation to follow
< 1 wk	Protocol and docs updated and agreed by TMG
< 2 wk	Summary information for patients
< 2 wk	Notify REC and MHRA (for information only)
< 1 m	Detailed discussions with industry partners
< 1 m	TMG review of processes

Prep: what if stop for safety?

Time	Action
< 1 wk	Phone all site PIs. Instructed to hand-amend PIS and CF. Updated documentation to follow
< 1 wk	Protocol and docs updated and agreed by TMG
< 2 wk	Summary information for patients
< 2 wk	Notify REC and MHRA (for information only)
< 1 m	Detailed discussions with industry partners
< 1 m	TMG review of processes

Prep: what if stop for safety?

Time	Action
< 1 wk	Phone all site PIs. Instructed to hand-amend PIS and CF. Updated documentation to follow
< 1 wk	Protocol and docs updated and agreed by TMG
< 2 wk	Summary information for patients
< 2 wk	Notify REC and MHRA (for information only)
< 1 m	Detailed discussions with industry partners
< 1 m	TMG review of processes

Prep: what if stop for LOB?

- LOB timelines same as for safety, except:

Time	Action
< 48 h	Alert CTU staff to potential queries
< 1 wk	Turn off randomisation to arms stopping early for LOB

- Safety and efficacy issues?
  - Act as if safety issues
- All arms continue
  - No changes required
  - Notify centres more leisurely

Activity Stage 1 analysis

- IDMC meeting: 30-Mar-2010
- Data frozen: 09-Feb-2010
- Accrual: **1469** patients total
- FFS events: **129** on control arm

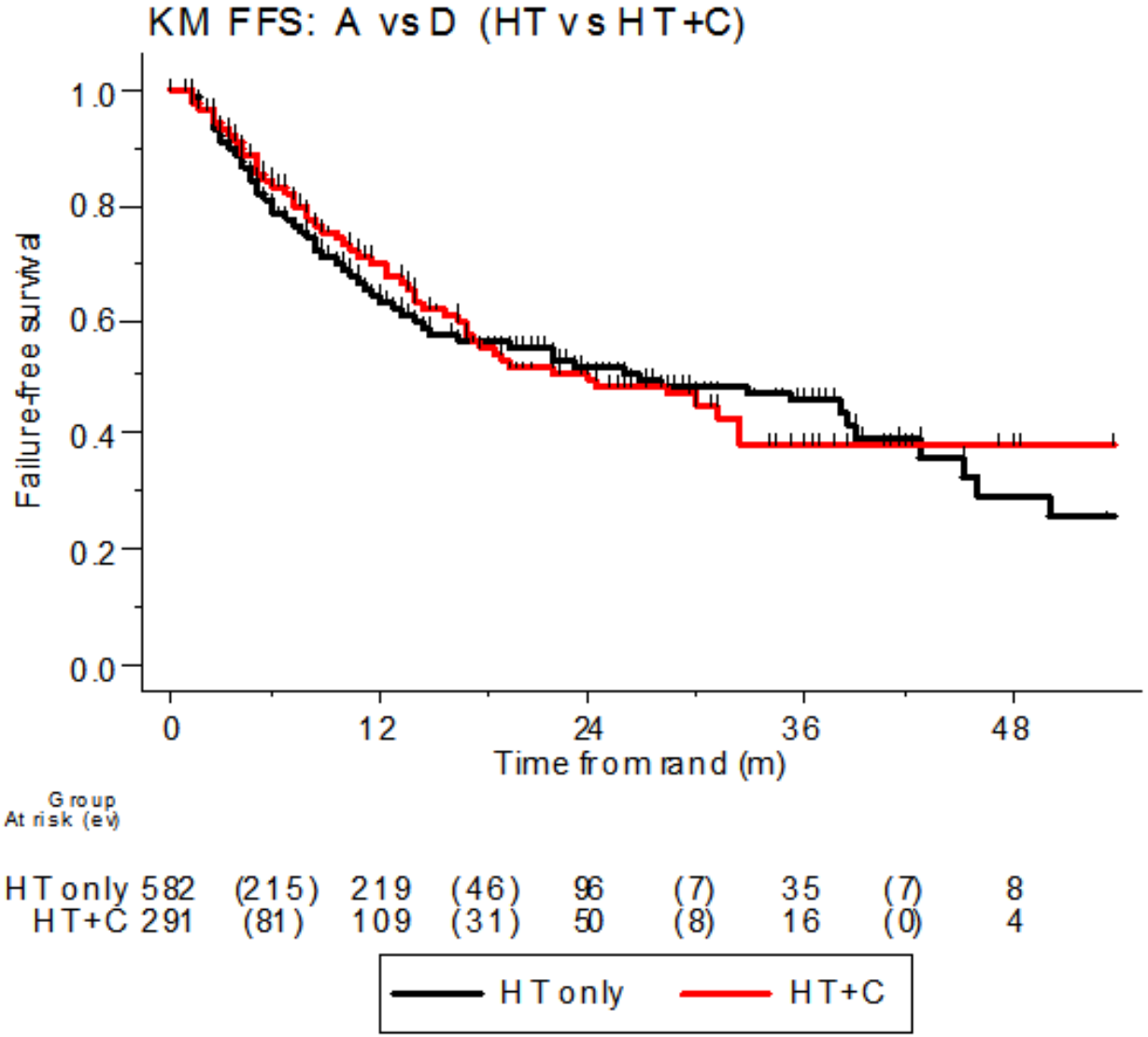
- IDMC recommended **all** arms continue accrual

Activity Stage 2 analysis

- IDMC meeting: 31-Mar-2011
- Data frozen: 01-Feb-2011
- Accrual: **2043** patients total
- FFS events: **209** on control arm

- IDMC recommended **changes:**
  - Stop recruitment to **2** research arms due to lack-of-benefit
  - Both celecoxib-containing arms (D and F) stop accrual
  - Accrual to continue to control + other **3** research arms

AS 2: ADT vs ADT + celecoxib



Target HR: 0.924

Adjusted HR: **0.98**
(95%CI 0.90-1.06)

(1-sided upper 75% upper CI 1.01)

Data from all other arms remains blinded, including Arm F

AS 2: Decisions

- TSC agreed with IDMC recommendations

1. Stop accrual to arms D and F

2. Encourage stopping treatment with celecoxib
   - Given risk:benefit profile

- Therefore, followed more accelerated timelines

AS 2: What did we do?

Day 0

- TSC meeting 06-Apr-2011
- Trial suspended for 6 hours until after TSC meeting
- Randomisation to D and F turned off
- Sites notified by email
  - Re-advise patients consented but not yet randomised
  - Mention stopping treatment at next visit (non-urgent)
- Temporary revised PIS agreed and sent to sites
  - Sites could print and use or just cross out manually

AS 2: What did we do?

Day 1

- Phone calls to all site PIs for info
- Summary for patients developed
  - For **all** patients, not just arms D and F
- Phone calls to all industry partners

Day 7

- REC notified with formally updated PIS
- MHRA notified

Week 8

- Protocol amendment formalised
  - Submitted as non-substantial amendment

When arms continue…

- Some implicit information about arms that continue
- Community not be taken out of equipoise
- Reinforces need to continue randomisation to gain stronger evidence!

STRUCTURE

1. Rationale for multi-arm, multi-stage (MAMS) RCTs

2. Overview of STAMPEDE

3. Stopping recruitment early to some trial arms
   - Methodological and practical issues
   - Following an intermediate analysis

4. Addition of new research arms during the trial
   - Methodological and practical issues

Flexibility and extension

- Design adapts to include further agents
  - Can add new research arms during trial
- Can be thought of as a new trial within STAMPEDE protocol
- Must be scientifically compelling case for inclusion

Principles

- First priority is to ongoing research arms
  - Must not hamper accrual so must **either**:
  1. Recruit better than predicted overall
  2. Wait for arms to stop

- Accept new arm will mature later than original research arms

- Only compare patients on new arms to patients recruited contemporaneously to control arm

Advantages?

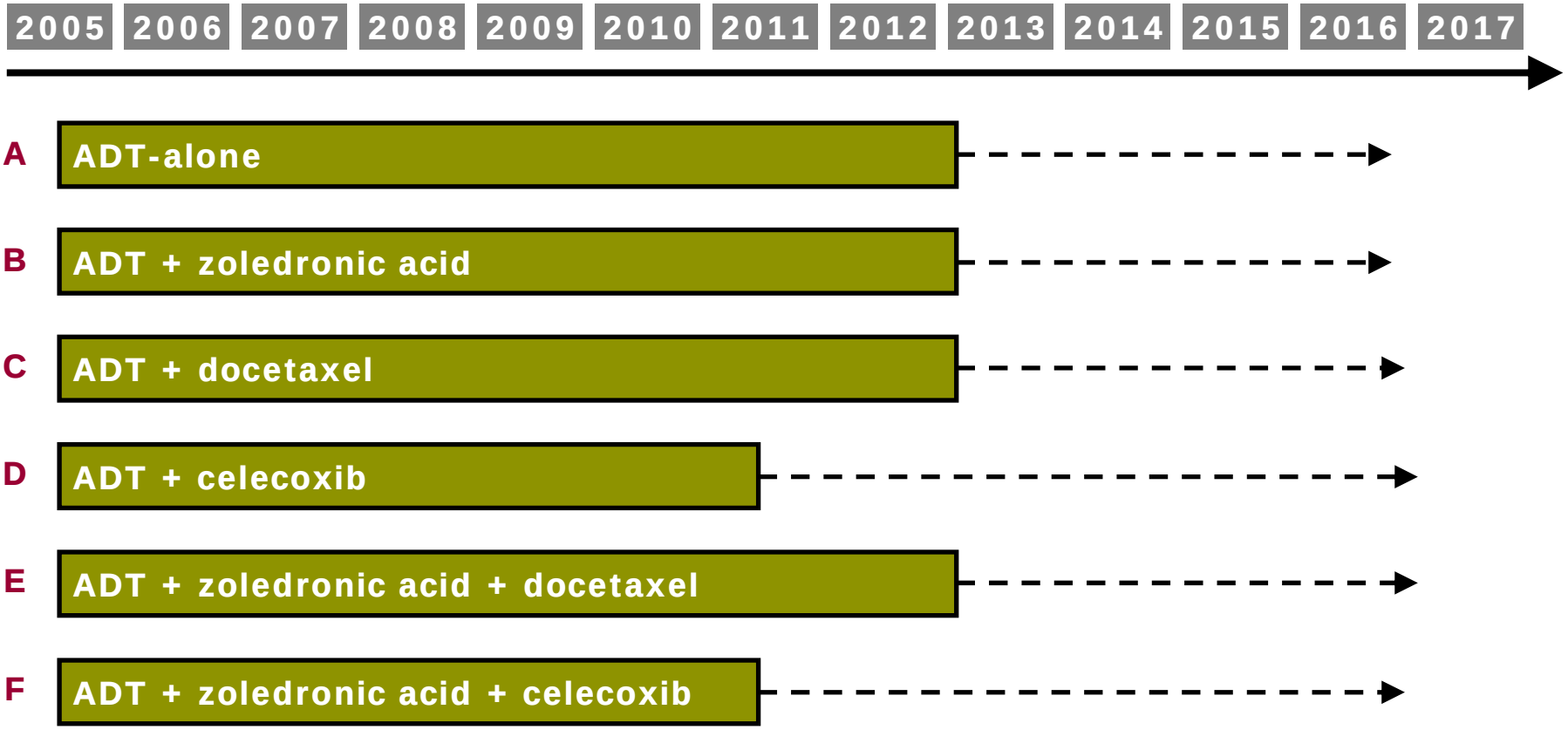
1. Can start recruiting quicker than a new trial
   - Updated protocol = simple, substantial amendment
   - Scientific review = amendment
   - Funding review = as required
2. Efficient use of volunteers
   - Patients contribute to more than one comparison
   - Reduce competing trials
   - Seamless accrual: no gaps between “trials”
   - Ongoing access to trial for patients
3. Efficient use of resources
   - Start at “full speed”
   - Cheaper than separate trial
   - Get answers more quickly

Disadvantages?

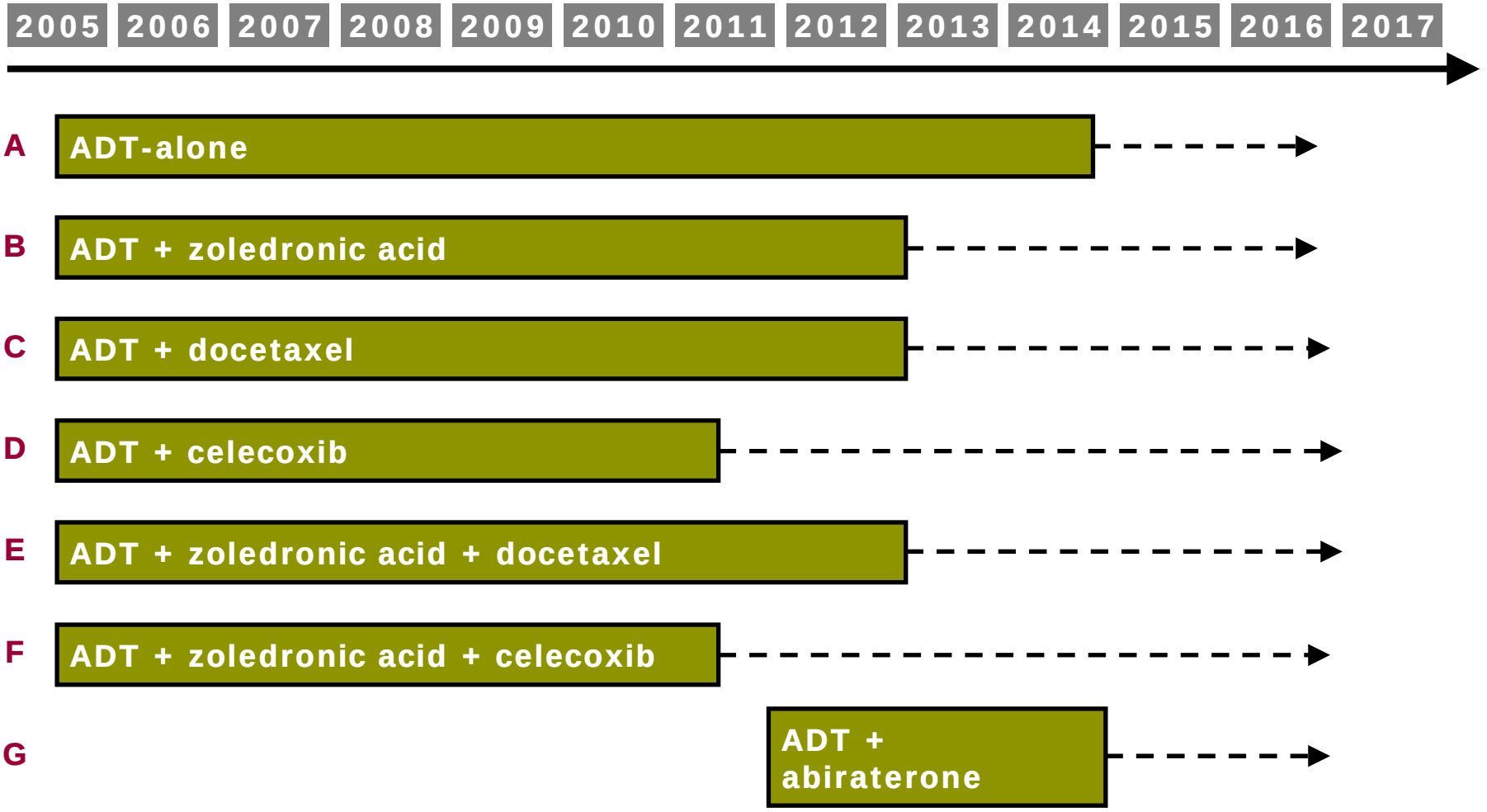
1. Original research arms could mature whilst new assessment ongoing
   - Consider as if data emerging from an external trial
   - Same as for other trials: trial team reacts if needed

2. Need to ensure enthusiastic researchers
   - Discuss with researchers from the outset
   - Run “hearts and minds” campaign
   - Encourage researchers to bring forward other ideas

STAMPEDE activity

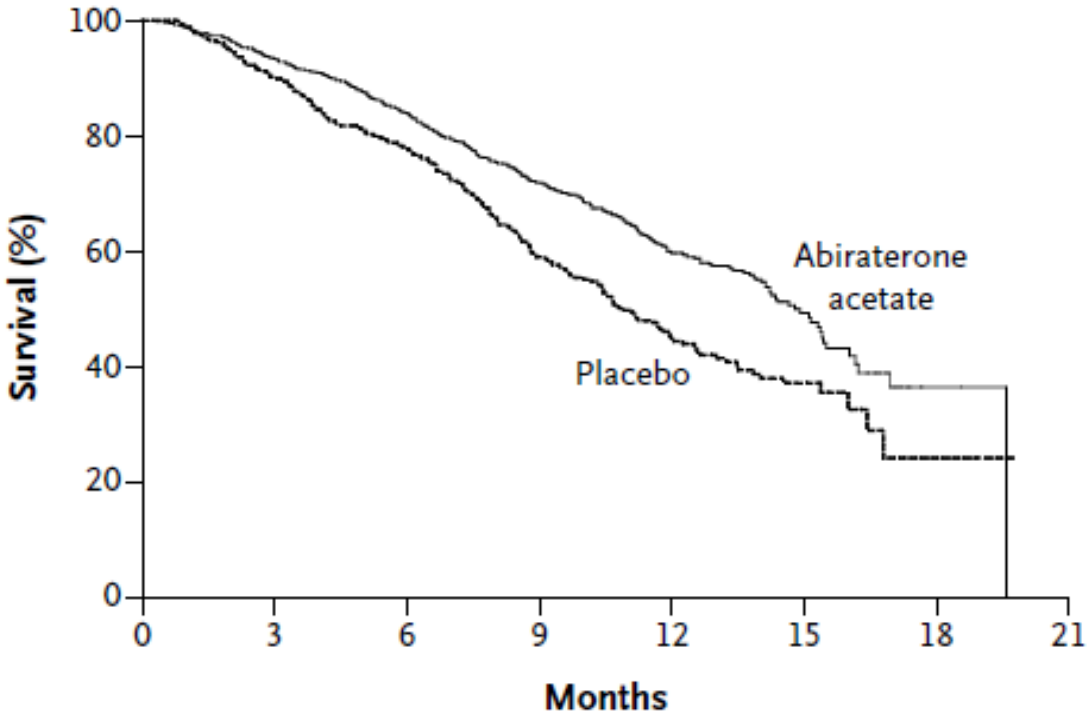


STAMPEDE activity



Adding abiraterone - rationale

- Discussions start when encouraging data in mCRPC
  - But is it better to give it sooner in the disease? STAMPEDE



Survival

HR: **0.66**
(95%CI 0.55-0.78)

De Bono et al
NEJM 2011 (364) p1995

No. at Risk								
Abiraterone acetate	797	736	657	520	282	68	2	0
Placebo	398	355	306	210	105	30	3	0

Adding abiraterone - design

- Chose to use the same design parameters as the original research arms

- Consider impact of:
  - Speeding or slowing accrual
  - Duration of co-accrual to original research arms
  - Allocation ratio for abiraterone
    - 2:1 like other arms?
    - 2:2 to maintain proportion on research treatments?
  - Addition of more research arms

If allocation ratio impacts on accrual rate...

Refft	Accrual rate	Alloc'n Ratio	Initial Overlap	Extra Arms	Accrual Duration	N pts alloc abl	Maturity
404	80	2:1	1 year	No	3 years	500	5.25 years
330	60	2:2	1 year	No	2.5 years	746	4.5 years
440	70	2:2	1 year	No	2.25 years	765	4.25 years

- If accrual slower because of lower allocation ratio
  - Accrual delay by around 1 year

If accrual is faster...

Refft	Accrual rate	Alloc'n Ratio	Initial Overlap	Extra Arms	Accrual Duration	N pts alloc abl	Maturity
330	60	2:2	1 year	No	2.5 years	746	4.5 years
802	70	2:2	1 year	No	2.5 years	870	4 years
891	70	2:2	1 year	No	2 years	660	4.75 years

If original research arms continue longer or shorter...

Refft	Accrual rate	Alloc'n Ratio	Initial Overlap	Extra Arms	Accrual Duration	N pts alloc abl	Maturity
320	80	2:2	0.5 year	No	2.0 years	643	4.75 years
329	60	2:2	0.5 year	No	2.5 years	825	4.0 years
888	60	2:2	1 year	No	2.5 years	746	4.5 years
847	60	2:2	1.5 year	No	2.5 years	669	5.0 years
940	80	2:2	1.5 year	No	3.0 years	847	4.25 years

- Overlap with original research arms beyond control
  - Minimal impact, easily offset by amending accrual duration

Adding abiraterone - design

- 2:2 allocation ratio
  - Good for accrual
- Cap accrual at 3yr or 1500pts
  - Original research comparisons will have around 1500pts
- Gives maturity in around 5 yr
  - Depends on mix of M0 and M1 pts
- Complete accrual before original arms mature

If allocation ratio impacts on accrual rate...

Refr	Accrual rate	Alloc'n Ratio	Initial Overlap	Extra Arms	Accrual Duration	N pts alloc abl	Maturity
404	50	2:1	1 year	No	3 years	500	5.25 years
330	60	2:2	1 year	No	2.5 years	746	4.5 years
449	70	2:2	1 year	No	2.25 years	765	4.25 years

- If accrual slower because of lower allocation ratio
  - Accrual delay by around 1 year

If accrual is faster...

Refr	Accrual rate	Alloc'n Ratio	Initial Overlap	Extra Arms	Accrual Duration	N pts alloc abl	Maturity
330	60	2:2	1 year	No	2.5 years	746	4.5 years
802	70	2:2	1 year	No	2.5 years	870	4 years
891	70	2:2	1 year	No	2 years	660	4.75 years

If original research arms continue longer or shorter...

Refr	Accrual rate	Alloc'n Ratio	Initial Overlap	Extra Arms	Accrual Duration	N pts alloc abl	Maturity
320	60	2:2	0.5 year	No	2.0 years	643	4.75 years
329	60	2:2	0.5 year	No	2.5 years	825	4.0 years
888	60	2:2	1 year	No	2.5 years	746	4.5 years
847	60	2:2	1.5 year	No	2.5 years	669	5.0 years
340	60	2:2	1.5 year	No	3.0 years	847	4.25 years

- Overlap with original research arms beyond control
  - Minimal impact, easily offset by amending accrual duration

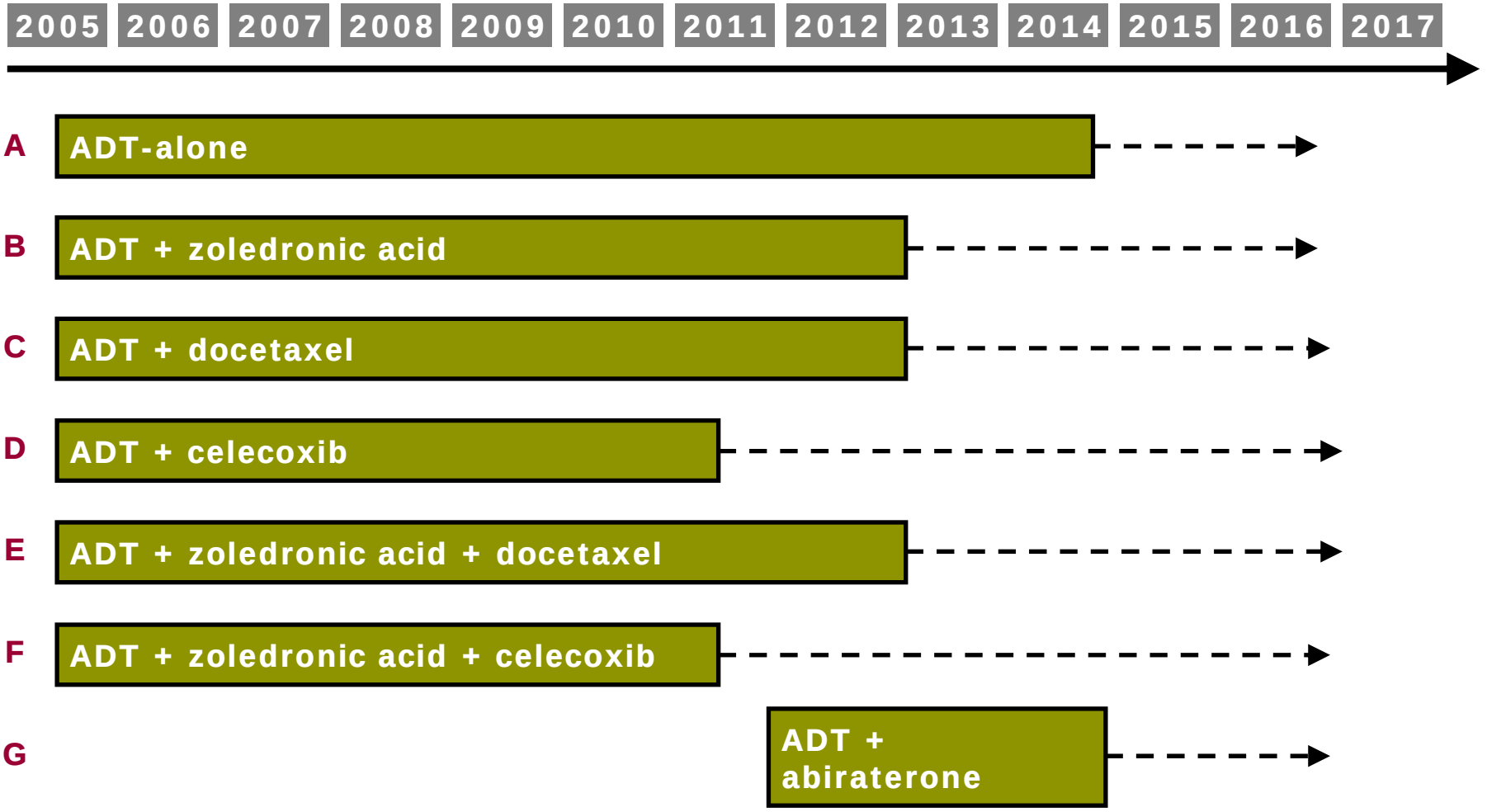
Adding abiraterone - timelines

- Formal discussions start: Mar-2010
- CTAAC approval for science: Jul-2010
- Abiraterone licensed: Sep-2011
- Contract with Janssen: Sep-2011
- Protocol v8 submitted: Aug-2011
  - REC approval: Sep-2011
  - MHRA response: expected by 10-Oct-2011
- Launch meetings: Sep/Oct-2011
- Switch-over date set: TBA (after MHRA approval)
- “First” patient in: ~Nov-2011

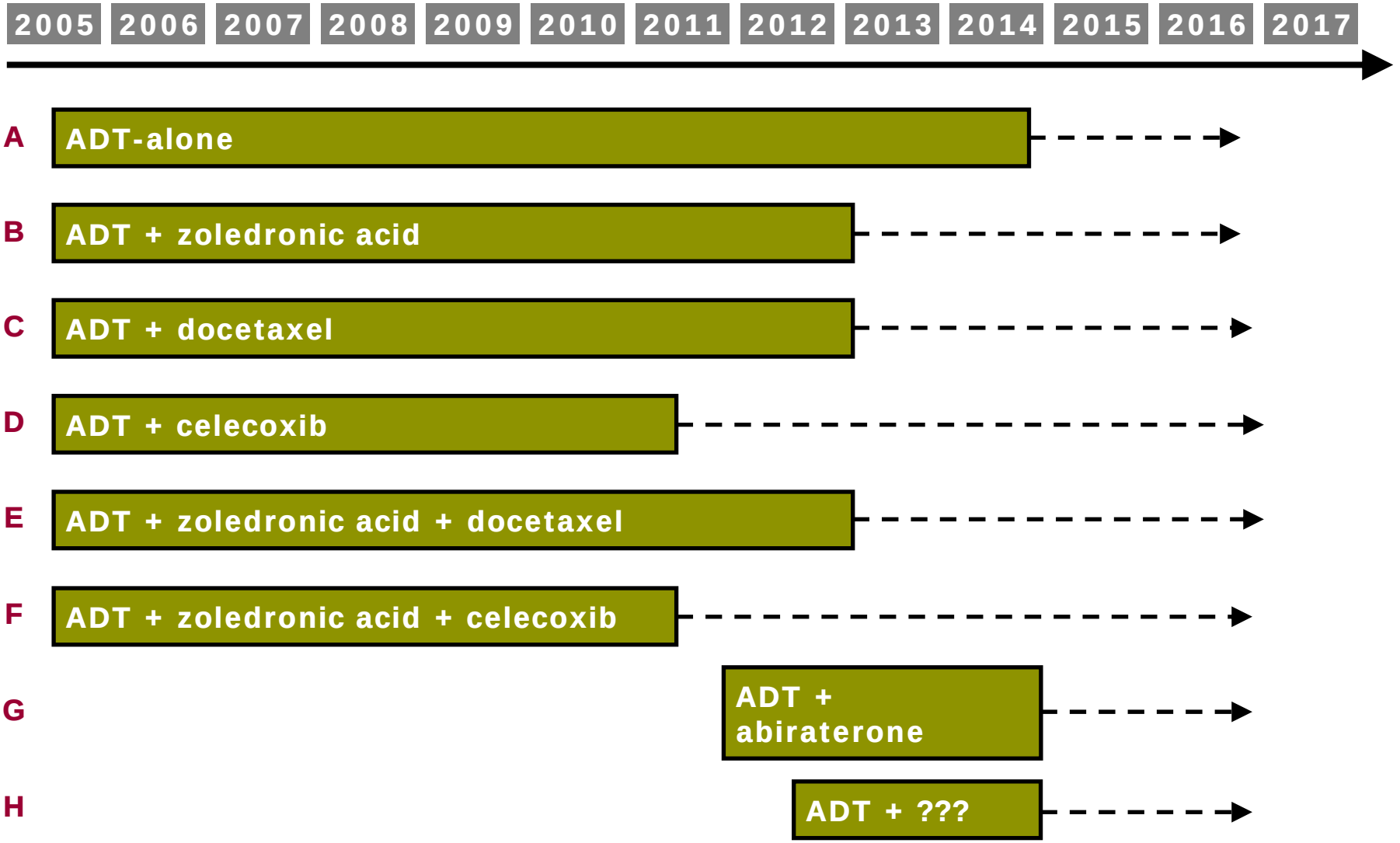
Adding abiraterone - next steps

- New arm “switched on” for whole trial on set date
- Sites will be given 4 weeks notice of switch-over
  - Starting from MHRA approval
- Sites must gain R&D approval for new version during this window
- Accrual will be seamless
  - In nearly all sites

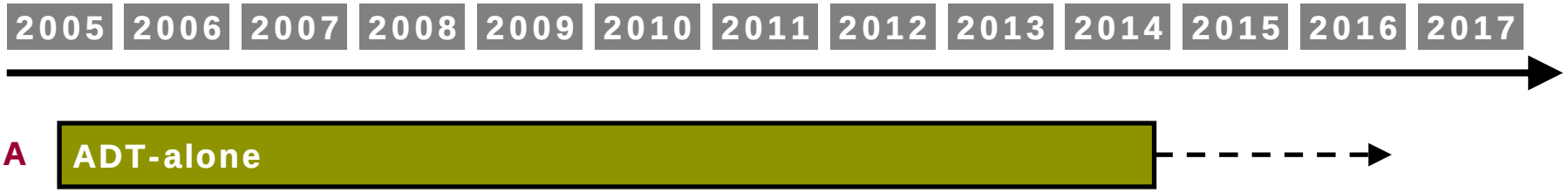
STAMPEDE activity



STAMPEDE activity



STAMPEDE activity



- TMG has initiated plans for arm H
  - And I, J, K…
- Achievable providing that accrual rates are maintained and appropriate questions are chosen

Conclusions

- MAMS trials speed evaluation of new treatments by:
  1. Testing many treatments simultaneously
  2. Using LOB analyses to focus research efforts
- Insufficiently active arms can successfully be stopped seamlessly in a MAMS trial
- Adding new research arms to an ongoing trial is achievable and desirable
- Fun and exciting design

Refs: MAMS trials

- Royston P, Parmar MKB, Qian W

  Novel Designs for Multi-Arm Clinical Trials with Survival Outcomes, with an Application in Ovarian Cancer. Statistic Med 2003; 22: 2239–2256

- Barthel FMS, Royston P, Parmar MKB

  A menu-driven facility for sample size calculation in multi-arm, multi-stage randomised controlled trials with a survival-time outcome. The Stata Journal 2009; 9 (4): 505-523

- Parmar MKB, Barthel F, Sydes MR *et al*

  Speeding up the Evaluation of New Agents in Cancer. J Natl Cancer Inst 2008; 100 (17):1204-1214

Refs: STAMPEDE methods

- Sydes MR, MKB Parmar, ND James *et al*

  Issues in applying multi-arm multi-stage (MAMS) methodology to a clinical trial in prostate cancer: the MRC STAMPEDE trial. Trials 2009; 10 (39)

Refs: STAMPEDE clinical data

- James ND, Sydes MR, Clarke NW *et al*

  STAMPEDE: Systemic Therapy for Advancing or Metastatic Prostate Cancer -- A Multi-Arm Multi-Stage Randomised Controlled Trial. Clin Oncol 2008; 20 (8):577-581

- James ND, Sydes MR, Clarke NW *et al*

  Systemic therapy for advancing or metastatic prostate cancer (STAMPEDE): a multi-arm, multistage randomized controlled trial. BJU Int 2009; 103 (4):464-469

- James ND, Sydes MR, Mason MD *et al*

  Celecoxib plus hormone therapy vs hormone therapy alone for hormone-sensitive prostate cancer: first results from STAMPEDE (MRC PR08) a randomised controlled trial EJC 2011 (ECCO conference abstracts); LBA#21

Software

- Free software available
  - `nstage` to design and plan MAMS trials
  - Available from MRC CTU
  - Implemented in Stata
  - Combined with `artpep` for increased flexibility

- MRC CTU staff happy to discuss proposals

Acknowledgements

- Funding:
  - Cancer Research UK (CRUK/016/09)
  - Novartis
  - Sanofi-Aventis
  - Pfizer
  - MRC

- All clinicians and hospital staff who have supported and continue to support the trial

- All patients who joined the trial and their families

Contact

Matthew Sydes
STAMPEDE Trial Statistician

Senior Scientist
MRC Clinical Trials Unit
Aviation House
125 Kingsway
London WC2B 6NH

Email STAMPEDE@ctu.mrc.ac.uk
Tel +44 (0)20 7670 4798
Mob +44 (0)7825 995251
Web www.ctu.mrc.ac.uk

Flexible trial design in practice – dropping and adding arms in STAMPEDE: a multi-arm multi-stage randomised controlled trial (MRC PR08, CRUK/06/019)

Matthew Sydes

MRC Clinical Trials Unit, London, UK

ND James, MD Mason, NW Clarke, C Amos, J Anderson, J de Bono, DP Dearnaley, J Dwyer, G Jovic, ASW Ritchie, M Russell, K Sanders, G Thalmann, MKB Parmar
on behalf of the STAMPEDE investigators