Improving outcomes as rapidly as possible for patients

Multi-arm, multi stage platform, umbrella and basket protocols

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The need for speed and change

- Development and testing process too slow (>10 years)
- Too often shows new is not better than standard
- In some diseases number of new therapies demanding evaluation is large
- Some diseases are being classified to smaller subsets using molecular characterisation
- Process of developing and starting a new trial is very time consuming – often a long gap between trials
- Many solutions proposed have been for phase I and II trials
- Our emphasis is on Phase III trials – longest and most expensive part of evaluation process
Principles underlying solutions

- Evaluate many primary hypotheses/treatments in the same protocol

- If there is a pilot/feasibility/phase II
  - seamless run through to the phase III and
  - include all phase II information in the phase III

- Conduct an adaptive trial, with only major adaptations, e.g.
  - Dropping arms
  - Adding arms
Multi-arm, multi-stage

Traditional Approach

Phase II
- T1
- T2
- T3
- T4

Phase III
- C
- T1
- C
- T3
- C
- T4

Multi-arm, Multi-stage

Phase II
- C
- T1
- T2
- T3
- T4

Phase III
- C
- T1
- T2
- T3
- T4
Need in prostate cancer

- 900,000 new prostate cancers in early 2000s, globally

- Standard treatment for high risk disease = hormone therapy – no change for 40 years
  - Median survival: ~5 years

- Many promising agents to evaluate
  - Different classes, different modes of action

- Use MAMS design to test many agents
  - Focus towards active agents with lack-of-benefit analyses
STAMPEDE design

Men with high-risk prostate cancer starting long-term hormone therapy

RANDOMISATION

A Androgen Deprivation Therapy | Control arm
---
B ADT + Zoledronic Acid
C ADT + Docetaxel
D ADT + Celecoxib
E ADT + ZA + Doc
F ADT + ZA + Cel

Treatment detail
Androgen Deprivation Therapy
:: Standard hormones
:: Given for >3 years
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

MRC PR08 -- ISRCTN78818544 -- NCT00268476
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<th>Stage</th>
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<td>Quality of life</td>
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Accrual: initial plans


Past accrual
Possible future accrual
Follow-up
Accrual: initial plans

Past accrual: Oct-2005
Possible future accrual: ADT-alone, ADT + zoledronic acid, ADT + docetaxel, ADT + celecoxib, ADT + zoledronic acid + docetaxel, ADT + zoledronic acid + celecoxib
Follow-up: 2005-2017
End of pilot phase (original arms)


A  ADT-alone
B  ADT + zoledronic acid
C  ADT + docetaxel
D  ADT + celecoxib
E  ADT + zoledronic acid + docetaxel
F  ADT + zoledronic acid + celecoxib

Apr-2007

Past accrual  Possible future accrual  Follow-up
Milestone: 500 patients in trial

Past accrual
Possible future accrual
Follow-up

Oct-2008

A: ADT-alone
B: ADT + zoledronic acid
C: ADT + docetaxel
D: ADT + celecoxib
E: ADT + zoledronic acid + docetaxel
F: ADT + zoledronic acid + celecoxib
Activity Stage 1 analysis (original arms)

- A: ADT-alone
- B: ADT + zoledronic acid
- C: ADT + docetaxel
- D: ADT + celecoxib
- E: ADT + zoledronic acid + docetaxel
- F: ADT + zoledronic acid + celecoxib

Past accrual: green
Possible future accrual: orange
Follow-up: dashed line

Apr-2010
Activity Stage 2 analysis (original arms)

A. ADT-alone
B. ADT + zoledronic acid
C. ADT + docetaxel
D. ADT + celecoxib
E. ADT + zoledronic acid + docetaxel
F. ADT + zoledronic acid + celecoxib

Apr-2011
**Abiraterone comparison activated**

- A: ADT-alone
- B: ADT + zoledronic acid
- C: ADT + docetaxel
- D: ADT + celecoxib
- E: ADT + zoledronic acid + docetaxel
- F: ADT + zoledronic acid + celecoxib
- G: ADT + abirat...

Past accrual: Green
Possible future accrual: Orange
Follow-up: Dashed line with arrow

Nov-2011

Activity Stage 3 analysis (original arms)

May-2012

- A: ADT-alone
- B: ADT + zoledronic acid
- C: ADT + docetaxel
- D: ADT + celecoxib
- E: ADT + zoledronic acid + docetaxel
- F: ADT + zoledronic acid + celecoxib
- G: ADT + abiraterone

Past accrual: 2005-2011
Possible future accrual: 2012-2017
Follow-up: May-2012
End of abiraterone pilot phase


A  ADT-alone
B  ADT + zoledronic acid
C  ADT + docetaxel
D  ADT + celecoxib
E  ADT + zoledronic acid + docetaxel
F  ADT + zoledronic acid + celecoxib
G  ADT + abiraterone (Follow-up)

Past accrual  Possible future accrual  Follow-up

Oct-2012
M1/RT comparison activated

- ADT-alone
- ADT + zoledronic acid
- ADT + docetaxel
- ADT + celecoxib
- ADT + zoledronic acid + docetaxel
- ADT + zoledronic acid + celecoxib
- ADT + abiraterone
- ADT + M1/RT

Jan-2013

Past accrual: Green
Possible future accrual: Orange
Follow-up: Dashed line

Accrual completed (original comparisons)

- A: ADT-alone
- B: ADT + zoledronic acid
- C: ADT + docetaxel
- D: ADT + celecoxib
- E: ADT + zoledronic acid + docetaxel
- F: ADT + zoledronic acid + celecoxib
- G: ADT + abiraterone
- H: ADT + M1/RT

Mar-2013

Past accrual: ADT-alone, ADT + zoledronic acid, ADT + docetaxel, ADT + celecoxib, ADT + zoledronic acid + docetaxel, ADT + zoledronic acid + celecoxib

Possible future accrual: ADT + abiraterone, ADT + M1/RT

Follow-up: Mar-2013
Enzalutamide comparison activated


A  ADT-alone
B  ADT + zoledronic acid
C  ADT + docetaxel
D  ADT + celecoxib
E  ADT + zoledronic acid + docetaxel
F  ADT + zoledronic acid + celecoxib
G  ADT + abiraterone
H  ADT + M1/RT
J  ADT + enzalutamide

Past accrual  Possible future accrual  Follow-up

End 2013, early 2014
2015: Docetaxel Survival Results

SOC
405 deaths
SOC + Doc
165 deaths

HR (95%CI) 0.76 (0.63, 0.91)
P-value 0.003

Non-PH p-value 0.51

Median OS (95% CI)
SOC 67m (60, 91m)
SOC + Doc 77m (70, NR)

Restricted mean OS time
SOC 58.8m
SOC + Doc 63.4m
Diff (95%CI) 4.6m (1.8, 7.3m)
STAMPEDE: SOC+DocP vs SOC

STAMPEDE: Docetaxel comparison

Recruitment: Oct-2005 to Mar-2013
Patients: 1184 SOC
592 SOC+DocP
Reported: ASCO 2015
Published: Lancet 2016
Allocation ratio: 2:1

HR (95%CI) 0.78 (0.66, 0.93)
P-value 0.006
Clinical Commissioning Policy Statement: Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer

- Already changed clinical practice
- Shortlisted for BMJ UK Research Paper of the Year

NHS England Reference: [B15/PS/a]
Control arm changed and new arm added

STAMPEDE: Metformin comparison introduced

Q2-2015: launch of metformin comparison
--- Trial recruits from population; powered in M1
**STAMPEDE: SOC+AAP vs SOC**

**STAMPEDE: Abiraterone comparisons**

- **Recruitment:** Nov-2011 to Jan-2014
- **Patients:** 957 SOC, 960 SOC+AAP
- **Reported:** ASCO 2017
- **Published:** NEJM 2017
- **Allocation ratio:** 1:1

**HR (95%CI) 0.63 (0.52, 0.76)**

**P-value 0.00000115**
MAMS Platform: further developments in STAMPEDE

STAMPEDE: Rucaparib comparison introduced

- Standard-of-care (SOC) = ADT (+/- RT) (+/- docetaxel)
- SOC+zoledronic acid
- SOC+docetaxel
- SOC+celecoxib
- SOC+zoledronic acid+docetaxel
- SOC+zoledronic acid+celecoxib
- SOC+(abi)^
- SOC+M1|RT {M1}
- (en+ab)#
- SOC+metformin
- SOC+tE2
- SOC+rucaparib [BioMk+]

Accrual - past
Accrual - future
FU and main analysis

First biomarker-stratified question for proportion of patients
Launch Q4-2017
STAMPEDE overview with rucaparib comparison (and possible future comparisons)

Eligible for STAMPEDE

Suitable for screening for biomarker screening

Biomarker stratifier

BIOmarker STRATIFIED

BRCA/ATM mutant

RANDOMISE

SOC

SOC + rucaparib

Safety Activity Efficacy

Future BM x +ve

RANDOMISE

[SOC]

[SOC + targeted treatment V?]

Biomarker -ve

Unstratified arms

RANDOMISE

SOC

SOC + M1[RT

SOC + metformin

[SOC + future unstratified question?]

[SOC + future unstratified question?]

Safety Activity Efficacy

Key

SOC: standard-of-care
STAMPEDE

• Will answer 12 major questions in 20 years (inc. phase II and phase III components)

• Has shown that Adaptive trials are
  • Feasible & practicable
  • Recruit well enough to overcome more arms
  • Efficient
  • Supported by patients, clinicians, funders, companies
MAMS platform

- EMA and FDA review & approval of MAMS platform design for RAMPART (about to be initiated)

- RAMPART – 4 arm randomised trial of immunotherapies in early renal cancer – 4th arm, blank at the moment
RAMPART – about to open

• International MAMS trial for renal cancer

Patients who have had their primary RCC resected and are at intermediate or high risk of relapse
n=1750

Arm A
Active Monitoring for 1 year

Arm B
Durvalumab 1500mg q4w for 1 year

Arm C
Durvalumab 1500mg q4w for 1 year
Tremelimumab 75 mg at day 1 and w4

Arm D
New agent/Combination of agents
Principles for trial design for biomarker defined subgroups of a specific disease: Umbrella Trial

Aim to include questions testing new treatments in all (or most) subgroups, using an adaptive approach and incorporate:

(i) refinement of the subgroups
(ii) introduction of new subgroups
(iii) ability to stop testing specific treatments and introduce new treatments
(iv) evaluation of the link between the biomarker and that treatment
FOCUS4 – umbrella trial design

Eligible patients:
- advanced or metastatic CRC
- fit for first-line chemotherapy
- consent to biomarker analysis

Standard chemotherapy for 16 weeks
=> Stable or responding disease

During first 16 weeks chemotherapy biomarker panel analysis*:
- on FFPE tumour block
- NGS: BRAF, PIK3CA, KRAS, NRAS, PTEN, POL-E mutation
- mRNA: EREG
- IHC: MSI/MMR, PTEN, H3K36me3

Registration period (Master protocol)

Molecular selection*

Patient selection

Synthetic lethality cohort

Trial period (Trial protocol)

Primary outcomes
PFS and/or OS from randomisation

Consent & randomisation

Consent & randomisation

Consent & randomisation

Consent & randomisation

Consent & randomisation

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Consent & randomisation

On progression recommence first-line chemotherapy

- BRAF
- MSI/MMR deficient/POL-E mutation
- PIK3CA mutation
- H3K36me3 loss
- KRAS + P53 mutation
- All wild type
- Non-stratified (Unclassified or when other stratifications are refused or unavailable)

- P
- No agent available at present
- PD-L1 inhibitor (in dev)
- Aspirin (300mg)
- No Rx
- WEE1 inhibitor (AZD1775)
- No Rx
- WEE1 inhibitor (AZD1775)
- No Rx
- No agent available at present
- Capecitabine
Add-Aspirin basket design

FOUR PARALLEL COHORTS WITHIN AN OVER-ARCHING PROTOCOL
Participants will have undergone primary treatment with curative intent

BREAST | COLORECTAL | GASTRO-OESOPHAGEAL | PROSTATE

REGISTRATION AND RUN-IN PERIOD
All participants take 100mg aspirin for 8 wks to assess adherence and tolerability

RANDOMISATION
Performed separately within each tumour cohort, double-blind

100mg ASPIRIN | 300mg ASPIRIN | PLACEBO

FOLLOW-UP
≥ 5 years, including long-term follow-up via routine health databases in the UK

Breast primary outcome: Disease-free survival
n=3100

Colorectal primary outcome: Disease-free survival
n=2600

Gastro-oesophageal primary outcome: Overall survival
n=2100

Prostate primary outcome: Biochem recurrence-free survival
n=2120
Add-Aspirin

- Recruited >3,500 patients in 2 year
- Recruitment has started in India, alongside capacity building work
- 150 recruiting centres in UK, with plans to expand that to more sites
Add Aspirin: basket protocol

• Looking to add further randomisations after 5 years of Aspirin
Applying these designs to infectious diseases

- **Truncate-TB**: funded
  - MAMS platform trial to shorten drug sensitive TB treatment to 2-3 months (starting with 5 arms)
  - Coordinated in Singapore, conducted in Asia

- **Vietnarms**: funded
  - Multi-arm trial assessing short courses of direct-acting antivirals to cure hepatitis C
  - Coordinated and conducted in Vietnam

- **HCV AVERT**: being developed
  - A stratified umbrella trial on how to prevent mother to child transmission of hepatitis C
  - Application for a development grant currently being considered by the MRC, for preparatory work in Egypt and Ukraine
Expanding to other diseases

- Working with a number of other groups nationally and internationally to design and deliver MAMS platform, umbrella and basket trials

- Major need to make progress in number of neurological diseases
  - Alzheimers
  - Motor Neurone Disease
  - Progressive Multiple Sclerosis
  - Parkinsons
Conclusions

• There is a real need to change how we do trials
  – To make faster progress
  – To respond to the many new opportunities