Multi-arm multi-stage platform trials in practice: the STAMPEDE trial

Miss Melissa Spears
Medical Statistician
MRC Clinical Trials Unit at UCL
20-May-2016
Who am I?

• MRC CTU at UCL since Oct-2012
• Medical Statistician
• STAMPEDE
  – Adding arms
  – Closing recruitment to arms
  – Reporting final results
Outline

• Design Concept
• Implementation
• Adaptation
• Moving forward

Disclaimer
This presentation will not cover:

- Scientific rationale for STAMPEDE research questions
- Details of the statistical design
STAMPEDE

• Prostate cancer
• High risk population
• Treat early; +Standard-of-care (SOC)
• Improve patient outcomes
• >8,000 participants
• 9 research questions
  – 5 evaluated & presented
  – 4 to mature in the future
‘Traditional’ Trial

- One research question
‘Traditional’ Trial

- One research question
- Single protocol
- Oversight committees

Control Arm A

Research Arm B
‘Traditional’ Trial

Recruitment

- One research question
- Single protocol
- Oversight committees
- Start →

Control Arm A
Research Arm B
‘Traditional’ Trial

- One research question
- Single protocol
- Oversight committees
- Start → Stop →
‘Traditional’ Trial

- **Recruitment**
  - Control Arm A
  - Research Arm B

- **Follow-up**

- **Analyse**
  - One research question
  - Single protocol
  - Oversight committees
  - Start → Stop → Analyse
‘Traditional’ vs MAMS Platform

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‘Traditional’ vs MAMS Platform

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- N research questions
- Single protocol
- Oversight committees
- Start → Stop → Analyse
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- **Recruitment**:
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- **Follow-up**

- **Analyse**
  - N research questions
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  - Oversight committees

- **Safety stage**
‘Traditional’ vs MAMS Platform

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- Single protocol
- Oversight committees
- Safety stage
- N interim analyses
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- **Follow-up**
  - N interim analyses

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**STAMPEDE 2\textsuperscript{nd} interim analysis on FFS Apr-2011** – recruitment stopped to celecoxib-containing arms
# ‘Traditional’ vs MAMS Platform

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Formal 3\textsuperscript{rd} interim analysis for ongoing arms only

All arms followed-up
‘Traditional’ vs MAMS Platform

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C: SOC+docetaxel
D: SOC+celecoxib
E: SOC+ZA+docetaxel
F: SOC+ZA+celecoxib
G: SOC+abiraterone

- N research questions
- Single protocol
- Oversight committees
- Safety stage
- N interim analyses
- Add new arms as new questions arise

added Nov-2011
‘Traditional’ vs MAMS Platform

- N research questions
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G: SOC+abiraterone
H: SOC+RT {M1}

added Jan-2013 {newly-diagnosed M1 pts only}
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- Add new arms as new questions arise

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H: SOC+RT {M1}
J: SOC+enz+abi

- Added Jul-2014
‘Traditional’ vs MAMS Platform

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- Add new arms as new questions arise

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H: SOC+RT \{M1\}
J: SOC+enz+abi
K: SOC+metformin

to be added Jul-2016 \{for non-diabetic pts only\}
‘Traditional’ vs MAMS Platform

- Only contemporaneous controls compared

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All for one | One for all

What?

• One overarching question
  – Early treatment, added to SOC
All for one | One for all

Why?

• Reduce patient numbers
• Rolling platform
• Broad eligibility
• Efficient use of resources: time & financial
• Shared processes
• Improve patient outcomes – more timely
All for one | One for all

Why?

• Reduce patient numbers
• Rolling platform
• Broad eligibility
• Efficient use of resources: time & financial
• Shared processes

• Improve patient outcomes – more timely
Result?

• Single protocol w/clear, defined objectives
• Platform asking same overarching question in differing, well-defined populations
• Attractive to patients – quick answers
• Embedded in MDT – triaging patients
• Maximise recruitment into research questions
STAMPEDE: Time to first patient after new comparison added -- by site

Sites with 1+ new randomisation

Time (months) to first new patient since new comparison added

>120 centres
9 yr

STAMPEDE Original research comparisons
– from trial initiation Oct-2005
All for one | One for all

STAMPEDE

• 1 trial, 10y, 8000pts VS 9 trials, 40y, 12000pts
• Average monthly recruitment >100pts
All for one | One for all

STAMPEDE

• 1 trial, 10y, 8000pts VS 9 trials, 40y, 12000pts
• Average monthly recruitment >100pts
• Updated SOC to include docetaxel (Dec-2015)
All for one | One for all

STAMPEDE

• 1 trial, 10y, 8000pts VS 9 trials, 40y, 12000pts
• Average monthly recruitment >100pts
• Updated SOC to include docetaxel
• Results now every 18 months
Operational Challenges

• Open dialogue with regulators around design
• Concurrent activities
  – Site perspective
  – Trials Unit perspective
• Open channels of communication
• Comparison Chief Investigators
• Working subgroups
Information Collection

- Too much VS not enough
Information Collection

- Too much VS not enough
- Impact on shared control arm
Information Collection

• Too much VS not enough
• Impact on shared control arm
• Changes over time
Information Collection

• Too much VS not enough
• Impact on shared control arm
• Changes over time
• Big data
• Routine data
Application in other areas

• Priority where:
  – SOC not changed in many years
  – Prospective therapies of interest & available for testing
• Therapies applicable to a broad eligible population
• Overarching question of interest
• Successfully implemented in:
  – FOCUS4 bowel cancer
  – ICON5 ovarian cancer
  – PanACEA MAMS tuberculosis
Moving forward

• What might STAMPEDE look like in 5-10 years?
Moving forward

• What might STAMPEDE look like in 5-10 years?
• Stratified medicine
Moving forward

• What might STAMPEDE look like in 5-10 years?
• Stratified medicine
• Immunotherapies
Moving forward

- What might STAMPEDE look like in 5-10 years?
- Stratified medicine
- Immunotherapies
- Machine learning
- Smart analytics
Moving forward

• What might STAMPEDE look like in 5-10 years?
• Stratified medicine
• Immunotherapies
• Machine learning
• Smart analytics
• Network meta-analysis
Thank you!