Ethics of Adaptive Trial Designs: What they are and what Research Ethics Committees (REC), Research regulators (UNCST, NDA) and research participants need to know

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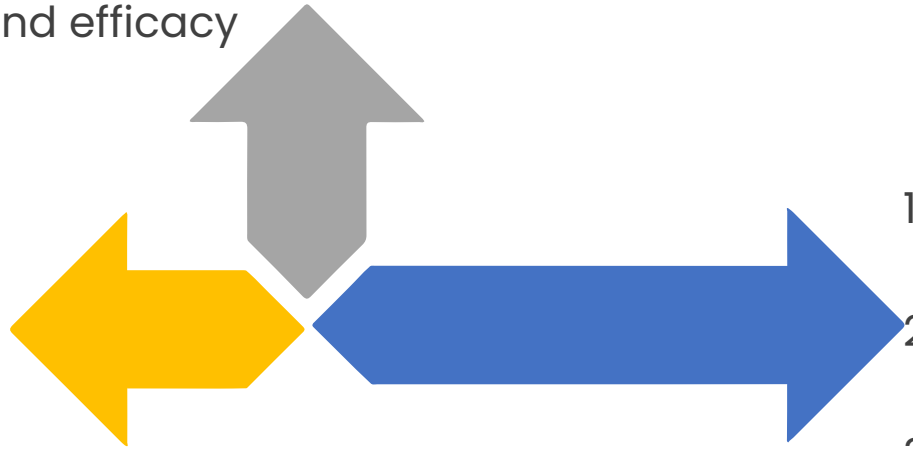
Acknowledgment: Prof. Noah Kiwanuka

Adaptive Clinical Trial Design: Definition

A study that includes opportunities to make modifications of one or more specified aspects of the study while the study is ongoing

Before a medicine/vaccine/diagnostic assay/medical device is approved and licenced for use in human beings:

Undergoes a rigorous scientific experimental testing to ensure safety and efficacy



Experiments – preclinical studies, clinical trials

Long and expensive process

1) 10 to 15 years or even more
2) Thousand of participants
3) Multiple ethics and regulatory reviews

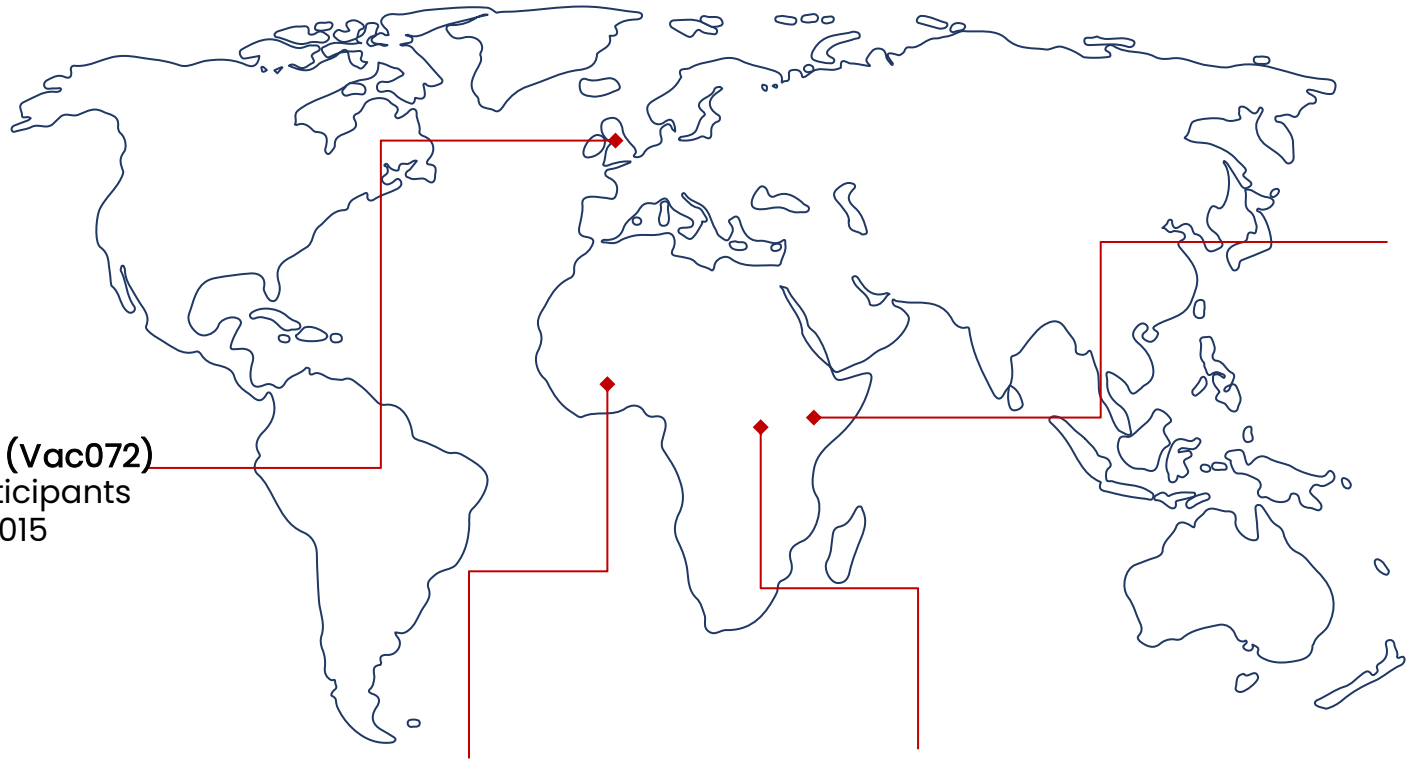
Clinical Trial Phases

	Pre-clinical Research	Phase 1	Phase 2	Phase III	Phase IV
Objective	Pharmacodynamic studies in animals	Assess safety, tolerability, PK and PD of drug	Drug disease interaction, efficacy of drug	Evaluate effectiveness and risk- benefit ratio	Monitor long term effects and effectiveness
Sample size	In animal models	20 to 80 individuals	100-500 individuals	1000- 3000 individuals	1000+ individuals
Duration	3-6 years	1-2 years	1-2 years	2-3 years	Ongoing

Rigorous scientific testing and multiple regulatory reviews


MINISTRY OF HEALTH
VACCINATE
AGAINST
MALARIA
AND OTHER
PREVENTABLE DISEASES.
"Protect your child for life"

Clinical Trials to Assess the R21 Malaria Vaccine



Phase I (Vac072)
64 participants
Date: 2015

Phase II (Vac076)
450 participants
Date: 2019

Phase III (Vac078)
>5000 participants
Date: 2021-2022

Phase IV

Date: Ongoing
Location: Mukono, Buikwe, Jinja, Tororo

1,000,000,000
USD

Rationale for Adaptive Clinical Trials

Allows clinical trials to be more flexible & efficient

Gives control to the investigators to improve the trial based on all available information while the trial is still underway

a hot issue in the drug dev't industry

Fast without undermining validity and integrity

Cost reduction
1)High cost of failed clinical trials drug development
2)About 10-20% of pathways reach success of drug licensure

Traditional Clinical Trials

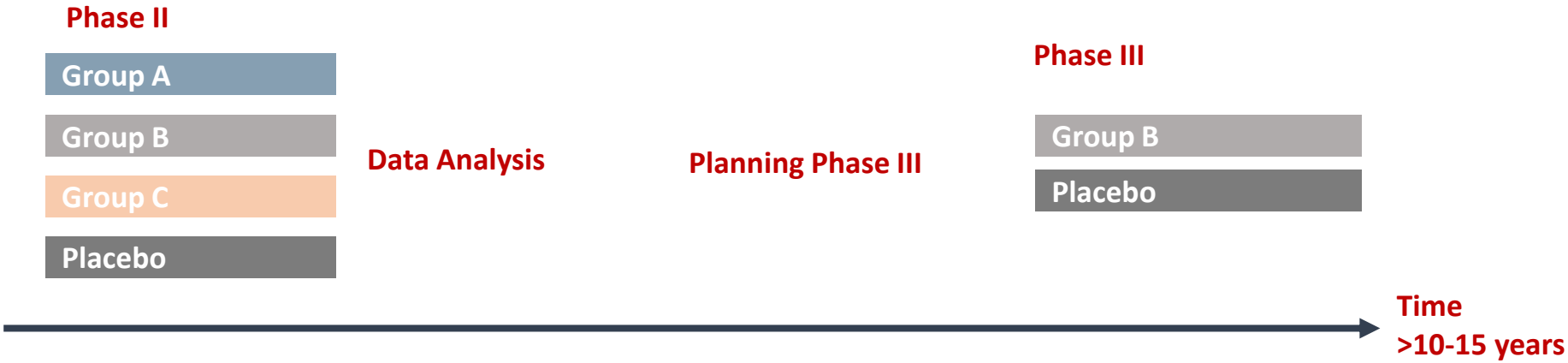
- Reject or fail to reject the null hypothesis in a well-defined population
- ≤3 study arms
- Standard phases (1-IV), clearly separated phase II & 3 & allows for little learning
- Standard statistical methods

Adaptive Clinical Trials

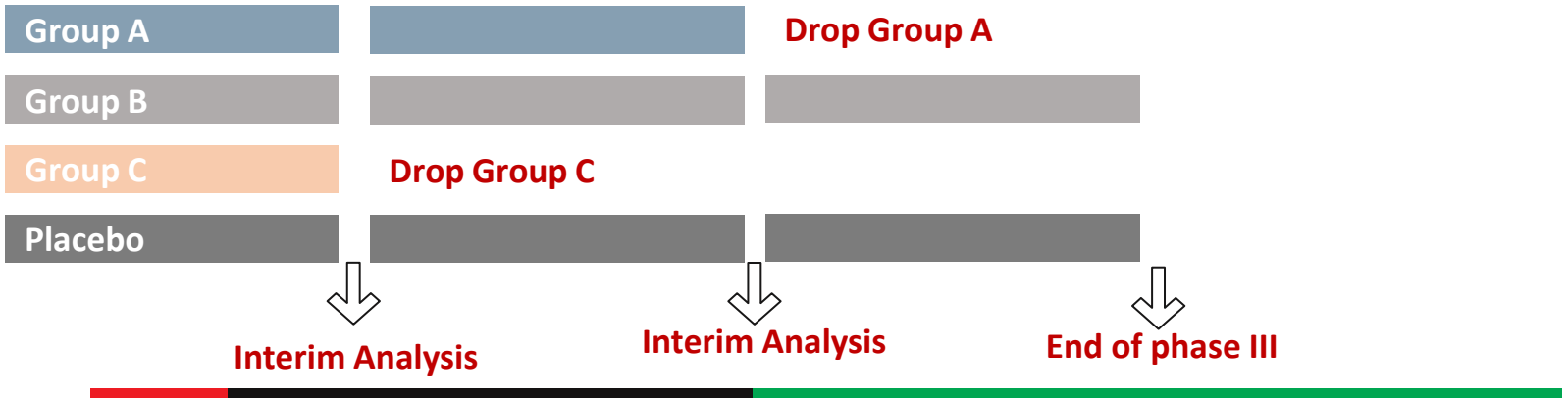
- Pre-specified modifications allowed based on interim analyses
- Many treatment arms
- Allows early detection / stop if warranted
- Different sets of risks and decision points

Adaptive Clinical Trial Designs: Seamless

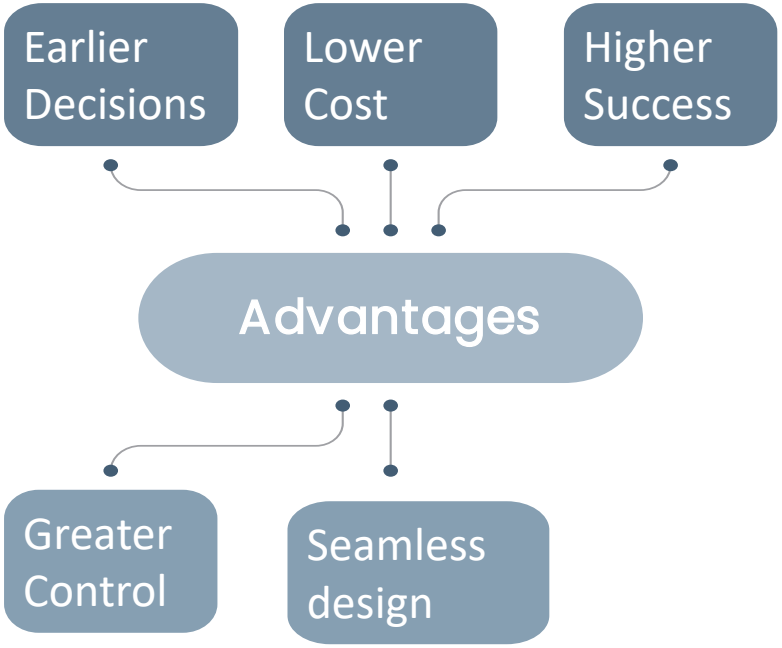
Traditional phase II & III studies



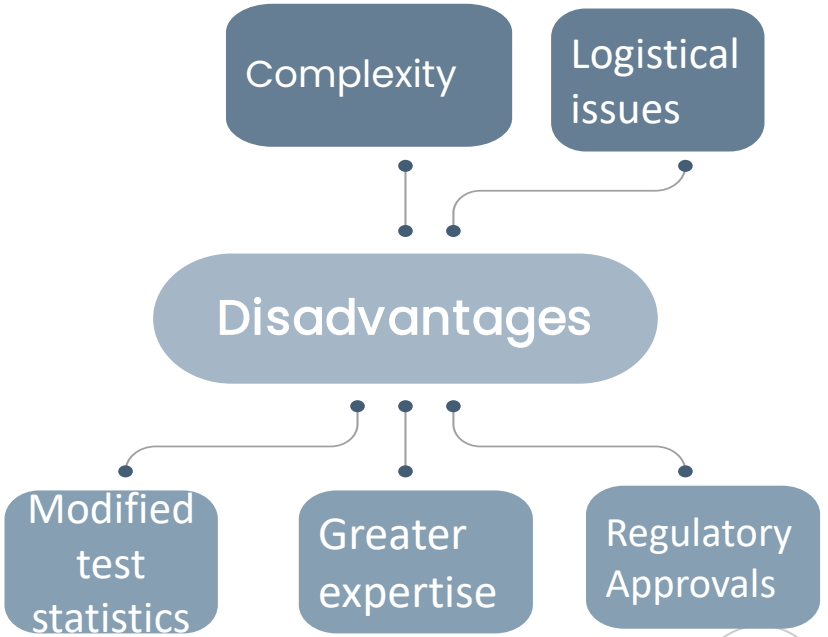
Adaptive design: Combined phase II & III



Advantages of Adaptive Clinical Trial Designs



Disadvantages of Adaptive Clinical Trial Designs



Adaptations

An adaptation is referred to a modification or a change made to trial and/or statistical procedure during the conduct of a clinical trial

Types of adaptions:

1. Prospective adaptation
2. Concurrent adaptation
3. Retrospective adaptation

Prospective Adaptation

Pre-planned during the design of the trial before implementation

Typical changes in:

1) Adaptive randomization
2) Stopping a trial early due to safety, futility or efficacy at interim analysis
3) dropping the losers (or inferior treatment groups)
4) Sample size re-estimation etc

priMe completes recruitment for a large African trial on prevention of tuberculosis in neonates

Portrait of a happy mother and daughter enjoying a piggyback ride outdoors

For its pivotal phase III trial of the novel tuberculosis vaccine VPM1002, the priMe project has completed recruitment of all participants. The priMe trial is a large, double-blind phase III

Concurrent Adaptations

- Generally, not pre-planned before start of the trial but their needs become apparent during the conduct of the trial

- Typical changes in:
  - Inclusion/exclusion criteria
  - Evaluability criteria
  - Dose/regimen and treatment duration
  - Changes in hypotheses and/or study endpoints
  - Etc.

Nankabirwa *et al. Trials* (2017) 18:322
DOI 10.1186/s13063-017-2050-0

Trials

STUDY PROTOCOL Open Access

Efficacy of umbilical cord cleansing with a single application of 4% chlorhexidine for the prevention of newborn infections in Uganda: study protocol for a randomized controlled trial

Victoria Nankabirwa[1,2*], Thorkild Tylleskär[2], Josephine Tumuhamye[2], James K. Tumwine[3], Grace Ndeezi[3], José C. Martines[2] and Halvor Sommerfelt[2,4]

ill. Severe illness is defined as illness that is associated with any of the following danger signs observed or verified by a study clinician: inability to feed or vomiting of all intake, lethargy or unconsciousness, severe lower chest in-drawing, axillary temperature of ≥37.5 °C or <35.5 °C, grunting, cyanosis, convulsions or a history of convulsions, and/or results in hospitalization and/or results in death. The data collection team records the presence or absence of omphalitis at each clinic visit. Signs for omphalitis include: pus, redness (inflammation) and swelling (edema) of the cord stump and the sur-

Retrospective adaptations

- Modifications and/or changes made to statistical analysis plan prior to database lock or unblinding of treatment codes

- In practice, prospective, ad hoc, and retrospective adaptations are implemented by study protocol, protocol amendments and regulatory reviewers' consensus

Types of Adaptive Designs

Multiple interim analyses Accrued data analysed at pre-specified points Trial may be stopped for efficacy or futility, or it continues Need to account for multiple analyses	Adaptive randomization design	Group sequential design	Sample size re-estimation design
	Drop the loser design	Adaptive dose-finding design	Adaptive treatment-switching
	Hypothesis adaptive design	Adaptive seamless Phase II/III	Multi adaptive design

Sydes *et al. Trials* 2012, **13**:168
http://www.trialsjournal.com/content/13/1/168

TRIALS

METHODOLOGY Open Access

Flexible trial design in practice - stopping arms for lack-of-benefit and adding research arms mid-trial in STAMPEDE: a multi-arm multi-stage randomized controlled trial

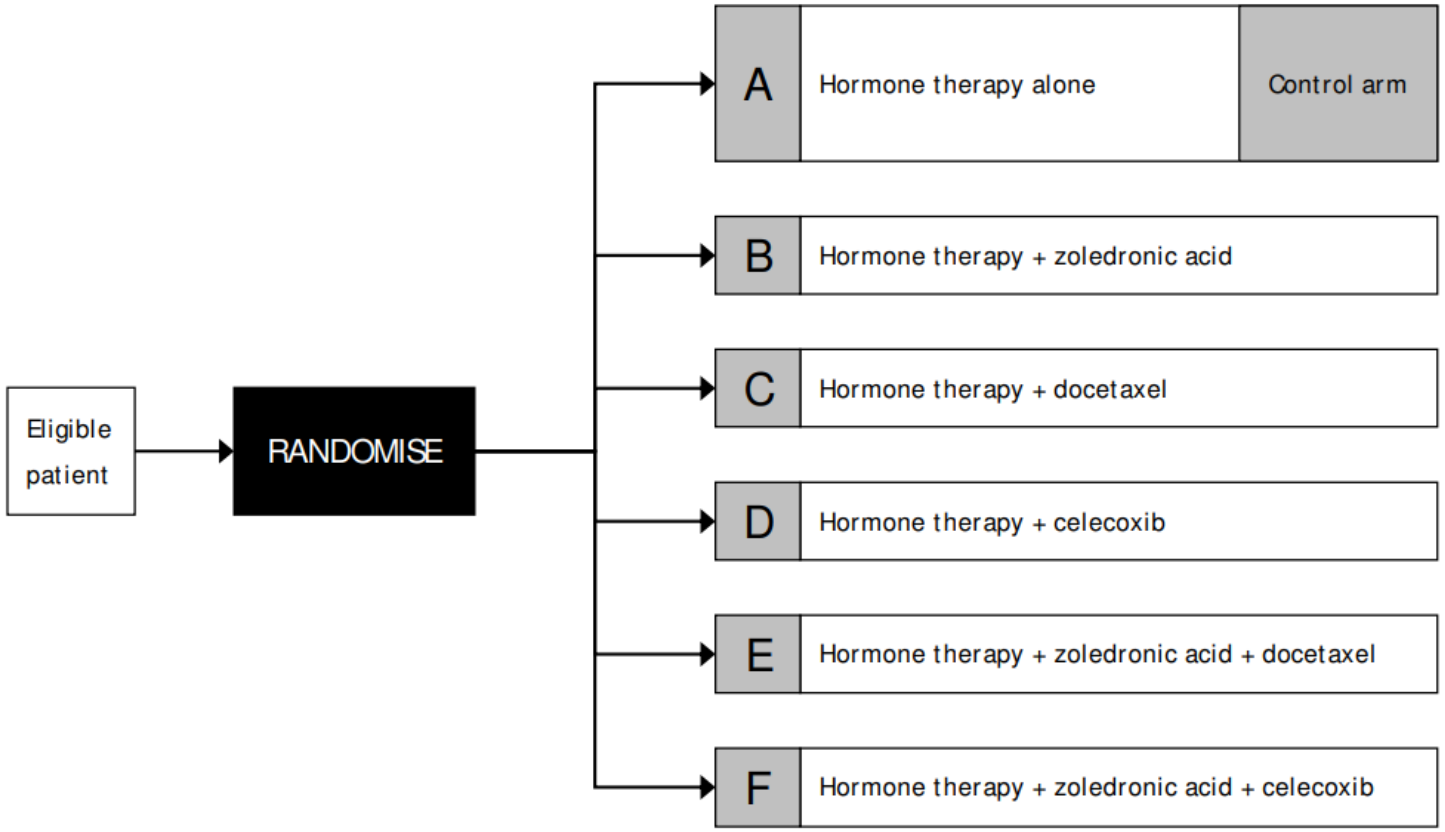
Matthew R Sydes[1*], Mahesh KB Parmar[1], Malcolm D Mason[2], Noel W Clarke[3], Claire Amos[1], John Anderson[4], Johann de Bono[5], David P Dearnaley[5], John Dwyer[6], Charlene Green[1], Gordana Jovic[1], Alastair WS Ritchie[1], J Martin Russell[7], Karen Sanders[1], George Thalmann[8] and Nicholas D James[9]

Abstract

Background: Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) is a randomized controlled trial that follows a novel multi-arm, multi-stage (MAMS) design. We describe

Sydes et al. Trials 2012

Multi Arm Multi Stage (MAMS) Trial



Sydes et al. Trials 2009

Table 2 Planned actions and timelines when accrual is stopped to trial arms

Action required	Timelines	
	Safety	LOB
Notify sites in writing of IDMC meeting date to pre-warn	-28 d	-28 d
Circulate prior letter from regulatory agency confirming that stopping early for LOB is not a substantial amendment, but part of trial design	-28 d	-28 d
IDMC meeting	-7 d	-7 d
IDMC notes and recommendations finalised	(<1 w)	(<1 w)
TSC meeting: stop / continue decision for each research arm	Day 0	Day 0
Turn off randomisation to arms stopping early for safety	<24 h	<1 w
Notify centres by email; patients to ignore irrelevant parts of PIS	<24 h	<24 h
Notify relevant industry partners	<24 h	<24 h
Notify TMG members	<24 h	<24 h
Alert trials unit staff to potential queries	<24 h	<48 h
Phone all site PIs. Instructed to hand-amend PIS and CF. Updated documentation to follow	<1 w	<1 w
Protocol and documents updated and agreed by TMG	<1 w	<1 w
Summary information for patients	<2 w	<2 w
Notify ethics committee and regulatory agency (for information only)	<2 w	<2 w
Detailed discussions with industry partners	<1 m	<1 m
TMG review of processes	<1 m	<1 m

Key: *LOB* = lack-of-benefit; *IDMC* = Independent Data Monitoring Committee; *TSC* = Trial Steering Committee; *TMG* = Trial Management Group; *PIS* = patient information sheet; *CF* = consent form; *h* = hour; *w* = week.
Note: the observed timelines broadly followed these plans.

Sydes et al. Trials 2012

Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

*Nicholas D James, Matthew R Sydes, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Melissa R Spears, Alastair W S Ritchie, Christopher C Parker, J Martin Russell, Gerhardt Attard, Johann de Bono, William Cross, Rob J Jones, George Thalmann, Claire Amos, David Matheson, Robin Millman, Mymoona Alzouebi, Sharon Beesley, Alison J Birtle, Susannah Brock, Richard Cathomas, Prabir Chakraborti, Simon Chowdhury, Audrey Cook, Tony Elliott, Joanna Gale, Stephanie Gibbs, John D Graham, John Hetherington, Robert Hughes, Robert Laing, Fiona McKinna, Duncan B McLaren, Joe M O'Sullivan, Omi Parikh, Clive Peedell, Andrew Protheroe, Angus J Robinson, Narayanan Srihari, Rajaguru Srinivasan, John Staffurth, Santhanam Sundar, Shaun Tolan, David Tsang, John Wagstaff, Mahesh K B Parmar, for the STAMPEDE investigators**

Summary

Background Long-term hormone therapy has been the standard of care for advanced prostate cancer since the 1940s. STAMPEDE is a randomised controlled trial using a multiarm, multistage platform design. It recruits men with high-risk, locally advanced, metastatic or recurrent prostate cancer who are starting first-line long-term hormone therapy. We report primary survival results for three research comparisons testing the addition of zoledronic acid, docetaxel,

Lancet 2016; 387: 1163–77

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James DN et al. Lancet 2016

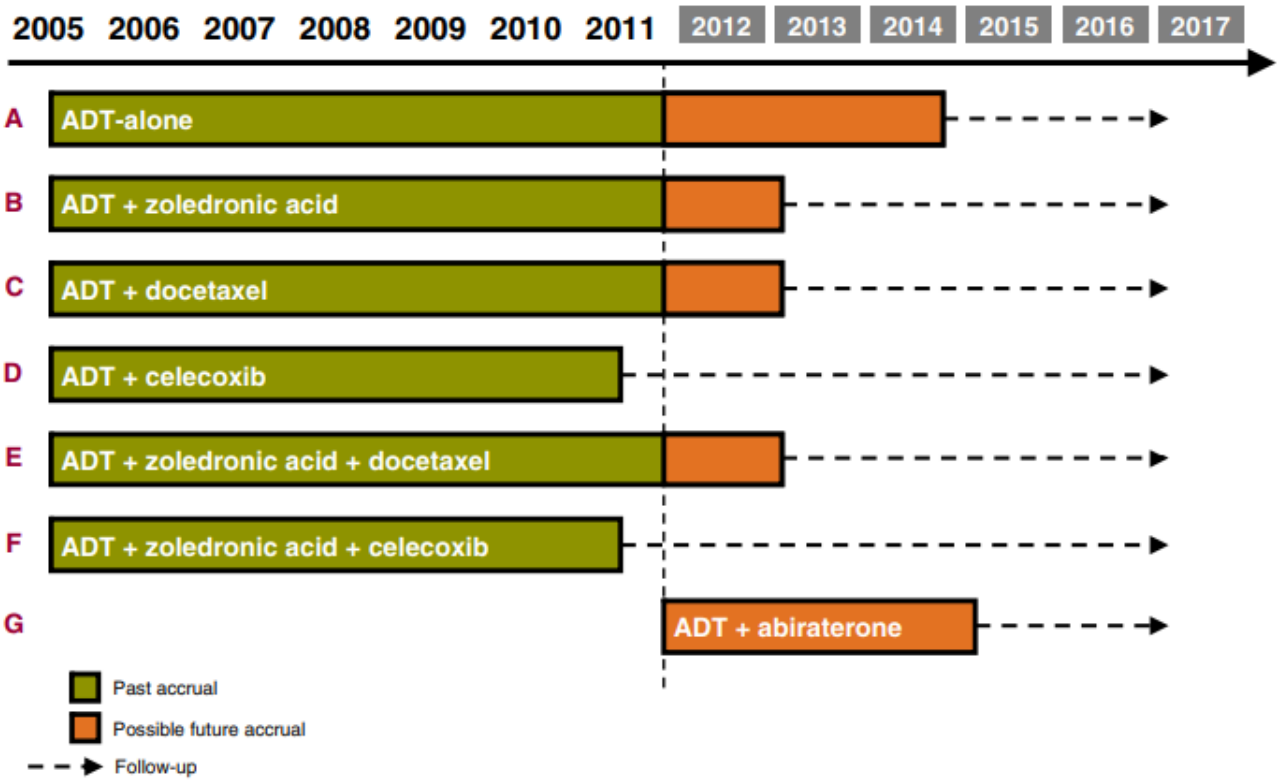

Figure 5 Trial arms open to allocat ion and fur ther t imelines as of Nov 2011.

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Management of Early Stopping

- Early stopping written into the protocol
- Notifications to RECs made although no immediate protocol amendment would be required
- Protocols updated as soon as practicable after changes to study arms to simplify activities for sites
- The Patient Information Sheets (PIS) would be updated immediately with removal of information that was no longer pertinent and sent to the ethics committee(s) for information

Changes in Treatments: Regulator Responses

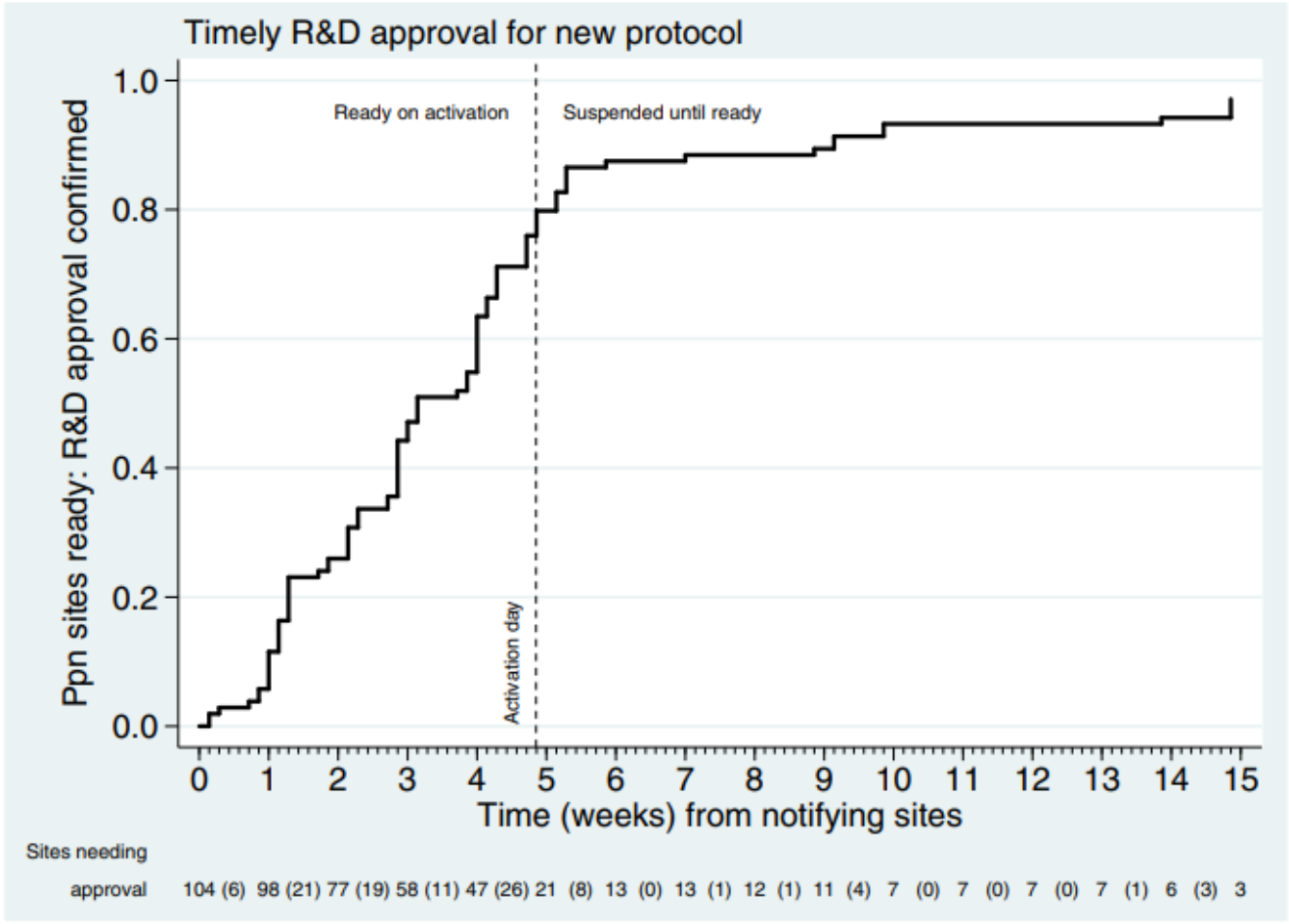

Figure 4 Activat ion of sites to new comparison.

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Issues Regulators (REC, NDA, UNCST) Need to Focus On (I)

- Purpose of adaptation
  - To enhance the trial and NOT to remedy inadequacies in planning
- Area of adaptation
  - Not all adaptations may be appropriate for every trial. Carefully consider which aspects can be “adaptive”
- Justification of adaptations
  - Must be scientifically justifiable and as much as possible prospectively planned and based on analysis of unblinded data

Issues Regulators (REC, NDA, UNCST) Need to Focus On (II)

Indicators of adaptation and focus areas

- Should be clearly stated, including their implications on the trial outcomes/endpoints

- Application of adaptive designs may result in a totally different trial that is unable to address the intended scientific/medical questions/hypothesis due to major differences in;
  - Actual trial population versus the original target population
  - Trial power and hypotheses tested and associated confidence intervals and or p-values
  - Trial endpoints/outcomes and their ascertainment and analysis before and after the adaptation

Table 1 Design parameters by trial stage for original research arms

Trial Stage	Type	Primary outcome measure	Target hazard ratio	Power	One-sided Significance level	Critical HR	Trigger events[1] (control)
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
Overall	-	-	-	83%	0.013	-	-

[1] Number of control arm events provoking analyses for the original research comparisons with a 2:1 allocation ratio in favour of control. The required number of events would be different for an equal allocation ratio.

Key: *FFS* = failure-free survival; *OS* = overall survival; *HR* = hazard ratio.

Note: these parameters are used for each pairwise comparison of research vs control.

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Issues Regulators (REC, NDA, UNCST) Need to Focus On (III)

- Study population post-adaptation
  - Do/does the pre-adaptation study population in the remaining trial groups contribute to final analysis?
  - Are the pre-adaptation study population in the dropped trial groups eligible for enrolment in the retained groups?
  - Does the adaptation scientifically justify change in the study population?

- Study design
  - Does the adaptation lead to a new design or new trial phase?
  - If a new trial phase is needed, is the a priori go-no-go criteria satisfied? (safety + intended effect)

Issues Regulators (REC, NDA, UNCST) Need to Focus On: (IV)

- Study outcome:
  - Is the primary outcome changing or getting modified? If yes, why and what is the impact on sample size, power and trial results?

- Sample size and power:
  - Original estimated SS & power; a priori interim analyses and their adjustments on SS & power; post-adaptation SS & power; final analysis SS & power

- REC approval for each adaptation
  - Each should be preceded by a presentation to the REC and approval. No blanket approval of all adaptations without returning to the REC for individual adaptation approval!

Thank You!

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