Current Statistical Considerations and Regulatory Perspectives on the Planning of Confirmatory Basket, Umbrella and Platform Trials

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Acknowledgments

Many slides in this presentation are from talks by:

Olivier Collignon (LIH, BSWP, EMA)

Anja Schiel (NoMA, BSWP)

And based on considerations from the BSWP task-force looking at these designs (Christian Gartner, David Brown, Bettina Haidich, Benjamin Hofner, Martin Posch, Olivier Collignon, Frank Pétavy, Inês Antunes Reis and Anja Schiel).

But despite this any opinions expressed are my own and do not necessarily reflect those of the MHRA or the EMA.

The Challenge

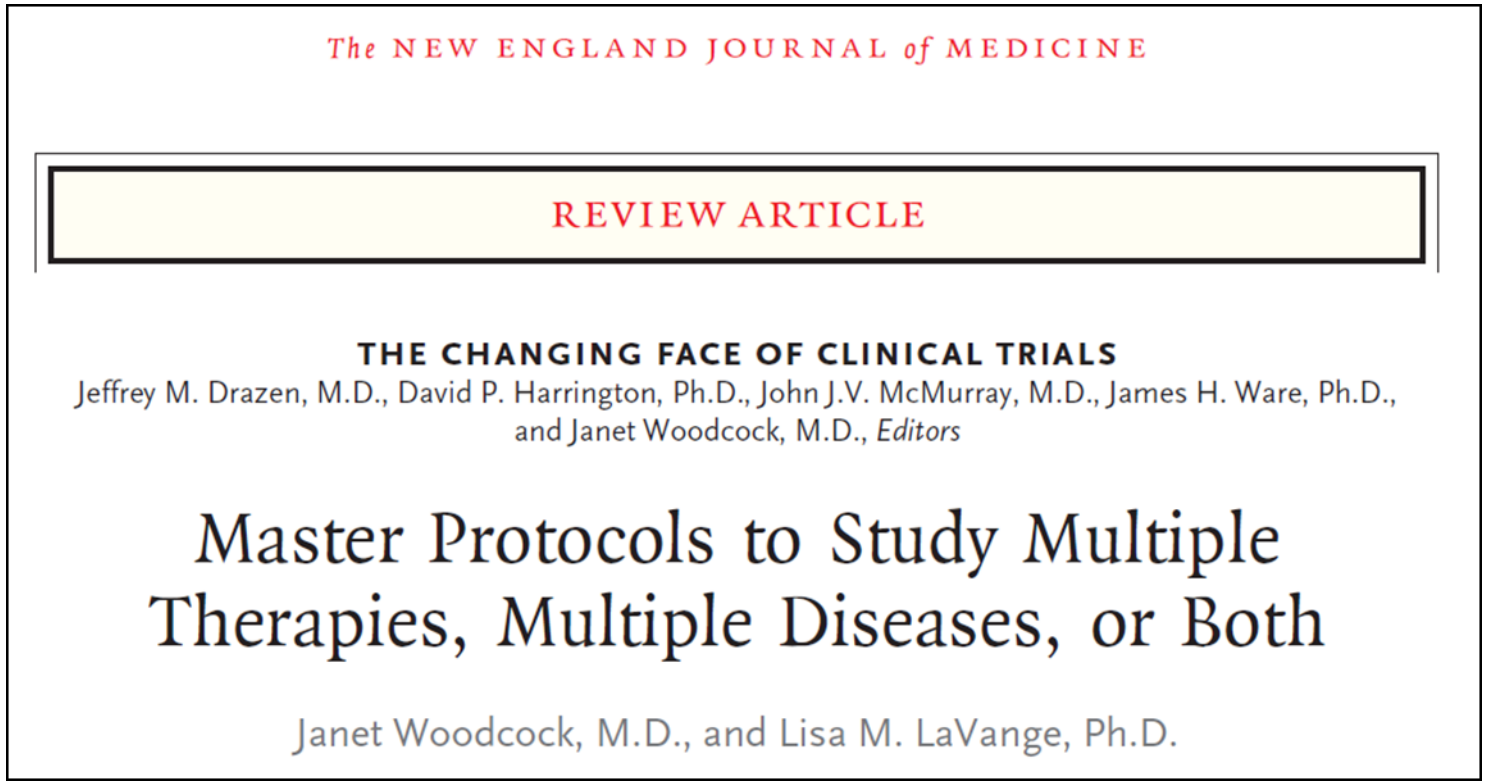
- A number of submissions to the EMA Scientific Advice Working Party (SAWP) led to a request to the Biostatistics Working Party (BSWP)
- Question: Do we need to be concerned with the control of the type I error rate in umbrella protocols?
- Type I error control is of major importance from the regulators' perspective
  - **Identify and collect examples discussed at SAWP**
  - **Conduct a literature review**

The first problem: Terminology

- Do we have a clear concept on the different trial designs?
- After a first round of literature search it was clear that there is a lack of common terminology
- Don’t get fooled by the wrapping

- How can we address the lack of common terminology?
- Define the trial design elements rather than put a label on the design (FDA)

Terminology



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

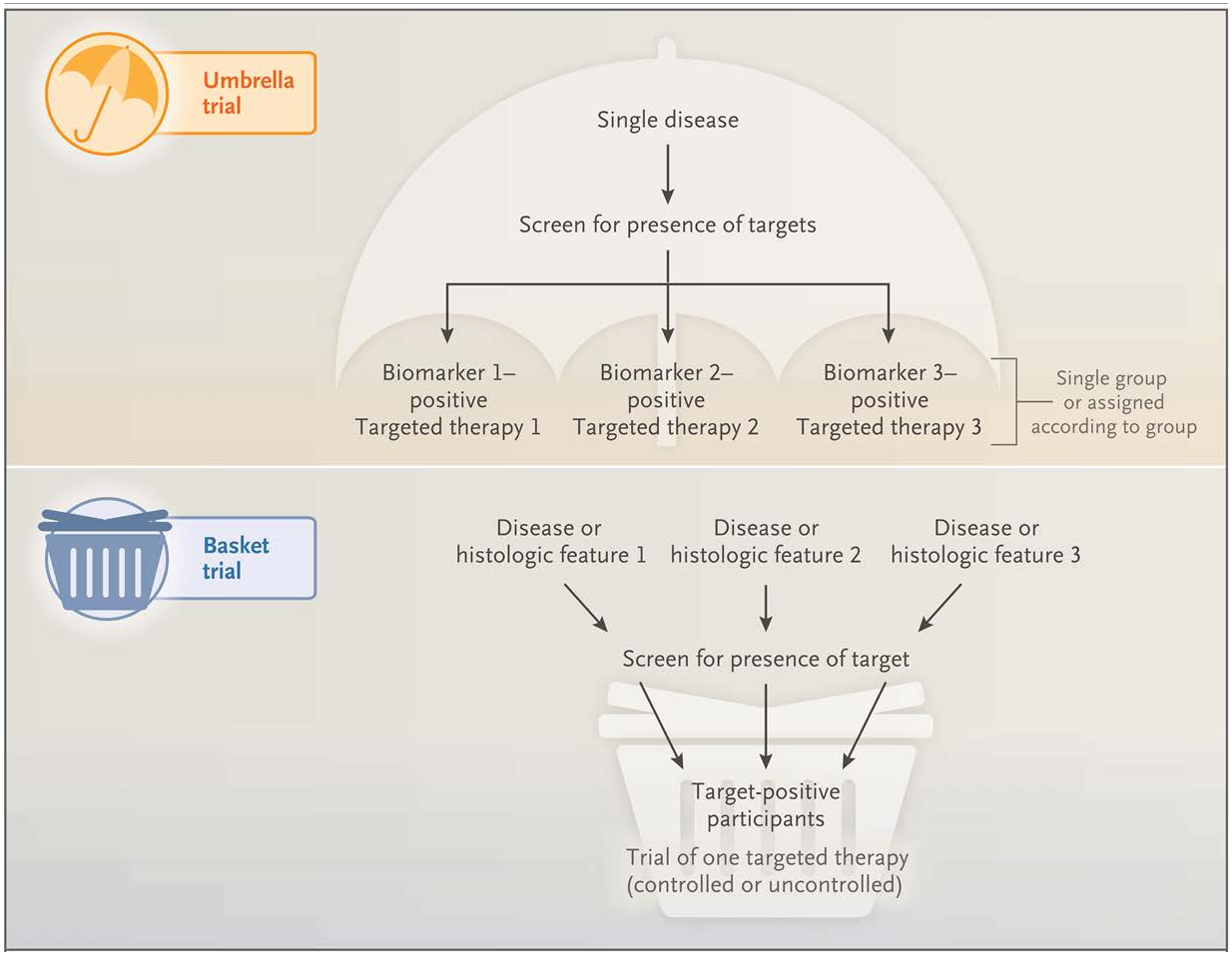
Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

Terminology

Table 1. Types of Master Protocols.

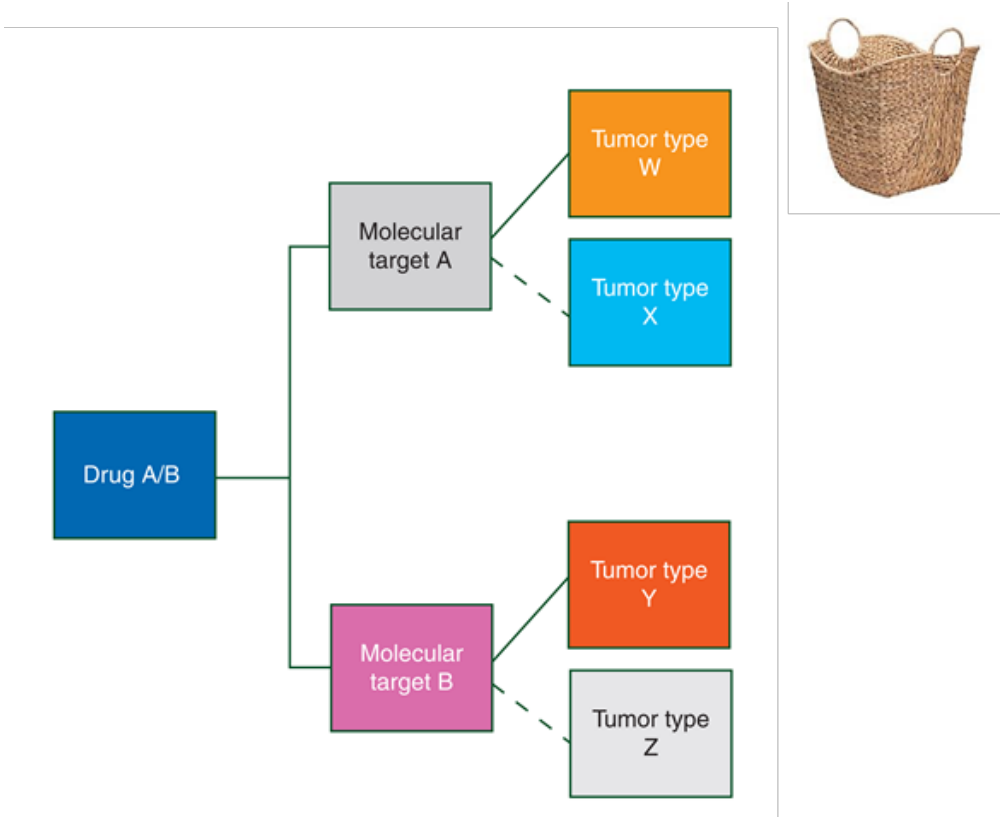
Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

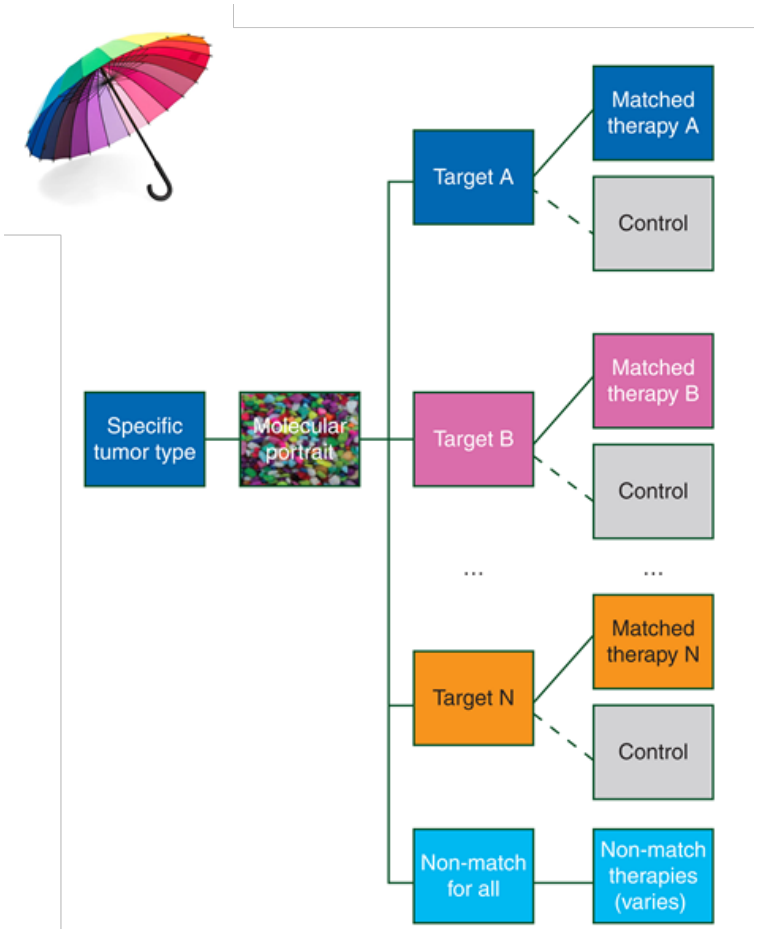

Umbrella trial
Single disease
Screen for presence of targets
Biomarker 1– positive Targeted therapy 1
Biomarker 2– positive Targeted therapy 2
Biomarker 3– positive Targeted therapy 3
Single group or assigned according to group
Basket trial
Disease or histologic feature 1
Disease or histologic feature 2
Disease or histologic feature 3
Screen for presence of target
Target-positive participants
Trial of one targeted therapy (controlled or uncontrolled)

Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples

L. A. Renfro* and D. J. Sargent

Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, USA


Drug A/B
Molecular target A
Molecular target B
Tumor type W
Tumor type X
Tumor type Y
Tumor type Z


Specific tumor type
Molecular portrait
Target A
Matched therapy A
Control
Target B
Matched therapy B
Control
...
...
Target N
Matched therapy N
Control
Non-match for all
Non-match therapies (varies)

Adaptive Design for a Confirmatory Basket Trial in Multiple Tumor Types Based on a Putative Predictive Biomarker

RA Beckman[1], Z Antonijevic[2], R Kalamegham[3,5] and C Chen[4]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 100 NUMBER 6 | DECEMBER 2016

UMBRELLA DESIGN

Multiple Drugs

One Indication
e.g. lung

Multiple Alterations

BASKET/BUCKET DESIGN

One Drug

Multiple Indications
e.g. lung, breast,colon..

One Alteration

Let’s try to simplify and look at the elements!

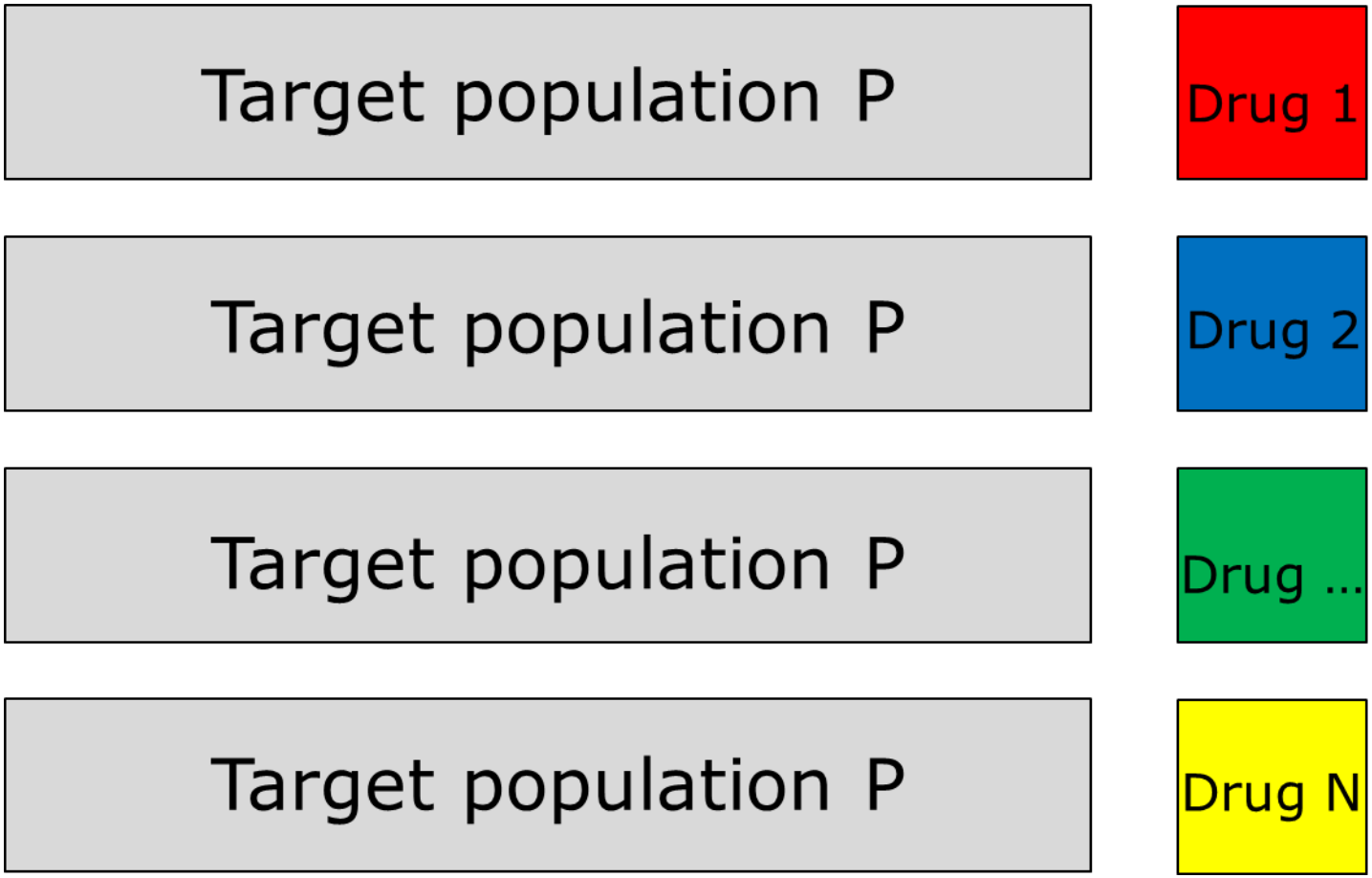
Basket trial

Advantages

- Molecular analyses done more efficiently and consistently within a single trial than if there were several trials, one for each tumour type.
- Exploiting expected correlation between arms could make trials more efficient – certainly true in phase 2 where separate baskets are sometimes combined
- General operational efficiency of only having one protocol etc.

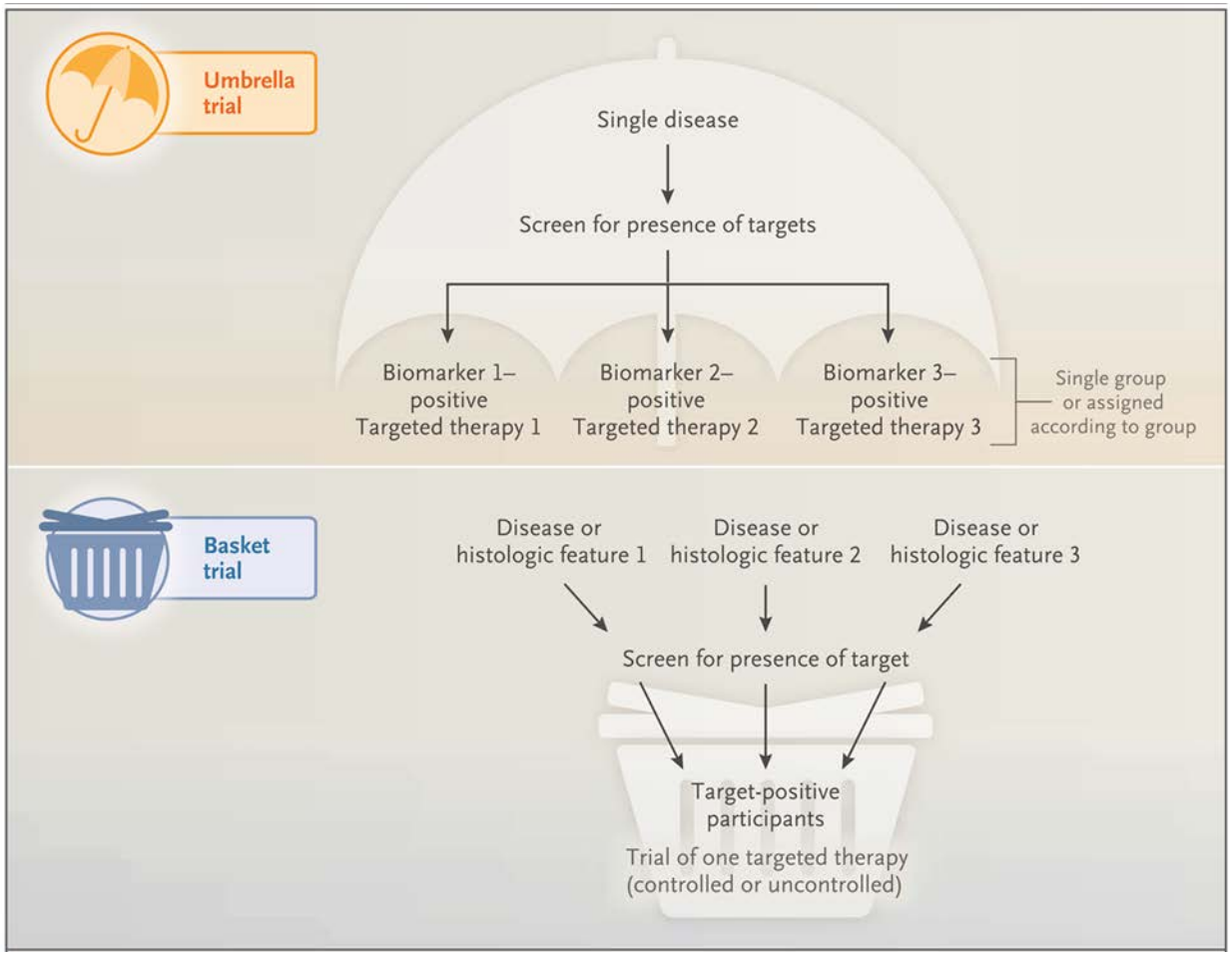
- The effect of a given drug D is being investigated in different target populations.
- This situation is not really different from a company pipeline in which a drug D would successively and independently be submitted to regulators for marketing authorization in different indications.
- Provided the studies corresponding to the different target populations are independent, no multiplicity adjustment would be required.
- Of note, if for each target population the design is randomised, the same comparator might not be used since standard of care might be different.

Umbrella Trial



Advantages

- Patients come in and are classified (biomarker) and then can be immediately enrolled in the appropriate sub-study.
- Operationally there are some big advantages – don’t have to re-screen patients several times for biomarkers to enrol into 4 separate trials.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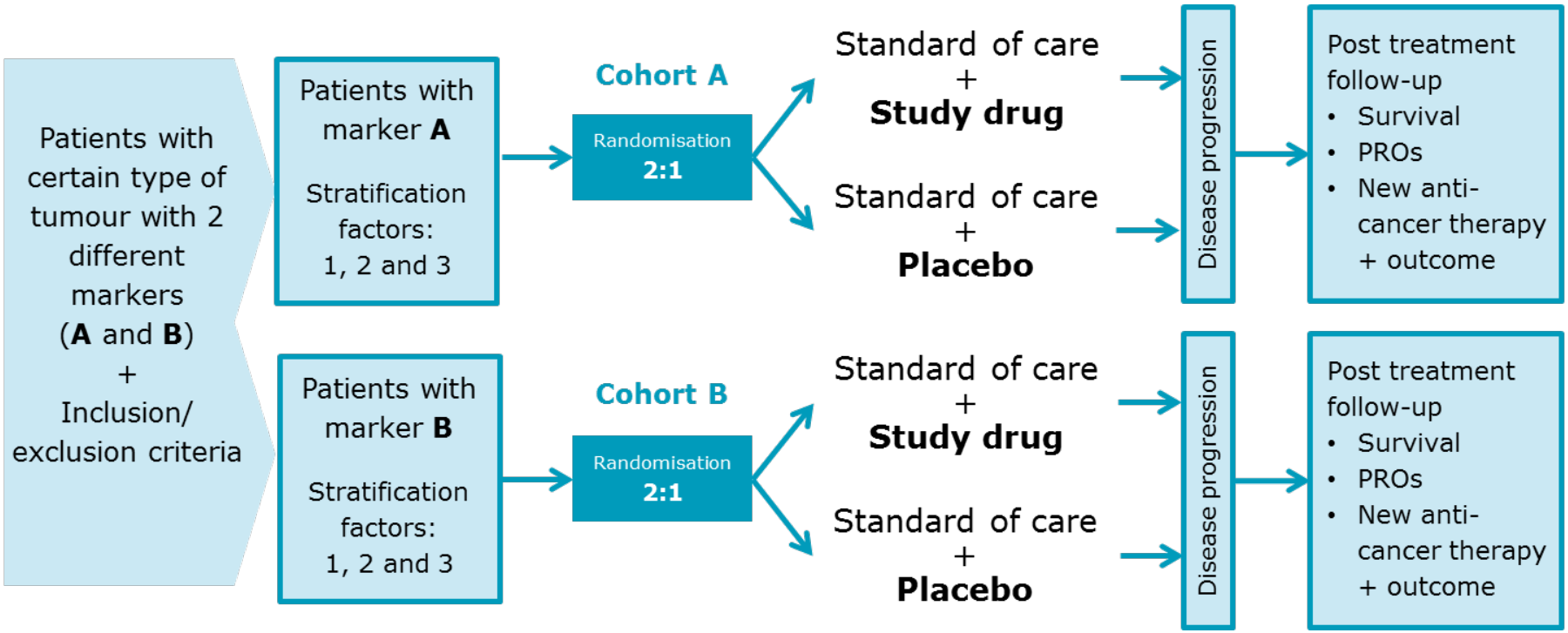
Disease or histologic feature 1
Disease or histologic feature 2
Disease or histologic feature 3
Screen for presence of target
Target-positive participants
Trial of one targeted therapy (controlled or uncontrolled)

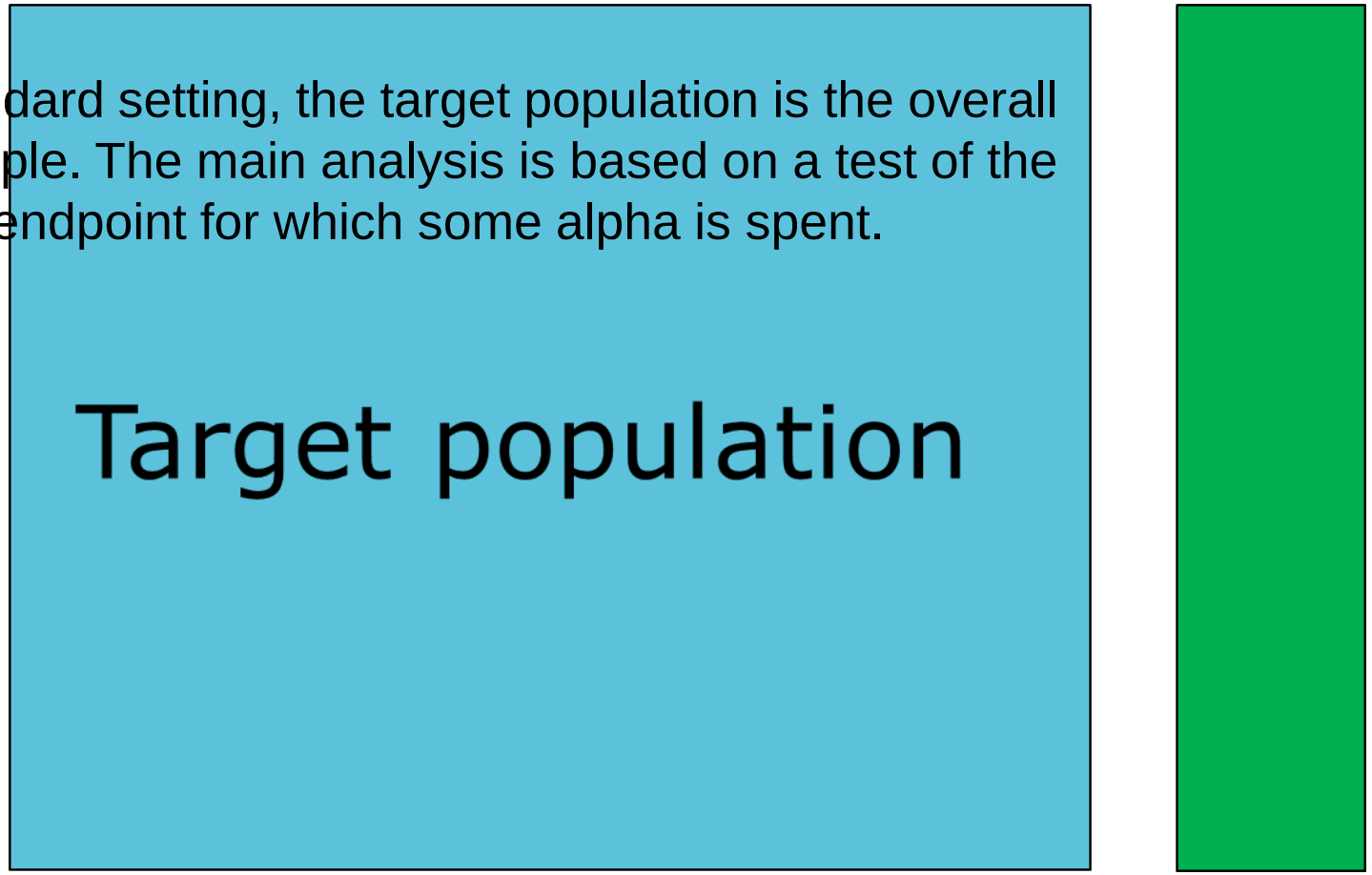
- In the ‘Umbrella’ trial, in each target population a different drug is tested.
- This situation is not really different from a company pipeline in which portfolio drugs would successively and independently be submitted to regulators for marketing authorization.
- Provided the studies corresponding to the different target populations are independent, no multiplicity adjustment would be required.
- Of note if the target population is the same for each drug 1,…,N tested, and if the corresponding designs are randomized, the comparator could be the same.

A recent example (anonymised) basket/umbrella

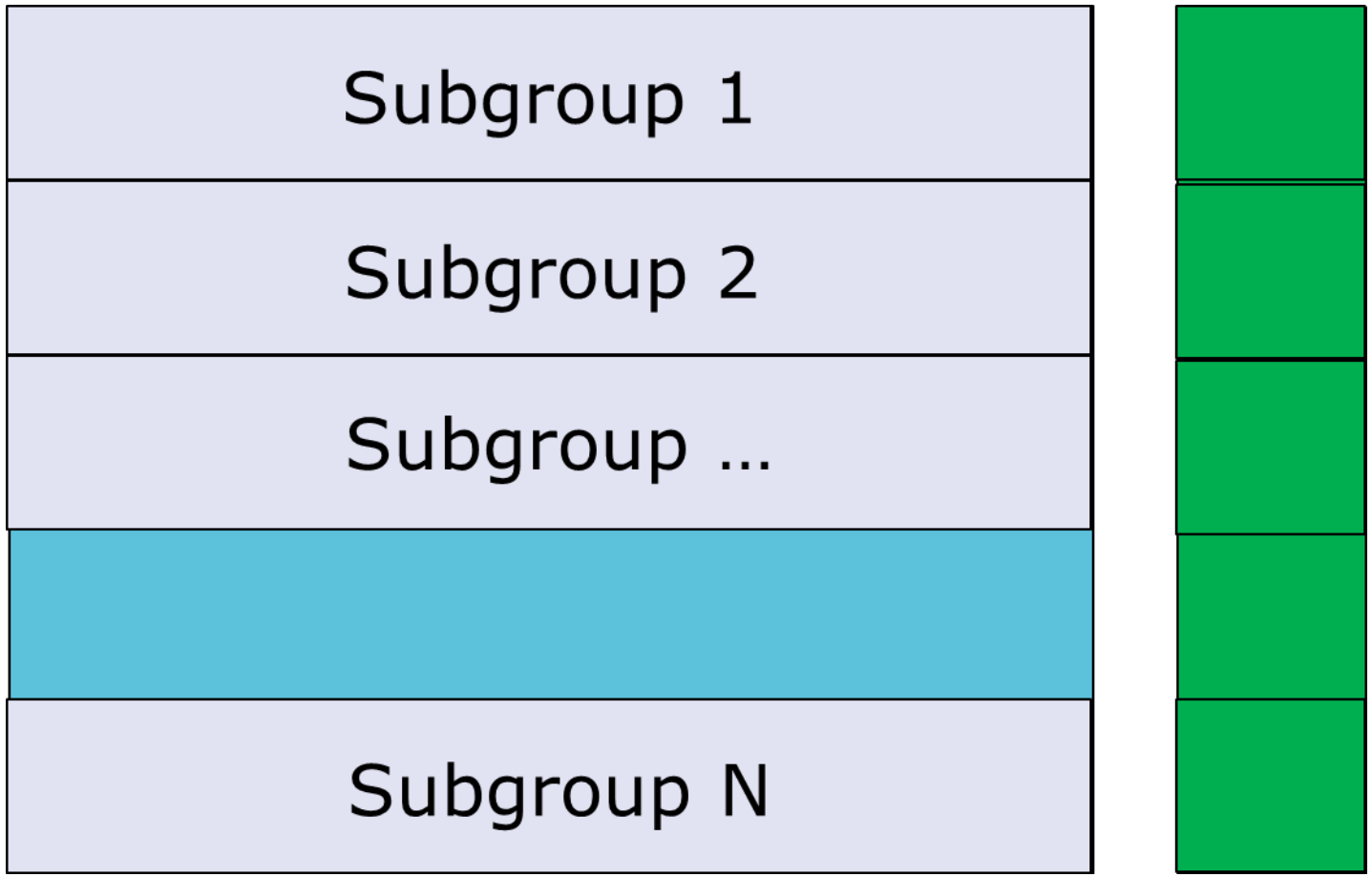


Why is this different from a subgroup analysis?

In a standard setting, the target population is the overall trial sample. The main analysis is based on a test of the primary endpoint for which some alpha is spent.



Depending then on the subgroup strategy, some alpha is devoted to the testing of the primary endpoint in each subgroup investigated.



- Basket trials shouldn’t be a strategy for avoiding spending some alpha to investigate the effect of the drug in different subgroups (which play the role of the target populations).

- If there is no strong clinical rationale for analysing the target populations separately, a standard trial with an appropriate subgroup analysis (corresponding to the planned target populations) might be more suitable.
- Pooling shouldn’t be used to rescue failed independent trials (corresponding to the target populations) on the ground of gaining power, especially if there is a strong clinical rationale for investigating them separately.

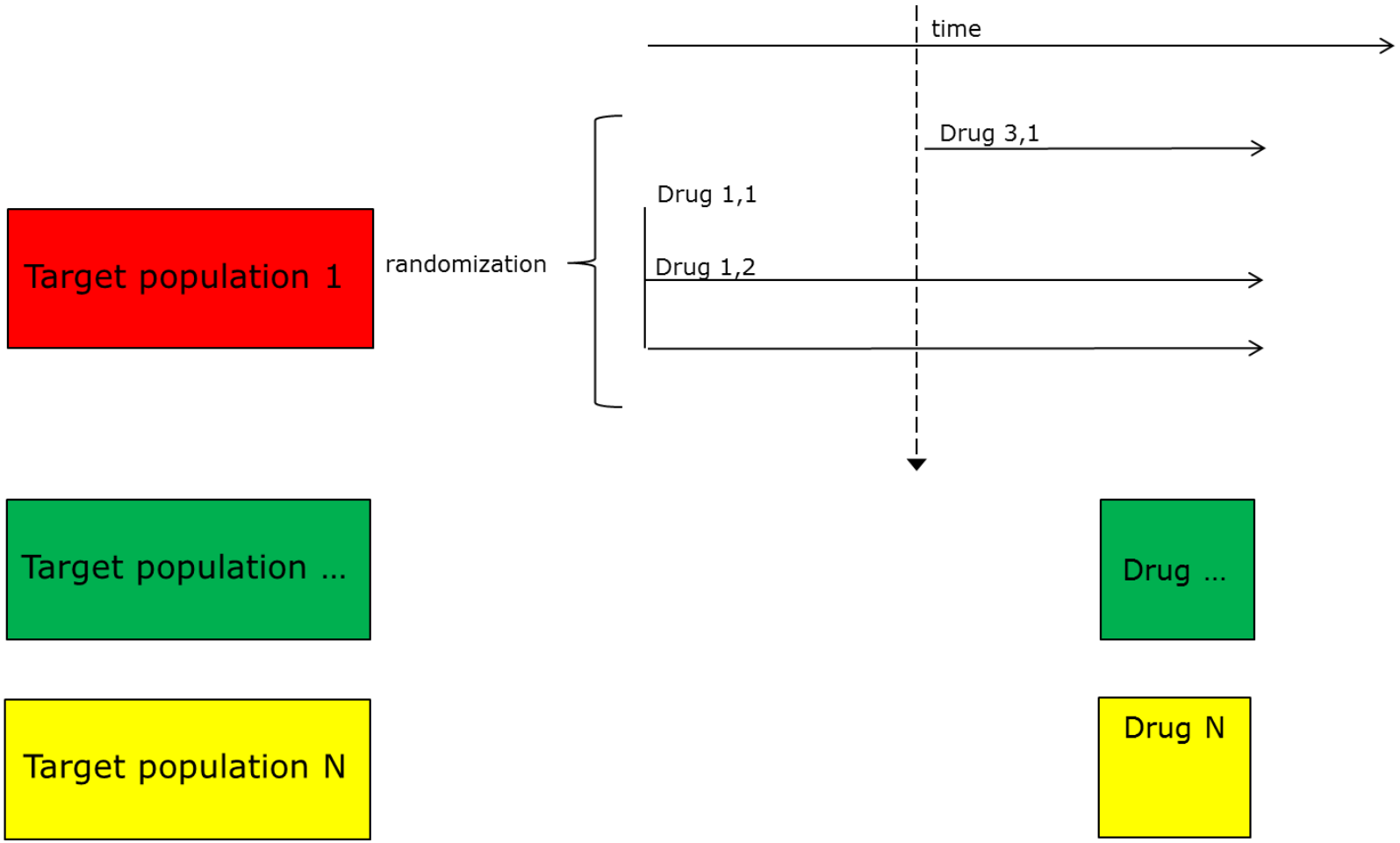
Pooling

- Pooling is often presented as one of the advantages of multi-arm, multi-drug trials (Particularly for basket trials)
- What is the planned pooling strategy; need for pre-specification (cherry picking must be avoided)
- If a ‘vast majority’ of the sub-trials corresponding to the different target populations are positive, can a global indication be obtained and how (this will depend on the unit of observation)
- What is the intended ‘indication’?
- Can pooling be clinically justified?
- Impact of the heterogeneity of the different pooled populations (risk of failure due to pooling)

Shared control

- A single sub-study could have a control group plus more than one experimental agent
- Sometimes the agents aren't from the same company
- Multiplicity issue here?
- But how different is this really to two separate trials – especially if it is two separate companies?

Platform trials



- In the same target populations, several drugs can be analysed concurrently by randomising corresponding patients to different treatment arms. Also, some additional treatment arms can be adjoined dynamically to the design.

- By definition, according to Renfro, another target population could also be added to the platform trial. Again, provided the corresponding trial is planned independently of the other ones, this should not lead no any multiplicity issues.

- Not really different from an umbrella trial provided all the trials corresponding to the target populations are independent with their own type 1 error.

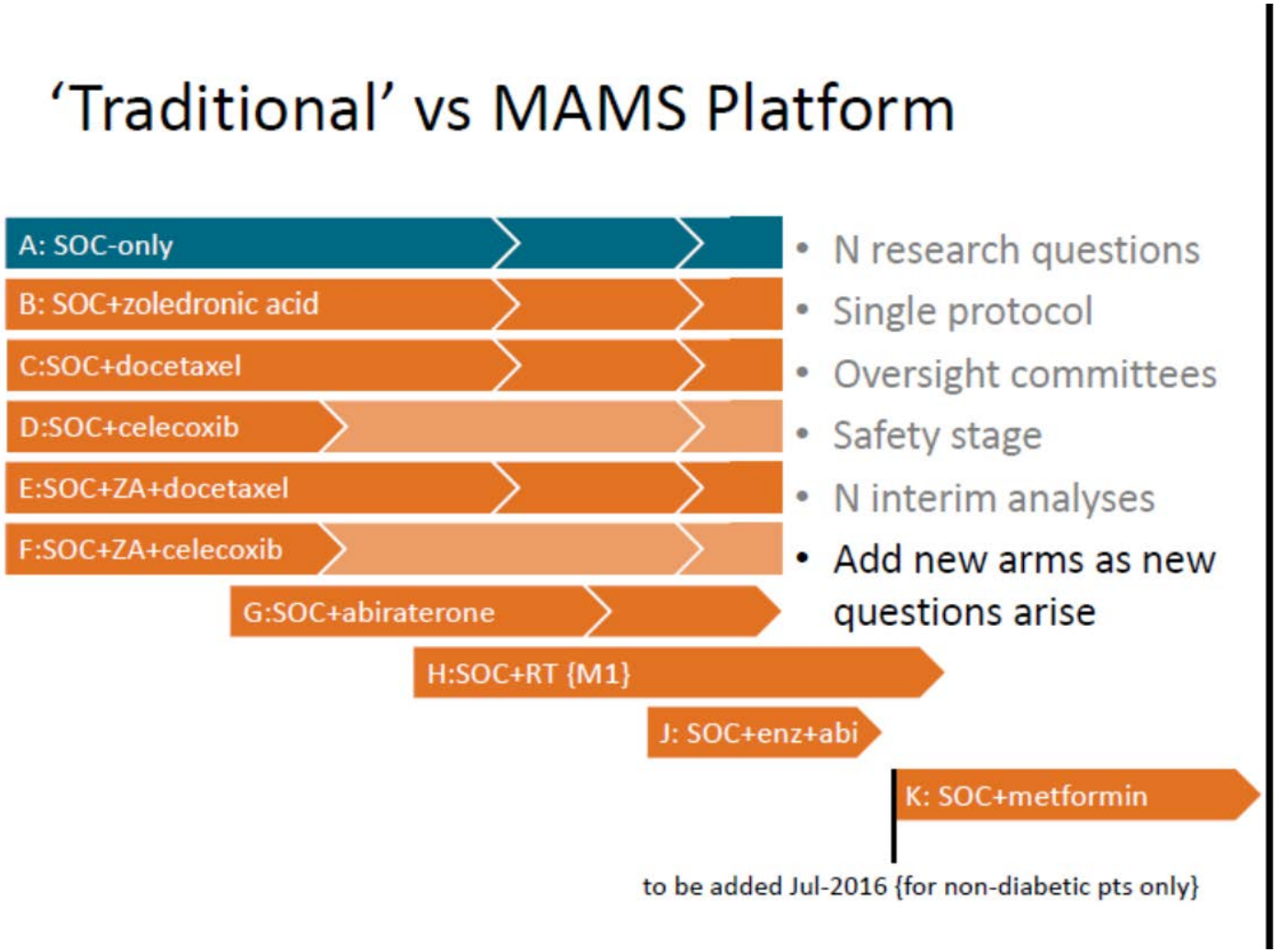
Platform design

- This approach essentially no different in terms of data generated than would be obtained from running several similar studies.
- Operationally there are some big advantages – don't have to re-screen patients several times for biomarkers to enroll into 4 separate trials.
- Some statisticians concerned about error control
- Issues from a CTA perspective

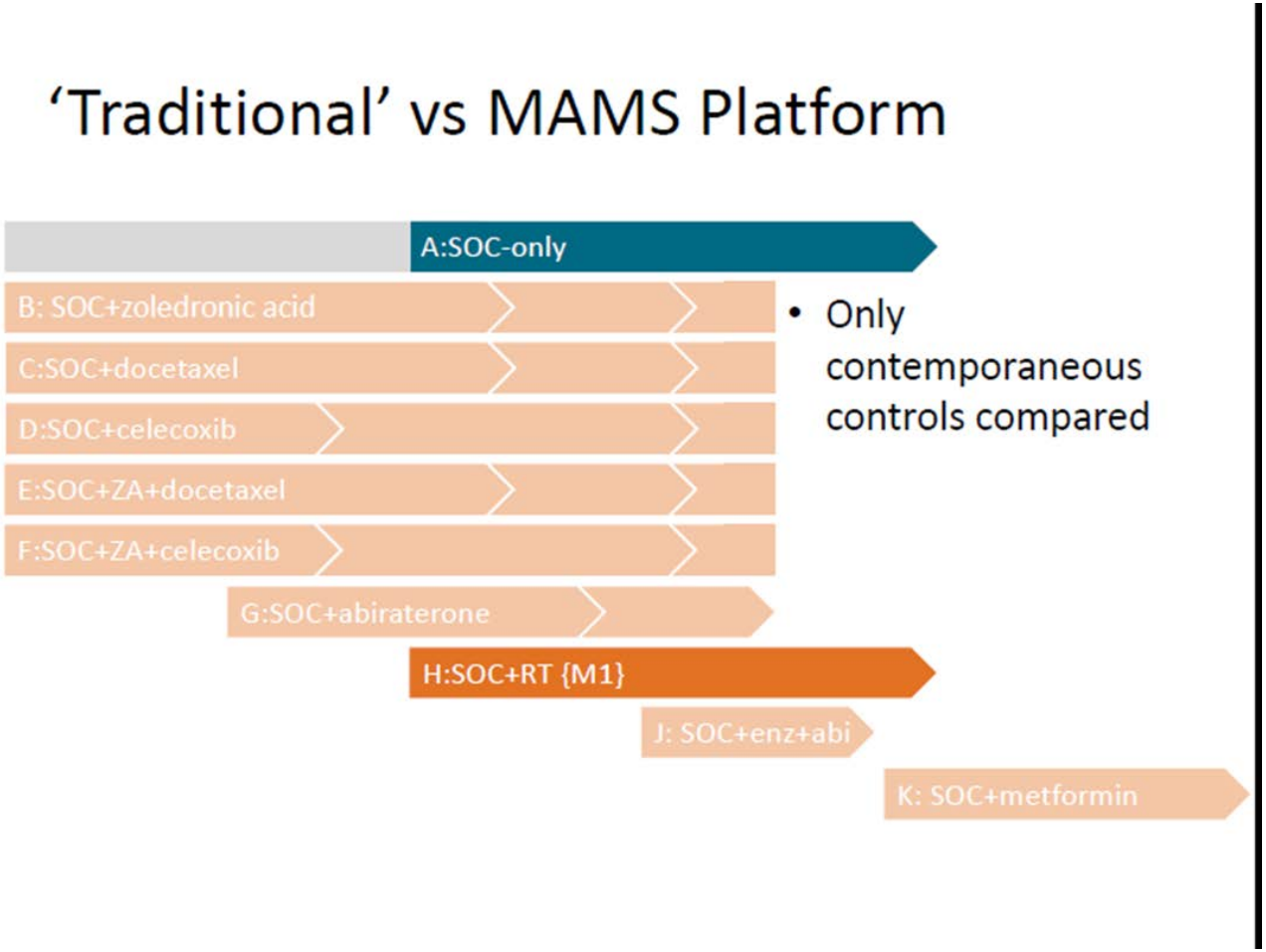
Multi-arm, multi-stage platform

- Shared control
- New interventions introduced and discontinued
- Patients randomised between all currently available interventions and control
- Control patients used in several comparisons – all that they were eligible for randomisation to.
- Different endpoints can be used at interim and final analysis

STAMPEDE trial



STAMPEDE study



Multi-arm, multi-stage platform

Clear gains in operational efficiency

Are these ‘infinite trials’? CTA issues.

Type I error control issues still under discussion

New ‘5%’ for each comparison – or need to adjust for multiplicity?

Is adjustment even possible without being able to predict the future.

Are there multiplicity issues?

The BSWP working hypothesis is:

- If we are looking at several **independent** trials **all controlled for type 1 error** relatively to their own design, then **no, we see no issues with multiplicity.**
- Possible violation of **independence** (still being debated):
  - no overlap of patients (ex: no switching from one sub-trial to the other?)
  - no overlap of treatment (ex: no common control arm)
  - no decision taken for one trial can impact the other ones (e.g. early stop for efficacy)
  - the only common points boil down to logistic/ethic/legal aspects
- If the same studies were presented as a development pipeline we wouldn't expect to see the type I error controlled across target populations.

Are there multiplicity issues?

Less clear the more complex the designs get

- Adding arms and/or drugs in time might cause problems with the concept of independence
- How many drugs can we test in the same indication or target population before we have a lucky hit?
- Dropping arms/drugs/target populations might not always be acceptable
- What is acceptable in the exploratory setting is not per se acceptable in the confirmatory setting