Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Master protocols: MHRA experience

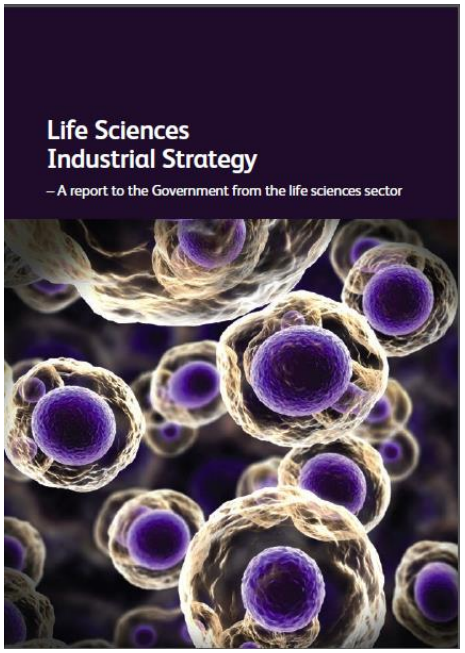
Khadija Rantell

Disclaimer

The views expressed in this presentation are those of the speaker and not necessarily those of the MHRA.

Life Sciences Industrial Strategy 2017 report to the UK Government:

Our goal



"As the UK seeks to do more **complex and innovative trials**, MHRA needs to continue engaging with sponsors to **assist with innovative protocol designs** and should facilitate efficient approval of complex trials and amendments to such trials, for example, to add new arms.

The **UK should attempt to lead the innovation** in clinical trial methodology, such as basket trials, and should also attempt to embed routine genomic analysis to make trials more targeted, smaller and more likely to deliver high efficacy."

Master protocols are new approaches to clinical trials driven by the need for enhanced efficiency (patients and resources).

Supporting innovative designs

- In the **UK**, the Experimental Cancer Medicine Centre (**ECMC**) Network is at the forefront of developing and delivering innovative trials.
- The **MHRA** has also a representative at the Clinical Trial Facilitation Group (**CTFG**) of the Heads of Medicinal Agencies (**HMA**).
- The **MHRA** welcomes and supports safe innovative approaches to clinical trials.
- Adaptations can be acceptable if safe and scientifically justified.
- However, the first hurdle in master protocols is **lack of common terminology.**

Terminology

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

- Approval of Clinical Trial Authorisation (CTA) applications is **a national responsibility.**
- **MHRA** assessment is based on **trial design elements** and not the name used to describe the study design.

Example1:
Umbrella trials (single disease)

One trial population: patients with ‘x’ tumour type

The trial population that will be divided in **sub-populations through genetic screening**. Patients will be matched with the best available treatment.

Primary Objective

To assess the safety and activity profile of therapies **(multiple therapies) targeting specific mutations** identified in patients with the ‘x’ tumour type

Note: Design may be randomised or use external controls depending on the disease.

Example 2:
Basket trials (single therapy)

Trial population: patients whose tumours harbour mutation ‘y’

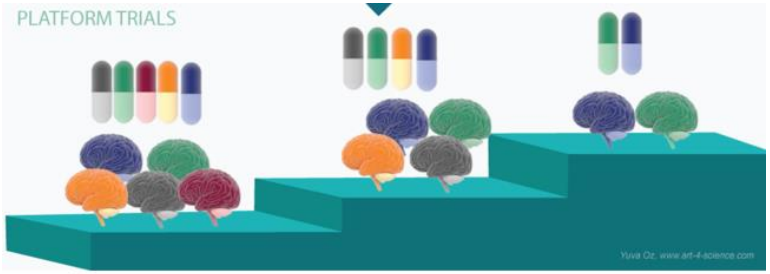
An IMP targeting mutation ‘y’ will be investigated **in all cancer patients with that mutation** and therefore potentially responsive to the IMP.

Primary Objective: to investigate the safety and efficacy of the IMP in all cancer patients with mutation ‘y’ **(multiple diseases or disease subtypes).**

Note: Use of a common control is not always suitable but may help to put the results into perspectives

Example 3: Platform trials

- Study of **more than one therapy** for a particular disease defined by both pathological and molecular criteria.
- Platform trials are similar to umbrella trials but have adaptive features; e.g. sequential testing with the possibility of stopping early for success or failure.
- Sub-studies can be **dependent** or **independent**



Example 4: Matrix trials

Phase 1-2 trial aimed at investigating the safety and preliminary efficacy of IMP ‘z’ alone or in combination with other cancer therapies in patients with advanced solid and haematological tumours.

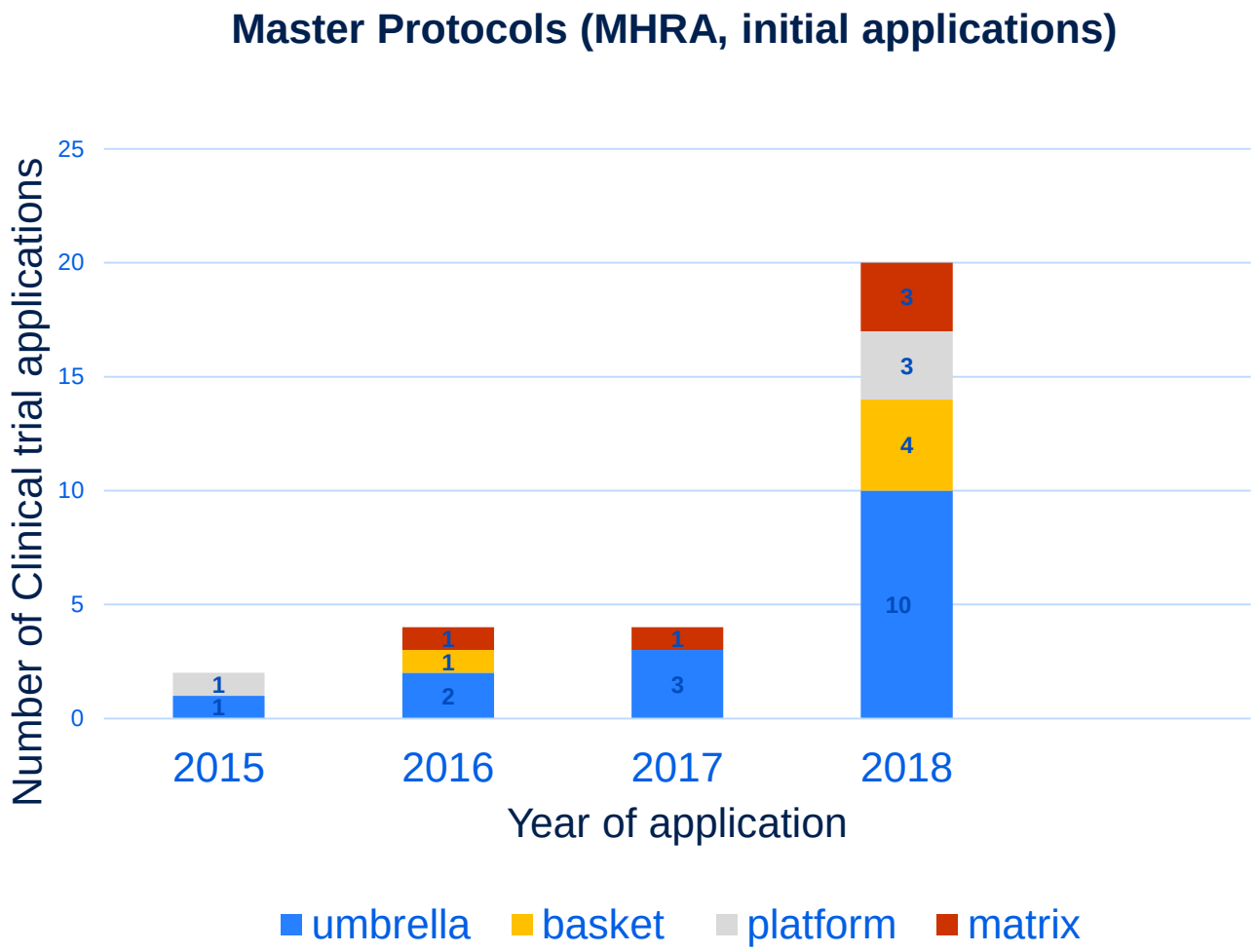
‘**n**’ IMPs/IMP combinations are possible

Plus

‘**N**’ trial populations

These can be acceptable in early phases but shouldn’t be presented as “never-ending” or as unlimited combinations in an unlimited number of advanced cancer indications.

MHRA experience



Characteristics of trials (MHRA CTA)

- **MHRA** experience (basket, umbrella, platform, matrix designs):
  - 11 x **Phase I/II** studies
  - 11 x **Phase II** studies
  - 5 x **Phase I** studies
  - 1 x **Phase IV** study
  - All trials were conducted in oncology patients.
  - Majority of CTA are approved or pending approval.

Common issues

- Allocation of single **EudraCT** number to a complex trial is challenging.
- Unharmonised decisions can be taken among the EU competent authorities.

- Approval is based on safety considerations, scientific rational and whether the Sponsor is be able to justify:
  - the choice of a complex trial design and explain why it is superior to a simpler, traditional design.
  - that future adaptations are consistent with the original trial hypothesis.
  - the statistical considerations (stopping criteria, Type I error control, bias, data pooling,…) are in place.
  - the trial has a beginning and an end. Never ending trials are not acceptable.

- The biggest barrier from our perspective for any clinical trial related issue/concern is not coming to ask our advice early enough (or at all!).

Let’s discuss together!

We can offer

- Scientific advice
- Regulatory advice
- Broader scope meetings
- Innovation office meetings - innovationoffice@mhra.gov.uk
- Email advice – clintrialhelpline@mhra.gov.uk
- Telephone assistance – 020 3080 6456

Acknowledgment

Dr Beatrice Panico (MHRA)
Dr Kirsty Wydenback (MHRA)
David Brown (MHRA)
Julia Saperia (MHRA)

Thank you!

Any Questions?

Additional slides.

Adaptations: initial Clinical Trial Authorisation application and requests for substantial amendments

Adaptations should be planned when deciding the original study design and adequately described and justified at the time of the initial Clinical Trial Authorisation (CTA) application.

Are ad-hoc adaptations ever acceptable?

Remember that a trial is an organised collection of data aimed at investigating a specific research hypothesis.

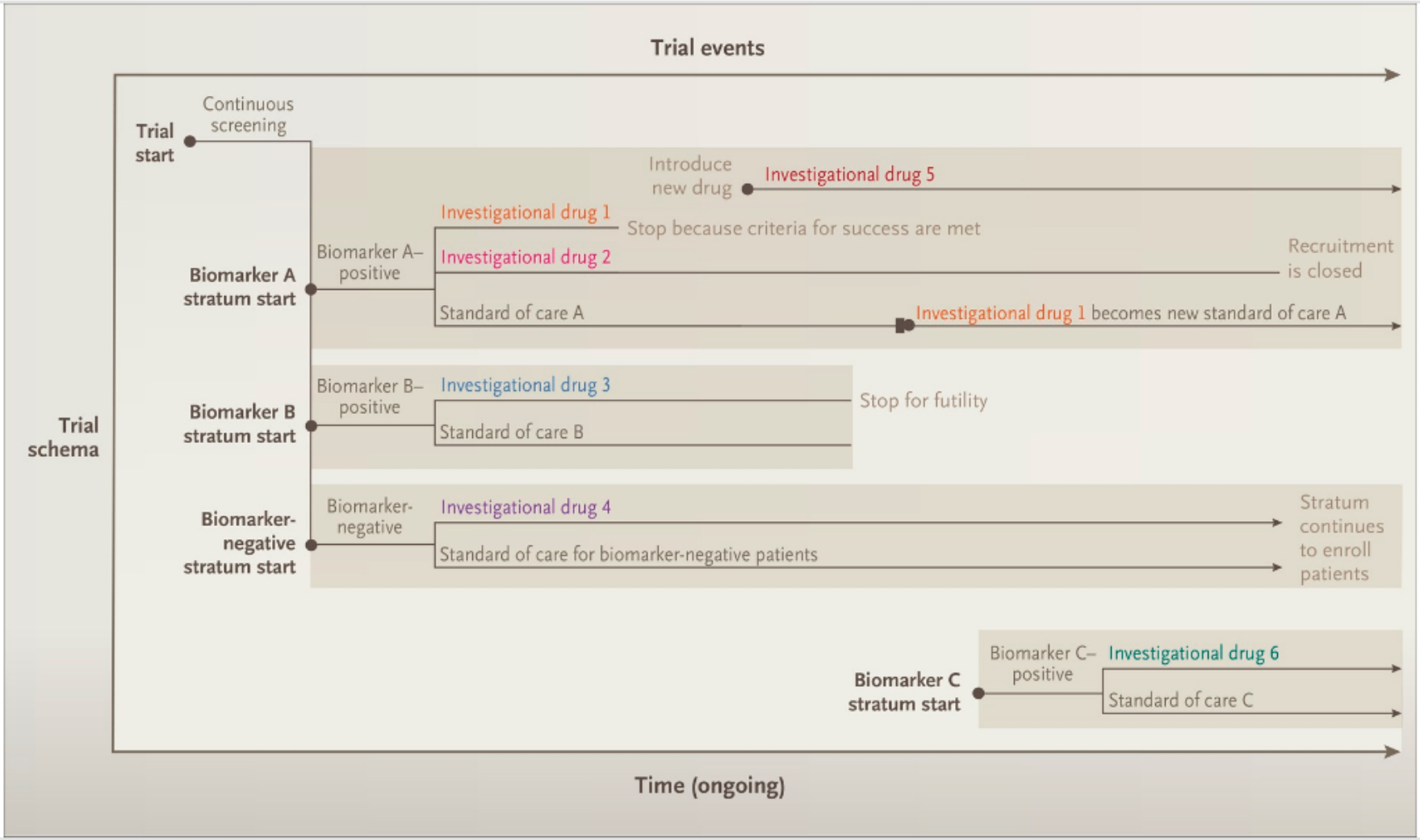
If the primary objective changes to an extent that is not in line with the original trial hypothesis, if changes make data obtained up to the point of the amendment inadmissible or make the sponsor lose control of Type 1 error

Isn’t this a new trial?

Adaptive study designs: Tips for Initial CTA applications

- Which are the ‘true’ trial objective(s) and how will they be achieved over time?
- List of the planned adaptations
- Why is it safe and scientifically acceptable to apply the adaptations and how will they allow the trial to meet its objective(s)? Organisational reasons are not an acceptable rationale!
- Does the trial design envisage additions of new Investigational Medicinal Products (IMPs) and/or new trial populations: justification needed
- Addition/removal of treatment arms: when will an arm be declared successful and further investigated in a separate Phase 3 trial? When is an arm closed?

Platform trials design



Examples of trials

Table 2. Examples of Master Protocols in Cancer.*

Trial	Description	Design	Drug or Drugs	Disease and Target	Study Population	End Points
B2225[6]	Basket trial to determine cancers responsive to imatinib	Phase 2, multicenter, open-label, noncomparative trial	Single: imatinib (400 or 800 mg per day)	40 cancers (solid tumors and hematologic cancers) with activation of imatinib target kinases	186 patients ≥15 yr of age	Tumor response (SWOG criteria and investigator's assessment)
BRAF V600[7]	Basket trial to evaluate the efficacy of vemurafenib in nonmelanoma cancers	Early phase 2, multicenter, open-label, noncomparative, adaptive trial using Simon's two-stage design	Vemurafenib monotherapy or (in some patients with colorectal cancer) vemurafenib plus cetuximab	Multiple nonmelanoma cancers with *BRAF* V600 mutations; eight tumor-specific cohorts plus an "all others" cohort	122 adults (≥18 yr of age)	Response rate (assessed by investigators according to RECIST or IMWG criteria) at wk 8
NCI-Match[8]	Umbrella trial to determine whether treating cancers according to molecular abnormalities is effective	Exploratory, multicenter, noncomparative trial	Multiple: 30 treatments (as of May 2016), both FDA-approved and investigational, that target gene abnormalities	Advanced solid tumor, lymphoma, or myeloma; DNA sequencing for actionable mutations	35 adults planned per substudy; pediatric study to begin in 2017	Tumor response (primary) and progression-free survival
BATTLE-1[9]	Umbrella trial to evaluate targeted therapies in chemotherapy-refractory NSCLC	Phase 2, single-center, comparative, adaptive randomization trial	Multiple: three monotherapies (erlotinib, vandetanib, and sorafenib) and one combination (erlotinib plus bexarotene)	Advanced NSCLC; targets included *EGFR* mutation, *KRAS/BRAF* mutation, VEGF expression, and RXRs/CyclinD1 expression	255 adults in whom ≥1 chemotherapy regimen had failed	Complete or partial response or stable disease according to RECIST criteria at wk 8 (primary), progression-free survival, overall survival, and toxicity
I-SPY 2[10-12]	Adaptive platform trial to identify treatment regimens for locally advanced breast cancer in the context of neoadjuvant therapy on the basis of biomarker signatures	Phase 2, multicenter, comparative, adaptive randomization trial	Multiple: standard chemotherapy and five new drugs (initially) as add-on to chemotherapy; 12 treatments tested to date, with latest (patritumab) added October 2016	Early, high-risk breast cancer; three biomarkers (hormone-receptor status, HER2 status, and MammaPrint risk score) define eight genetic subgroups	1920 women (estimated) with invasive tumor ≥2.5 cm in diameter	Pathological complete response
Lung-MAP[13-15]	Master protocol to evaluate biomarker-matched therapies in rare squamous-cell subsets of NSCLC	Phase 2–3 comparative trial	Multiple: four investigational drugs plus one therapy for no-match control group (initially); three investigational drugs remain	Squamous-cell NSCLC; multiple targets (four molecular targets initially; three remain)	100–170 patients planned for phase 2 (40 are now enrolled); 300–400 planned for phase 3	Objective response rate, progression-free survival, and overall survival

* BATTLE-1 denotes Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination 1, IMWG International Myeloma Working Group, I-SPY 2 Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2, Lung-MAP Lung Master Protocol, NCI-MATCH National Cancer Institute Molecular Analysis for Therapy Choice, NSCLC non–small-cell lung cancer, RECIST Response Evaluation Criteria in Solid Tumors, and SWOG Southwest Oncology Group.