

# Adaptive trials: acceptability, versatility and utility

Summary of a FORUM workshop held on  
23 January 2019

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The Medicines and Healthcare products Regulatory Agency regulates medicines, medical devices and blood components for transfusion in the UK. The Agency is an executive agency, sponsored by the Department of Health and Social Care and includes three expert business centres: the Clinical Practice Research Datalink (CPRD), the National Institute for Biological Standards and Control (NIBSC) and the MHRA regulatory centre (MHRA).

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The Academy's FORUM was established in 2003 to recognise the role of industry in medical research, and to catalyse connections across industry, academia and the NHS. Since then, a range of FORUM activities and events have brought together researchers, research funders and research users from across academia, industry, government, and the charity, healthcare and regulatory sectors. The FORUM network helps address our strategic challenge 'To harness our expertise and convening power to tackle the biggest scientific and health challenges and opportunities facing our society' as set in our Strategy 2017-21. We are grateful for the support provided by the members and are keen to encourage more organisations to take part. If you would like further information on the FORUM or becoming a member, please contact [forum@acmedsci.ac.uk](mailto:forum@acmedsci.ac.uk).

Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Academy of Medical Sciences or its Fellows, the Medicines and Healthcare products Regulatory Agency, the Medical Research Council or the National Institute for Health and Care Excellence.

The Academy is grateful to the Medicines and Healthcare products Regulatory Agency, the Medical Research Council and the National Institute for Health and Care Excellence for their organisational input and support of this event.

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# Executive summary

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**Adaptive clinical trials make use of innovations and advances in statistics and computing to enable the trial protocol to be adapted and updated as evidence is generated. Such approaches can make trials more likely to answer the key research questions they hope to address, as well as offer benefits in speed and efficiency. However, adaptive designs break some of the paradigms of randomised controlled trials that have been established over the last 50 years and so developing and applying these new methodologies is not without its challenges.**

On 23 January 2019, the Academy of Medical Sciences, the Medicines and Healthcare products Regulatory Agency, the Medical Research Council and the National Institute for Health and Care Excellence held a FORUM workshop examining the utility, versatility and acceptability of adaptive clinical trials. Using a series of case studies, participants explored the challenges and opportunities for adaptive trials from the perspectives of industry, academia, funding bodies and regulatory bodies. Key themes to emerge from the workshop include:

- Adaptive trials have the **potential to make clinical research faster, more efficient and more clinically relevant**. A range of designs, and the ability to make a variety of adaptations, make them suited to a range of applications, from first in man dosing studies through to large real world effectiveness studies.
- Case studies of the **usefulness and flexibility of adaptive designs** are beginning to emerge, but their use is still infrequent compared to standard randomised controlled trials. The rate of increase in their use is relatively slow due to a number of factors, such as a limited, but growing, expertise base, and a lack of awareness of the potential benefits of using such designs.
- **A number of perceived challenges held by different sectors may be inhibiting the use of adaptive trials**. These include perceptions that adaptive trials are complex, expensive, and not accepted by regulators, among others. However, most of these were thought to be either misconceptions or are otherwise surmountable.
- **Cultural differences between industry, academia and the NHS remains a barrier** to effective collaboration and cooperation. Breaking down some of these cultural barriers is vital to innovation in trial design, and building confidence in adaptive trials to facilitate widespread use.
- **However, there are also some practical challenges** that make adaptive trials more challenging to carry out than traditional randomised controlled trials. These include; a lack of flexible funding for adaptive trials and challenges with intellectual property and disclosure when working with multiple trial sponsors, for example, when multiple investigative medicinal products are being studied in a single trial.

- Innovation in adaptive trial design should be encouraged through **knowledge exchange, dedicated funding and innovation in the use of data sources.**
- Underpinning the effective use of adaptive designs is a **requirement for a skilled, informed clinical research workforce throughout industry, academia and the NHS** who can take advantage of the benefits that adaptive designs bring.

This meeting was convened as part of the Academy's FORUM programme, which was established in 2003 to recognise the role of industry in medical research and to catalyse connections across industry, academia and the NHS. We are grateful for the support provided by the members of this programme and are keen to encourage more organisations to take part. If you would like information on the benefits of becoming a FORUM member, please contact [FORUM@acmedsci.ac.uk](mailto:FORUM@acmedsci.ac.uk).

# Introduction

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**Randomised controlled trials (RCTs) are the primary source of evidence for assessing the safety and efficacy of new medicines and medical interventions, but the high costs and lengthy timelines can be challenging.<sup>1</sup> The effective use of traditional RCTs may be especially challenging in situations such as very small patient populations, rare diseases, or complex interventions where endpoints and outcomes are less easily defined. Adaptive RCTs may provide advantages over standard RCTs, such as ensuring the correct sample sizes, incorporating information from outside the trial and integrating across heterogeneous patient populations or within patient subgroups.<sup>2</sup> Finally, the strength of traditional RCTs is in providing robust, unbiased evidence but it may be difficult to generalise beyond the RCT to the real world use of an intervention.**

The research community is developing novel and tailored trial designs to overcome some of the challenges outlined above. These trial designs may include new adaptive 'versions' of umbrella, basket and platform designs, which have recently emerged as innovative types of RCTs.<sup>3,4,5,6</sup> They also include more complex adaptive trials with the ability to alter methodologies, design or sample size during the trial.

However, there is currently uncertainty around the acceptability, and applicability in different contexts, of adaptive designs and the strength of the evidence that they generate for regulators, health technology assessment (HTA) bodies and commissioners. These uncertainties are driven by outstanding questions around evidence thresholds for aspects such as, error rates, feasibility studies or acceptable methodologies for very small patient populations. There are also challenges in implementing adaptive designs. For example, features such as the planned adaptations or the use of historical or shared controls groups

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<sup>1</sup> Academy of Medical Sciences (2011). *A New Pathway for the Regulation and Governance of Health Research* <https://acmedsci.ac.uk/file-download/35208-newpathw.pdf>

<sup>2</sup> Adaptive trial – a clinical trial that incorporates the flexibility to make pre-specified changes based on accumulating data.

<sup>3</sup> Umbrella trial – a clinical trial that evaluates multiple targeted therapies for at least one disease.

<sup>4</sup> Basket trial – a clinical trial that evaluates one targeted therapy on multiple diseases or multiple disease subtypes.

<sup>5</sup> Platform trial – a clinical trial that evaluates several targeted therapies for one diseases perpetually, and further accept additions or exclusions of new therapies during the trial.

<sup>6</sup> ABPI & MHRA (2015). *MISG New Technologies Forum on Umbrella/Basket Protocols*.

[www.abpi.org.uk/media/1350/misg-new-technologies-forum-report-umbrella-basket-protocols.pdf](http://www.abpi.org.uk/media/1350/misg-new-technologies-forum-report-umbrella-basket-protocols.pdf)

must be used carefully to ensure that they do not compromise the validity of the trial. Some examples of adaptations that might be made are outlined in **Box 1**. New adaptive designs are also continuing to emerge, and may become commonly used. It is therefore important to ensure that the research community, regulators, HTA bodies and commissioners are prepared for them. This will require the right skills and expertise as well as appropriate infrastructure.

Recent work by the Academy on accelerating access to innovation, endpoints in oncology research and real world evidence has considered the need for new methodologies and sources of evidence to assess therapeutics and medical interventions.<sup>7,8,9</sup> In addition, the Medical Research Council (MRC), as key funder of innovative trials, and the Medicines and Healthcare products Regulatory Agency (MHRA) as a key evaluator of the protocols and outcomes of trials, have made it a priority to ensure that the potential benefits of adaptive trials are realised.

## Box 1 - Examples of trial adaptations

A number of potential adaptations can be incorporated into the methodologies of an adaptive trial. These include:<sup>10,11</sup>

1. Sample size reassessment to ensure the trial meets statistical thresholds.
2. Dose escalation to determine safety and efficacy.
3. Modifying allocation ratios to enable more patients to receive superior treatments, for example in the ALIC<sup>4</sup>E trial described in Case Study 1.
4. Incorporating new molecular biomarkers, genetic markers or surrogate endpoints, for example in the FOCUS4 trial described in Case Study 2.
5. Adding new treatment arms as new investigative medicinal products (IMPs) become available, for example in the EPAD Consortium described in Case Study 3.
6. Dropping inferior treatment arms for futility or side-effects.
7. Enabling seamless transition from Phase I to Phase II or from Phase II to Phase III, for example in the STAMPEDE trial described in Case Study 4.
8. Stopping the whole trial at an early stage for success or lack of efficacy.

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<sup>7</sup> Academy of Medical Sciences (2017). *Accelerating access to medical innovation: a research agenda for innovation science*. <https://acmedsci.ac.uk/file-download/80863587>

<sup>8</sup> Academy of Medical Sciences (2017). *Looking to the future: oncology endpoints*. <https://acmedsci.ac.uk/file-download/41135280>

<sup>9</sup> Academy of Medical Sciences (2018). *Next steps for using real world evidence*. <https://acmedsci.ac.uk/file-download/7021031>

<sup>10</sup> Thorlund K *et al.* (2017). *Key design considerations for adaptive clinical trials: a primer for clinicians* *BMJ* **360**:k698

<sup>11</sup> Pallmann P *et al.* (2018). *Adaptive designs in clinical trials: why use them, and how to run and report them* *BMC Med* **16**(1):29

# Why use adaptive designs?

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**Professor Roger J. Lewis, Professor and Chair, Emergency Medicine, Harbor-UCLA Medical Center and Senior Medical Scientist, Berry Consultants, LLC, gave an introductory presentation on the motivations for doing adaptive trials, as well as some of the advantages and challenges that they bring.**

He explained that when designing an RCT, there are uncertainties within the parameters set that may reduce the likelihood of getting a confirmatory result (whether positive or negative). These include parameters such as the event rate, dosing regimen, length of the trial and the target populations selected for randomisation. Historically, it was believed that these parameters needed to be decided upon in advance of the trial and kept constant throughout the trial to help protect against bias and to control error rates in the statistics. However, if parameters are not optimal, trials may not answer the key research questions they are attempting to answer. Professor Lewis suggested that as a consequence many trials, despite great expense and length, failed to answer their intended research questions, and in some cases may actually have had little chance of answering these questions in the first place.

Adaptive trials allow these parameters to be adjusted throughout a trial to maximise the chances of answering the research questions. They do this by accumulating information as a trial progresses and using it to make appropriate (and pre-specified) adaptations to the trial design. These adaptations could include, for example, stopping active arms early due to futility or success, modifying randomisation strategies or incorporating new arms or biomarkers. To make these adaptations, adaptive trials are reliant on algorithms that define the allocation or sampling rules. These algorithms determine when adaptations are necessary, or when a trial has met its goal in answering its research question. The algorithms may be quite sophisticated in their nature, increasingly relying on Bayesian statistics, and are developed in collaboration between clinical trial design and implementation specialists, statisticians and computer scientists.<sup>12</sup> This collaboration is vital to ensuring that the algorithm performs appropriately to meet the needs of the trial.

Because the resulting algorithm may be complicated, it is important that the statistics involved and produced by the algorithms are understandable and can be scrutinised in order to test their strengths and limitations. To help this, development and understanding of the algorithms must take place through trial simulations which can then inform trial design. These simulations use different scenarios and show the trajectory taken by an iterative algorithm which depends on the data being accumulated. Simulations of many different scenarios, and thousands of individual trials under each scenario determine the expected operating parameters of the trial, and therefore the expected adaptations. Simulations also allow the assessment of threats to statistical integrity, such as bias and errors, and allow researchers to develop solutions proactively. It also allows better understanding of what adaptations might be feasible, and necessary, to help the trial answer its research questions, a vital step as

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<sup>12</sup> Bayesian statistics – a field of statistics whereby the probabilities of outcomes are subjective (ie. a range of values) and are updated and refined as additional data is collected.



potential adaptations must be predefined in trial planning, and not incorporated ad-hoc.

Professor Lewis noted that currently there is overreliance on particular aspects of statistics, such as  $p$ -values, and that other statistical methods have the potential to contribute to the evidence supporting conclusions. A variety of statistical approaches can be used which are well suited to adaptive designs, especially those built on complex designs such as platform trials. Bayesian statistics and approaches are useful as they can provide probability ranges for clinically important measures and outcomes, and inferential models are more flexible than frequentist approaches, making it easier to mitigate risks. However, these statistical methods may appear alien to some clinical trial researchers, and so efforts should be made to help spread awareness of their utility, as well as their limitations.

Professor Lewis concluded that adaptive trials allow new evidence to rapidly improve trial efficiency in a seamless process. By applying adaptive designs to trial architectures such as platform trials, they can be applied beyond single treatments and homogeneous populations to make trials more efficient and more likely to answer research questions.

During the following discussions, it was noted that adaptive designs can assist patient recruitment by better predicting the required recruitment and updating this as data are gathered, helping to ensure a statistically significant result (whether confirmatory or not). Similarly, this approach means that over-recruitment, which would waste time and resources, is not an issue, as the trial can be stopped once statistical significance has been achieved regardless of the recruitment size. This is in contrast to traditional RCTs where the recruitment target is defined at the start of the trial.

## MHRA perspectives on adaptive trials

Dr M. Beatrice Panico, Medical Assessor, Clinical Trials Unit, MHRA gave an overview of the MHRA perspective of adaptive trials, and where the challenges and opportunities for their application lie. She clarified that the MHRA supports innovation and several trials with innovative designs are already ongoing in the UK. Some innovative trials are 'adaptive design trials': modifying the conduct of ongoing trials increases the chance of the trial formally being a success (i.e. that the null hypothesis can be rejected). A central tenet of adaptive design protocols is that the adaptations are pre-specified in the protocol and are not made on an ad-hoc basis. Trials have to be safe and scientifically sound. It is therefore crucial that sponsors of adaptive design trials provide the regulators with a strong scientific rationale as to why an innovative design is the best solution to address the trial objectives rather than a more traditional approach. The rationale should also discuss how the trial integrity will be maintained despite continuous adaptations.

Adaptations that can prove challenging under current regulation are the addition of new Investigational Medicinal Products or new trial populations and some seamless Phase 2-3 trials (see **Case Study 4**). These additions can require substantial amendments to allow for trial adaptation. If the proposed changes are so extensive that they change the nature of the initially approved trial (for example, they are not in line with the original research hypothesis, they make the data obtained up to the point of the amendment inadmissible or make the sponsor lose control of Type 1 errors) then a new clinical trial application would probably be necessary.<sup>13</sup> The decision is always on a case-by-case basis both for initial protocols and later amendments.

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<sup>13</sup> Type 1 Error – The rejection of a true null hypothesis, also known as a false positive result.

The MHRA, along with partners including the Experimental Cancer Medicines Centres Network, are developing a consensus paper that highlights the challenges of complex innovative designs (Box 2).

**Dr Panico also reminded the audience that amendments are a 'yes or no' scenario where no interaction with the Sponsor is possible while review is ongoing. She concluded by stating that adaptations can be acceptable if safe and scientifically justified. Early engagement with regulators is strongly recommended in order to address potential issues of concerns.**

## Box 2 - ECMC Network consensus paper

Dr Kirsty Wydenbach, Deputy Unit Manager, Clinical Trials Unit, MHRA gave an overview of a consensus paper being developed by the Experimental Cancer Medicines Centres Network and partners.

This paper aims to highlight the challenges of complex innovative design trials, which use adaptations, and, drawing from best practice examples, show how they may be overcome. The paper, which focuses on adaptive cancer trials, is due to be published in late-2019.

The paper will cover considerations for trial planning, design, conduct and delivery as well as evaluating the impact of trial post-hoc. Dr Wydenbach outlined that the key messages are in five consensus statements:

1. Early engagement with regulators and other key stakeholders is key for success.
2. All parties need to understand the aims, risks and expected outcomes of a trial and this needs to be communicated with clarity, consistency and flexibility.
3. Complex innovative design trials need to be appropriately resourced to answer multiple research questions.
4. Research questions, once answered, should be publically reported as soon as possible thus allowing improvement in trials at an accelerated rate.
5. Training and upskilling of trialists, funders and support staff is vital to improve the uptake and delivery of complex innovative design trials.

# Perceptions and cultural challenges

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**Throughout the workshop, participants noted that there was a perception of barriers to the use of adaptive trials, although these were not all substantiated, and could therefore be overcome through better communication, education and collaboration and changing attitudes and approaches to adaptive trials within the research community.**

## Perceived barriers to adaptive trials

Participants gave their impressions of what they thought the perceived barriers to the use of adaptive trials are. Within industry, it is possible that the use of adaptive designs may be avoided due to inherent conservatism and, as innovative approaches represent a risk, when they fail the innovation itself is often blamed regardless of the real cause. It was noted that there were a number of misconceptions that may either dissuade consideration of their use, or result in mismatched expectations when they are pursued. For example, those deciding on the trial methodologies to use may perceive adaptive designs to be logistically challenging and overly complex. This may be because some adaptive trials rely on sophisticated statistical methods, such as Bayesian statistics, which are unfamiliar to many working in clinical trials, or because there is a need for additional pre-planning work when compared to a normal RCT that follows a well-established methodology. In addition, adaptive methodologies are often not published in easy to interpret and understandable forms. However, just because a trial is adaptive in nature does not mean it is significantly more complicated than a standard RCT, despite perceptions.

The impression of complexity may stem from the need for continual decision-making that drives the adaptations made throughout the trial. Similarly, some adaptive trials may have the ability to 'grow' beyond their initial design, owing to their ability to add trial arms, a feature not often found in standard RCTs. In addition, platform trials that incorporate multiple arms may appear complex due to having multiple randomisation arms, and potentially large patient cohorts.

It was also noted that key decision makers may have perceptions that there are additional challenges for intellectual property and ensuring the integrity of adaptive trials. Pre-competitive collaboration was cited as a key driver of innovation but trial sponsors may be apprehensive to enter such partnerships due to the complexities for intellectual property. Although adaptive trials may be more complex than RCTs, the many adaptive trials already conducted demonstrate that these perceived barriers are not insurmountable.

Participants described that committees overseeing funding decisions may not yet have the

experience or expertise to be able to effectively assess funding applications for adaptive trials, especially if the number of adaptive trials being conducted significantly increases. As securing funding is vital to a trial being undertaken, it is important to ensure that funding decision committees fully understand adaptive trials to be able to critique them appropriately. Upskilling funding committees to ensure they can effectively assess adaptive trials would address this.

Finally, the perceptions that adaptive trials were either discouraged, or poorly understood, by regulatory bodies was discussed. Key decision makers may feel that there is a greater risk of an adaptive trial being rejected by regulatory bodies, either in the planning stage, or more seriously, rejecting the results of the completed trial. It was also noted that this perceived risk extended to HTA bodies, where it was perceived that adaptive designs may not be effectively or fairly incorporated into HTA processes. However, as outlined below, contrary to these perceptions, regulatory and HTA bodies are working to incorporate adaptive designs into their processes.

## Case study 1 – ALIC<sup>4</sup>E

Professor Chris Butler FMedSci, University of Oxford described the ALIC<sup>4</sup>E trial – an adaptive design open-label platform trial of influenza medicines in primary care settings.<sup>14</sup>

The trial aimed to identify the differential benefits of antivirals in different population groups and in different severities of disease and to determine the cost-effectiveness of prescribing antivirals. The trial was designed so that new antivirals could be incorporated into the trial as it progressed, which was important in case the new antivirals superseded existing antivirals as the standard of care. This meant the trial could continue running despite new antivirals being developed.

The trial recruited 3259 patients over three flu seasons in 16 countries. After each flu season, the data monitoring committee considered whether adaptations should be made, for example to increase allocation to the best performing arms. The trial successfully identified that antivirals were of most benefit to those who were older or had more severe illness.

Ultimately, as no new antivirals emerged as the trial progressed, no adaptations were required to be made. However, Professor Butler reflected that the data monitoring committee who oversaw adaptations had been significantly upskilled through working with Oxford Clinical Trials Unit and Berry Consultants to learn how to

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<sup>14</sup> <https://www.phc.ox.ac.uk/phctrials/trial-portfolio/alic4e>

make adaptations. He also said that the biggest challenges were logistical, including the drawing up of contracts. It was highlighted that trials such as these can be useful for pandemic preparedness, including sharing learnings with LMICs and countries with endemic or epidemic communicable diseases.

## Alleviating these barriers

Participants discussed ways to overcome perceived barriers and misconceptions about adaptive trials.

### Increasing understanding and acceptance

It was suggested that a shift in culture within industry to be more understanding and accepting of adaptive trials may help reduce scepticism and separate perceived risks from real risks. This could be achieved through increased dialogue of industry with regulatory and HTA bodies, which was considered vital to dispel any perceptions about the acceptability of adaptive designs. Such dialogue should take place early on in development programmes and be on an ongoing basis as expectations and experiences evolve.

### Consistent guidance from regulators

It was noted that those wishing to use adaptive designs have received inconsistent advice from different regulators. The level of guidance offered by regulators also differs, with some regulators, such as the FDA, publishing dedicated guidance, and the EMA expected to publish guidance in the near future.<sup>15</sup> It was suggested that an inter-regulatory consensus, and guidance resulting from this, would be beneficial to the wider community, and that those using adaptive designs would benefit from assurance that their methodologies will be acceptable across international regulatory bodies.

It was also noted that there is inconsistency in the language used which adds to potential confusion and misinterpretation. Different terminology is used by international regulators as well as between different sectors and by individuals, and it was agreed that a general and international consensus on terminology would aid discussions within and across sectors and borders.

The European Medicines Agency published adaptive trial guidelines in 2007, however, adaptive designs have developed since then to include designs such as platform trials. It is expected that these guidelines will be updated in the near future.<sup>16</sup> The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is expected to release guidance on adaptive designs in the near future.

### Knowledge exchange and networks

The publication and dissemination of case studies was noted as being important to improving confidence among industry and others intending to use adaptive designs. Many innovative trials are being developed or are taking place that are not publicised widely, or disseminated

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<sup>15</sup> <https://www.gmp-compliance.org/gmp-news/revision-fda-guideline-on-adaptive-designs-for-clinical-trials>

<sup>16</sup> <https://www.ema.europa.eu/en/methodological-issues-confirmatory-clinical-trials-planned-adaptive-design>

through academic publications only after the trial has concluded. Case studies may improve that lack of visibility of adaptive trial methods.

They may also dispel apprehension around perceptions of being the 'first' to use a particular study design. Those considering adaptive designs may not realise that similar designs have already been developed and received regulatory scrutiny, and the opportunities to learn and build on the precedent from these are missed.

### **Enduring and shared infrastructure**

It was noted that the infrastructure required to conduct larger adaptive trials, such as those incorporating platform, basket or umbrella designs, can be complicated and expensive to set up, but that, once established, this infrastructure can be enduring and be used by many trials. Public funders, such as the National Institute for Health Research, might be able to invest in such infrastructure, and such investment may initially focus on funder prioritised areas where adaptive designs are likely to have the largest impact. It was suggested that the adaptive trial community could discuss what these areas might be and reach a consensus to aid funding bodies in their strategic decisions.

## **Case study 2 – FOCUS4**

Dr Louise Brown, University College London described the FOCUS4 adaptive umbrella-platform trial for metastatic colorectal cancer.<sup>17</sup>

The FOCUS4 trial relied on molecular stratification using biomarkers to recruit and stratify patients. Each biomarker subgroup, which utilised biomarkers such as BRAF and PIK3CA mutations, was individually randomised and powered with the aim of testing novel agents active in the identified subgroups. The adaptive nature of the design allowed for arms and biomarkers to be added and dropped as the study developed and new biomarkers or novel agents emerged. It also incorporated a seamless Phase II/III design to allow highly performing novel agents to continue to Phase III.

Throughout the trial, several adaptations were made, including the introduction of new novel agents through industry partnerships, and new biomarkers as biological understanding emerged. In addition, the study switched to using next generation sequencing by adapting the protocol and laboratory manual.

Dr Brown noted that industry engagement was challenging throughout the trial, with typically 18 months spent in discussions to create collaborations that ultimately fell through. Also challenging was keeping up with promising biological discoveries that could be incorporated into the trial. She also suggested that the size of the

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<sup>17</sup> <http://www.focus4trial.org/>

trial, involving 104 sites, meant that coordinating contracts and staff was a challenge. However, she noted that it provided several successful learning opportunities, including the ability to test many drugs and biomarkers through single regulatory and ethics approvals, the successful adaptation of the design as it progressed and the building of strong collaborations within and beyond the trial management group. Dr Brown also noted that a supportive and collaborative clinical research network along with supportive funders was key to the success of the trial.

# Promoting innovation in trial design

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**One of the key concerns amongst participants was that innovation in trial design was not developing quickly enough, despite advances in statistical methods, computational power and proven case studies. Although some adaptive designs are becoming widespread, innovation in new designs should be encouraged to widen their application and utility.**

## Encouraging innovation in adaptive trial design

### **Funding to promote innovation**

Participants noted that, while funding does exist for adaptive trials as part of wider funding for clinical trials, there is a lack of dedicated funding for the development of new methodologies. They welcomed the steps that funders, such as the MRC, have taken to promote adaptive designs, for example the MRC Hubs for Trials Methodology with a dedicated adaptive design stream, and the MRC Clinical Trials Unit at University College London, a centre for innovation in trial design.<sup>18,19</sup> Participants felt that there was scope for further hubs and networks to promote innovation across the wider clinical trials sector in the UK.

Due to the nature of innovative trials, greater emphasis must be placed on the 'pre-work' that takes place before the trial begins. This includes not only methodology development, but the development and analysis of the simulations required to select the most appropriate adaptive design. It was felt that current funding structures did not always accommodate such pre-work, especially when it is done proactively rather than with the intention of using the methodology in a specific trial. It was suggested that the funding of such pre-work will result in more rapid innovation in trial designs.

Robust clinical trial infrastructure that can accommodate adaptive designs is essential to encourage their use. It was suggested that if such infrastructure were readily available to be used by companies wishing to conduct adaptive trials, then the development and uptake of adaptive designs would likely increase as costs and set-up times decreased. Such infrastructure could be funded as part of the routine clinical trial infrastructure awarded to Clinical Trial Units.

Participants noted that in some cases medical research charities could be a key funder for

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<sup>18</sup> <https://www.methodologyhubs.mrc.ac.uk/research/working-groups/adaptive-designs/>

<sup>19</sup> <https://www.ctu.mrc.ac.uk/>



development and innovation in adaptive designs. The MS Society and Cancer Research UK are already working to co-design adaptive trials.<sup>20</sup> It was acknowledged that medical research charities are often disease specific, and not all therapy areas have charities with sufficient resources to fund such research.

### **New sources of data to promote innovation in design**

Adaptive trials are often reliant on innovative data sources to guide decision making. This includes the use of biomarkers for stratification of patient populations for randomisation, biomarkers that may act as surrogate endpoints for deciding if arms should be expanded or stopped for futility, and incorporating new biomarkers that are required when new classes of IMPs are introduced. These biomarkers need to be validated for each mechanistic pathway before being used during an adaptive trial. Adaptive trials may not be possible without an understanding of the biology of a biomarker so it can be accurately and reliably measured, and the clinical significance of these measurements determined.<sup>21</sup> Participants therefore felt that the development of novel biomarkers was important in supporting an environment where innovation in adaptive design would be encouraged. Without these tools, patient stratification, Bayesian incorporation of data and the use of surrogate markers may all be more challenging.

Participants agreed that genomics was a principal tool for stratification of patient populations for randomisation, as well as for discovering new biomarkers. It was noted that genomics is likely to be especially impactful for trials which aim to test a range of IMPs that operate through different biological mechanisms in the appropriate sub-populations. For example, the FOCUS4 trial (see **Case Study 2**) used genomics for molecular stratification of patients for drug selection.

Participants noted that patients are key proponents of the use of adaptive designs and, when the nature of adaptive designs are explained to patients, they generally view them as a positive thing. It was remarked that this enthusiasm could be harnessed to help improve adherence and retention in Phase III trials, and that patients could even act as advocates for adaptive trials, potentially improving recruitment. This could be especially important for trials in disease areas where patient numbers are small, and therefore a high recruitment rate is required for the success of the trial. Patients are often surprised to learn that trials are not generally adaptive, and that it represents a potential risk to patient trust and engagement to not use adaptive designs where they are available and effective.

### **Building the skills base to enable innovation**

While the UK has a world-leading clinical research environment, with a highly skilled workforce, the development of adaptive designs and methodologies requires new skills that are underrepresented at present in the academic and clinical research workforce. Equipping researchers with the appropriate skills, and creating the networks to allow knowledge exchange, would allow individuals, institutions and consortia to innovate more effectively and on a larger scale.

Participants noted that the UKCRC Clinical Trials Unit network consists of 51 clinical trials units that come together to share experiences, and within this network is a range of specialisms, including data scientists, statisticians and quality assurance staff, among others, who can collaborate effectively.<sup>22</sup> The network allows for efficient knowledge transfer and could be a key conduit for upskilling staff to conduct adaptive trials.

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<sup>20</sup> <https://www.cancerresearchuk.org/funding-for-researchers/how-we-deliver-research/our-research-partnerships/stratified-medicine-programme>

<sup>21</sup> Buyse M (2011). *Statistical validation of surrogate outcome measures*. *Trials*. **12(Suppl 1)**:A93

<sup>22</sup> <https://www.ukcrc-ctu.org.uk/>

## Case study 3 – EPAD Consortium

Dr Melanie Quintana, Berry Consultants described the European Prevention of Alzheimer's Disease (EPAD) Consortium, which is funded through the Innovative Medicines Initiative.<sup>23</sup>

The Consortium includes 39 partner organisations across Europe, and consists of a primary cohort of over half a million people with varying risk of dementia who can participate in research, a selective longitudinal cohort study of those at higher risk, and an adaptive platform Phase II component for testing new therapies.

The trial component is designed to make use of the two cohorts for rapid recruitment and patient stratification, and its long-term nature allows it to be enduring as new therapies emerge that may operate via currently unknown or non-investigated biological pathways.

Dr Quintana described that a master protocol platform methodology was chosen as it allows the use of a core common protocol with adaptations.<sup>24</sup> This enables a network of trial sites, and the data they generate, to be more easily streamlined. She described how the master protocol does not name specific treatments, but is structured to define how patients are enrolled and how new arms enter and exit the trial. Appendices to the master protocol then describe protocols for each drug or individual trial. These allow adaptations such as new endpoints and analyses for futility. The platform design also allows the use of shared, non-concurrent controls between trials across the Consortium.

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<sup>23</sup> <http://ep-ad.org/>

<sup>24</sup> Master protocol – a clinical trial protocol created for evaluating multiple hypotheses of sub-studies that are concurrently conducted.

# Practical, operational and logistical challenges and solutions

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**In order to use adaptive trial designs widely in clinical research successfully, there may be some practical, operational and logistical challenges that need to be overcome. Participants shared their experiences of using adaptive trial designs and how some of these challenges might be solved.**

## Practical challenges of conducting adaptive trials

### **Upskilling of the clinical research workforce**

Participants agreed that key to the delivery of adaptive clinical trials are the individuals working to deliver trials, both those working in clinical settings and those supporting them. As outlined earlier, adaptive protocols differ from traditional RCTs. Clinical trial staff who are familiar with running RCTs may need additional training or support to effectively implement an adaptive protocol and to adopt adaptations effectively and in a timely manner. Again, it was remarked that this may improve over time as more staff become familiar with adaptive designs, but that the current 'early adopters' of clinical trials may find this a barrier at present.

It was also remarked that this need for upskilling has to be extended to trial data monitoring committees, who have oversight of the trial and make decisions on when to make adaptations. The committee needs to understand the reasons for making adaptations and the implications of doing so to ensure that adaptations are made appropriately. Although trials may provide this learning opportunity, as exemplified by the ALIC<sup>4</sup>E trial (see **Case Study 1**), such upskilling of data monitoring committees should be proactive and pre-empt any specific trial. It is not clear who should fund or provide training, but it was felt by attendees that there is a clear need.

While not unique to adaptive trials, it was noted that the logistics of setting up trials with complicated or novel protocols can be challenging, which may lengthen the time to first treatment administration. For adaptive trials, part of this delay may come from lengthier or more complicated contractual negotiations with participating clinical trial sites. This is amplified when the trials are large, multi-site or international in scope. If the clinical trial site is unfamiliar with the trial design, this may lead to unnecessary delays, though it was felt that once sites become more familiar and comfortable with adaptive designs this problem should be somewhat mitigated.

The statistical methodologies that power some adaptive trials are complex and sophisticated, and in many cases are still being developed and improved. As the number of adaptive trials increases, there may be an increased demand for statisticians who are skilled in the use of these methodologies. The dissemination of methodologies and the upskilling of statisticians was therefore suggested as a priority.

### **Flexible funding – a solution to many challenges**

The delivery of any clinical trial requires sufficient funding to enable staff to recruit participants, conduct the clinical work and collect and analyse the results. The costs, and therefore the funding, for adaptive clinical trials can vary depending on the adaptations that are made or are expected to be made. For example, introducing additional treatment arms, or expanding cohorts will both increase costs, whereas stopping arms for futility will result in decreased costs.

When applying for funding, a specific predicted figure and the costs that determine that figure need to be defined. Consequently, if more adaptations are required than anticipated, the trial may be costlier than the funding level initially bid for and acquired. Conversely, if fewer adaptations are required, the trial may fall under budget, which has its own negative implications. To fit the current funding structure, adaptive trial applications may have to over anticipate adaptations to ensure sufficient funding is available. This could lead to adaptive trials appearing more expensive than they truly are and not being approved due to this overestimation. Consequently, the funding bid may be less likely to be successful as the trial may appear to be poorer value for money.

In the cases where a trial is under budget, it was noted that the underspend could not be retained for other uses, and so there is little incentive for investigators to keep costs down. It was noted that for ongoing, open-ended trials, which do not have a defined endpoint, bidding for and acquiring funding can be even more complicated. For example, the termination of funding for a living trial (see **Case Study 3**) could result in the trial ending even though the infrastructure it has established could have additional benefits. It was suggested that dedicated, flexible funding might alleviate these issues. It was also remarked that adaptive trials may be expected to be cheaper than traditional RCTs amongst some funders; it was noted that while adaptive designs can have the potential to save costs, this is not always a key reason for doing them.

It was noted that in many cases, clinical trial staff are contracted for a specific trial. However, when an adaptive trial becomes less resource intensive due to adaptations such as dropping arms, staff can be impacted. As adaptations are meant to be responsive to acquired data, the aim is generally to implement them in a timely manner once the data are available. This may mean that some staff have uncertainty over their contract length. In addition, if such an adaptation is made and impacts staff, the nature of contracts mean that staff cannot easily be moved to another trial.

### **Challenges in reporting adaptive trials**

Reporting of the results of adaptive trials can be problematic. For a traditional RCT, results are published at the end of the trial, once all treatment arms have been concluded, which is not always the case for adaptive trials. Some adaptive trials may use a common control group shared by multiple active arms. If an arm is either stopped for futility or for evidence of benefit, it would be expected that the results from this arm will be reported before the end of the trial to allow the research community to benefit from the findings. Other arms may be ongoing, and disclosure of the details of terminated or completed arms may compromise the integrity of the ongoing arms.

The adaptive nature of these trials may raise concerns for ensuring integrity through good firewall practices.<sup>25</sup> In a standard RCT, staff involved in a trial are only privy to certain information to reduce the risk of bias. However, adaptations may by their nature reveal information about the outcomes of the trial that may impart bias. Participants felt that ensuring trial integrity to prevent these biases was essential in building and maintaining confidence in adaptive trials, as bias mitigation is an essential component to a trustworthy and robust clinical trial.

The contracted research organisation sector, as a major conductor of clinical trials, holds responsibility for ensuring adequate reporting of the trials they are involved in. By adhering to minimum reporting standards such as the ACE Consort Extension (**Box 3**), methodologies and learnings can be better shared amongst the community, accelerating innovation and use of adaptive trials.<sup>26</sup>

### **Working with multiple sponsors**

One potentially challenging aspect of adaptive trials that study multiple IMPs is the need to coordinate and collaborate with the multiple industry trial sponsors who are developing and testing the different IMPs. This is challenging due to both the perceived barriers, as outlined above, and because of the practical implications of working with multiple sponsors at once, including the associated contracts, and reporting, business intelligence and intellectual property implications. Multiple industry co-sponsors have worked together successfully on a single trial, such as the ISPY-2 trial which included multiple companies contributing drugs.<sup>27</sup>

### **Regulatory uncertainties**

Despite general enthusiasm and acceptance among regulatory bodies for adaptive trials, participants recognised that there were still some areas where regulatory bodies needed additional reassurances to feel comfortable with some designs. For example, adaptive trials cover a huge range of potential designs, so ensuring that they adequately control for errors and bias is essential. In addition, the use of simulations to predict errors and bias, whilst effective, will need to be communicated to regulators in a manner that reassures them of the validity and integrity of the simulations.

For health technology assessment, participants noted that the use of surrogate endpoints, whilst beneficial if they represent clinical benefit, can lead to uncertainty about the long-term clinical benefits of the medicine. This can increase the difficulty in effectively assessing the cost-effectiveness of the medicine. In addition, if no surrogate endpoints are available, or if the time to gather data on an endpoint is too long, adaptive trials become more challenging due to the long lag times in gathering data.

It was also noted that patient safety should always be the priority, and that the correct expertise is required to ensure that any increased complexity does not impact this.

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<sup>25</sup> Firewalls refer to procedures and governance that restrict access to information to ensure the integrity of a trial and maintain blindness.

<sup>26</sup> Dimairo M *et al.* (2018) *Development process of a consensus-driven CONSORT extension for randomised trials using an adaptive design* BMC Medicine **16**: 210

<sup>27</sup> <https://www.ispytrials.org/>

## Case study 4 - STAMPEDE

Matt Sydes, University College London, described the STAMPEDE multi-arm, multi-stage (MAMS) seamless Phase II/III adaptive platform protocol for prostate cancer patients starting long-term hormone therapy.

The platform approach allows for a structure in which new comparisons, in the form of additional research arms, can be added in to investigate new research questions without the need for a brand-new trial. STAMPEDE has so far resulted in three practice-changing findings supporting the use of docetaxel, abiraterone and, most recently, prostate radiotherapy for metastatic disease.<sup>28,29,30</sup>

The trial started in 2005, and is currently on version 20 of the protocol. Matt acknowledged that all protocol amendments are burdensome for sites, but ensure the trial runs appropriately and captures the right information using the right protocol.

As of early 2019, over 11,000 patients have been recruited to the trial, and adaptations made so far include adding new arms and dropping arms for insufficient activity. The latest protocol adaptation has enabled trial follow-up to stop for 1500 patients, simplifying participation for patients and releasing capacity for sites to focus on other participants.

Matt noted two of the drivers of success for STAMPEDE were good clinical leadership and collaboration between investigators leading to shared recognition in success. While STAMPEDE has been very successful, to replicate it on multi-national basis would be even more challenging due to the differences in capacity and capability of regulatory bodies across the world.

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<sup>28</sup> James ND *et al.* (2016). *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.* *Lancet* **387(10024)**:1163-1177

<sup>29</sup> Sydes MR *et al.* (2018). *Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol.* *Ann Oncol* **29(5)**:1235-1248

<sup>30</sup> Parker CC *et al.* (2018). *Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial* *Lancet* **392(10162)**:2353-2366

Researchers involved in the trial have published papers sharing their experiences and learnings; such publications are vital to sharing learnings from novel trials such as these.<sup>31,32,33</sup>

## Improving uptake of adaptive trials

A number of practical steps were suggested that stakeholders could take to facilitate the greater use of adaptive trials.

### Knowledge exchange and signposting

There is a database of trial statisticians to help create connections with clinical trial experts. A dedicated database, or an addendum, that outlined those statisticians who were skilled and experienced in adaptive designs would enable those wishing to conduct adaptive trials to better access the expertise required, and better enable the dissemination of methodologies and skills.

It was also felt that the opportunities for secondments and skills exchange could help upskill staff across the clinical trial infrastructure network. Skills exchange could also take the form of shadowing staff who are working on adaptive trials to gain insights and experience.

Participants agreed that industry needs to be more intimately involved in the development, planning and execution of adaptive clinical trials. It was suggested that greater engagement with industry colleagues would be a vital aspect of facilitating collaborations and industry sponsorship of trials. Knowledge exchange and networking opportunities, including FORUM events and others, could be a key part of this.

### Dedicated infrastructure

As outlined above, participants suggested that dedicated funding for infrastructure would encourage the use of adaptive trials, especially in those disease areas where adaptive trials are likely to have the most impact in the short to medium term. In addition, it would help to have dedicated funding for biomarker development and for 'pre-work', such as simulations. Such infrastructure would initially be most beneficial where there has been little progress through conventional trial approaches, such as dementia, or where there are large pipelines of new therapies in development that would benefit from faster, and more effective clinical development through adaptive trials.

### Standards for reporting

As outlined in Dr Dimairo's talk (see **Box 3**), it would be beneficial to have standardised reporting of adaptive trials. The reporting of detailed methodologies will allow others to use or build upon them, contributing to the wider knowledge base. Effective reporting will also increase confidence in those who are considering using adaptive designs for the first time.

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<sup>31</sup> Schiavone F *et al.* (2019). *This is a platform alteration: a trial management perspective on the operational aspects of adaptive and platform and umbrella protocols*. *Trials*. **20(1)**:264.

<sup>32</sup> Hague D *et al.* (2019). *Changing platforms without stopping the train: experiences of data management and data management systems when adapting platform protocols by adding and closing comparisons*. *Trials*. **20(1)**:294.

<sup>33</sup> Morrell L *et al.* (2019). *Mind the gap? The platform trial as a working environment*. *Trials*. **20(1)**:297.

Additionally, reporting could go beyond methodologies to include summaries of the challenges encountered and how they were addressed, so that others can learn from these experiences.

## Box 3 - Reporting adaptive trials – the Adaptive designs CONSORT Extension (ACE)

Dr Munya Dimairo, University of Sheffield, presented on behalf of the ACE steering committee. The Consolidated Standards of Reporting Trials (CONSORT) Statement provides guidance for the transparent reporting of trials.<sup>34</sup> However, adaptive trials have several unique features that the CONSORT guidelines do not cover. The ACE steering committee is developing additions and modifications to the guidance specifically for adaptive trials.<sup>35</sup>

The project began with a review of the reporting of existing adaptive trials and found that most were inadequately reporting methodologies and results. A development paper has been published, with the full guidance to be published in late 2019.

The guidance consists of generalisable principles that state the minimum reporting guidelines that were built using a consensus-driven approach through stakeholder engagement. The long-term goal is for the guidelines to enhance transparency and adequate reporting of adaptive trials to help mitigate concerns around methodologies, bias or reporting for future trials.

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<sup>34</sup> <http://www.consort-statement.org/>

<sup>35</sup> Dimairo M *et al.* (2018) *Development process of a consensus-driven CONSORT extension for randomised trials using an adaptive design* BMC Medicine **16**:210



# Conclusions

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In her closing statements, the workshop chair, Professor Deborah Ashby OBE FMedSci, Professor of Medical Statistics and Clinical Trials, Imperial College London applauded the encouraging progress that has been made in the use of adaptive trials in recent years, noting the success exemplified in the case studies, as well as the general consensus that academia and industry are beginning to make more widespread use of adaptive designs.

Professor Ashby emphasised that there were still challenges to be overcome across the entire pathway from development of methodologies, through to the execution of trials and the evaluation of their outcomes. She highlighted that progress in upskilling the clinical trial workforce, and generating the infrastructure to support complex adaptive designs was essential to their widespread deployment. Flexibility of funding and breaking down cultural barriers would accelerate the development of further innovative designs that can contribute to the existing portfolio of designs. Finally, earlier, constructive conversations between academia, industry and regulatory and health technology assessment bodies will help ensure that designs are appropriately chosen and the results can be evaluated with integrity.

Professor Ashby closed by noting that patients could be a key driver for the further use of innovative adaptive designs, especially as trials begin to require more discrete and stratified patient populations. Patients are supportive of adaptive designs and their engagement and support can enable trials that incorporate co-design and have better patient recruitment, adherence and engagement. Professor Ashby suggested that patient facing charities could be a key ally in supporting the use of adaptive trial designs.

# Annex I - Agenda

09.00-09.30	<b>Registration and refreshments</b>
09.30-09.40	<b>Welcome and introduction</b> Professor Deborah Ashby OBE FMedSci (Chair), Professor of Medical Statistics and Clinical Trials, Imperial College London
<b>The current landscape for adaptive trials</b>	
09.40-10.00	<b>Introduction to adaptive trials</b> Professor Roger J. Lewis, Professor and Chair, Emergency Medicine, Harbor-UCLA Medical Center and Senior Medical Scientist, Berry Consultants, LLC
10.00-10.15	<b>Regulatory challenges for adaptive trials</b> Dr Maria Beatrice Panico, Medical Assessor, Clinical Trials Unit, MHRA
10.15-10.30	<b>Innovative trial design: ECMC concept paper</b> Dr Kirsty Wydenbach, Deputy Unit Manager, Clinical Trials Unit, MHRA
10.30-11.30	<b>Experiences of conducting adaptive trials</b> <i>Case studies of experiences in developing and conducting adaptive trials.</i> <ol style="list-style-type: none"> <li>1. Professor Chris Butler FMedSci, Professor of Primary Care, University of Oxford</li> <li>2. Dr Louise Brown, Principal Research Associate, University College London</li> <li>3. Dr Melanie Quintana, Statistical Scientist, Berry Consultants</li> <li>4. Matt Sydes, Reader in Clinical Trials, University College London</li> </ol>
11.30-11.50	<b>Tea and coffee</b>
11.50-12.20	<b>Parallel breakout session 1 – current challenges and opportunities</b> <i>Parallel breakout sessions where, in light of the case studies, participants can consider the current and future challenges, and necessary preparations for novel trial design. Participants will be asked to consider what we have got right so far, and what further progress is needed from each of the following sectors, and the steps they need to take, to advance the use of adaptive trials. Participants can choose to attend one session from the following:</i> <ul style="list-style-type: none"> <li>• Regulatory and health technology assessment bodies</li> <li>• Academia</li> <li>• Industry sponsors</li> <li>• Funding bodies (Research commissioning)</li> </ul>
12.20-12.30	<b>Moving between rooms</b>
12.30-13.00	<b>Parallel breakout session 2 – current challenges and opportunities</b> <i>Parallel breakout sessions where, in light of the case studies, participants can consider the current and future challenges, and necessary preparations for novel trial design. Participants will be asked to consider what we have got right so far, and what further progress is needed from each of the following sectors, and the steps they need to take, to</i>

	<p><i>advance the use of adaptive trials. Participants can choose to attend one session from the following:</i></p> <ul style="list-style-type: none"> <li>• Regulatory and health technology assessment bodies</li> <li>• Academia</li> <li>• Industry sponsors</li> <li>• Funding bodies (Research commissioning)</li> </ul>
13.00-13.45	<b>Lunch</b>
13.45-14.45	<p><b>Reporting back to the group and discussion</b></p> <p><i>The chairs of each theme will report back their 2-3 key challenges and how they could be addressed, and there will be opportunity to discuss and debate these challenges and needs from each sector with the audience – what are the criteria needed for adaptive trials?</i></p>
14.45-15.00	<p><b>Reporting adaptive trials – the Adaptive Designs CONSORT (ACE) extension</b></p> <p>Dr Munya Dimairo, Research Fellow, University of Sheffield</p>
15.00-15.15	<b>Tea and coffee</b>
<b>Preparing for the future</b>	
15.15-15.35	<p><b>What does the future hold for adaptive trials?</b></p> <p>Professor Roger J. Lewis, Professor and Chair, Emergency Medicine, Harbor-UCLA Medical Center and Senior Medical Scientist, Berry Consultants, LLC</p>
15.35-16.50	<p><b>Panel discussion with the audience – meeting future challenges</b></p> <p><i>Each panel member will be asked to give a 3-5 minute response to some of the challenges highlighted thus far, and to reflect on what they consider the key upcoming issues for adaptive trials to be, followed by discussion around these issues and how they might be addressed.</i></p> <ol style="list-style-type: none"> <li>1. Dr Liz Allen, Vice President Early Clinical Development, IQVIA</li> <li>2. Dr Jacqueline Bouvy, Senior Scientific Advisor, National Institute for Health and Care Excellence</li> <li>3. Professor Julia Brown, Professor of Medical Statistics, University of Leeds</li> <li>4. Professor Andy Grieve, Head of Statistical Innovation Centre of Excellence, UCB</li> <li>5. Dr Rob Hemmings, Statistics and Pharmacokinetics Unit Manager, Medicines and Healthcare products Regulatory Agency</li> <li>6. Professor Hywel Williams FMedSci, Director, National Institute for Health Research Health Technology Assessment Programme</li> </ol>
16.50-17.00	<p><b>Summary from chair</b></p> <p>Professor Deborah Ashby OBE FMedSci (Chair), Professor of Medical Statistics and Clinical Trials, Imperial College London</p>
17.00	<b>Close</b>
17.00-18.30	<b>Drinks and networking reception</b>

# Annex II – Participant list

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## Chair

**Professor Deborah Ashby OBE FMedSci**, Chair in Medical Statistics and Clinical Trials, Imperial College London

## Speakers

**Dr Jacoline Bouvy**, Senior Scientific Advisor, Science Policy and Research Programme, National Institute for Health and Care Excellence

**Dr Louise Brown**, Principal Research Associate, University College London

**Dr Munya Dimairo**, Research Fellow, University of Sheffield

**Professor Andy Grieve**, Head of the Statistical Innovation Centre of Excellence, UCB

**Mr Rob Hemmings**, Statistics and Pharmacokinetics Unit Manager, Medicines and Healthcare products Regulatory Agency

**Professor Roger Lewis**, Professor of Emergency Medicine and Vice Chair, University of California, Los Angeles

**Dr Beatrice Panico**, Medical Assessor, Medicines and Healthcare products Regulatory Agency

**Dr Melanie Quintana**, Statistical Scientist, Berry Consultants

**Mr Matt Sydes**, Reader in Clinical Trials, University College London

**Professor Hywel Williams FMedSci**, Director, National Institute for Health Research Health Technology Assessment Programme

**Dr Kirsty Wydenbach**, Deputy Unit Manager / Senior Medical Assessor, Clinical Trials Unit, Medicines and Healthcare products Regulatory Agency

## Attendees

**Dr Virginia Acha**, Executive Director - Global Regulatory Policy (EU, EMEA, APAC), MSD

**Dr Liz Allen**, Vice President Early Clinical Development, IQVIA

**Dr Emma Arriola**, Scientific Director, Oncology Development, Abbvie

**Mr Mike Batley**, Deputy Director - Research Programmes, Department of Health and Social Care

**Professor Julia Brown**, Professor of Medical Statistics, University of Leeds

**Professor Chris Butler FMedSci**, Professor of Primary Care, University of Oxford

**Dr Helen Campbell**, Portfolio Manager, Department of Health and Social Care

**Ms Sophie Cooper**, Scientific Adviser, Science Policy and Research Programme, National Institute for Health and Care Excellence

**Mr Thomas Devine**, Head of Procurement, Royal Papworth Hospital NHS Foundation Trust

**Ms Stephanie Ellis**, Chair, London - Hampstead Research Ethics Committee, Health Research Authority

**Professor Richard Emsley**, Professor of Medical Statistics and Trials Methodology, King's College London

**Dr Emma Gray**, Head of Clinical Trials, MS Society

**Dr Lisa Hampson**, Statistician, Novartis

**Dr Ali Hansford**, Head of Science Policy, Association of the British Pharmaceutical Industry

**Mr Jordan Holland**, Senior Policy Adviser, Office for Life Sciences

**Professor Thomas Jaki**, Professor in Statistics, Lancaster University

**Dr Jonathan Jones**, Senior Medical Director Europe North, Vertex Pharmaceuticals  
**Dr Justin Lindemann**, Group Director Senior Physician, AstraZeneca  
**Mr Adam Lloyd**, Senior Principal, Health Economics and Outcomes Research, IQVIA  
**Ms Emma Lowe**, Senior Research Policy Manager, Department of Health and Social Care  
**Dr Adrian Mander**, Director of Hub for Trial Methodology Research, University of Cambridge  
**Dr Kathleen Meely**, Senior GCP Inspector, Medicines and Healthcare products Regulatory Agency  
**Dr Ilaria Mirabile**, Head of the ECMC Programme Office, Experimental Cancer Medicine Centres  
**Dr Rhoda Molife**, Senior Clinical Director - Oncology, MSD  
**Mr Nuru Noor**, PhD Student, University College London  
**Ms Daniela Palazzolo**, Principal, Pricing & Market Access, PAREXEL  
**Professor Max Parmar**, Director, MRC Clinical Trials Unit, University College London  
**Professor Sue Pavitt**, Professor in Translational & Applied Health Research, University of Leeds  
**Dr Sarah Rappaport**, Policy Adviser, Wellcome  
**Dr Alexander Renziehausen**, Programme Manager, NCRI  
**Dr Sam Rowley**, Programme Manager - Methodology and Clinical Research, Medical Research Council  
**Ms Susan Sandler**, Director, EMEA Policy Lead, Global Regulatory Policy & Intelligence, Janssen  
**Professor Nigel Stallard**, Professor of Medical Statistics, University of Warwick  
**Professor Ann Marie Swart**, Professor of Medicine, University of East Anglia  
**Professor Sue Todd**, Professor of Medical Statistics, University of Reading  
**Dr George Wang**, Senior Associate, PAREXEL  
**Professor James Wason**, Professor of Biostatistics, Newcastle University  
**Professor Chris Weir**, Personal Chair of Medical Statistics and Clinical Trials, University of Edinburgh

**Academy staff and secretariat**

**Dr Shaun Griffin**, Interim Head of Policy, Academy of Medical Sciences  
**Dr James Squires**, FORUM Policy Manager, Academy of Medical Sciences  
**Beverley Wilson**, Policy Intern, Academy of Medical Sciences  
**Cristiana Vagnoni**, Policy Intern, Academy of Medical Sciences  
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