OPINION

Adaptive platform trials: definition, design, conduct and reporting considerations

The Adaptive Platform Trials Coalition

Abstract | Researchers, clinicians, policymakers and patients are increasingly interested in questions about therapeutic interventions that are difficult or costly to answer with traditional, free-standing, parallel-group randomized controlled trials (RCTs). Examples include scenarios in which there is a desire to compare multiple interventions, to generate separate effect estimates across subgroups of patients with distinct but related conditions or clinical features, or to minimize downtime between trials. In response, researchers have proposed new RCT designs such as adaptive platform trials (APTs), which are able to study multiple interventions in a disease or condition in a perpetual manner, with interventions entering and leaving the platform on the basis of a predefined decision algorithm. APTs offer innovations that could reshape clinical trials, and several APTs are now funded in various disease areas. With the aim of facilitating the use of APTs, here we review common features and issues that arise with such trials, and offer recommendations to promote best practices in their design, conduct, oversight and reporting.

There is a need for more efficient evaluation of the clinical benefits of new therapeutics and the comparative effectiveness of interventions in current use. Traditional randomized controlled trials (RCTs) are the gold-standard approach to generate evidence regarding the benefits and harms of potential medical therapies. However, they can be slow, inefficient and limited in the questions they address[1]. Awareness of these limitations has led to growing interest in novel trial designs, particularly those that use 'master protocols', which can be classified as basket, umbrella and adaptive platform trials (APTs)[2]. APTs represent the largest departure from traditional RCT design[3] in that they 'study multiple interventions in a single disease (or condition) in a perpetual manner, with interventions allowed to enter or leave the platform on the basis of a decision algorithm'[2]. APTs also incorporate within-trial adaptations (typically using, but not limited to, Bayesian approaches) such as response-adaptive randomization (RAR) rules to preferentially assign interventions that perform most favourably, rules to trigger the addition or termination of a study arm, or rules to transition from one study phase to another.

APT innovations create opportunities for more efficient knowledge generation, novel funding and investment strategies, and the engineering of 'learning health systems', in which knowledge generation is embedded in routine clinical practice to drive continuous improvements. With their common platform and infrastructure, their efficient use of control arms and their ability to streamline the launch of new study interventions, APTs can offer numerous advantages in both pharmaceutical and device development and comparative effectiveness settings, helping to bridge the knowledge translation gap between traditional RCTs and clinical practice[4,5]. Reflecting this potential, several APTs are now funded in various disease areas, testing over 30 experimental agents (TABLE 1). With this growing experience, common features and issues for APT design are becoming apparent. For example, APTs require considerable pretrial evaluation through simulation to assess the consequences of patient selection and stratification, organization of study arms, within-trial adaptations, overarching statistical modelling and miscellaneous issues such as modelling for drift in the standard of care used as a control over time. In addition, once APTs are operational, transparent reporting of APT results requires accommodation for the fact that estimates of efficacy are typically derived from a model that uses information from parts of the APT that are ongoing, and may be blinded.

As several groups are launching APTs, the Adaptive Platform Trials Coalition was formed to generate standardized definitions, share best practices, discuss common design features and address oversight and reporting. This paper is based on the findings from the first meeting of this coalition, held in Boston, Massachusetts in May 2017, with additional development by the group in the months following (BOX 1). We first briefly overview design elements and nomenclature of APTs and then discuss key considerations in study design, documentation, oversight and reporting, which are covered in the Coalition's recommendations presented at the end of the article. For illustration, we also use three case studies: I-SPY 2, a phase II APT investigating neoadjuvant therapies for breast cancer (BOX 2); REMAP-CAP, which is testing alternative interventions within multiple domains of care for severe pneumonia (BOX 3); and GBM AGILE, a phase II/III APT investigating approaches for the management of glioblastoma (BOX 4).

Design elements and nomenclature

The focus of an APT is a disease or condition, rather than a particular intervention[3]. As such, the overarching design can be created before any specific experimental arms are defined. Philosophically, the APT is a platform or engine that can be used continuously, and potentially ad infinitum, to facilitate comparisons of alternative interventions, often within multiple different clinical or biomarker-defined subtypes, thus supporting an ever-improving evidence base for optimal treatment. Most APTs use Bayesian inference models because they are well suited for iterative updating or adaptations. However, frequentist statistical

and machine learning reinforcement approaches have also been proposed[6].

APTs have been constructed as phase II, III, IV and seamless phase II/III settings (TABLE 1). A typical APT design is shown in FIG. 1. After establishing the starting conditions regarding patient entry criteria and strata, initial experimental arms and outcomes, the APT commences enrolment and randomization. As data accrue from enrolled patients, they are used to iteratively update a pre-specified model. The updated results of the model trigger thresholds for the end of a particular experiment and provide updated randomization instructions for the ongoing APT. A particular experiment typically ends because a pre-specified probability of success or failure for an experimental arm is triggered. Updated randomization typically occurs via RAR (BOX 5), where the randomization weight is proportional to the probability that a therapy is superior[7]. This process continues iteratively. Modifications to this loop can be made with the introduction of new experimental arms or other trial adaptations. Design features used in APTs to date can be grouped into five broad areas, as described below and in TABLE 2.

Patient selection and enrichment strategies. Because APTs often enrol a broad population, they may, at enrolment, stratify the cohort into different subtypes based on presenting clinical or biomarker criteria[8]. Stratification may then be used to limit interventions to select subtypes, define separate control arms or test whether there are larger treatment effects among particular subtypes or combinations of subtypes. The choice of enrichment strategy is disease and trial-specific[9]. For example, because human epidermal growth factor receptor 2 (HER2) status affects breast cancer treatment options, I-SPY 2 uses HER2 status to both define possible experimental and control regimens and to create subtypes where randomization probabilities are allowed to vary (BOX 2). By allowing randomization probabilities to vary by biomarker subtype, enrichment also occurs during the trial through adaptation (see below).

Table 1 | **Design features of select funded adaptive platform trials**

Feature	I-SPY 2	REMAP-CAP	GBM AGILE	INSIGhT[13]	EPAD	DIAN	Precision Promise	PREPARE FLU
Registration number	NCT01042379	NCT02735707	NCT03970447; Alexander et al.[42]	NCT02977780	Ritchie et al.[45]	NCT01760005	NA[a]	ISRCTN27908921
Population	Breast cancer	Severe pneumonia	Glioblastoma	Glioblastoma	Alzheimer disease	Alzheimer disease	Pancreatic cancer	Influenza
Phase	II	IV	II/III	II	II	III	II/III	IV
Proportion of experimental agents	14/16	0/9[b]	1/2	3/4	3/3	3/3	NA[a]	NA
Time of primary outcome	6 months	3 months	TTE	TTE	4 years	>4 years	TTE	1 week
Patient selection								
Subtype stratification	Y	Y	Y	Y	Y	N	Y	N
Study arms								
Multiple arms	Y	Y	Y	Y	Y	Y	Y	Y
Multiple domains	N	Y	N	N	N	N	N	N
Common control	Y	Y	Y	Y	Y	Y	Y	Y
Within-trial adaptations								
RAR	Y	Y	Y	Y	N	N	Y	Y
Interim frequency	2 weeks	Monthly	Monthly	Monthly	Quarterly	Biannually	Monthly	Weekly
Staggered arms	Y	Y	Y	Y	Y	Y	Y	Y
Integration								
Bayesian model	Y	Y	Y	Y	Y	Y	Y	N
Miscellaneous								
Longitudinal model	Y	N	Y	N	Y	Y	N	N
Time machine	Y	Y	Y	N	N	N	Y	Y
Embedding	N	Y	N	N	N	N	N	N

N, no; NA, not applicable; RAR, response-adaptive randomization; TTE, time to event; Y, yes. [a]In the planning phase, with multiple experimental arms and a control arm proposed. [b]For corticosteroid, antibiotic and macrolide domains.

Organization of study arms. APTs use several tools and features to study multiple interventions. The simplest feature is the use of multiple arms, with a single experimental therapy per arm. More complex designs include testing different interventions within multiple domains in the same patient. Each patient is then assigned a therapeutic regimen that reflects a particular combination of interventions within each domain. In REMAP-CAP (BOX 3), for example, patients are simultaneously assigned separate treatment options within antibiotic, immunomodulation and ventilation domains. Other options are alternative sequences of interventions within the same patient, potentially dependent on response.

Within-trial learning and adaptations. The most typical within-trial learning tool is re-weighted randomization probabilities proportional to updated probabilities of success based on accrued trial data (RAR), a feature in all three case studies. Biomarker enrichment can occur during the course of the trial as a therapy that begins in a trial as being biomarker-agnostic becomes biomarker-specific through updated randomization probabilities. The converse is also possible: a biomarker-specific therapy could generate evidence supporting value in a broader population[10]. This flexibility allows APTs to combine what had previously been thought of as two separate trials. For example, glioblastoma RCTs typically test new interventions in either newly diagnosed or recurrent tumours, but not both. By considering these two presentations as a biomarker, GBM AGILE (BOX 4) can study an intervention in both groups simultaneously: if the effect is limited to newly diagnosed patients, the RAR algorithm steadily decreases the probability of recurrent patients being randomized to the drug (ultimately to zero) while simultaneously confirming the effect in newly diagnosed patients.

Another adaptation feature is the activation of trial arms that are only triggered by the performance of related arms (for example, the triggering of a higher dose of a drug if a lower dose shows efficacy but no safety concerns). The relationship between different endpoints can also be investigated, with the ability to switch to earlier or more easily obtained endpoints once they are demonstrated to have adequate proxy characteristics. For example, I-SPY 2 (BOX 2) includes a model that 'learned' that demonstration of response on a magnetic resonance image is predictive of the primary endpoint of pathological complete response, and therefore the Bayesian model incorporates early magnetic resonance imaging findings into subsequent RAR decisions, increasing overall trial efficiency.

Integration of patient selection, study arms and adaptations. When testing multiple interventions across multiple subtypes or subtype combinations, an APT can use an overarching model to provide more robust estimates of within-subtype intervention effects, presuming there are adequate patients assigned within each subtype to each intervention or control being compared. The construction of the model requires careful consideration of which intervention-by-subtype and intervention-by-intervention-by-subtype interactions should be considered. A model that is too simple may fail to tease out important interactions, but a model with too many terms will compromise study power. In REMAP-CAP (BOX 3), interactions are considered between shock status at presentation, antibiotic assignment and steroid assignment because the effect of steroids may depend on shock status and on the choice of antibiotics. However, REMAP-CAP does not consider interactions between the ventilation strategy and choice of antibiotic or steroid, based on consensus within its steering committee that such interactions would be negligible, and avoiding their inclusion preserves study power.

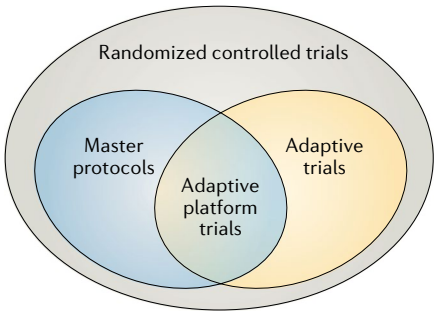
Miscellaneous features. Increasingly, the efficient conduct of an APT requires consideration of its incorporation into clinical care or the electronic health record (see 'Embedding APTs in clinical practice' below). APTs that run over a prolonged period may encounter drift in usual practice or background care, which may pose an important threat to the ability to leverage randomization as a vehicle for causal inference. A 'time machine' used to model the effect of time on the control arm is a feature of both I-SPY 2 and GBM AGILE[11]. Patient data may also accrue too slowly for interim updates to randomization assignments, requiring a mechanism to rely on partial, incomplete and potentially inaccurate follow-up.

Evaluating alternative design choices

Crucially, many of the design features described above can alter the APT's performance characteristics. Thus, these features must be evaluated through extensive pretrial simulation[12–15], typically using

Box 1 | **Consensus process and rationale for the term 'adaptive platform trial'**

Consensus process



This work was generated by a writing committee from the Adaptive Platform Trials Coalition. Two members of the committee (B.M.A. and D.C.A.) invited the leadership of several adaptive platform trials (APTs) to generate the agenda, invitees, structure, purpose and funding for an initial meeting. Representatives were identified from all known APTs via a snowballing technique. We also invited stakeholders not involved in APTs from the US Food and Drug Administration, industry, patient organizations and academia. The initial 3-day meeting was split into sessions that consisted of introductory talks followed by proctored discussions (see Supplementary Box 1). To ensure broad engagement, sessions used rotating moderators and voting where necessary. D.C.A. and B.M.A. drafted the manuscript and circulated for input from all authors.

Rationale

The coalition endorsed the term APT because it conveyed three crucial elements (see figure). First, an APT is a prospective experiment — a trial — of alternative care strategies. Second, it is a platform, with a master (or core) protocol, upon which multiple questions can be asked about the effectiveness of interventions for a particular disease or condition[34]. In this way, the design is similar to basket or umbrella trials. However, the third element, 'adaptive', distinguishes this class because, like other adaptive trials, it uses information generated during trial conduct to alter subsequent operations in a pre-specified way (see below). In other words, APTs differ from traditional trials in that they use a master, rather than a stand-alone, protocol and they use adaptive, rather than fixed, design features. Both elements (master protocol and adaptive design features) add complexity, but with the intent of improving the efficiency of knowledge generation. There are clear examples of platform trials under master protocols (for example, Lung-MAP[35] (NCT02154490) or NCI-MATCH[36] (NCT02465060)) and stand-alone trials that use Bayesian updating (for example, Sepsis-ACT[37] (NCT02508649)) that would not be considered APTs. By combining elements of both, APTs generate a unique set of opportunities and challenges.

Box 2 | **Case study of I-SPY 2**

The most established adaptive platform trial (APT) is I-SPY 2 (Investigation of Serial studies to Predict Your therapeutic response with imaging and molecular analysis 2; NCT01042379), which began enrolling in 2011 and is expected to enrol 1,920 patients at 16 centres in Canada and the USA. I-SPY 2 is an open-label phase II trial evaluating the efficacy of combining experimental drugs in conjunction with standard chemotherapy as compared with standard chemotherapy alone for women diagnosed with local metastatic breast cancer before surgical resection. The trial is designed to investigate therapies across ten subsets of patients (called 'drug signatures') based on combinations of MammaPrint and human epidermal growth factor receptor 2 (HER2) and oestrogen receptor status[22,23,38]. Following biomarker assessment, eligible subjects without exclusion are randomized to receive one of the available interventions.

The primary outcome for I-SPY 2 is the identification of combinations of experimental drug and standard chemotherapy increasing the likelihood of pathological complete response (pCR), an early surrogate endpoint, as compared with standard chemotherapy alone. Use of an early surrogate endpoint permits assessment of the potential efficacy of the experimental interventions more quickly than clinical endpoints would afford. Secondary outcomes include relapse-free survival at 3 and 5 years, overall survival, tumour volume via magnetic resonance imaging, defining predictive and outcome characteristics, and establishing adverse event and laboratory abnormality profiles for each experimental drug.

A key adaptive feature of I-SPY 2 is the use of a response-adaptive randomization matrix across the multiple drug signatures, which permits changing allocation probabilities over time to different experimental arms within different drug signatures. A related feature is that the sample size is not predetermined, but rather continues until a predefined statistical trigger is breached. The superiority trigger is the finding within a particular drug signature that the experimental arm would have >85% Bayesian predictive probability of success if tested in a subsequent phase III trial of 300 patients with the same signature. The futility trigger is a finding of <10% probability of success in a subsequent phase III trial for all ten signatures.

I-SPY 2 has assessed multiple therapies in multiple signatures, using pCR[29,39] as the primary outcome to change randomization assignment in favour of those interventions that appear most promising. MK-2206 (Merck), TDM1 + pertuzumab (Genentech/Roche), veliparib (AbbVie), neratinib (Puma Tech), pembrolizumab (Merck) and pertuzumab (Genentech) have demonstrated superior results and will be further evaluated within the I-SPY 3 trial[22,23,38,40,41]. Currently, five study arms remain open.

Monte Carlo simulations drawing from likely population distributions for the disease or condition under study, including consideration of the likely frequency of subtypes of interest together with estimates of likely event rates, accrual rates, anticipated treatment effects and interaction terms.

During these simulations, design features such as the 'responsiveness' of the RAR can be adjusted to achieve a balance that allows variable weighting over time without overly aggressive swings in response to spurious observations, especially early in the trial. Additional simulations should be conducted as more becomes known about actual accrual patterns, availability of treatment and other pretrial assumptions. The output of these simulations is a multiple-component assessment of trial operating characteristics, such as the sample size, time to completion, probability of accurately determining success or failure and so on.

Optimal design requires good communication between the clinical and statistical experts in the research team, and engagement in an iterative process not only within the research team but with other key stakeholders.

Documentation

Trial registration. Because most APTs are modular, with staggered additions of new appendices, it is crucial not only that the APT be registered on an appropriate website, such as ClinicalTrials.gov, but also that there be a commitment to regularly update the registration when there are material changes. Updates that change the range of therapeutic options as arms are added or dropped are particularly important. Organization of websites to provide easy access to information on available arms is critical. One potential problem is that registration sites sometimes do not have adequate flexibility to describe some APT features. For example, ClinicalTrials.gov asks for information regarding a single sponsor for a study, which can be confusing when there are multiple sponsors and funding sources.

Study protocol. We recommend describing an APT in a master (or core) protocol. This protocol should contain the governing rules for the APT, such as eligibility, the mechanism for random assignment, study endpoints, the overarching analytical approach and all other design elements that are generic to the APT and not related specifically to the interventions being studied in individual arms. The initial experimental arms (interventions) or suite of arms (for example, within a particular domain of care) can then be defined in appendices to the protocol. As the APT evolves, new study questions, domains or experimental arms can be defined in subsequent appendices. Similarly, if there are region-specific elements to the APT, they can be defined in a region-specific appendix.

Statistical analysis plan. Like all RCTs, an APT requires a comprehensive statistical analysis plan (SAP) addressing all of the typical issues, such as specification of analysis data sets, handling of missingness, description of interim analyses and so on. In addition, there are some particularly important issues for APTs. When designing an APT, the investigators must choose from several statistical design features. These choices should be informed by simulations of alternative possible trial trajectories to understand their trade-offs. However, what defines 'possible trial trajectories' is somewhat arbitrary. If an overly narrow set of possible scenarios is simulated, then researchers may fail to understand the consequences of their design choices. Therefore, we recommend that either the SAP (perhaps in an appendix) or a separate publicly available document (for example, a published paper of the study design) includes a description of the design choices that were considered, which possible trajectories were simulated and what the trial performance characteristics were when using the different design choices under the different simulated trajectories.

Particular design issues whose consequences should be evaluated through simulation include: the data and distributions used to inform the Bayesian priors (assuming a Bayesian model is used); the decisions to include terms in the model (or not), such as intervention-by-subtype interactions or 'time machine' features; the proposed RAR rules, endpoints and any longitudinal models for endpoints; robustness to missing data of various forms, variable proportions and accrual of patients within any subtypes; and false positive and false negative rates. Particular simulation issues include defining null conditions and partial effects, as well as ensuring that the range of possible eventualities is adequately broad and comprehensive. The SAP may also have modular appendices to handle any differences for different arms in the trial.

Box 3 | **Case study of REMAP-CAP**

REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; NCT02735707) is an international phase IV clinical trial assessing multiple combinations of conventional care and experimental treatment options for adults diagnosed with severe community-acquired pneumonia (CAP). Unlike I-SPY 2 (BOX 2), REMAP-CAP's study design includes multiple domains within which alternative interventions are compared. As such, patients are assigned to regimens consisting of specific interventions within each domain. Patients can also be eligible for random assignment in some domains even if ineligible for participation in other domains. REMAP-CAP is launching with four domains. Domain #1 is the antibiotic domain, comparing five separate antibiotic strategies to treat severe pneumonia. Domain #2 is the extended macrolide domain, comparing extended macrolide for its combined immunomodulatory and antimicrobial properties with no extension. Domain #3 is the corticosteroid domain, comparing alternative dosing strategies of corticosteroids for their cardiovascular and immunomodulatory effects. Finally, domain #4 is the ventilation domain, comparing alternative mechanical ventilation strategies.

REMAP-CAP has the capacity to add additional interventions within each domain and to add additional domains. Given the international nature of this clinical trial, the modular nature of domains within REMAP-CAP is particularly useful as it permits geographical variation in intervention implementation due to regulatory status, reimbursement coverage determination or local prescribing practice differences. REMAP-CAP emphasizes embedding of trial operations into usual care to ensure rapid and complete capture of all possible patients, both to generate an adequate sample size and as a preparedness strategy in the event of pneumonic pandemics. The study is designed to enrol adults admitted to an intensive care unit (ICU) within the last 48 hours with suspected severe CAP, and has funding to recruit 6,800 subjects.

The primary outcome is all-cause mortality at 90 days. Secondary outcomes include ICU and hospital mortality, ICU and hospital length of stay, organ failure-free days, destination at hospital discharge, ICU readmission and 6-month survival, disability and quality of life. The trial is enrolling in Europe, Australia and New Zealand, with recent funding to commence enrolment in Canada.

Oversight

Prelaunch regulatory and scientific review. One concern for an APT is the broad flexibility regarding design features and potential trajectories, with no standard, comprehensive way to review the trade-offs associated with different design decisions. Consider, for example, an APT using an overarching model to generate effect estimates for multiple interventions against a common control that exposes two patient strata (subtypes) to the various interventions. A choice must be made about whether the superiority of any intervention over control should be estimated in aggregate across the two strata or whether effects should be estimated for each stratum. If the latter choice is made, a further choice is whether the within-stratum effects are estimated just from those patients within the stratum or whether estimates can borrow information from the performance of the interventions and control in the other stratum. The merits of each choice differ under different circumstances with regard to whether an intervention-by-stratum effect actually exists. With similar trade-offs for the many other design decisions, determination of the strengths of the overall design quickly becomes a non-trivial task.

Currently, the only pretrial oversight and approval process is via expert peer review, such as statistical and content review at the US Food and Drug Administration (FDA). The FDA developed policy guides for the critique and approval of both master protocols[2,16] and adaptive trials[17], and similar guidelines exist or are being developed by other oversight groups. However, there is no explicit and transparent review process for APTs, and therefore no mechanism for standardized evaluation across different national and international oversight and review bodies.

We recommend that a standardized process begins with a critique of the overarching design, as contained within the master protocol and the SAP, yet with considerable focus on the performance of the adaptive design choices as illustrated in simulations across the range of the most plausible trajectories likely to occur for numerous theoretical interventions. Regulatory review should include careful review of the algorithms driving RAR rules and perhaps also the software or any custom coding used to run the models and to generate the simulations. Ideally, the FDA or similar oversight bodies may want to generate standard parameters or rules regarding parameter selection for simulation. Once agreement is reached over the function of the overarching design, each particular domain or intervention can be assessed independently through review of the relevant appendix. This process will require considerably more effort in pretrial evaluation of the statistical methods and simulations than for a standard RCT. However, the investment in time and interaction should yield long-term gains because subsequent modifications, through the addition of individual appendices, should be easier.

Prelaunch ethical review. Several features of APTs may appear to be very complex, including multiple strata or subtypes at enrolment, exposure to multiple interventions, complex or unfamiliar statistical techniques and the potential for non-balanced randomization that changes over time. Although each component may be well defended, the trial in aggregate may thus appear overwhelming for an institutional review board, and concern may be raised that patients, by extension, will be confused and therefore perhaps unable to give truly informed consent. That said, the first APT (I-SPY 2) was launched with strong patient advocacy, and many aspects of APTs address issues that are quite intuitive. For example, using RAR to adjust the odds of being assigned a particular therapy to favour those interventions performing best is arguably more intuitive to patients than maintaining 50:50 random assignment throughout. However, RAR is primarily a vehicle for efficient learning: although probabilities may be weighted in favour of a well-performing therapy, there is

Box 4 | **Case study of GBM AGILE**

Currently under development, GBM AGILE (Glioblastoma Multiforme Adaptive Global Initiative Learning Environment) will be a phase II/III-like clinical trial enrolling adult patients who are both newly diagnosed or have recurrent isocitrate dehydrogenase wild-type glioblastoma multiforme[42]. The enrolment of this stratified patient population is unique to GBM AGILE's study design. Like REMAP-CAP (BOX 3), GBM AGILE is an international trial with emphasis on the capture of all possible patients, with a projected enrolment of 3,000 subjects.

The design includes an adaptively randomized 'learn' stage to identify effective interventions and associated biomarker-defined signatures, followed by seamless transition (graduation) to a fixed randomized 'confirm' stage for interventions that show promise. As overall survival is the primary endpoint of GBM AGILE, the pooled data from experimental arms that have graduated and been confirmed in the trial could be used as the foundation for new drug application or biologic license application submissions and registration.

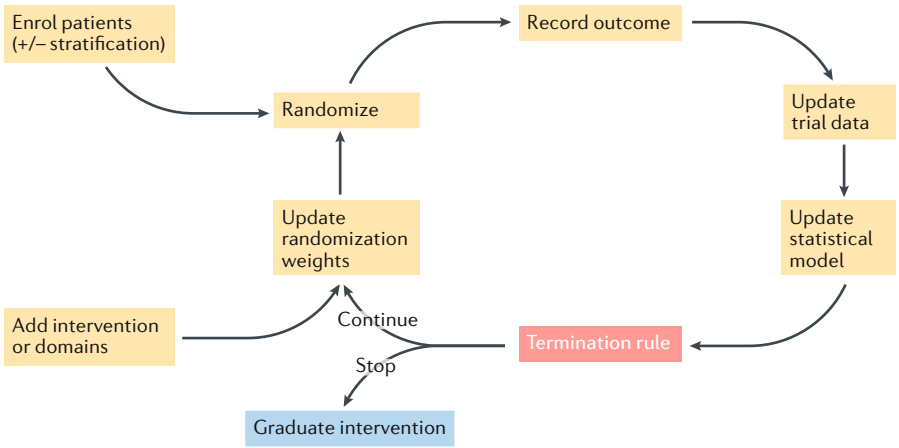


Fig. 1 | **General operational flow of an adaptive platform trial.** Although specifics vary for each identified step and additional features may be added, most adaptive platform trials (APTs) have a common set of activities. Enrolling patients, randomization, recording outcomes and updating trial data are in common with traditional randomized controlled trials. In APTs, however, this information is used in real or near-real time to update a statistical model that is then used to make decisions about termination for graduation (for example, demonstration of superiority) or futility of one part of the trial (for example, a comparison of one particular therapy to control) and for updating consequent randomization probabilities. Not shown: randomization and randomization updates are often specific for different patient subtypes.

no guarantee that a patient will receive the best-performing therapy.

We therefore propose that ethical review addresses three broad questions. First, are the key features of the APT design, such as RAR, adequately described in lay terms during the consenting process? Second, is the information exchange managed in a way that minimizes patient burden and overload? Use of a modular format or multiple consents aligned with the different appendices may help in this regard. Third, are the risks related to exposure to the individual experimental interventions adequately described and managed? Management of study risks should involve ensuring that the trial addresses meaningful uncertainty in the relevant expert medical community[18]. To address these areas in sufficient detail, the modular format can be used to review each set of experimental interventions in blocks, separate from the overarching design issues. Use of a central institutional review board may also help, given the complexity of APT review. Finally, including patient stakeholders in APT design and implementation may help to ensure ethical issues are appropriately addressed.

Oversight during study conduct. Once a trial launches, study conduct falls under all usual Good Clinical Practice standards for RCT execution, and thus most oversight issues are similar to those for any Good Clinical Practice data safety and monitoring plan[19]. One key issue, therefore, relates to ensuring the Data Safety and Monitoring Board (DSMB) has adequate expertise to 'watch' the trial unfold. For example, an APT that uses RAR will have frequent interim updates that are largely automated. The DSMB can review these updates, but is not expected to intervene except when a trajectory unfolds that was not anticipated in pretrial simulation and is associated with potential harm. When such a circumstance occurs, the trial steering committee should be informed and additional simulations should be conducted to better understand their potential consequences. The ability of the DSMB to appreciate this situation probably requires a high level of APT expertise. A related issue is ensuring the correct mechanisms for firewalls and blinding are in place. However, these issues are not very different from the monitoring of adaptive trials in general.

Reporting results

Many standards and principles for the reporting of traditional RCTs, such as International Committee of Medical Journal Editors and CONSORT (CONsolidated Standards of Reporting Trials) statements on reporting, apply to APTs[20,21]. There are, however, some features unique to APTs. Perhaps the most important issue is that APTs are designed to produce definitive results about a particular experiment (for example, the triggering of stopping rules for the comparison of a particular therapy with one or more alternatives within one or more subtypes) while other parts of the APT are still running. Consider again the example from above of an APT testing multiple interventions in two patient subtypes, with each intervention's treatment effect within each subtype generated from an overarching model that uses information from all patients. When an intervention is found to be superior within one subtype, it is unclear which data should be presented in the report. If only those patients in the subtype are reported, the reader may reasonably claim there are inadequate data presented to support the primary findings (a model estimate derived from patients not reported in the paper). If information on all enrolled patients is included, the reader may feel appeased, but now the entire trial will have been unblinded even though many evaluations are not yet complete.

The only experience with reporting from APTs to date is from I-SPY 2. In two reports[22,23], I-SPY 2 presented a flowsheet documenting how many patients were screened and enrolled, how many patients were randomly assigned to either the experimental arm or control arm being compared in the report (along with follow-up rates and the numbers considered evaluable) and the number of patients randomly assigned into other arms not being presented in the report. For those enrolled, randomized to the reported experiment or control and considered evaluable, the report provided detailed information on baseline characteristics and on safety data. However, for efficacy, only estimates from the overarching model were presented, and no 'raw' outcome data were included, on the justification that the model provided the most accurate estimate of treatment benefit.

The I-SPY 2 approach attempts to comply, where possible, with existing reporting standards while protecting the integrity of the study's design. However, failure to report raw outcome data differs from the traditional standard for high-quality reporting, emphasizing the need to consider APT-specific standards. Such standards may endorse the I-SPY 2 approach or perhaps encourage the reporting of raw results as a sensitivity analysis. To date, reporting was limited to instances where experimental and control arms were concurrently randomized, but we foresee a need for novel reporting paradigms when reporting experimental arm comparisons with non-concurrent or mixed controls. If a long-running APT has only been reported via a series of individual experiment-to-control comparisons within subtypes of

patients, there may be value in the periodic publication of the entire trial up to specific points in time, such as when a new arm is about to be added, to aid understanding of the overall trial.

Embedding APTs in clinical practice

A major opportunity for APTs is to nest or embed them in clinical practice, leveraging efficiencies in clinical trial operations and narrowing the translational gap between evidence generation and clinical care. Most APTs so far were not designed for comparative effectiveness questions of existing practice. Instead, they focused on phase II decision-making for unapproved experimental interventions, using traditional approaches to recruit patients and execute study procedures. However, the randomized embedded multifactorial adaptive platform (REMAP) design, used in REMAP-CAP, is explicitly intended to be embedded in clinical practice, merging APTs with so-called 'point-of-care clinical trial' designs both to leverage efficiencies in trial execution and to provide continually updated randomized evidence on best practice within a learning health system[24].

Interest in APTs as a bridge to real-world evidence is growing. However, the major barriers are similar to those for the embedding of any clinical research into clinical practice, and relate to overcoming social and cultural barriers between the clinical research and clinical care enterprises, to removing financial and logistical disincentives and to determining how to leverage the electronic health record[24,25].

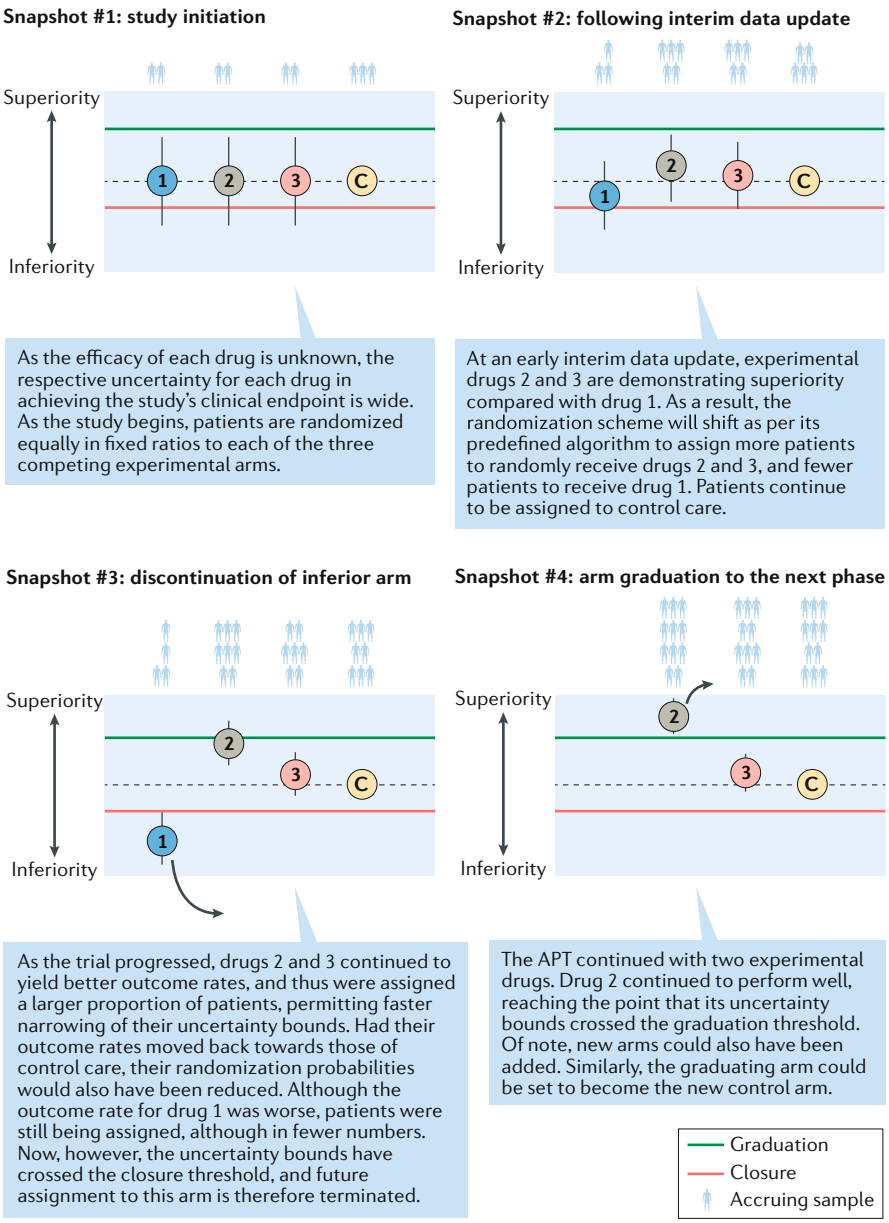
Sponsorship

When evaluating experimental therapies, the typical approach approved by the FDA is for a single entity to hold overall Investigational New Drug (IND) approval with cross-reference to INDs for the experimental arms. Different kinds of organizations can sponsor APTs. Non-profit organizations are a natural sponsor for APTs, as in this situation the APT can act as a trusted third party between industry and regulators and even work with regulators before commercial partners are identified. Disease-specific platform trials[26] sponsored by disease-specific philanthropic organizations are common in this regard. Alternatively, not-for-profit entities (qualifying in the USA as a 501(c)3 organization) formed more specifically to foster APTs can serve as sponsors. The Quantum Leap Healthcare Collaborative sponsorship of I-SPY 2 and the Global Coalition for Adaptive Research sponsorship of GBM AGILE are two examples[27].

Box 5 | Response-adaptive randomization

Adaptive clinical trials (APTs) have typically included response-adaptive randomization (RAR). RAR is not essential to an APT, but is simply one type of 'within-trial' adaptation. Importantly, RAR does not confer advantages over fixed randomization in all situations, and, to perform properly, does require pretrial simulation. Inaccurate or slow accrual of patient outcome data can affect the performance of the RAR, and must therefore also be anticipated and modelled in pretrial simulation.

The figure provides an overview of a typical RAR scheme for an APT. This particular APT is testing three experimental agents (labelled 1–3) against control (C) care (for example, three novel experimental agents for a particular cancer compared with the chemotherapeutic agent commonly used to treat this specific cancer). Four snapshots represent the starting condition (snapshot #1) followed by interim updates (for example, after accrual of a pre-specified number of patients). The relative proportions of accruing patients per arm are represented in the upper portion of each snapshot. The height of each agent relative to control represents the estimate of benefit or harm relative to control, and the vertical line represents uncertainty (akin to error bars or confidence limits) around the estimate. In this example, the control group is kept constant, but an alternative approach is to set a minimum proportion. The central horizontal line represents equivalence to control care. The upper and lower lines represent the thresholds that must be cleared by the uncertainty bounds around an experimental agent to trigger graduation or closure. In this example, inferiority is set as an easier threshold to cross than superiority, but this decision is arbitrary. See REFS[43,44] for further detail.



There are also potential reasons for industry to sponsor APTs directly. One clear scenario would be if an industry sponsor had a multi-product pipeline for a given indication. Even in these rare instances, however, different products would probably have different development timetables. If the expected efficiencies of a platform are great enough, several sponsors may find value in forming a consortium to pool resources. Testing several combination strategies against a common therapeutic backbone may be a desirable research strategy in either a single-organization or a consortium model. One emerging example

Table 2 | **Key features of adaptive platform trials**

Feature or term	Description
Patient selection	
Enrichment	The process of using clinical or molecular biomarkers to create subtypes (also called subgroups) for whom interventions will be assigned differently. An APT may exclude a subtype from assignment or allow treatments to be assigned as part of a general or subtype-specific RAR rule as the trial progresses
Subtypes	Comprising patient or disease-specific strata, subtypes are mutually exclusive and exhaustive of the patient/biomarker space. As a patient can belong to only one subtype, it is the natural unit to allow randomization probabilities to vary
Strata	Single patient or disease-specific characteristics that can be used alone or in combination to define subtypes
Signatures	In contrast to subtypes, signatures are therapy-specific and define specific indications for which the therapy may be efficacious. Signatures may be defined by subtypes or combinations of subtypes
Study arms	
Domain	An area within which several interventions are compared
Intervention	A therapy or approach being tested by the APT
Common control arm	By comparing multiple experimental arms with a single 'common' control arm, the sample size is preserved in comparison with traditional 1:1 designs
Regimen	A particular combination of interventions (therapies) across domains
Within-trial adaptations	
RAR	A method by which accumulating data are used to change the assignment of additional patients. RAR is a randomized assignment, but the randomization weights are linked to estimates of treatment effect generated from previously enrolled patients via a pre-specified model. In this way, patients can be assigned to treatment arms that appear more promising based on accumulating evidence without interference by the investigators in real time. In addition to a common control arm, RAR can increase the overall efficiency of APTs and be an attractive feature for patients
Adaptive sample size/ perpetual enrolment	In a traditional RCT, sample-size calculations use treatment effect estimates based on limited data, with the risk of overestimation (leading to high risk of β-error) or underestimation (leading to unnecessary time, cost and patient exposure). In an APT, accumulating evidence can be used to re-estimate the optimal sample size and an experimental arm can leave the trial as soon as the data permit
Interim updates	Interim updates are the act of updating the APT model or parameter estimates with data accumulating within the trial
Integration	
Bayesian inference model	An overarching statistical model used to generate estimates for the true distributions of outcomes for different patient groups, given prior estimates and their observed outcomes in the APT. This model is typically used to drive both within-trial adaptations and termination decisions for parts of the trial, although frequentist statistical and machine learning reinforcement approaches have also been proposed
Multifactorial designs	Designs that seek to understand the marginal effects of multiple interventions, alone and in combination, overall and by subtype
Simulations	As APTs use data generated during the trial to alter their subsequent conduct in a pre-specified way, the results of any one APT are probabilistic and dependent on several parameters. Therefore, trial simulations are performed during the design phase to estimate the APT's operating characteristics. Input parameters such as the accrual rate, event rate, time to event and effect size are used to simulate how a trial might run. By repeating this exercise thousands of times, investigators are able to understand how many times an APT would lead to various results
Miscellaneous	
Longitudinal model	A response model that incorporates patient or disease measures to estimate therapeutic effect on an endpoint before the endpoint occurs. Longitudinal models are updated with information generated within an APT, can be used to increase overall efficiency of RAR and may generate data use to support surrogate endpoint development
Time machine	A statistical model used to estimate how a control arm has evolved over time. A time machine can add robustness to control estimates and improve the precision of therapeutic effect estimates from different trial eras
Embedding	Embedding refers to incorporating clinical trial elements into more routine clinical practice, perhaps leveraging the electronic health record. Embedding is a critical element of the transition to a learning health system
Documentation	
Master (core) protocol	A document containing the governing rules for the APT, such as patient eligibility, randomization rules, endpoints, the overarching statistical model and rules for study arm graduation. The protocol specifies all generic elements of the APT, rather than those related to a specific non-constant feature, such as a particular experimental arm or study region
Protocol appendices	The documents appended to the master protocol that specify any non-constant feature of the design, such as a particular domain, intervention or region

APT, adaptive platform trial; RAR, response-adaptive randomization; RCT, randomized controlled trial.

Box 6 | **Proposed design, documentation, oversight and reporting recommendations for adaptive platform trials**

Design

- Consider alternative choices within each of the five broad design areas for an adaptive platform trial (APT)
  - Patient selection and stratification
  - Organization of study arms
  - Within-trial adaptations
  - Integration of patient selection, study arms and adaptations
  - Miscellaneous considerations (for example, embedding into the electronic health record or use of 'time machine' for drift in usual care)
- Specify parameters to be varied in simulation
  - Underlying distributions of subtype frequencies
  - Event rates
  - Accrual rates
  - Size of relative and absolute treatment effects
  - Possible interactions between interventions, subtypes and other features (for example, time or region)
- Generate operating characteristics of different design choices across the range of simulations
  - Sample size, time to completion and probabilities of designation as success or failure for different true assumptions by signature
- Engage in an iterative design build with close communication between clinical experts, patient advocates, regulators, drug/assay and/or device companies, funders and biostatisticians

Documentation

- Trial registration
  - Update with each amendment or material change to the randomization scheme or study conduct
- Study protocol
  - Use modular format
  - Summarize all generic elements in a master protocol
  - Organize each individual experiment or trial alteration as a separate appendix
- Statistical analysis plan (SAP)
  - Include detailed summary of alternative design choices, simulation parameters and resultant performance characteristics of the different design choices across the different simulated trajectories

Oversight

- Regulatory review
  - Use a modular format to separately review the master protocol and SAP from individual appendices
  - Provide documentation of the design process (along with software and coding for model, algorithms and simulations)
- Ethical review
  - Use a modular format to ensure separate review and explanation of design issues from risks and benefits of individual interventions
  - Use a centralized institutional review board
- Data safety and monitoring plan
  - Ensure the Data Safety and Monitoring Board (DSMB) is adequately experienced or instructed to understand critical design features and appropriately oversee updating rules
  - Ensure appropriate firewalls between the trial steering committee, the biostatistical team responsible for updating rules and biostatistical support to the DSMB

Reporting results

- Report results of parts of APT when they trigger formal stopping rules
  - Include detailed accounting of the number of patients screened, enrolled, randomized to the reported experiment and randomized to other parts of the APT
  - Report baseline characteristics of patients enrolled in the experimental components that are being reported
  - Report safety data on these patients
  - If primary efficacy results are from an overarching model, provide details of the model methods as well as the results from the model
  - Consider also including 'raw' results from those patients presented in the report as a sensitivity analysis if the rest of the APT is not considered to be jeopardized by such reporting
- Consider reporting the entire APT results periodically (for example, before introduction of major new appendix/amendment)

is the immuno-oncology space, where the number of trials being opened probably outstrips the capacity for patient enrolment. An APT may be a solution where several therapeutic approaches can be studied in a way that minimizes the overall risk of low and/or insufficient accrual if many trials are conducted in parallel. Finally, academic institutions, contract research organizations and government-sponsored cooperative groups[28] may all be possible sponsors for APTs.

Financing APTs

APTs do not lend themselves to traditional funding models. National Institutes of Health grants, for example, typically require known trial sizes and timelines to calculate and distribute budgets. A trial design intended to enrol perpetually, with an unclear — and theoretically unbounded — number of enrollees, does not fit this paradigm. Similarly, APTs that test multiple experimental interventions must overcome the financial and legal hurdles that arise when approaching multiple pharmaceutical companies to participate in a single trial. In this scenario, the APT sponsor would interact with industry by offering various financial terms to participate in the trial. For smaller trials without registration potential, this might take the form of investigator-initiated studies through the usual channels. For larger trials with potential for registration, more significant financing is required. This may take the form of a fee-for-service arrangement whereby industry partners pay a per-patient or per-arm cost to participate (a form of 'pay-to-play'). I-SPY 2 was initially funded through federal support and donations, but has now evolved to a pay-to-play model. REMAP-CAP has thus far focused on comparative effectiveness questions and is funded by government grants from multiple countries. GBM AGILE is funded via donations and a pay-to-play model.

Other innovative financing models and new types of clinical research arrangement with different risk-sharing options are possible as well. For example, the APT sponsor may raise additional funding to subsidize or entirely finance an experimental arm in exchange for a licensing or royalty agreement should the experimental arm prove to represent a commercial therapeutic. Through common screening procedures, shared control arms, a perpetual infrastructure that accelerates the time to first patient enrolled and other innovations, non-profit disease-specific APTs may incentivize industry entrants into a disease area by reducing the cost and time for development.

Additionally, as an ongoing platform, the APT could itself be seen as a financial entity whose worth relates to its capacity to generate new knowledge about a particular disease or group of patients and do so efficiently. This creates value in addition to the traditional learning that occurs through

studying the therapy considered in each individual arm of the trial. As an integrated vehicle for assessing multiple interventions, a platform may be a safer investment instrument than the owners of any single product being tested by the APT[29,30]. Platforms can generate data and insights that could be valuable for both academic and industry researchers as well as other parties in the health-care system such as payers[31].

Selecting an APT versus an RCT design

There will be many instances where APTs do not offer adequate net benefit over traditional designs. For example, if only two approaches are being compared, there is often no advantage to RAR[32]. Similarly, if a trial must begin immediately, there may not be enough time for the pretrial steps required for an APT. Given the need for thoughtful protocol design and time-intensive planning before implementation of an APT, knowing when to consider use of an APT study design, rather than a traditional RCT design, is pivotal. With their ability to evaluate multiple interventions concurrently as well as sequentially, use of an APT for such studies, whether the multiple therapies are experimental, usual care or a combination of the two, is often desirable. In addition, once an APT is implemented, its study design permits the rapid addition of new interventions of interest to the existing domains as well as the incorporation of new domains of interest. Likewise, as the RAR rules typical of APTs permit the shifting of randomization allocations towards those intervention arms demonstrating superiority through interim data updates, thereby achieving statistical significance with fewer patients, APTs may be particularly beneficial in studies with limited patient populations either due to the rarity of the underlying disease/condition or due to the restrictions of the study's inclusion/exclusion criteria.

In contrast, those studies desiring completion of patient enrolment within an abbreviated timeframe (that is, only a few weeks) may not experience the full benefit of an APT, not only due to the shortened study duration during which insufficient time exists for successive interim data updates to provide insight but also due to the significant up-front planning and expense associated with this kind of study.

Conclusion and recommendations

Two rising movements in medicine — patient-centred precision medicine and the learning health system[33] — will probably drive continued interest in, and adoption of, APTs. APTs are purpose-built to efficiently test multiple interventions in multiple disease subtypes, a key thrust of precision medicine. The APTs' perpetual nature, with use of features such as RAR, also provides a strategy for continuous quality improvement with respect to the comparative effectiveness (and adoption of) existing interventions, a key thrust of the learning health system.

Although still early in their evolution, APTs are already encountering a set of common issues as they are designed and implemented. This initial effort summarizes some of these design, conduct, oversight and reporting issues and offers preliminary recommendations (BOX 6). Nonetheless, we anticipate a need for considerably more effort in this area, both to speed adoption of APTs across all applicable areas of medicine and to promote an emerging best practice for APT deployment.

The Adaptive Platform Trials Coalition

A list of participants and their affiliations appears at the end of the article.

https://doi.org/10.1038/s41573-019-0034-3

Published online: 28 August 2019

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Acknowledgements
The authors are grateful to the Harvard/Massachusetts Institute of Technology (MIT) Center for Regulatory Science for hosting the meeting, and to the Harvard/MIT Center for Regulatory Science, the University of Pittsburgh, the PREPARE consortium, REMAP-CAP and Berry Consultants for financial support towards travel, lodging and expenses. They thank C. D'Avanzo, L. Dilworth, L. Maliszewski (Harvard University), R. Rice (University of Pittsburgh) and J. Clenell (Berry Consultants) for organizational and administrative support and J. Vates (University of Pittsburgh) for detailed review and editing.

Competing interests
B.M.A. reports employment at Foundation Medicine, Inc.; personal fees from Bristol-Myers Squibb, Schlesinger Associates and Precision Health Economics; and unpaid leadership as president and CEO of the Global Coalition for Adaptive Research, a non-profit research organization. S. Berry reports being a part owner of Berry Consultants, LLC (a company that designs and implements platform and adaptive clinical trials for pharmaceutical companies, medical device companies, National Institutes of Health cooperative groups, international consortia and non-profit organizations) and providing consulting for platform trials. M. Buxton, M. Paoloni and K. Viele are currently employees of Berry Consultants, LLC. R. Lewis is a senior medical scientist at Berry Consultants, LLC. D. A. Berry is a co-owner of Berry Consultants, LLC. B. Hyman has current research support from AbbVie, Amgen, Denali, Fidelity Biosciences, Eli Lilly, Merck and co. and Arvinas; serves as a consultant for Biogen, Ceregeen, Genentech, Roche, Eli Lilly, Neurophage, Novartis, Takeda and Sunovian; and owns stock in, as well as having a family member who works for, Novartis. M. Krams is an employee of Johnson & Johnson. A.W. Lo has personal investments in biotechnology companies, biotech venture capital funds and mutual funds; serves as an adviser to BridgeBio Capital; is director of Roivant Sciences Ltd. and chairman emeritus and senior adviser to AlphaSimplex Group; has during the past 6 years received speaking/consulting fees or honoraria from AIG, AlphaSimplex Group, BIS, BridgeBio Capital, Citigroup, Chicago Mercantile Exchange, Financial Times, Harvard University, IMF, National Bank of Belgium, Q Group, Roivant Sciences, Scotia Bank, State Street Bank, University of Chicago and Yale University; and is a director of the Massachusetts Institute of Technology Whitehead Institute for Biomedical Research and a member of the Board of Overseers of Beth Israel Deaconess Medical Center. C. Ritchie provides consultancy and/or receives grant funding from Actinogen, Allergan, Biogen, Eisai, Alector, Janssen, MSD, Lundbeck, Prana Biotechnology, AbbVie, Roche, Eli Lilly and Pfizer. B. Spellberg in the last 12 months consulted for Bayer, Forge, Shionogi, Alexion, Synthetic Biologics, Paratek, TheoremDx, Bioversys and Acurx; and owns equity in Motif, BioAIM, Synthetic Biologics, Mycomed and ExBaq. M. Trusheim is owner of Co-Bio Consulting LLC, which provides services to biomedical companies, and has received speaking fees over the past 6 years from Cowen Group, Merck & Co. and Shire. P. Y. Wen reports receiving research support from Eli Lilly, Puma and Celgene and serving on advisory boards for Eli Lilly and Puma. The remaining authors declare no competing interests.

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Supplementary information
Supplementary information is available for this paper at https://doi.org/10.1038/s41573-019-0034-3.

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[1]University of Pittsburgh School of Medicine, Pittsburgh, PA, USA. [2]Harvard Medical School, Boston, MA, USA. [3]Berry Consultants, Austin, TX, USA. [4]Berry Consultants, San Francisco, CA, USA. [5]University of California Los Angeles, Los Angeles, CA, USA. [6]Monash University, Melbourne, Australia. [7]Massachusetts General Hospital, Boston, MA, USA. [8]Arizona State University, Tempe, AZ, USA. [9]Anderson Cancer Center, Houston, TX, USA. [10]University Medical Center of Utrecht, Utrecht, Netherlands. [11]Veterans' Affairs Boston Healthcare System, Boston, MA, USA. [12]University of Oxford, Oxford, UK. [13]University of California San Francisco, San Francisco, CA, USA. [14]Boston University, Boston, MA, USA. [15]Dana-Farber Cancer Institute, Boston, MA, USA. [16]Harvard University, Cambridge, MA, USA. [17]Multiple Myeloma Research Foundation, Harvard Business School, Cambridge, MA, USA. [18]University of Antwerp, Antwerp, Belgium. [19]Johnson and Johnson Pharmaceuticals, New Brunswick, NJ, USA. [20]Massachusetts Institute of Technology, Cambridge, MA, USA. [21]The US Food and Drug Administration, Washington, USA. [22]Stanford University, Palo Alto, CA, USA. [23]Carnegie Mellon University, Pittsburgh, PA, USA. [24]Pancreatic Cancer Action Network, Dallas, TX, USA. [25]Auckland District Health Board, Auckland, New Zealand. [26]Harvard School of Public Health, Boston, MA, USA. [27]Gemini Group, Ann Arbor, MI, USA. [28]Duke University, Durham, NC, USA. [29]University of Edinburgh, Edinburgh, UK. [30]ICNARC, London, UK. [31]New York University, New York, NY, USA. [32]IQVIA, Durham, NC, USA. [33]University of Southern California, Los Angeles, CA, USA. [34]Harvard Business School, Cambridge, MA, USA. *e-mail: angusdc@upmc.edu; Brian_Alexander@dfci.harvard.edu