As currently designed and conducted, randomised controlled trials rarely address the complexity of patient characteristics that need to be taken into account when making clinical decisions in primary care. We introduce the concept of a response-adaptive platform trial design, as this approach may be better suited to answering patient-centred primary care research questions.

LIMITATIONS OF TRADITIONAL TRIAL DESIGNS IN INFORMING DECISION MAKING IN PRIMARY CARE

The primary question addressed by a traditional clinical trial is whether a treatment is beneficial in the average patient. However, the question that trials should ideally provide would instead answer the question:

“What is the best treatment for each individual patient, given all of their characteristics that could influence the effectiveness, or otherwise, of the treatment?”

Although sub-group analyses are often performed in traditional trials to determine if the treatment effect is associated with certain patient or disease characteristics (for example, comorbidities, age, or illness severity), these analyses are typically post-hoc, underpowered, and usually consider only one patient characteristic at a time. Thus we might learn something about the influence of age in general on the outcome of treatment from sub-group analysis of a traditional trial, but not about the influence of age, illness severity, and symptom duration combined. Furthermore, participants in traditional clinical trials are often selected to be homogeneous in terms of their illness and to be free of comorbid conditions and any concomitant medications that might complicate the assessment of the effect of a treatment. This leads to a lack of applicability of trial findings to many complex primary care patients.

Most registration trials (those intended to support regulatory approvals of new medications) also fail to address important comparative effectiveness questions such as which therapy or combination of therapies may be the most or least effective, or which therapy, out of all of the available therapies, has the best compliance or tolerability. The traditional randomised trial is also typically limited in the number of comparisons: they include only one, or at most, a few comparator arms. Many registration trials are sponsored by industry, and so there is little incentive to pit a new therapy against a competitor’s, or to investigate a new therapy in combination with an existing competitor’s therapy. These considerations often result in a series of standalone trials, perhaps with comparison with placebos or other controls that are not used in routine clinical practice.

THE PLATFORM TRIAL

A platform trial is essentially a lasting trial infrastructure that operates under a master protocol. This allows for interventions to be added in, or dropped, as data for effectiveness, or futility, meet pre-specified thresholds of precision. Platform trials are well established in oncology, where there may be a large number of promising early-phase interventions suitable for evaluation at any one time; where the disease is heterogeneous and patients with a wide range of characteristics can benefit from having treatment tailored to their specific disease sub-type; and where new candidate interventions may soon become available for clinical evaluation. Moreover, this process is intended and designed to be ongoing. Patients are randomised to a common control arm or to one of multiple treatment arms. Analyses are conducted frequently during patient accrual, in an ongoing manner, rather than when a pre-specified sample size has been reached and all follow-up is complete. Arms may graduate by achieving a pre-specified level of access either overall or in predefined sub-groups. Conversely, treatment arms can be dropped if shown to lack effectiveness during the trial. Furthermore, as new therapies become available, these can be added without interrupting the trial. The latter possibility is usually governed by a trial steering committee.

RESPONSE-ADAPTIVE RANDOMISATION

Response-adaptive randomisation is a strategy in which the proportion of participants randomised to each arm are periodically updated during a trial, usually to favour the better-performing arms. This approach has been shown to be more efficient than equal or fixed randomisation between arms in estimating the efficacy of the best-performing treatment when there are three or more treatment arms.

Because platform trials are dynamic learning environments, planning and set-up are more complex and usually take longer than a simple two-armed trial. There is not a single sample size calculation. Instead, the performance of the platform trial design is assessed using intensive computer simulations that enable the trialists to understand the trial’s operating characteristics, such as the expected sample size, the proportion of patients likely to be randomised to each intervention, under what circumstances this might change, intervention is erroneously identified as beneficial, or erroneously dropped for being apparently ineffectual. With consideration of the operating characteristics, the proposed trial’s rules can be tuned and the simulations re-run until the design behaves optimally. For example, if truly effective therapies are too commonly being dropped from the theoretical study in the simulations, the first interim analysis may be planned for too early on in the trial, before sufficient patients have been enrolled. By delaying plans for the first interim analysis, there may be less natural variability, and the likelihood of dropping a desirable therapy decreases.

As platform trials may also enrol a heterogeneous group of patients, the adaptive randomisation algorithm can take a patient’s predictive or prognostic factors into account as well. This means that participants within a trial can be preferentially randomised to the therapies that may perform better for them, rather than the treatment that is performing better in the trial, on average. For example, it may be that younger patients receive a greater benefit from a particular therapy than older patients. As this becomes clear during the trial, younger patients could be preferentially randomised to one treatment while older patients are preferentially randomised to another. Such characteristics of interest that may modify treatment effects are pre-specified in advance to ensure questions of treatment benefit in these sub-groups are prospectively answered in adequately powered analyses. Hence adaptive randomisation with the consideration of patient characteristics allows trials to explore a more complex space of therapeutic benefit than traditional designs, and will help directly answer the questions about which therapy is best for patients with particular characteristics.
The nature of certain primary care research questions seems well suited to this design, especially when relevant risk factors and circumstances are constantly changing, for example, in studies of acute infections where clinical outcomes are often available in the short term and where levels of antimicrobial sensitivity and resistance mechanisms in common infectious agents are constantly changing. Such a dynamic situation requires that evaluation of existing and new interventions, or their combination, are of necessity an ongoing project.

We have been unable to identify published trials from primary care that have used this approach, though one recent example uses data from a historical trial and shows that it would have been more efficient had it been designed as an adaptive trial.

Thus, in response-adaptive platform trials:

- multiple treatment arms can be included simultaneously — patients are randomised to a common control arm, or to one of multiple treatment arms;
- as new therapies become available, these can be added without interrupting the trial;
- analyses are conducted as data accumulate, rather than simply when a pre-specified sample size has been reached and all follow-up is complete — treatment arms can be dropped if shown to be ineffective;
- as signals emerge for effectiveness, or otherwise, of an intervention, the proportion of patients randomised to that arm may be altered, thus increasing the chances of trial participants receiving the best treatment within the trial; and
- sub-groups of interest are pre-specified and the dynamic nature of the trial can ensure that there is enough power to determine effectiveness or otherwise for patients each with a range of pre-specified characteristics (for example, children with more acute onset or more severe illness).

**IMPLICATIONS FOR GENERATING EVIDENCE TO SUPPORT THE PATIENT-CENTRED CLINICAL METHOD**

As people live longer, often with a greater number of acute and chronic health and social care needs, primary care clinicians face unprecedented challenges in delivering evidence-based, effective, and personalised care to the diverse community they serve. Adaptive platform trials are naturally suited for addressing patient heterogeneity in treatment response, and for simultaneously comparing outcomes from a wide range of interventions (including combinations) using the same measures. This method of evaluation therefore resonates with the realities of making clinical decisions in primary care, where patients are usually complex and clinicians often say that traditional trial results are all well and good, but their patients are often not like those in the trials. It matches the clinical reality of clinicians building on their experience of individual patient complexity, context, their experience of a wide range of interventions they and the colleagues in their networks have tried, and scientific data to identify the one (or combination of treatments) that seems to work best for the particular patient in front of them.

Furthermore, this research process resonates with the philosophy of primary care, which is to use all available multisource data as soon as they become available, to ensure that a particular individual receives the intervention that is the best possible for them given their particular relevant characteristics, including even, or especially, when they volunteer for a clinical trial.

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**COMPETING INTERESTS**

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