Thank you.

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| Host department:Oxford |
| Project Title: |
| Consideration of using non-concurrent controls and time trends in adaptive platform trials: The what, the why and the how |
| Proposed supervisory team  |
| Ly-Mee YuOther members of the supervisory team Jane Holmes, Chris Butler |
| Potential for cross consortium networking and educational opportunities: |
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| Project description: |
| During the COVID-19 pandemic, the impetus to find potentially effective interventions as quickly as possible has driven an increased interest in adaptive design trials. Platform designs, in particular, have many attractive features and are more efficient compared to traditional two-arm parallel randomised clinical trials (RCTs). The trial design has the flexibility to allow additional interventions to be added in, or to replace existing interventions according to pre-specified criteria. It also allows simultaneous comparison of multiple potential invention groups against a single control. (Berry, Connor and Lewis, 2015).This has the potential to increase efficiency in terms of the numbers of participants recruited and the time to reach conclusions about efficacy and futility. An additional advantage lies in the opportunity to further reduce sample size by including non-concurrent controls in the analysis. This means that participants who are randomised to the control group before a treatment arm is active can contribute to the analysis of that treatment. However, there are divided opinions on when and how these controls should be included due to the potential negative effects of doing so under the occurrence of time trends. This is more likely to be an issue for trials that take a long time to complete (e.g. cancer trials such as I-SPY (Barker *et al* (2009), and STAMPEDE (Sydes *et al* (2012)) or ones that are conducted in a rapidly changing environment such as a pandemic. Time trends may affect all treatments and control equally, but there may also be a different drift in different arms. This could be due perhaps to an interaction with baseline characteristics and the recruited population changing over time. Several papers have discussed this in the specific context of platform trials including work by Lee and Wason (2020), Bofill Roig *et al* (2022) and Saville *et al* (2022). The issue of time trends has also been discussed in the adaptive randomisation literature, for example Villar *et al* (2018) who look at the implications for rare diseases. However, the different methods have not been directly compared nor is it clear which method to use in which situation. Lee and Wason (2020) performed simulations to explore the benefits and disadvantages of using non-concurrently randomised controls when either a linear or a step trend was present in the data. They found that including non-concurrent controls increases power if there is no time trend and that the advantages are greater when a new treatment is added at a later time point. They also found there is a greater risk of bias in the presence of a step trend as compared to a linear trend and when the trend is non-linear that adjusting for a linear trend may lead to spurious findings. They conclude that if strict control of the type 1 error is necessary then non-concurrent controls should not be included. Saville *et al* (2022) assumes the trend follows the same pattern across all arms and models the time course of the control arm using hierarchical models to smooth the trend across time intervals. They use simulations with binary data and find that adjusting for time increases power and precision. Bofill Roig et al (2022) compare model-based methods for binary and continuous data for trends that are equal across arms, differ by arms, and where it is not additive on the scale of the model. They suggest that other methods, such as dynamic models that include historical data, could also be explored and conclude that whether to include non-concurrent controls should be on a case by case basis.This leads to the conclusion that no one size fits all. Different methods may be appropriate in different scenarios. Is the extra effort of using hierarchical models worth it for scenarios where it can be assumed that the time trend is the same in all treatment arms, and how does this method cope with a step change? Other than the methods described here, are there any other methods that could perform better, such as those used to include historical data? Are there any instances where the methods perform so badly that only concurrent controls should be included? How often and how large a trend are we likely to see in practice? What are the implications for the design of such a trial? All these are questions which are currently unanswered.The aims of the project are 1. to understand how the time trend and non-concurrent controls have been incorporated in platform trials
2. to determine how different models are used to handle different types of time trends occurring in different types of trial design
3. to compare the performance of these models when incorporating non-concurrent controls in the presence of time drift and to explore methods that have been used to incorporate historical data
4. to develop a guidance document and open source code using the results from objectives 1, 2 and 3 above
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| Indicative project costs:  |
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| Training and development provision by host: |
| *Formal training:*  |
| *Informal training:*  |
| *PPIE*:  |