# Title of Project

# A Practical Adaptive Designs Toolkit

## 1 Abstract

***Background***

Adaptive designs (ADs) can help improve trial efficiency. However, the lack of practical knowledge in ADs among diverse clinical trials stakeholders is hampering their routine use, although it is steadily increasing. We developed an online, open-access, comprehensive, flexible, and practical educational toolkit on ADs for a broad audience including non-statisticians.

***Methods***

We iteratively developed practical educational material covering several different topics relating to ADs. This was informed by prior work and diverse practical knowledge and experience of the project team in ADs and non-adaptive trial designs. The **P**ractical **A**daptive and **N**ovel **D**esigns & **A**nalysis (PANDA) toolkit was developed using "Ruby on Rails" with a React frontend and is hosted on the University of Sheffield servers. We sought feedback from potential users on the toolkit design, webpage content and structure throughout the project. Further feedback will also be collected from users after launch to continuously improve the toolkit.

***Results***

The PANDA toolkit is accessible via: https://panda.shef.ac.uk/. PANDA allows self-paced practical learning that is easily accessible to anyone involved in clinical trials research. PANDA users can learn remotely about ADs at a time that suits them, and easily find content relevant to them at different stages of a trial with the aid of the search function. Feedback on PANDA can be provided via panda.team@sheffield.ac.uk.

***Conclusions***

The PANDA toolkit, though developed in the UK, is a globally accessible resource that will evolve in response to research needs and feedback from users. We hope it will be a vital educational resource to help improve practical knowledge and appropriate uptake of adaptive trials for years to come.

# 2 Introduction

There is a need to streamline the conduct of randomised trials to address research questions as efficiently as possible. Lessons from the COVID-19 pandemic reinforce this. Adaptive designs (ADs) can improve efficiency by adding controlled flexibilities to the design and conduct of the trial. Planned changes can be made to certain aspects of the trial (e.g., increasing the initial sample size, dropping treatment arms, or stopping the trial early) based on accruing outcome data while the trial is ongoing. ADs are increasingly being used (1–3) or at least considered at the design stage(4). However, they are not routinely used in practice as they should be. The lack of practical education and experience, especially among researchers, is one of the leading obstacles hampering the uptake of ADs (1,5,6).

Recent initiatives to address the skills and knowledge gap in ADs include research fellowships (e.g., (7,8) and NIHR-SRF-2015-08-001), reporting guidance (9,10), and the development of software resources (11,12), educational publications (13,14), and outreach activities to support UK Clinical Trials Units (CTUs), many of which were led by the MRC-NIHR Trials Methodology Research Partnership (TMRP) Adaptive Designs Working Group (ADWG). However, a few courses focused on practical issues in ADs were available, some of which were expensive, infrequently offered and focused on statistical audiences. Therefore, accessible education resources that include practical guidance and software recommendations, and can readily be updated, are needed to improve practical knowledge and AD use (1), especially among diverse stakeholders in clinical trials research (e.g., trialists, clinicians, statisticians, funders, and ethics committees).

Therefore, we developed an online, open-access, comprehensive, flexible, and practical educational toolkit on ADs for a broad audience including statisticians, clinicians, grant development support staff, proposal developers, trial managers, trialists, and data managers. We primarily focused on ADs in randomised trials, with a view to extend to other trial types in the future.

# 3 Methods

## 3.1 Design of the PANDA toolkit

The **P**ractical **A**daptive and **N**ovel **D**esigns & **A**nalysis (PANDA) toolkit is hosted on the University of Sheffield (UoS) servers and was developed in collaboration with a UoS

software development company (epiGenesys) using "Ruby on Rails" with a React frontend. Ethics approval (ref: 012041) was granted by the Research Ethics Committee of the School of Health and Related Research (ScHARR) at the UoS.

The project team brainstormed the structure of the online toolkit via face-to-face and online meetings and email correspondence. The guiding principles were:

- ease of content navigation,
- ease of use by content managers,
- flexibility to expand content and add new functionalities,
- the need for diverse stakeholders to quickly access content relevant to them and,
- ease of linkage to other external resources.

We had extensive discussions with software developers who advised on several aspects such as mapping information flow based on their experience of developing similar platforms.

## 3.2 Development of content

The project team members had diverse practical knowledge and experience in ADs and non-adaptive trial designs. The educational needs were informed by experiences of the project team, prior work on barriers and facilitators to the use of ADs (7), and qualitative feedback from surveys of multidisciplinary stakeholders during the Adaptive designs CONSORT Extension (ACE) project (15). We brainstormed the scope and breadth of content that should be covered with a more practical focus through face-to-face and online meetings and email correspondence. Educational content was drafted and reviewed iteratively by the project team.

Initially, we focused on five types of ADs: sample size re-estimation, group sequential, multi-arm multi-stage, adaptive population enrichment, and response adaptive randomisation. Additional areas to be covered across all types of ADs included:

1. what is an AD, the goals of different types of ADs, research questions or goals they can help address, and when they are appropriate;
2. potential benefits and limitations of ADs;
3. case studies and examples showing the thought process, how to design, communicate, monitor, and analyse different adaptive trials;
4. general considerations at the design, conduct, analysis, and reporting stages;
5. communicating ADs to key stakeholders;

6. practical guidance (e.g., on costing adaptive trials; writing trial protocols and statistical analysis plans; and reporting);
7. measures to minimise operational and statistical bias in an adaptive trial;
8. statistical methods underpinning different ADs;
9. how to include health economics analysis in trials using an AD;
10. available statistical software to help with the design, monitoring, and analysis.

## 3.3 How feedback was sought and how it influenced the development process

Formal and informal feedback was gathered throughout the development process of the portal and content. Also, a functionality in the toolkit allows users to provide feedback via a project team email (panda.team@sheffield.ac.uk).

In May 2020, we tested six colour themes and layouts of the toolkit landing page to gauge preference among potential users within the Design, Trials and Statistics (DTS) section of ScHARR (UoS) and the project team. Based on feedback from 31 responders, the most preferred colour theme and layout of the landing page was chosen.

On 11 June 2020, we organised a webinar session at the NIHR Statistics Conference on "*Making adaptive designs more accessible*" and presented PANDA to gather feedback from statisticians and clinicians. A demo version with selected draft content was released to registered attendees three days before the webinar to give them enough time to explore the toolkit. We asked them to complete a short survey on their satisfaction with the landing page colour scheme, content structure, how content was accessed from the landing page, and the ease of navigation within the toolkit. We also asked them about the usefulness of the content from the perspective of a user learning about ADs and sought any feedback they had.

Feedback was very positive during the webinar discussions and some suggestions were made including a wish list of aspects that could be incorporated in the future. Twenty-one responded to the survey after the webinar. Most responders were either satisfied or very satisfied with the structure of content [17 (81.0%)], the way to access content from the landing page [16 (76.2%)], and colour themes of the landing page [17 (81.0%)] - with the remainder being fine with each of these. Nineteen (90.5%) found it moderately easy or very easy to navigate within the toolkit and only one had moderate difficulty. Ten (47.6%), 9 (42.9%), and 2 (9.2%) found draft material extremely, very, or somewhat helpful for someone learning about ADs, respectively. Notably, this was only based on draft material

covering general considerations and multi-arm multi-stage ADs. The demo version was disseminated via Twitter and improvements were made to the toolkit based on qualitative feedback received during and after this webinar. It was also presented to diverse stakeholders at the NIHR virtual symposium on "*Delivering Complex and Innovative Design (CID) Studies*".

Targeted users from the Sheffield CTRU (e.g., statisticians, data managers, and trial managers) were asked to review content relevant to them and provide feedback. We also sought feedback from five purposively selected registered CTUs that were felt to represent those that could benefit the most and project team members had connections with. The opportunity to provide feedback will be given to all CTUs once the final toolkit is launched. The gathering of feedback to improve content quality is a process that will continue beyond the toolkit going live.

# 4 Results and Conclusion

The developed online PANDA toolkit is accessible via: https://panda.shef.ac.uk/. This toolkit allows self-paced practical learning that is easily accessible to anyone involved in clinical trials research. Users can learn remotely about ADs at a time that suits them, and they can easily find content relevant to them at different stages of a trial. The search tool also facilitates ease of access to relevant content.

To ensure long-term sustainability, PANDA can be updated to include new and emerging content (e.g., new types of ADs, trial examples, new software). Although the original scope was on adaptive randomised trials, the toolkit can be easily expanded to cover non-randomised early phase ADs in the future. In addition, the current content can be updated to remain relevant as research evolves. Statistical code to illustrate the design and analysis is embedded within the toolkit or linked from other resources. The intention is for the toolkit to be a "one-stop shop" repository hosting essential resources on ADs with a practical flavour from other related work; for example, recently developed guidances on reporting (9,10) and costing of adaptive trials (NIHR130351), statistical software, statistical analysis plans, health economics evaluation aspects (DRF-2015-08-013), and protocols. Users can contribute to the toolkit content in several ways in a moderated manner by the project team. For example, they can share their positive and negative practical experiences on design and running an adaptive trial through an internal blog for other users to learn from or suggest material that should be

included. The toolkit records anonymised usage information that can be used to monitor areas frequently accessed and help improve content.

The PANDA toolkit, though developed in the UK, is a globally accessible resource that will evolve in response to research needs and feedback from users. We hope it will be a vital educational resource to help improve practical knowledge and appropriate uptake of adaptive trials for years to come.

# 5 Dissemination

The PANDA toolkit is open access and accessible via https://panda.shef.ac.uk/. We will actively promote the toolkit through several approaches and platforms such as via:

- a series of webinars organised by the research team,
- contributed webinars/workshops at national and international clinical trials conferences,
- social media platforms such as Twitter,
- targeted newsletters such as the MRC-NIHR TMRP,
- the UK CRC network of registered CTUs,
- the MRC-NIHR TMRP ADWG,
- established international contacts from previous related projects.

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The following project team members contributed to the grant application, the design of the portal, and the development of toolkit content throughout the project:

**Dr Munya Dimairo**; *Research Fellow in Medical Statistics, CTRU, ScHARR, University of Sheffield.*
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**Dr Graham Wheeler**; *Senior Lecturer and Deputy Head of Statistics, Imperial Clinical Trials Unit, Imperial College London (previously Senior Statistician, CRUK & UCL Cancer Trials Centre, UCL).*

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# 8 Appendices

None.

# 9 Conflict of interest declaration

No conflict of interest to declare.