MRC Network of Hubs for Trials Methodology Research: Final Report

Reference: N85

Title: Guidance to optimise pilot study design and conduct: A joint HTMR and NIHR HTA 'Research on Research' proposal

Actual cost: £24,510

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1. Background and rationale

Internal and external pilot studies are recognised to be methodologically different. An external pilot/feasibility study is widely accepted to be a standalone piece of work done to explore the feasibility of performing a definitive randomised controlled trial. Outcome data from an external pilot is, therefore, not routinely combined with outcome data from the future definitive trial, owing typically to substantial changes to the definitive study design and conduct following the external pilot. An internal pilot, however, is designed and conducted as the first phase of a randomised controlled trial, and outcome data from this preliminary phase will always be included in the main analysis, should the trial progress beyond the internal pilot phase. However, in which circumstances to choose one design over the other is not clear or well understood.

For studies with an internal pilot phase, little is also known about the selection and reporting of key 'progression criteria' (sometimes referred to as 'decision' or 'stop/go' criteria) that are typically used to evaluate the viability of proceeding to a main trial (1, 2). Progression criteria are typically set around key areas of uncertainty or risk relating to the viability of the main trial, such as trial recruitment, protocol adherence and outcome data (1). However, a structured literature review found that there is considerable variation in the selection and application of progression criteria and a lack of detailed reporting around decision-making processes for stopping, amending or proceeding to a main trial (1). Ideally, progression criteria are agreed and progress against them reviewed by the trial team and trial steering committee, jointly with the funding body. Little is known, however, about how decisions to proceed, amend or abandon the main trial are made in practice.

This proposal aimed to address these two key unanswered questions in the field: when to do an internal or external pilot, and; how to apply progression criteria for internal pilots. We undertook an analysis of protocols of NIHR HTA funded RCTs with an internal pilot to consider decision-making around progression criteria. In parallel, we conducted in-depth qualitative interviews to explore the understanding, views and practices of funding body representatives involved in funding applications for pilot/feasibility studies for RCTs and reviewing and implementing progression criteria for main trials with an internal pilot phase. In combination, these two pieces of work informed the organisation and content of a one-day workshop, bringing together key stakeholders to discuss and debate the challenges surrounding the design and conduct of internal and external pilot studies.

References
1. Avery KN, Williamson PR, Gamble C, O'Connell Francischetto E, Metcalfe C, Davidson P, et al. Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. BMJ open. 2017;7(2):e013537.
2. NIHR. http://www.invo.org.uk/posttypejargon/pilot-studies/

2. Aim

To provide clear guidance for trialists to inform the selection and design of pilot work prior to a definitive main study assessing the effect of an intervention, and to provide guidance for selection of progression criteria in RCTs with an internal pilot design.

3. Objectives

a) To review the decision-making process regarding progression to a full trial from an internal pilot study in HTA funded trials;
b) To explore and understand the practices and views of funding body panel representatives, regarding; i) funding different types of pilot and feasibility work and; ii) the process of selecting, reviewing and implementing progression criteria to inform main trials with an internal pilot phase;
c) To conduct a one-day workshop, bringing together key stakeholders to discuss the challenges and limitations around designing and conducting internal and external pilot studies, and formulate solutions for improving future research practice;
d) To submit a peer-reviewed publication, detailing the results of this work, with emphasis on guiding the choice of pilot study design and improving future funding practices for pilot and feasibility studies.

NB: The original objectives proposed a 2-day workshop with an overnight stay for delegates. This was not deemed necessary to complete the objectives of this study and accounts for most of the underspend on the initial budget (final budget submitted previously).

4. Summary of project achievements

a) **Analysis of protocols of funded trials** (Rosala-Hallas, Trials 2019)**:** an analysis was performed of a cohort of 57 protocols of clinical trials with an internal pilot, funded by the NIHR HTA programme in 2017 (*objective 3a: work performed by Anna Rosala-Hallas, Carrol Gamble, Jane Blazeby, Paula Williamson*). Progression criteria included: target number for recruitment, rate

of randomisation, retention/primary outcome ascertainment rate, rate of treatment adherence and consent rate. All but one study was permitted to continue to the main trial despite 25% of studies not meeting their outlined progression criteria. Changes were made to the design of the main trial for 25% of studies, mainly in terms of addressing challenges to recruitment. This work illustrated that, while progression criteria are sometimes not met in full, funding committees involved in the reviewing process will generally support continuation to the main trial, usually accompanied by a second review or close monitoring.

b) **Qualitative work:** in-depth interviews were conducted to explore the views and perceptions of 19 funding body panel representatives towards funding pilot work (*objective 3b: work performed by Katherine Fairhurst, Kerry Avery, Alicia O'Cathain, Pat Hoddinott, Jane Blazeby*). Purposive sampling identified participants from UK funding panels including NIHR (HTA/RfPB/EME/PGfAR) CRUK, CSO and ARUK. Maximum variation sampling ensured inclusion of multiple characteristics, including chair/deputy chair/member positions on different funding panels and various methodological roles. Semi-structured interviews were performed face-to-face or by telephone and informed by a topic guide. Most participants agreed an external pilot design should be chosen when substantial uncertainty exists about one or more design parameters. Of these parameters, a stable, deliverable and acceptable intervention was perceived by most as essential for proceeding to a main trial. Some funders discussed how staged funding for external pilot studies proceeding to a main trial could improve efficiency and limit waste. Others also felt that an open-ended funding strategy presented significant logistical difficulties, despite its appeal.

c) A one-day workshop was organised and convened on 16th May 2019 at Engineer's House, Clifton, Bristol (*objective 3c: work informed by all co-applicants and collaborators*). Further details of the workshop content and format is provided in Appendix A. The workshop was attended by 32 delegates, including representatives from most UK funding body panels and clinical trials units. The day comprised of a series of lectures from members of the working group (Fairhurst, Eldridge, Hopewell, Rosala-Hallas, Thabane), which stimulated extensive discussion amongst the group. In the afternoon, breakout groups chaired by working group members facilitated engagement from all participants in discussing the key factors in choosing between an external and internal pilot study design.

5. Summary of outputs from this project

Oral presentations: International Clinical Trials Methodology Conference, Brighton, October 2019

Findings from the protocol analysis and qualitative interviews (*objectives 3a and 3b*) were presented to a wide methodology audience at ICTMC, October 2019.

- PS4A - O1 Internal pilots in clinical trials: Current practice in design and assessment
- PS5A - O1 When to do an external or internal pilot study: Findings from an interview study with research funders

Publication in a peer-reviewed journal

- Rosala-Hallas, A., Gamble, C., Blazeby, J. *et al.* A review of current practice in the design and assessment of internal pilots in UK NIHR clinical trials. *Trials* **20,** 571 (2019) doi:10.1186/s13063-019-3669-9 (*Objective 3d*)

6. Next steps and future outputs

A further publication is in progress which will detail the overall findings of this work, the implications for future practice and offer guidance on the choice of pilot/feasibility study design (*objective 3d*). It is anticipated that this work will be submitted for publication in early 2020.

7. Appendices

A. Workshop agenda (see embedded and next page)

Appendix A_HTMR PAFS Workshop age

NIHR | Bristol Biomedical Research Centre

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MRC Hubs for Trials Methodology Research Workshop

When to do an external or internal pilot study

Thursday 16th May 2019

Engineers House, The Promenade, Clifton, Bristol BS8 3NB

10:30 **Registration and refreshments**

11:00 **Welcome, introductions and aims of the workshop**
Jane Blazeby

Chair of morning session – Paula Williamson

11:15 **"One of the biggest questions is when should one do an external pilot" - an interview study exploring funding body views and practices**
Kit Fairhurst
10 mins talk, 10 mins questions

11:35 **When to do external pilot / feasibility studies: a conceptual framework**
Sandra Eldridge
10 mins talk, 10 mins questions

11:55 **Reporting of external pilot / feasibility studies: an extension to CONSORT guidelines**
Sally Hopewell
10 mins talk, 10 mins questions

12:15 **Discussion**
Paula Williamson

12:45 **LUNCH**

Chair of afternoon session – Jane Blazeby

13:30 **Overview and purpose of breakout groups**
Jane Blazeby

13:35 **Breakout groups**
Key factors in choosing between an external & internal pilot

P T O

14:00	**Feedback from breakout groups**
14:20	**Current practice in the design and assessment of internal pilots in clinical trials** Anna Rosala-Hallas *10 mins talk, 10 mins questions*
14:40	**Skype Discussant** Lehana Thabane *10 mins talk, 10 mins questions*
15:00	**Summary of the day** Paula Williamson/Jane Blazeby
15:30	**CLOSE**