Effective use of Pilot studies

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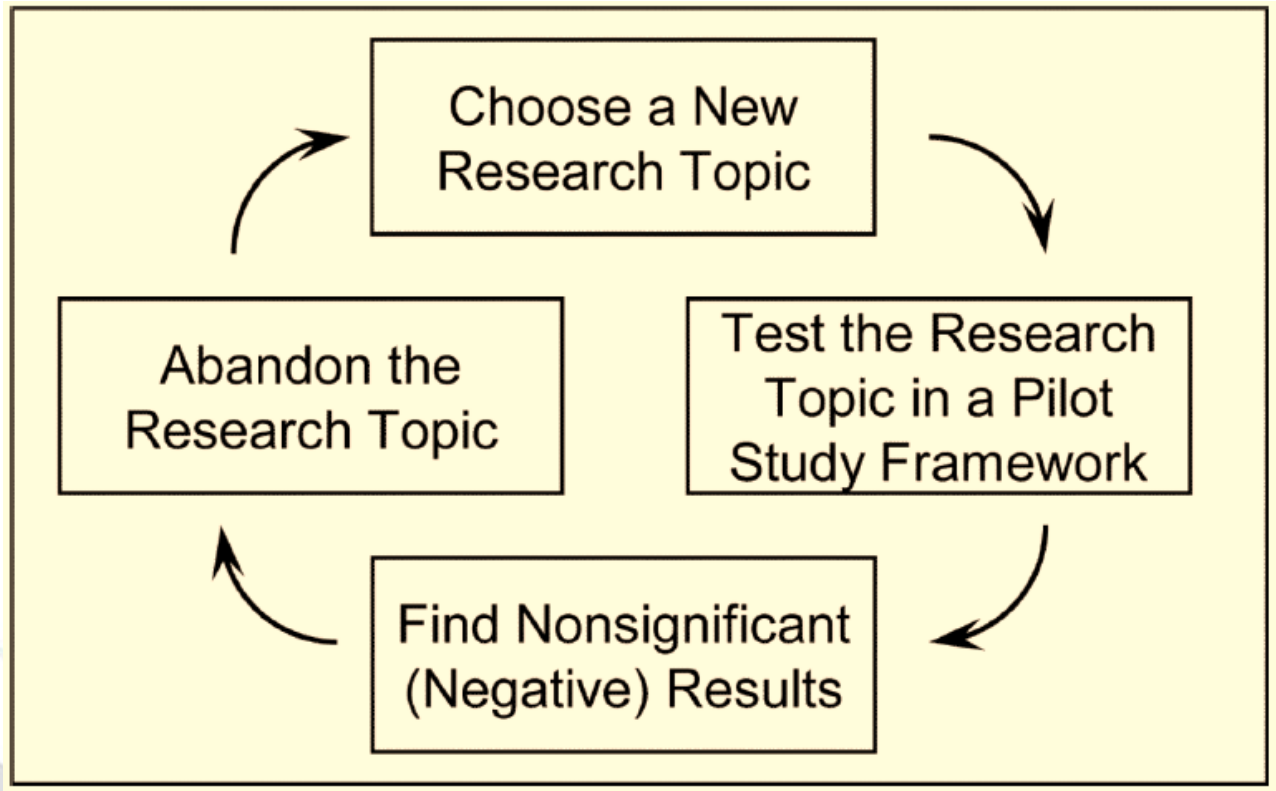
Misconceptions about pilot studies

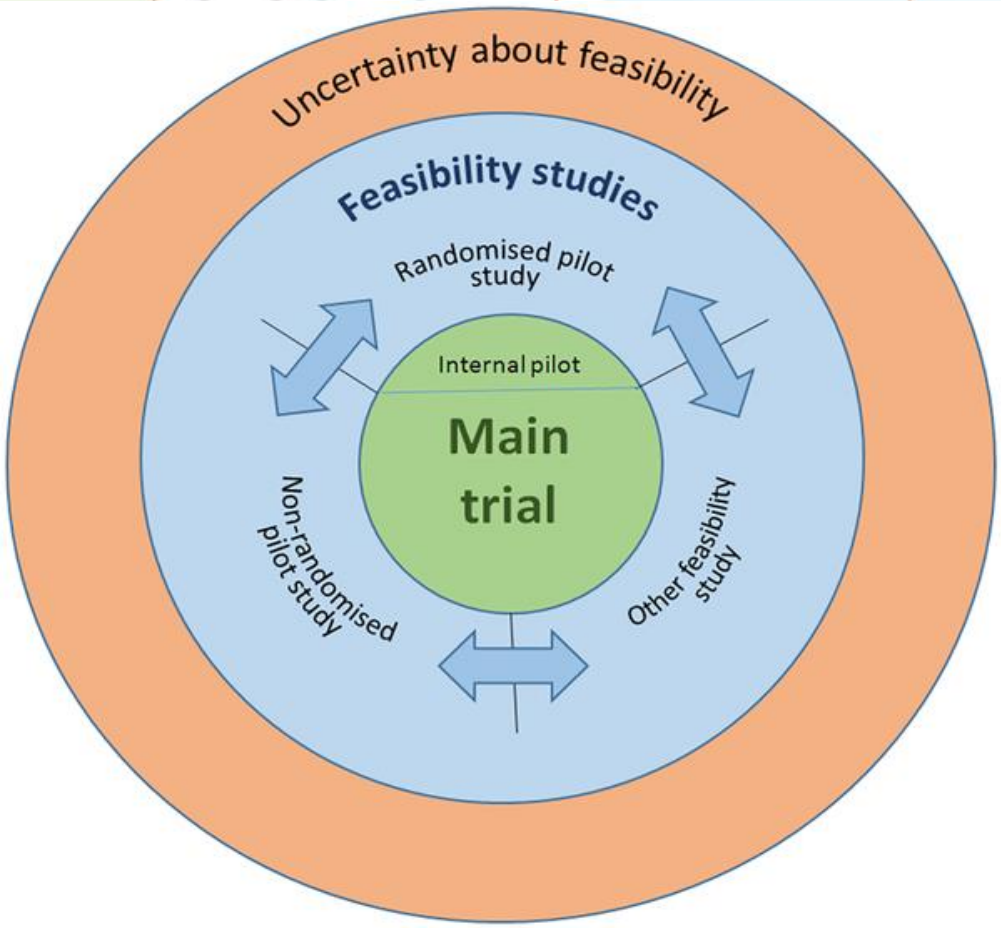
- a study with little or no funding
- a label for vague, poorly developed research proposals
- a study that precedes a costly study

Non-productive scientific strategy involving the use of pilot studies



Is it a pilot or a feasibility study?

Pilot or Feasibility: a conceptual framework



PLOS ONE

Eldridge SM, Lancaster GA, Campbell MJ, Thabane L, Hopewell S, et al. (2016) Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development of a Conceptual Framework. PLoS ONE 11(3): e0150205. doi:10.1371/journal.pone.0150205 http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0150205

Case 1: Randomized pilot study

- Investigators assessed whether
  - an RCT of the management of reduced fetal movement was ***feasible*** in relation to
    - recruitment and retention
    - acceptability and
    - adherence to protocol
  - They also examined the prevalence of poor perinatal outcomes

Heazell AE, Bernatavicius G, Roberts SA, Garrod A, Whitworth MK, Johnstone ED, et al. A randomised controlled trial comparing standard or intensive management of reduced fetal movements after 36 weeks gestation—a feasibility study. BMC pregnancy and childbirth. 2013; 13:95. Epub 2013/04/18. doi: 10.1186/1471-2393-13-95 PMID: 23590451; PubMed Central PMCID: PMCPmc3640967

Case 2: Non-randomized pilot

- Investigators developed an intervention to avoid use of syringes and contamination of materials among injecting drug users.
  - Intervention had 4 components. PIs examined the *adoption* of each component in sample of 37 drug users.
  - *Does intervention merit further testing?* PIs assessed whether the extent of blood residues had reduced sufficiently from baseline to post-intervention.

Colon HM, Finlinson HA, Negron J, Sosa I, Rios-Olivares E, Robles RR. Pilot trial of an intervention aimed at modifying drug preparation practices among injection drug users in Puerto Rico. AIDS and behavior. 2009; 13(3):523–31. Epub 2009/03/25. doi: 10.1007/s10461-009-9540-3 PMID: 19308722

Case 3: Feasibility, not a pilot

- Is it feasible to conduct an RCT comparing operative with non-operative treatment for femoroacetabular impingement surgery?
- Questionnaires sent to surgeons and patients to determine their opinion about feasibility of RCT

Palmer AJ, Thomas GE, Pollard TC, Rombach I, Taylor A, Arden N, et al. The feasibility of performing a randomised controlled trial for femoroacetabular impingement surgery. Bone & joint research. 2013; 2(2):33–40. Epub 2013/04/24. doi: 10.1302/2046-3758.22.2000137 PMID: 23610700; PubMed Central PMCID: PMCPmc3626218.

Recommendations

DESIGN, CONDUCT AND ANALYSIS OF PILOT STUDIES

Reasons for conducting a pilot study

- Evaluate ***feasibility*** of
  - recruitment, randomization, retention, assessment procedures, adequacy of instrumentation, implementation of novel intervention
- Obtain ***preliminary estimates*** of treatment effect

Design and analysis of pilot studies

– DESIGN:
  - have clear feasibility objectives
  - have a clear analytic plan
  - have explicit “go/no go” criteria

– ANALYSIS
  - mainly descriptive
  - focus on confidence interval estimation

Domains of feasibility

- **Process**: feasibility of processes that are key to success of main study
- **Resources**: time and resource problems that can occur during the study
- **Management**: capacity; potential human and data management problems
- **Scientific**: preliminary data on safety, dose, response, effect and variance of the effect

Formulate pilot objectives based on uncertainties

- **Randomized pilot**: *To assess feasibility of RCT of management of reduced fetal movement*
  - Recruitment, retention, acceptability, adherence to protocol and prevalence of poor perinatal outcomes
- **Non-randomized pilot**: *To pilot an intervention to avoid the use of syringes and contamination of materials among injecting drug users*
  - Adoption rate of each of 4 components
  - Do pre-post changes indicate that intervention merited further testing?
- **Feasibility study, not a pilot**: *To determine feasibility of RCT comparing operative with non-operative treatment for femoroacetabular impingement surgery*
  - Surgeon and patient opinion on randomization via a questionnaire

Quantification of feasibility outcomes

Study component	Feasibility quantification
Screening	Number screened per month
Recruitment	Number enrolled per month
Randomization	Proportion of screen eligible who enroll
Retention	Treatment-specific retention rates
Treatment adherence	Rates of adherence to protocol for each intervention
Treatment fidelity	Fidelity rates per unit monitored
Assessment process	Proportion of planned ratings that are completed; duration of assessment visit

Pre-specify “go/no go” criteria

DECISION study, Leblanc et al. 2011

Main study:

- Optimal use of antibiotics for treating acute respiratory infections in primary care

Intervention:

- Education in shared decision-making among family physicians and patients

Objective of pilot trial:

- to assess feasibility and acceptability of study design, procedures and intervention

Pre-specify “go/no go” criteria

- **Go / No go criteria**
  - Family medicine groups participating ≥ 50%
  - Recruited physicians participating in all 3 workshops ≥ 70%
  - Mean satisfaction level regarding workshops ≥ 65%
  - Missing data in each completed questionnaire <10%

- **Result**: participation rate of 24%.

- **Conclusion**: Not meeting the pre-set criteria does not necessarily indicate non-feasibility, but rather underlines changes to be made to the protocol.

Using pilot results to plan main study

- **A** process for **De**cision-making after **p**ilot and feasibility **t**rials (ADePT)
  - development following a feasibility study of a complex intervention for pelvic organ prolapse (Bugge 2013)

- Acceptance checklist for clinical effectiveness pilot trials: a systematic approach
  - checklist to decide whether pilot data can be carried forward to the main dataset without compromising trial integrity (Charlesworth 2013)

Justify the sample size

All pilot studies should have a sample size justification.

But not all studies need to have a sample size calculation.

Justifying pilot sample size

- Without statistical power calculation
  - Small samples (about 10) may be appropriate for
    - pilot-testing a database management system
    - demonstrating ability to execute a specific research protocol
- With statistical power calculation
  - Feasibility objective warrants it
    - Testing instrumentation for primary endpoint measurement:
      Is RNA assay more accurate and precise than the antigen assay?
    - Estimating acceptability of intervention: Is the taste of a novel dietary supplement acceptable to at least 95% of target population?

Justifying pilot sample size

- **Rule of 12**

  At least 12 participants for estimating the average and variability to plan subsequent studies (van Belle 2002 and Julious 2005)

- **Rule of 30**

  A general rule of thumb is to take 30 patients or greater to estimate a parameter (Browne 1995)

- **On using SD estimates from pilot study**

  Construct an 80% one-sided confidence interval and use upper limit rather than the point estimate itself

Notes on pilot sample size

- On preliminary estimates of safety using proportion of observed SAEs in a pilot study:
  - **If none of the participants experience SAEs,**

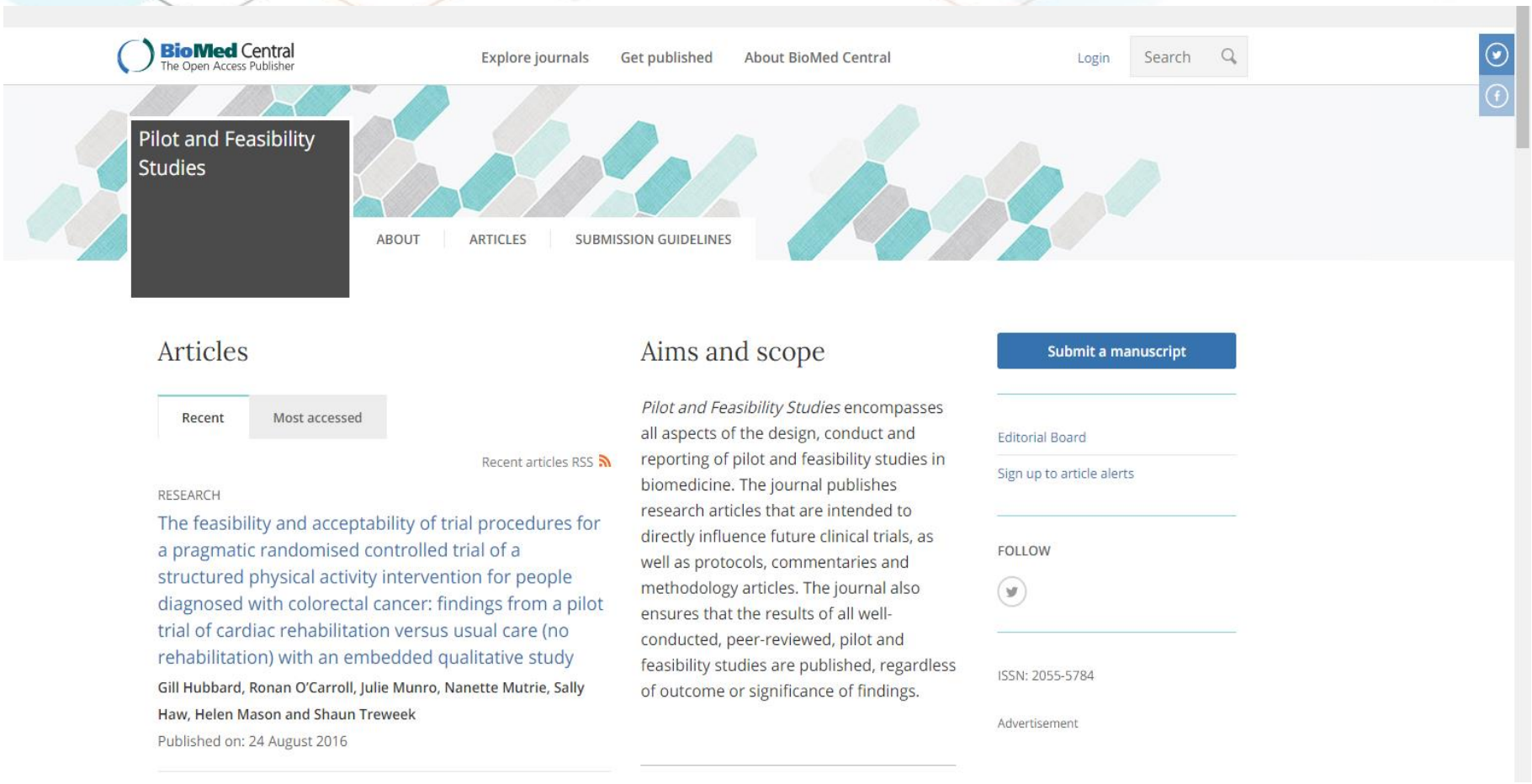
n	Confidence level	Confidence interval
5	90%	0% - 37%
10	90%	0% - 21%
20	90%	0 – 11%

- **The 3/n rule**

  Suppose n=15, and no participant reports an AE. Then the 95% CI for the AE rate is given by (0% to 20%), where 3/15 = .20 (Jovanovic and Levy, 1997)

Publishing the results of pilot studies

Journal: Pilot and Feasibility studies



Checklist for reporting the results of pilot studies

Table 3 Pilot Study - Checklist: Items to include when reporting a pilot study

PAPER SECTION	Item	Descriptor	Reported on Page #
TITLE *and* ABSTRACT	1	Does the title or abstract indicate that the study is a "pilot"?	
INTRODUCTION			
Background	2	Scientific background for the main study and explanation of rationale for assessing feasibility through piloting	
METHODS			
Participants and setting	3	• Eligibility criteria for participants in the pilot study (these should be the same as in the main study – if different, state the differences)	
		• The settings and locations where the data were collected	
Interventions	4	Provide precise details of the interventions intended for each group and how and when they were actually administered (if applicable) – state clearly if any aspects of the intervention are assessed for feasibility	
Objectives	5	• Specific scientific objectives and hypotheses for the main study	
		• Specific feasibility objectives	
Outcomes	6	• Clearly defined primary and secondary outcome measures for the main study	
		• Clearly define the feasibility outcomes and how they were operationalized – these should include key elements such as recruitment rates, consent rates, completion rates, variance estimates, etc	
Sample size	7	Describe how sample size was determined	
		• In general for a pilot of a phase III trial, there is no need for a formal sample size calculation. However, confidence interval approach may be used to calculate and justify the sample size based on key feasibility objective(s).	
Feasibility Criteria	8	Clearly describe the criteria for assessing success of feasibility – these should be based on the feasibility objectives	
Statistical Methods	9	Describe the statistical methods for the analysis of primary and secondary feasibility outcomes	
Ethical Aspects	10	• State whether the study received research ethics approval	
		• State how informed consent was handled – given the feasibility nature of the study	

Checklist for reporting the results of pilot studies

RESULTS		
Participant flow	11	Flow of participants through each stage (a flow-chart is strongly recommended). • Describe protocol deviations from pilot study as planned, together with reasons • State the number of exclusions at each stage and reasons for exclusions
Recruitment	12	Report the dates defining the periods of recruitment and follow-up
Baseline data	13	Report the baseline demographic and clinical characteristics of the participants
Outcomes and estimation	14	For each primary and secondary feasibility outcome, report the point estimate of effect and its precision (*e.g.*, 95% confidence interval [CI]) – if applicable
DISCUSSION		
Interpretation	15	Interpretation of the results should focus on feasibility, taking into account • the stated criteria for success of feasibility; • study hypotheses, sources of potential bias or imprecision – given the feasibility nature of the study • the dangers associated with multiplicity of analyses and outcomes
Generalizability	16	Generalizability (external validity) of the feasibility. State clearly what modifications in the design of the main study (if any) would be necessary to make it feasible
Overall evidence of feasibility	17	General interpretation of the results in the context of current evidence of feasibility • Focus should be on feasibility

Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC medical research methodology. 2010; 10:1. Epub 2010/01/08. doi: 10.1186/1471-2288-10-1 PMID: 20053272; PubMed Central PMCID: PMCPmc2824145

SUMMARY

When planning the next pilot study…

- Identify main uncertainties in main study
  - **Formulate** objectives based on the uncertainties
  - **Quantify** your feasibility objectives
- Pre-specify “go/no go” criteria
- Justify the sample size
- Publish the results of your pilot study

Thank you!

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