On The Need For Pilot Trials

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Objectives

• To outline the scope of pilot studies
• To review the rationale for, merits of, and challenges of pilot studies

The design and interpretation of pilot trials in clinical research in critical care

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Adapted from CCM 2009
Context is Key
Pilot Randomized Trials

Canadian Institutes for Health Research

• Pilot trial: an important, stand-alone, scientific endeavour with specific objectives

• Designed to
  – encourage research preparation
  – build convincing large grant applications
  – ensure a high return on investment
Lexicon 2
Lazy Lexicon of ‘Pilot Studies’

- Confusing terminology
  - Background work, exploratory work
  - Pilot work, Pilot study, Pilot trial
  - Run-in study
  - Feasibility study
  - Phase I, Phase II, some Phase III studies

- Vague definitions
  - National Cancer Institute: ‘the initial study examining a new method or treatment’
Pilot Projects

Pilot work
• Work done in preparation for a study (e.g., pretesting a survey instrument)

Pilot study
• A stand-alone project in preparation for a study (e.g., development and validation of a survey instrument)

Pilot studies are under-discussed, under-used, under-reported.
Prescott & Soeken, 1989
The Weight of Pilot Trials

Cheap & cheerful

Costly & rigorous
Pilot Study

• A stand-alone, scientific endeavour
• Many possible objectives & designs
  – lab study to examine mechanism
  – survey to learn knowledge, attitude, beliefs
  – practice audit to examine utilization
  – observational study to evaluate a test
  – qualitative study to understand phenomena
  – randomized trial to evaluate surrogate
• Specific objectives & specific outcomes
Run-In Pilot Studies
Run-In Pilot Study

• Goal: to implement and evaluate whether a complex algorithm or procedure can be used successfully at all participating centers

• If patients are randomized in a run-in trial
  – If minor protocol modifications needed, patients can be ‘rolled over’ into large RCT
  – If major protocol modifications needed, patients not typically chronicled in large RCT

• If patients are not randomized in a run-in study
  – Whether protocol modified or not, they are not typically included in the larger RCT report
Objectives: to enrol 2 patients/center & adjudicate the ability of

• investigators to adhere to protocols of cooling, rewarming and management

• research coordinators to complete follow-up and timely accurate case report forms
Results of a Run-In Pilot Study

• Outcomes
  – Time from patient identification to consent
  – Time from randomization to target T (8h, 3h)
  – Rewarming rate
  – Temperature deviations
  – Safety

• Overall compliance in 18 centers:
  – 1 center enrolled 1 patient, did not join RCT
  – 3 centers asked to enrol 4 additional patients
  – 15 invited to in full trial
Informing Feasibility
Possible Pilot Trial
Feasibility Objectives

- Screening & recruitment
- Consent
- Protocol implementation
- Acceptability

- Selection of primary outcome
- Follow-up
- Community interest
- Making it happen outside your own backyard
OSCILLATE Pilot Trial Objectives

Focused on feasibility

1) Assess adherence to ventilation protocols
2) Gauge ability of protocol to limit cross-overs
3) Estimate recruitment for future trial and understand recruitment barriers
4) Document ability to achieve 6 month follow-up for quality of life & mortality
The PIC-UP Pilot RCT [M Duffett]

**Design:** Blinded pilot RCT

**Inclusion:** 4 mo-18 y 
>48 h expected MV

**Intervention:** Pantoprazole 1 mg/kg or placebo

**Outcomes:**
1. Effective screening
2. Satisfactory enrolment
3. Protocol timeliness
4. Protocol adherence

**Funding:** CIHR, Hamilton Health Sciences, IWK Health Centre

7 centers

85 of 120 children randomized
RESEARCH QUESTION:
Is it feasible to enroll newly mechanically ventilated adults in a multi-centre pilot RCT of early in-bed cycling plus routine physiotherapy versus routine physiotherapy alone to inform a larger RCT?

CYCLE Pilot RCT
Feasibility Outcomes

1. **Accrual**: Following orientation, the overall average accrual rate will be 3 pts q 2 mo/ site

2. **Protocol delivery**: The cycling protocol can be implemented with >80% protocol delivery

3. **Outcome Measures**: >80% of outcomes will be measured as scheduled

4. **Blinded Outcome Assessment**: >80% of outcomes at hospital discharge will be assessed by personnel blinded to group allocation
75% of all eligible patients are not randomized due to PT resources.
Age of Blood Evaluation (ABLE) Pilot Trial

‘A Group of People Does Not Constitute a Research Team’
Examining Proof of Principle
Acidified Enteral Feeds

- Do acidified enteral feeds decrease pH and gastropulmonary colonization?
- Double-blind RCT of patients ventilated for 48h
- Acidified EN (pH 3.5) vs standard EN (pH 6.5)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Acid Feeds (N=49)</th>
<th>Standard (N=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric pH</td>
<td>3.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Gastric colonization</td>
<td>26 (53%)</td>
<td>35 (76%)</td>
</tr>
<tr>
<td>Tracheal colonization</td>
<td>25 (51%)</td>
<td>29 (63%)</td>
</tr>
<tr>
<td>VAP</td>
<td>3 (6%)</td>
<td>7 (15%)</td>
</tr>
</tbody>
</table>

Heyland et al, CCM 1999
Examining Exclusion Criteria
Exclusion Criteria

47% Strongly justified (e.g., patient may be harmed)
16% Potentially justified (e.g., patient may be noncompliant)
37% Poorly justified (e.g., chronic comorbidity, SES)
**INCLUSION**
- ICU patient ≥ 18 yrs
- Expected adm > 72h

**EXCLUSION**
- Trauma, ortho, cardiac surgery
- DVT, PE ≤ 3 mo
- Contraindication to heparin
- Therapeutic anticoagulation
- Platelets < 75 x 10⁹/L
- Cr Clearance < 30 ml/min

**PROTECT**

LMWH
- DVT, PE
- Bleeding, HIT

UFH

![Canadian Critical Care Trials Group](CIHR_IRSC.png)
Informing Costs
PROTECT-TIMES
(Time-in-Motion Evaluation Study)

• **Objective:** To describe the daily tasks and time required by Research Coordinators to implement the PROTECT protocol and manage patient enrolment and follow-up

• **Methods:** Prospective, observational, time-in-motion study using a piloted real-time daily management log to document study-related Research Coordinator activities
Time Engaged In Trial Activities

- screening
- consenting
- charting
- CRFs
- communicating
- trial management
- log
- miscellaneous
PROTECT-TIMES

• 50 patients enrolled in 10 centers

• Per patient: 6.4h [3.9-10.2h] (median [IQR])

• Study day 1 activities: 2.2h [1.3h]

• Average study day: 0.9h [0.95h]

• Activities related to enrolled patients decreased over time
PROTECT-TIMES

• Documented diverse Research Coordinator activities to prepare, implement, and manage PROTECT patients
• Showed a range of personnel costs for research conducted in the start-up phase
• Assisted future sites in realistically planning and implementing the PROTECT protocol
• Helped to justify budget
Analysis
Analytic Plan & Reporting: A Priori Inferences

• Pilot trials should have hypotheses
  – the informed consent rate will be 80%
  – x patients will be enrolled in y months
  – microbiome diversity will decrease over time

• Hypotheses for treatment effects are tricky
  – focus on confidence interval estimation
  – outcomes could be irrelevant if feasibility problems
  – feasibility could be irrelevant if outcome problems
Analytic Plan & Reporting: Avoid Over-interpretation

• Endpoints
  – feasibility outcomes
  – ‘proof of principle’ or surrogate outcomes (physiologic, biochemical, mechanical)
  – (underpowered) clinically important outcomes

• Consider reporting clinical outcomes
  – by blinded group assignment
  – as a single cohort
Analytic Plan & Reporting: A Priori Inferences

• Decide strategy for refining the protocol of the large RCT based on results of the pilot

• Develop threshold criteria for success
  – Strategy for GO vs NO GO!
Limitations of Using Pilot Trials To Estimate or Establish Treatment Effects
Interim analyses every $q$ patients or events

Stopping boundary
True beneficial effect
No effect
Recombinant tissue factor pathway inhibitor
1754 patients with severe sepsis:
Rolling 3 month average

Acidified Enteral Feeds

• Do acidified enteral feeds (pH 3.5) compared to standard feeds (pH 6.5) decrease pH and gastropulmonary colonization among patients ventilated for 48h?
• Yes, ‘proof of principle’ established
• But more deaths
  – Acid feeds = 15/49 (30.6%)
  – Standard feeds = 7/46 (15.2%)
• RR = 2.01 (0.90, 4.49), p=0.09

• Mortality risk factors:
  – acid feeds (OR 5.1)
  – US center (OR 3.9)
  – age (OR 1.1)

Heyland et al, CCM 1999
Establishing Treatment Effects: Tempting But Dangerous!

- Imbalances in baseline characteristics and random variation can lead to unreliable effects (type 1 or 2)
- De-emphasizing results of underpowered analyses for clinical endpoints will help to decrease risk of over-interpretation
- Consider declaring only
  - ‘potential efficacy’ if the 95%CI around estimated treatment effect includes a pre-defined minimal important difference
  - ‘potential harm’ if the 95%CI around estimated harm effect lies outside the upper confidence limit for safety
Publishing Pilot Trials
Calls To Publish Pilot Studies

• “Everybody needs pilot studies – not just their own, but those of other researchers in the field” [van Teijlingen et al, J Advanced Nursing 2001]

• “An amnesty for unpublished trials” [Smith and Roberts 1997]
Challenges Finding Published Pilot Trials

• Trial Registries
  – Pilot trials infrequently registered
  – If trials are registered, poorly labelled

• Peer review literature
  – Publication bias
  – If pilot trials published, poorly labelled
Reasons To Publish Pilot Studies

• To share protocols
• To record implications for conducting the larger study
• To help others avoid similar pitfalls, thus enhancing responsible future research
• To honour participant contributions
• Not to promote the clinical outcomes
Theoretical Reasons Not To Publish Pilot Studies

- Raise doubt at granting agencies
- Slow the progress to a full trial
- Concerning consent process
- Patients only contribute to answering the clinical research question if they are ‘rolled over’ in an internal pilot
Pilot Reports & Publication Rates of Follow-up Reports

- Follow-up publication rate of full reports of abstracts was 50%
  Scherer et al, JAMA 1994

- Follow-up publication rate of full reports of pilot studies was 29% (1992-1999)

- Similar for positive & negative studies

- Time lag:
  - 50% by 2 years
  - 98% by 6 years

  Cloft et al, Academic Medicine 2001
32 (12%) of 262 Pediatric Critical Care RCTs were Pilot Trials

4 led to larger trials

- 2 published
- 3 in progress

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pilot Trials (n=32)</th>
<th>Other Trials (n=230)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children randomized</td>
<td>30 (20, 43) min=6, max=156</td>
<td>50 (32, 98) min=8, max=4947</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multi-centered</td>
<td>6 (22)</td>
<td>39 (18)</td>
<td>0.60</td>
</tr>
<tr>
<td>Studied medications</td>
<td>15 (56)</td>
<td>140 (63)</td>
<td>0.53</td>
</tr>
<tr>
<td>Blinding</td>
<td>13 (48)</td>
<td>112 (51)</td>
<td>0.84</td>
</tr>
<tr>
<td>Commercial funding</td>
<td>5 (19)</td>
<td>35 (16)</td>
<td>0.78</td>
</tr>
<tr>
<td>Any funding reported</td>
<td>18 (67)</td>
<td>123 (56)</td>
<td>0.31</td>
</tr>
<tr>
<td>Stopped early</td>
<td>3 (11)</td>
<td>29 (13)</td>
<td>1.00</td>
</tr>
<tr>
<td>High risk of bias</td>
<td>15 (56)</td>
<td>93 (42)</td>
<td>0.22</td>
</tr>
</tbody>
</table>
Summary

Pilot trials should have

• suitable objectives and criteria for success
• specific outcomes that address the objectives
• a thoughtful analysis to prevent misuse of results
• cautious interpretation
  – surrogate outcomes
  – clinical outcomes

.....to avoid undue enthusiasm or pessimism
Summary

• Rigorous pilot trials can inform the design and implementation of future large RCTs
• Pilot trials should be subject to the same scrutiny and requirements as full RCTs, including public registration
• Further methodologic work is required to identify optimal pilot trial design, indexing, and reporting
Summary

Pilot trials are particularly helpful for
1. New drug, device or program
2. New investigator
3. New research team
4. A complex protocol
5. Financial planning
6. Founding a research program
Thank you for the Invitation!