Renal Supportive Care Research methodological challenges

Dr Fliss Murtagh FRCP PhD MRCGP MD
Cicely Saunders Institute
King’s College London
Disclosure of Interests

Clinical Academic at the Cicely Saunders Institute, King’s College London. Research and service development grants:

• National Institute for Health Research, UK – research grants:
  • C-CHANGE: RP-PG-1210-12015
  • C-CHANGE development: RP-DG-0709-10162
  • Non cancer place of death: SDO-FR-08-1813-257

• NHS Kidney Care, Department of Health, UK – previous service development grant:
  • The Advanced Renal Care project (2010-12)
What to research? Domains of quality care
National Consensus Project for Quality Palliative Care 2004

1. Structure and processes of care
2. Physical aspects of care – physical outcomes
3. Psychological and psychiatric aspects of care – psychological outcomes
4. Social aspects of care – social outcomes
   – Family communication and care
   – Post-bereavement care
5. Spiritual, religious and existential aspects of care
6. Care of the imminently dying patient – end of life outcomes
7. Ethical and legal aspects of care – ethical outcomes

All outcomes need to be patient- (or family-) centred
The purpose of research

- To build new knowledge in order to improve care and outcomes
  - Effectiveness research - compares how different treatments or interventions work
    - Simple interventions/Complex interventions
  - Epidemiological research - patterns, causes, and effects of disease conditions in defined population
  - Health services research - how people access health care services, how much care costs, and what happens to patients as a result of this care
Where do the gaps lie?

- Limited understanding of population, their needs, evolution of needs over time
- Little or no evidence of comparative effectiveness of interventions, especially more complex (e.g. models of care)
- No evidence of cost-effectiveness
- Few attempts to assess the acceptability (patient-centeredness) of interventions
  - informed by patient priorities and preferences
Overview

- Routine clinical data
- Population
- RCTs
- Other designs
- Complex interventions
Routine collection of outcomes data

- Not discussed but important
- Needs to include outcomes, as well as process measures
- Use for quality improvement
- If collected systematically can underpin research
  - Routine clinical data for research
Defining and identifying the study population

- Defining conservative care population
- Reporting who is not in the study
- Research in relation to end of life
  - Death is only known retrospectively
  - Study all? Identify the sickest? Use prognostic indicators to stratify and select?
- Recruiting widely increases clinical relevance but maximises resource requirements
Difficulties with RCTs

- Difficult to implement in advanced illness/end of life
- Narrow “window of equipoise”
- May not be ethical e.g. dialysis v conservative RCT
- Findings poorly applicable to typical patients - difference between efficacy and effectiveness e.g. in ESRD near end of life - impaired capacity
- Translational research gaps (Phase 2 and 3)
  - (Phase 1 bench to bedside)
  - Phase 2 effectiveness, acceptability
  - Phase 3 wider policy & public health implications
RCTs important

- Current RCT approaches
  - Interim analysis often helpful

- Adopting adaptive approaches
  - Introduce new treatment strategies as they evolve
  - Unequal randomisation – weight to
    - Interventions most likely to work
    - Uncovering important but clinically small differences
    - Focusing on clinically important subgroups

- Pragmatic clinical trials
  - Broadly inclusive (‘real world’)
  - Patient outcomes (QoL)
  - Patient/family involvement
Adapting and refining RCTs

• Fast track RCT
• Use of mixed methods
  – 30/100 Cochrane RCTs associated QUAL (Lewin BMJ 2009)
    • Importance of theoretical basis
    • Justification and integration
  – Cognitive interviewing
  – Longitudinal dimensions – understanding natural course first to inform timing of outcomes
Other designs

• Quasi-experimental
  – Controlled trial without randomisation
  – Confounding a major issue - pre-post testing (tests done before data collection to try and identify confounding factors within participants)

• ‘Before and after’ design
  – Change over time a major issue, repeated measures to offset

• Geographical comparisons

• Cohort, cross-sectional, retrospective studies
Tackling complex interventions

- Harder to understand and evaluate
- Much harder to build robust evidence
  - what components work and why?
- Needs different methods:
  - careful modelling and description of intervention
  - different research designs
  - usually multiple research outcomes
- Issues of generalizability
  - Local adaptation is critical, but only possible if nature/interaction of components understood
Defining the intervention

• In any non drug trial, defining the intervention may be challenging

• For example:
  – Renal end of life care service
  – Patient educational programme
  – Family caregiver support service

• Without careful definition, there is no real possibility of:
  – Replicability
  – Identification of what is working (or not) and why
Simplified model of an intervention

- Phenomenon under review
- Structure
- Population

Processes

OUTCOMES
Framework for evaluation of complex interventions

Pre-clinical
- Explore relevant theory to ensure best choice of intervention and hypothesis and to predict major confounders and strategic design issues

Phase I
- Modelling
  - Identify the components of the intervention, and the underlying mechanisms by which they will influence outcomes to provide evidence that you can predict how they relate to and interact with each other

Phase II
- Exploratory Trial
  - Describe the constant and variable components of a replicable intervention AND a feasible protocol for comparing the intervention to an appropriate alternative

Phase III
- Definitive RCT
  - Compare a fully-defined intervention to an appropriate alternative using a protocol that is theoretically-defensible, reproducible and adequately controlled, in a study with appropriate statistical power

Phase IV
- Long-term Implementation
  - Determine whether others can reliably replicate your intervention and results in uncontrolled settings over the long term

Continuum of increasing evidence
### Standard trials vs Complex intervention evaluations

<table>
<thead>
<tr>
<th>Pre-clinical work</th>
<th>Theory – develop best choice of intervention and hypotheses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I – first in man (volunteers)</td>
<td>Modelling – understand components of intervention and underlying mechanisms to influence outcomes</td>
</tr>
<tr>
<td>Phase II – first in patients</td>
<td>Exploratory trial – describe the constant and variable components and work out feasibility of trial</td>
</tr>
<tr>
<td>Phase III – full scale evaluation</td>
<td>Definitive RCT – compare intervention with alternative</td>
</tr>
<tr>
<td>Phase IV – post marketing</td>
<td>Long term implementation – can others reliably replicate and longer term</td>
</tr>
</tbody>
</table>
Tackling the challenges

- Define the intervention: structure, process, intended outcomes (all components)
- Conceptualise how components might interact (theoretical modelling)
- Consider the behaviours required by those delivering or receiving the intervention
- Consider the groups involved in the intervention
- How much local modification of intervention is required i.e how standardised
- Select primary and secondary outcomes very carefully (patient informed)
- Select ways to monitor how intervention does or doesn’t operate as expected
Cohort study

• longitudinal study used to analyse risk factors
• follows a group of people and uses correlations to determine the absolute risk of disease/event (e.g. developing depression, having dialysis, death)
  – also observational over time
• Especially useful when little is known about course of illness over time
• Can inform
  – Patient-centred outcomes
  – Timing of outcome measurement
  – Response shift
  – Relationship of outcomes to death
Use of proxy data

• Widely used in palliative care research

• Missing data
  – frequently missing not at random but due to changing health status

• Proxies – families, other care-givers, professionals
  – May be poor correlation (not helpful)
  – May be consistent bias (can be addressed)
Research burden

• Crucial
  – Detailed piloting
  – Use of cognitive interviewing
  – Avoid collecting more data just because it can be collected!
  – Inverse relationship between research burden and amount of missing data
  – How much missing data is too much?
Attrition and follow up

• ‘Front end’ support for study participation
• Recruitment of iller patients possible but needs additional time and resource
• Resonant connections with participants to maximise longitudinal follow up
• Patient/family carer dyads
Conclusions

• The importance of matching Method → Outcomes to research question
• Methodological challenges but some solutions emerging
• Need to think “outside the box”
• Collaborative research is paramount
• Programme work is important
• Adapted RCTs, other methods, and mixed methods have much to offer