Improving Long-Term Outcomes Research for Acute Respiratory Failure

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Create and nationally disseminate resources to assist Acute Respiratory Distress Syndrome (ARDS)/Acute Respiratory Failure (ARF) researchers in designing trials that appropriately evaluate long-term patient outcomes

Presenters

- Alison E. Turnbull, PhD, DVM, MPH
  - Assistant Professor – JHU PCCM & Epidemiology
- Victor D. Dinglas, MPH
  - Research Associate – JHU PCCM
- Elizabeth Colantuoni, PhD
  - Associate Scientist – JHSPH Biostatistics

R24 Grant Aims

Aim 1: National web-based electronic database of validated and recommended survey instruments and clinical testing methods for long-term outcomes - Turnbull

Aim 2: Practical resources for maximizing retention in long-term, longitudinal research - Dinglas

Aim 3: Statistical methods & programs for evaluating functional outcomes in the presence of high patient mortality ("competing risk of mortality") - Colantuoni
Outcome measurement in ICU survivorship research from 1970-2013: a scoping review of 425 publications

Peer-reviewed published studies 1970 - 2013
• ≥ 20 adult ICU survivors assessed after hospital discharge

Excluded
• Qualitative studies
• Studies only assessing survival
• Psychometric evaluations of measurement instruments or tests
• >50% of patients had neurologic injury
• >50% of patients had cardiac surgery

Outcome measurement in ICU survivorship research from 1970-2013: a scoping review of 425 publications

525 Studies
• 116 Cross-sectional studies
• 168 Cohort studies w/ 1 follow-up
• 110 Cohort studies w/ multiple follow-up assessments
• 31 Trials

Randomized Trials N = 31

| Months to last assessment median (IQR) | 12 (5-12) |
| No follow-up assessments median (IQR) | 1 (1-2) |
| N at last follow-up median (IQR) | 87 (32–199) |
Outcome measurement in ICU survivorship research from 1970-2013: a scoping review of 425 publications


425 peer-reviewed papers
- Outcomes assessed using 250 different measurement instruments

Why is this a problem?
- Important outcome domains may not be assessed
- Difficult to compare results
- Barrier to meta-analyses
- Selective outcome reporting bias
What do other scientists do?

National Institute of Standards and Technology

OMERACT: Outcomes Measures in Rheumatology

OMERACT strives to improve endpoint outcome measurement through a data driven, iterative consensus process involving relevant stakeholder groups

CORE OUTCOME SETS (C.O.S)

Core outcome set: A minimum collection of measures reported in all studies within a specific field.

A COS does NOT prevent investigators from collecting data on additional outcomes.

Definitions

- Core domain - a concept, health-related condition, or aspect of health that must always be measured within a specific field of research
  
  *(What outcomes should we all measure?)*

- Core outcome set (COS) - a *minimum* set of agreed-upon outcome measures
  
  *(How should we measure them?)*

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Core Outcome Measurement in Effectiveness Trials - COMET

Existing COS
COS under development

Our goal

Develop a COS for survivors of acute respiratory failure (including acute respiratory distress syndrome) after hospital discharge using a rigorous methodology and an international panel of relevant stakeholders.

Systematic reviews

- Scoping review of outcomes 1970-2013
  425 articles (Crit Care Med. 2016;44:1267)
- Qualitative studies of ICU survivorship
  22 articles; (Critical Care. 2016;20:345)
- Anxiety symptoms in ICU survivors
  27 studies; (Gen Hosp Psychiatry. 2016; In Press)
- Depression symptoms in ICU survivors
  38 studies; (Crit Care Med. 2016;44:1744)
- Evaluation of measurement properties
  20 ICU studies evaluated 21 instruments; COSMIN rating
New psychometric analyses

- Impact of Event Scale - Revised
  Criterion validity (Chest. 2013;144:24-31)
- Hospital Anxiety and Depression Scale
  Internal consistency (J Crit Care. 2015; 30:793-8)
- MID of HADS and IES-R
  (Gen Hosp Psychiatry. 2016;42:32-5)
- SF-36 & mental health symptoms
- 6MWT vs. cognitive tests battery
  Criterion validity (Critical Care. 2015; 19:220)
- Validity and MID of 4-Meter Gait Speed Test
  Internal construct validity, responsiveness; MID (Crit Care Med. 2016; 44:859-68)
- Physical performance-based measures vs. patient-reported outcomes
  2 studies of ARDS survivors, 13 hospitals in 5 states – in progress
- Dual energy X-ray absorptiometry (DXA)
  5-centers in US, n=120 ARDS survivors – in progress

Instrument information sheets

- >70 cards available on www.improveLTO.com

Interviews and Surveys

- Qualitative interview of ARF survivors
  • 30 minute semi-structured interviews; n=38 (under peer-review)

- Domain survey – ARDS survivors, family, researchers
  • 78 patients, 80 family members, 121 international ICU outcomes researchers (under peer-review)

  • Clinicians/researchers n=44 in USA & n=85 in Australia

Modified Delphi Consensus Process

Delphi Method

- Recruit a panel of informed experts
- Maintain anonymity of panel members
- Provide a summary of results after each round of voting
- a priori consensus criteria
### Delphi – Expert Panel

**Stakeholder groups**

1. **Clinical researchers** (n=35)
   - All International Forum for Acute Care Trialists (InFACT) members including USCIITG
   - Random sample of 6 corresponding authors from scoping review
   - 9 authors of internationally recognized ARF research
   - 16 countries represented

2. **Clinicians/professional associations** (n=19)
   - ICU physicians, ICU nurses, rehabilitation clinicians
   - Australia, Canada, UK, & US

3. **Patients/caregivers** (n=17)
   - Australia, Canada, UK, & US

4. **Funding bodies** (n=4)
   - AHRQ, NIA, NICHD, National Library of Medicine

### Dissemination & Adoption

COS success depends on the research community adopting and enforcing a minimum standard

- Funding bodies
- Journal Editors
- Clinical researchers
- Peer-reviewers


### Get involved

- **ATS NHLBI session May 24, 2017**
  - 12:15 – 13:15

### Aim 2

**PRACTICAL RESOURCES FOR COHORT RETENTION**
Cohort retention in Post-Hospital Studies of ICU survivors (1970-2013)

<table>
<thead>
<tr>
<th>Cohort Studies</th>
<th>Cohort Studies with One Follow-Up Assessment</th>
<th>Cohort Studies with More Than One Follow-Up Assessment</th>
<th>Randomized Controlled Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 118 (23%)</td>
<td>n = 168 (29%)</td>
<td>n = 119 (26%)</td>
<td>n = 21 (7%)</td>
</tr>
<tr>
<td>Months from discharge to last assessment, median (IQR)</td>
<td>31 (18-55)</td>
<td>6 (6-12)</td>
<td>12 (12-15)</td>
</tr>
<tr>
<td>No. of follow-up assessments, median (IQR)</td>
<td>2 (2-3)</td>
<td>1 (1-2)</td>
<td></td>
</tr>
<tr>
<td>No of participants assessed at last follow-up time, median (IQR)</td>
<td>61 (37-125)</td>
<td>107 (53-255)</td>
<td>83 (40-149)</td>
</tr>
<tr>
<td>Loss to follow-up reported (%)</td>
<td>25 (13-29)</td>
<td>22 (2-37)</td>
<td>14 (2-26)</td>
</tr>
<tr>
<td>Loss to follow-up, median (IQR) (%)</td>
<td>25 (13-29)</td>
<td>22 (2-37)</td>
<td>14 (2-26)</td>
</tr>
</tbody>
</table>

- Threat to validity, results in loss of statistical power
- In RCTs, potential bias if differential loss to follow-up btw trt groups

Follow-up of ARDS Network’s ALTA, EDEN, OMEGA, and SAILS Trials

Threat to validity, results in loss of statistical power
In RCTs, potential bias if differential loss to follow-up btw trt groups

Myth: Follow-up = bothersome

After 280 questions & repeated calls/mailing, 92% “bothered” no more than a little bit

R24 Grant – Aim 2 (cohort retention)

1. Systematic review of retention methods
2. Semi-structured interviews of JHU researchers for unpublished retention methods
3. Empirical analyses of existing data - ongoing
   - Factors assoc. w/ incomplete visits
   - Factors assoc. w/ requiring home visits
   - Estimation of bias from missing data
   - Empirical analyses of pt contact effort and patient satisfaction
Systematic Review of Cohort Retention Strategies

- 21 studies of 3,068 citations eligible
- Inclusion criteria: data on retention from a study, and information on strategies used for retention
- Analyzed 368 strategies & found 12 themes
- Studies analyzed reported a median of 17 strategies across median of 6 themes
- Studies that utilized more strategies had retention rates greater than mean rate of 86%


Updated Systematic Review of Cohort Retention Strategies

- identified 88 studies – 67 since our last review
  - 6/88 (7%) were designed to compare strategies
  - 82/88 (93%) were designed to describe strategies


Updated Systematic Review of Cohort Retention Strategies

- Comparative studies
  - financial/cash incentives = retention rates
- Descriptive studies
  - Number of strategies used = retention rates
- Themes of “contact and scheduling” and “visit characteristics” represented largest & most frequently used
- Created searchable DB of all 618 strategies and 12 themes:
  - http://www.improvelto.com/sysrevstrategies/


Semi-structured interviews
- unpublished retention methods

- 19 studies from JHU:
  - ≥200 pts, ≥80% retention rates; ≥1 year follow-up
- Most common strategies involve:
  - Study reminders, study visit characteristics, emphasized study benefits, & contact/scheduling strategies
- Other key findings:
  - Well-functioning, organized, and persistent research teams
  - Strategies tailored to cohort and individual pts
  - Adapting & innovating strategies over time
“Menu” of tools – R24 Aim 2

http://www.improvelto.com/cohort-retention-tools/

- Participant Contact Information Form
- Communication Templates and Manuals
- Retention Strategies from Systematic Review
- Locating Participants
- Follow-up Protocols
- Staff Training
- Other Tools
- Presentations

To Aim 3

Detailed Contact Info Sheet Template

Communication Template

Home Visit Scheduling Script:

"I understand that it would be very difficult for you to get to the research study/hospital. We would be willing to visit you at home for your follow up visit."

Note: Identify a mutually agreeable time for the person doing the home visit - consider driving time to and from appointment as well.

"We could visit you at your home on ___(Day/Time options): ___ would any of these times work for you?"

If caller is unsure of availability for home visit:

"I will need to connect ___(Follow-up Supervisor’s first and last name): ___ the follow-up supervisor, to find out when he/she is available to visit you at home. Can I call you back either later today or tomorrow to verify a time that will work for you?"

Note: If the participant has indicated that a home visit is not possible due to work schedule or any other limitations, use the following script:

Searchable Database of Retention Strategies (systematic review)
STATISTICAL TOOLS TO ACCOUNT FOR COMPETING RISK OF MORTALITY

Aim 3

In designing clinical trials measuring LTOs within critically ill patient populations, researchers must consider the potential impact of mortality.

BIG QUESTION: How do we evaluate the effect of interventions on LTOs when some patients die?

1. Evaluate commonly used and novel statistical methods to analyze LTOs in the presence of high mortality
2. Create statistical software to analyze LTOs in the presence of high mortality
**“Competing risk” of mortality**

Randomized trial in mechanically ventilated adult ICU patients

**LTOs “truncated due to death”**

Randomized trial in ALI/ARF adult ICU patients

**Systematic Review**

- Identified all RCTs published during 2014 in five high-impact general medicine journals
- Eligibility criteria: RCT, mortality reported for all treatment groups, and mortality ≥10% in at least one treatment group
- Evaluated the RCTs for:
  - One or more primary or secondary LTOs included
  - What statistical method, if any, was used to address potential bias due to patient mortality
  - Presence of missing data and appropriate method to account for this
Systematic Review

Most commonly used method

**“Survivors only” analysis**
- Compare the mean LTO among survivors

**Advantages:**
- Simple to implement and explain
- If mortality rates are similar across the interventions, then unbiased

**Disadvantages:**
- If mortality differs across the interventions, may be biased
- Violates the intention to treat principle

Survivor Average Causal Effect

- Can we somehow “balance” mortality across the interventions, thus creating a situation where mortality is independent of intervention
- Survivor Average Causal Effect (Rubin, 2000)
  - Compare the mean LTO among “always survivors”, patients who would have survived regardless of what treatment they receive
- **Advantages:**
  - Estimates the direct effect of the intervention on the LTO among the “always survivors”
  - Randomization is preserved within the subset of “always survivors”, so the treatment comparison is unbiased

Survivor Average Causal Effect

- **Disadvantages:**
  - Requires assumptions which are not directly testable
  - Treatment comparison is made within the “always survivors”, a subset of patients that is not directly identifiable
  - Violates the intention to treat principle
Composite endpoint method

- Traditional composite endpoint for LTO may be defined as: survived to 12-months with clinically relevant improvement in quality of life compared to hospital discharge
- Ranking approach (Lachin, 1999)
  - Rank the patients
  - Compare the average rank across the interventions using Wilcoxon rank-sum test.
- Patient ranking:
  - Earlier death is worse than later death
  - Death is worse than survival
  - Poor LTO worse than good LTO among survivors

Composite endpoint method

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>25th</td>
<td>Experienced death by 60 days</td>
<td>Experienced death by 12 days</td>
</tr>
<tr>
<td>50th</td>
<td>Survive to 12-months with QOL ≤ 30</td>
<td>Experienced death by 71 days</td>
</tr>
<tr>
<td>75th</td>
<td>Survive to 12-months with QOL ≤ 45</td>
<td>Survive to 12-months with QOL ≤ 40</td>
</tr>
<tr>
<td>90th</td>
<td>Survive to 12-months with QOL ≤ 49</td>
<td>Survive to 12-months with QOL ≤ 47</td>
</tr>
</tbody>
</table>

Recommendations

- When it is biologically unlikely that the intervention to impact mortality
  - Survivors only analysis
- When mortality is the primary endpoint
  - It is hypothesized that there will be a difference in mortality across intervention groups
  - Analyses of LTOs should consider alternative methods (survivor average causal effect or composite endpoint method).
Software development

- In collaboration with other Johns Hopkins University researchers, we have developed an application that
  - Implements the methods described above
  - Implements a multiple imputation approach
  - Sensitivity analysis to the multiple imputation assumptions

- Developed using C++, R and Shiny
  - i.e. you don’t have to have these software installed on your computer

R24 Project Team Members

PI: Dale M. Needham, FCPA, MD, PhD
Co-investigators and faculty:
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  - Kitty Chan, PhD – Psychometrician
  - Elizabeth Colantuoni, PhD – Biostatistician
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  - Victor Dinglas, MPH – Research Associate/Manager
  - Michelle Eakin, PhD – Qualitative researcher/psychologist
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Project website

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