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OACIS

JOHNS HOPKINS MEDICINE

Improving Long-Term Outcomes Research for Acute Respiratory Failure

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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*

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NHLBI Grant: R24HL111895

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

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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

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Resources available at:
www.improveLTO.com

Very brief registration

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

Turnbull et al. *Crit Care Med.* 2016;44:1267-77

Peer-reviewed published studies 1970 - 2013

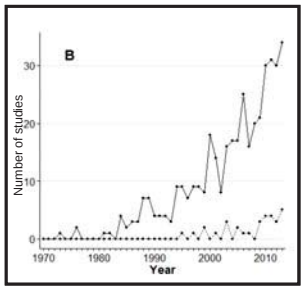
- ≥ 20 adult ICU survivors assessed after hospital discharge

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

Turnbull et al. *Crit Care Med.* 2016;44:1267-77



Studies of ICU survivor outcomes included in the scoping review. Dashed line = trials

425 Studies

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

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

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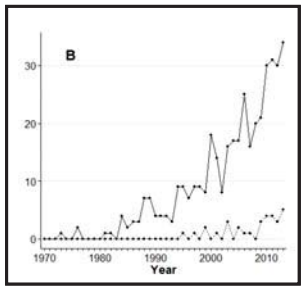

Studies of ICU survivor outcomes included in the scoping review. Dashed line = trials

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

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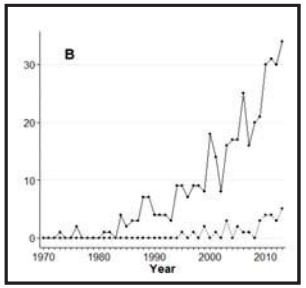


Studies of ICU survivor outcomes included in the scoping review. Dashed line = trials

425 peer-reviewed papers

- Outcomes assessed using 250 different measurement instruments

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

Turnbull et al. *Crit Care Med*. 2016;44:1267-77

PTSD symptoms[a] (*n* = 70; article to instrument ratio = 4.7)	
IES	26 (37)
PTSS 10-Questions	17 (24)
IES-Revised	13 (19)
Clinician-Administered PTSD Scale for *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition	8 (11)
Symptom Checklist-90-R	5 (7)
PTSD Checklist-Civilian Version	5 (7)
PTSS 14-Questions	4 (6)
Post-Traumatic Stress Diagnostic Scale	4 (6)
Other named instruments assessing PTSD symptoms[f]	7 (10)

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

Turnbull et al. *Crit Care Med*. 2016;44:1267-77

TABLE 5. Articles With Any Assessment of Participation Restriction (*n* = 196)

Measurement of Participation Restriction	1970–2013 (*n* = 196)
Instruments used to assess participation restriction (%)	
Return to work	87 (44)
Katz Activities of Daily Living	41 (21)
Glasgow Outcome Scale	16 (8)
Lawton Instrumental Activities of Daily Living	15 (8)
Karnofsky Performance Status Scale	11 (6)
Barthel Index	11 (6)
Functional Independence Measure	6 (3)
New York Heart Association Functional Classification	5 (3)
Cerebral Performance Category Scale	5 (3)
Modified Rankin Scale	3 (2)
Other named instruments[c]	32 (16)
Custom-made instrument	28 (14)

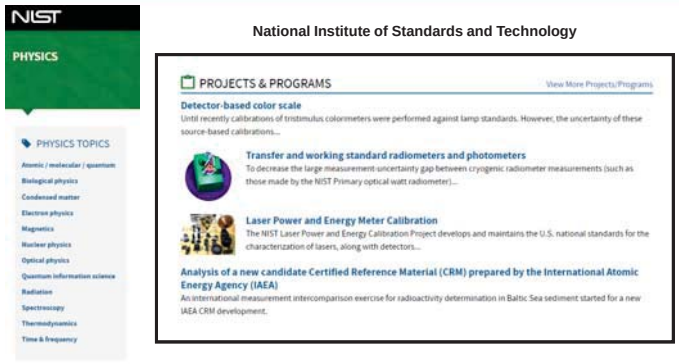
Outcome measurement in ICU survivorship research from 1970-2013: a scoping review of 425 publications

Turnbull et al. *Crit Care Med*. 2016;44:1267-77

Why is this a problem?

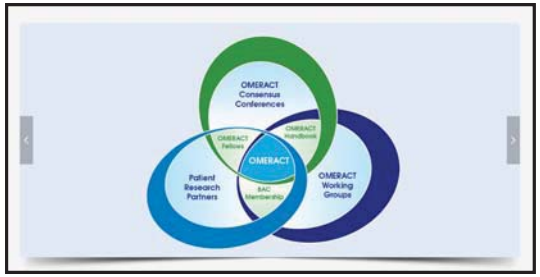
- Important outcome domains may not be assessed
- Difficult to compare results
- Barrier to meta-analyses
- Selective outcome reporting bias

What do other scientists do?



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

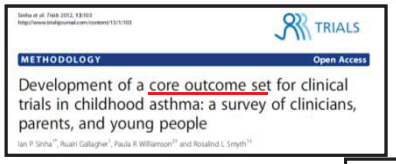
- **Core domain** - a concept, health-related condition, or aspect of health that must always be measured within a specific field of research

  (***What*** *outcomes should we all measure?)*

- **Core outcome set (COS)** - a *minimum* set of agreed-upon outcome measures

  *(**How** should we measure them?)*

COS in other fields



ORIGINAL ARTICLE
Connective tissue disease related interstitial lung diseases and idiopathic pulmonary fibrosis: provisional core sets of domains and instruments for use in clinical trials Saketkoo LA, *et al. Thorax* 2014;**69**:428–436.

Original article
Development of a core outcome set for research and audit studies in reconstructive breast surgery *BJS* 2015; **102**: 1360–1371

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
  (*J Clin Epidemiol*. 2016; In Press)

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
  SF-36 MH domain correlated with psych symptoms but non-specific (*Ann Am Thorac Soc*. 2016;13:1343-50)
- MMSE vs. cognitive tests battery
  Criterion validity (*Critical Care*. 2015. 5;19:220)
- Validity and MID of 6-Minute Walk Test
  Internal construct validity, responsiveness; MID (*Chest*. 2015;147:1316-26)
- Validity and MID of 4-Meter Gait Speed Test
  Validity, responsiveness, test-retest & inter-rater reliability; 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

Instrument	Impact of Events Scale - Revised
Acronym	IES-R
Core Domain	Mental Health Conditions and Symptoms
Area assessed (Number of questions)	Total questions: 22 Intrusion: 7 Avoidance: 8 Hyperarousal: 7
Description	A self-reported question/naire designed to measure the subjective distress caused by traumatic events.
Versions	The original version contains 15 questions, consisting of the intrusion and avoidance subscales. The revised version is more commonly used in current research.
Recall Period	Past week
Scoring information	Items are rated on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). Total scores are summed with higher scores indicating greater distress with regards to a specific event.
Estimated time to complete	6 minutes
Administer to	Patient
Require trained administrator	No
Mode of administration	In-person, Phone, Mail
Order from	Contact co-creator, Daniel S. Weiss Ph.D.: daniel.weiss@ucsf.edu Department of Psychiatry University of California - San Francisco PO Box F-0984 San Francisco, CA 94143-0984 Phone: (415) 476-7557 Email: daniel.weiss@ucsf.edu hugos@lppi.ucsf.edu
Licensing Fee Fees and licensing information is effective as of 2016, but is subject to change over time	No Cost
Equipment required	Survey form and pen
Number of published Critical Care publications using instrument *	39
Highest COSMIN** rating (from a systematic review***)	Bienvenu, 2013 •Internal Consistency (Cronbach's α = 0.96, n = 60); COSMIN: POOR •Criterion Validity (Person r =0.80, Spearman r=0.69, n=60); COSMIN: FAIR
Additional comments	None
Online Example:	http://www.emdrhap.org/content/wp-content/uploads/2014/07/VIII-E_Impact_of_Events_Scale_Revised.pdf

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)*

– Domain survey – Pilot (Hodgson CL *et al*. *Physical Therapy Journal*. 2016; In Press)
  - 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)
   i. All International Forum for Acute Care Trialists (InFACT) members including USCIITG
   ii. Random sample of 6 corresponding authors from scoping review
   iii. 9 authors of internationally recognized ARF research
   iv. 16 countries represented
2. Clinicians/professional associations (n=19)
   i. ICU physicians, ICU nurses, rehabilitation clinicians
   ii. Australia, Canada, UK, & US
3. Patients/caregivers (n=17)
   i. Australia, Canada, UK, & US
4. Funding bodies (n=4)
   i. 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

Copsey B, et al.: Appraising the uptake and use of recommendations for a common outcome data set for clinical trials: a case study in fall injury prevention. *Trials* 2016; 17:131

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)

(*Crit Care Med*. 2016;44:1267-77)

Methodological Characteristics	Cross-Sectional Studies[a] n = 116 (27%)	Cohort Studies With One Follow-Up Assessment[a] n = 168 (39%)	Cohort Studies With More Than One Follow-Up Assessment[a] n = 110 (26%)	Randomized Controlled Trials n = 31 (7%)
Months from discharge to last assessment, median (IQR)[b]	31 (18–52)	6 (6–12)	12 (12–12)	12 (5–12)
No. of follow-up assessments, median (IQR)			2 (2–3)	1 (1–2)
No. of participants assessed at last follow-up time, median (IQR)[c]	65 (37–125)	107 (53–255)	80 (46–146)	87 (32–199)
Loss to follow-up reported (%)[d]	80 (69)	129 (77)	40 (36)	20 (65)
Loss to follow-up, median (IQR) (%)[d]	22 (11–38)	22 (7–37)	14 (2–25)	13 (6–25)

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

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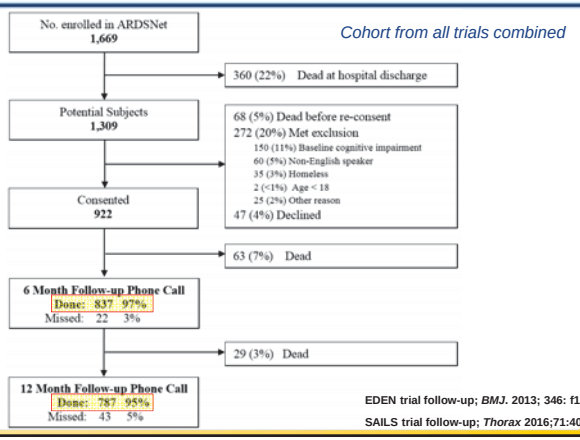
Follow-up of ARDS Network's ALTA, EDEN, OMEGA, and SAILS Trials



Cohort from all trials combined

EDEN trial follow-up; *BMJ*. 2013; 346: f1532.

SAILS trial follow-up; *Thorax* 2016;71:401-410

Myth: Follow-up = bothersome

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

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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

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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%**

Robinson, Dennison, Wayman, et al. *J Clin Epidemiol* 2007; 60:757-765.

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

Robinson, Dinglas, Sukrithan, et al. *J. Cli.n Epi.* 2015; 68:1481-7.

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/

Robinson, Dinglas, Sukrithan, et al. *J. Cli.n Epi.* 2015; 68:1481-7.

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

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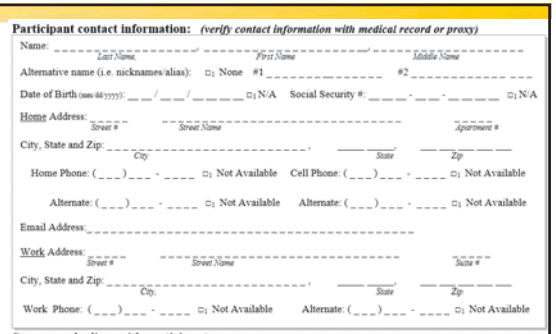
Detailed Contact Info Sheet Template



Participant contact information: *(verify contact information with medical record or proxy)*

Name: _____ (Last Name), _____ (First Name) _____ (Middle Name)

Alternative name (i.e. nicknames/alias): ☐1 None #1 _____ #2 _____

Date of Birth (mm/dd/yyyy): ___/___/_____ ☐1 N/A Social Security #: ___-___-_____ ☐1 N/A

Home Address: _____ (Street #) _____ (Street Name) _____ (Apartment #)

City, State and Zip: _____ (City), _____ (State) _____ (Zip)

Home Phone: (___)___-____ ☐1 Not Available Cell Phone: (___)___-____ ☐1 Not Available

Alternate: (___)___-____ ☐1 Not Available Alternate: (___)___-____ ☐1 Not Available

Email Address: _____

Work Address: _____ (Street #) _____ (Street Name) _____ (Suite #)

City, State and Zip: _____ (City), _____ (State) _____ (Zip)

Work Phone: (___)___-____ ☐1 Not Available Alternate: (___)___-____ ☐1 Not Available

Someone who lives with participant:

Name: _____ (Last Name), _____ (First Name) _____ (Middle Name)

Home Phone: (___)___-____ ☐1 Not Available Work Phone: (___)___-____ ☐1 Not Available

Cell Phone: (___)___-____ ☐1 Not Available Alternate Phone: (___)___-____ ☐1 Not Available

Relationship to Patient (e.g., wife, father): _____

Someone with different address from participant: *(obtain complete information for 2 people)*

Name: _____ (Last Name), _____ (First Name) _____ (Middle Name)

Address: _____ (Street #) _____ (Street Name) _____ (Apartment #)

City, State and Zip: _____ (City), _____ (State) _____ (Zip)

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Communication Template

Home Visit Scheduling Script:

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

Note: Identify a mutually agreeable time [verify the availability 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 contact [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 limitation, use the following script:

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Searchable Database of Retention Strategies (systematic review)

Show 100 entries Search:

First Author	Publication Year	Theme	Strategies extracted from paper
Anastasi	2005	Reminders	The study coordinator gave each participant a reminder telephone call before each study visit.
Anastasi	2005	Contact and Scheduling Methods	The contact information for the study coordinator was also incorporated into the daily food diaries to provide an easy and accessible mechanism to reach the study team for questions or other issues.
Anastasi	2005	Contact and Scheduling Methods	Study participants were required to provide the study coordinator with instructions on leaving telephone messages at home, in the event a roommate, partner, or answering machine was available to take messagesThis procedure was instituted to protect the confidentiality of study participants' HIV status.
Anastasi	2005	Visit Characteristics	Flexible office hours

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Hard-to-Find Participant Checklist

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Step 1 – Calling phone numbers

(Disconnected and other non-working phone numbers should be called frequently to check if the numbers are working again).

If neither participant nor proxies have returned our phone calls within 3 days OR there are NO working phone numbers, immediately do the following:

- send a "Hard to find" letter to the participant (see "Step 3 – Sending mail" further below), then
- complete "Step 2 – Online searching," and
- If appropriate, investigate if there have been any recent hospitalizations and/or new contact info (e.g., review your medical records system).

Did you call all available phone numbers for the participant? ***Note: if you need to call from a different number, use Google voice.***	☐ Done. Additional notes:
Did you call all available phone numbers for the proxies?	☐ Done. Additional notes:

Step 2 - Online searching

(Online searches should be repeated every 1-2 weeks, to check for updates).

Did you "reverse search" the participant using name, phone number and address (e.g., using Superpages.com)?	☐ Done. Additional notes:
Did you "reverse search" all proxies using name, phone number and address (e.g., using Superpages.com)?	☐ Done. Additional notes:

Step 3 – Sending mail

If you have performed all of the above steps and have not made contact with a subject within 2 weeks of the *initial* call:

- Send a "Hard to Find" (HTF) letter (see example at www.ImproveICU.com)
- If no response to above, send "Signature Required Letter" (SRL) via USPS 1 week later
- Discuss with study supervisor or investigator regarding whether to send a "Hard to Find" (HTF) letter to any searched address.

Did you send a Hard To Find letter to the participant?	☐ Done. Additional notes:
Did you send a Hard To Find letter to each proxy?	☐ Done. Additional notes:
Did you send a Signature Required Letter to the participant?	☐ Done. Additional notes:

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Escalation of Retention Strategies

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Stage 1:

Phone participant ***# weeks*** *before due date*

1. If participant is not available, leave a message
2. If contact information is not valid, do "reverse search" for phone number using participant's address on Superpages.com

**If none of the subject's contact data is valid, proceed to telephone proxy(s)

Stage 2:

If no response from participant after ***# daily*** *attempts at phone contact, by* ***# weeks*** *before due date:*

1. Send letter to participant via regular mail
2. Phone proxies (if done in Stage 1, mail proxy now)

Stage 3:

If no response by ***# weeks*** *before due date:*

- Send signature-required letter to participant and regular letter to all proxies (use signature-required letter for proxy if regular letter sent in Stage 2)

Stage 4:

If no response from by ***# - # weeks*** *before due date:*

1. Mail signature-required letter to all proxies
2. Re-check Superpages.com for any updated information
3. Follow the Hard-to-Find Participant Checklist Manual and Hard-to-Find Participant Checklist
4. Immediately discuss participant status with senior research team members (e.g., investigator), and have other staff attempt contact with the participant
5. Discuss plans for home visit (if feasible/applicable)

Reminder:

Always document any communication with participant and/or proxy on Participant Contact Attempt and Locate Log

Ensure to utilize the Hard-to-Find Participant Checklist for specific resources and strategies.

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Aim 3

STATISTICAL TOOLS TO ACCOUNT FOR COMPETING RISK OF MORTALITY

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R24 Grant – Aim 3 (competing risk mortality)

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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

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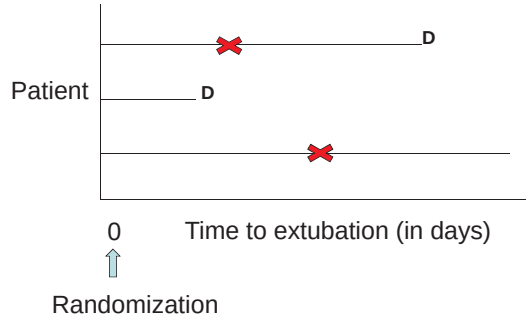
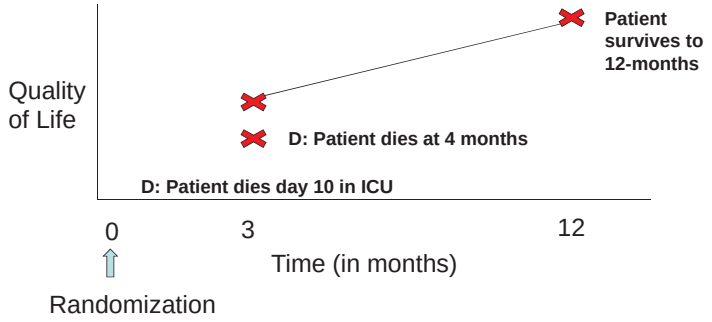
"Competing risk" of mortality

Randomized trial in mechanically ventilated adult ICU patients

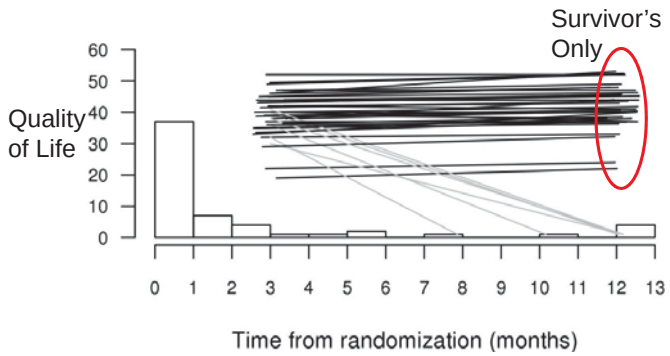


LTOs "truncated due to death"

Randomized trial in ALI/ARF adult ICU patients



LTOs "truncated due to death"



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

Percentile	Intervention	Control
25th	Experienced death by 60 days	Experienced death by 12 days
50th	Survive to 12-months with QOL ≤ 30	Experienced death by 71 days
75th	Survive to 12-months with QOL ≤ 45	Survive to 12-months with QOL ≤ 40
90th	Survive to 12-months with QOL ≤ 49	Survive to 12-months with QOL ≤ 47

Composite endpoint method

- Advantages
  - Simple to implement and explain
  - Provides a hypothesis test for comparing interventions
  - Adheres to the intention to treat principle
- Disadvantages
  - Requires a ranking scheme
  - Does not directly allow for separating out the effects of interventions on mortality and the LTO, i.e. provides a global test

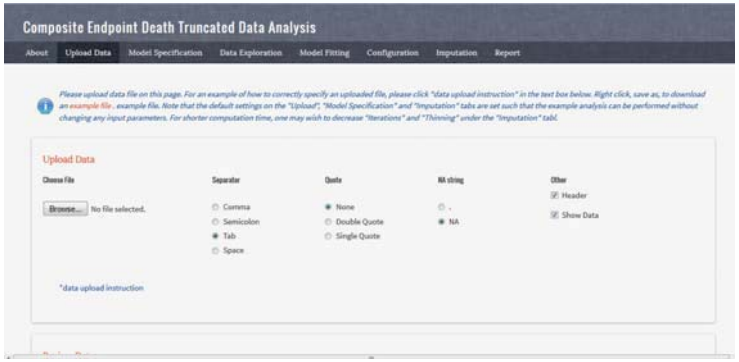
Recommendations

- 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
- Can be downloaded as a standalone application
  - i.e. you don't have to have these software installed on your computer

Software development



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