Ascertaining Death and Hospitalization Endpoints: The TRANSFORM-HF Experience

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Presentation Outline

- Death Endpoint
  - Explanatory vs. Pragmatic trial
  - Data collection options
- TRANSFORM-HF Case Study
  - Study design
  - Death Hybrid Data Collection Plan
  - Hospitalization Hybrid Data Collection Plan

Death Endpoint

Introduction

- Death Endpoint Rationale
  - Delaying death is major health care objective.
  - Objectively measured (unbiased)
- Death Identification and Adjudication Process
  - Differs in explanatory and pragmatic trials
  - Has implications for how death endpoints are acquired and measured
- Primary death measurement Issues
  - Lack of national death data source
  - Available sources incomplete
  - Difficult to access

Death Identification and Adjudication Processes

- Explanatory Trial
  - Sites
    - *Responsible for identifying patient deaths*
    - *When patient cannot be contacted*
      - *Proxy contacted to schedule visit or*
      - *Searches internet for patient location*
    - *Process varies between sites*
    - *Forwards source documents to CEC*
  - Centralized Clinical Events Committee (CEC)
    - *Responsible for adjudicating cause of death*
    - *Uses CEC procedure and source documents*

Death Identification and Adjudication Processes

- Pragmatic Trial
  - Responsibilities
    Sites not responsible for identifying all deaths
    Frequently rely upon secondary data sources
  - EHRs and patient devices
    Record only care-related events
    Unless patient dies during care event, death not recorded
  - National / Regional Death Databases
    Most not timely and/or not comprehensive
    Not easily linked with patient health records
    Cause of death not reliable

Death Rates Vary By Data Source

Source	Living	Deceased	% deceased
Accurint	5000	470	8.6
Social Security Death Master File	5140	330	6.0
National Death Index	4870	600	11.0
NORC's final disposition after 2014 locating effort	4820	650	11.9
Deceased according to any of the four sources	4740	730	13.3
Deceased according to all four sources	5190	280	5.1

- Data source completeness?
  - Patients in these databases likely have died.
  - Patients not in databases not necessarily alive.
- Search criteria availability and timing?

Warren JR, 2017

Death Event Identification Planning Steps

- Determine data required from death event
  - "Fact of Death" – patient has died
  - Date of death
  - Cause of death
  - Related conditions
  - Occupation or education level
  - Patient alive
- Single or hybrid death data source
  - Multiple sources may yield better results
    Completeness, timing, additional data
  - If hybrid, how adjudicate discrepancies

Michael Hogarth, MD, 2018

Death Data Sources

- States / Territories
  - Collect vital events (e.g., death)
  - Report vital event statistics
- National Databases
  - Social Security Administration Death Master
  - Medicare Master Beneficiary Summary File
  - NCHS National Death Index
- Other Sources
  - Individual state vital event statistics
  - National Association of Statistics and Information Systems (NAPHSIS) FOD web service.

Death Data Responsibilities

- US Constitution, Article I, Section 2
  - Congress empowered to carry out census in "such manner as they shall by Law direct."
- Vital Statistics (birth, death, marriage, etc.)
  - Federal authority limited because not explicitly outlined in US Constitution
  - States / Territories

    Collect vital event statistics (e.g., death)

    Report to National Center for Health Statistics (NCHS)
  - Since 1933, all states and territories have required vital events registration

Death Data Responsibilities

- National Center for Health Statistics – CDC
  - Charged with collecting and aggregating vital event data at federal level.
  - Data obtained via the Vital Statistics Cooperative Program (VSCP) that pays state / territories for these data.
  - Federal vital events include: birth, death, and fetal deaths.

Death Data National Aggregation Challenges

- Timeliness
  - Electronic death registration systems (EDRS)
    - *46 jurisdictions had EDRS in 2018*
      - *Only 39 with >75% of death events registered via EDRS*
    - *Rarely use the same EDRS*
- State Laws
  - State laws govern vital records release
  - Causes redactions from the death master file

Death Data National Aggregation Challenges

- Data Quality
  - EDRS-EHR integration is rare

    Only California and Utah had demonstrated as of 2018.

    >$50,000 California health system cost may be prohibitive
  - NCHS Cause of Death

    25% of cases require manual coder review.

    US model death certificate has 4 narrative 'underlying causes of death' blocks.

    NCHS uses semi-automated process to classify a single 'cause of death.'

National Death Data Files

- SSA Death Master File
  - Data sources: family members, funeral homes, financial institutions, postal authorities, states and other federal agencies.
  - Patient Identifier: Social Security Number
  - Limitations

    Before 2011, DMF was the timeliest, most comprehensive, and least expensive patient death data source.

    In 2011, SSA agreed with closed record states that the Social Security Act did not supersede state laws that limited the disclosure of state records.

National Death Data Files

- SSA Death Master File
  - Resulted in the exclusion of 40% of new death from the DMF.
  - Public DMF version

    Does not include state death data.

    Does include information from other sources.

    Source for Ancestry.com, Legacy.com.
  - Death data incomplete:

    Death are deaths.

    Absence of death not mean patient is alive.

Death Data Files

- Medicare Master Beneficiary Summary File
  - Data sources: Medicare claims, family members, online date of death edits, Medicare beneficiary information.
  - Patient Identifier: Medicare Beneficiary Number
  - Standard linking approach: SSN / Medicare ID, date of birth, and sex
  - Limitations

    Available 9-months after calendar year close.

    Only Medicare beneficiaries.
  - Death data incomplete:

    Non-beneficiaries not included.

Death Data Files

- NCHS National Death Index
  - Data sources: State vital statistics offices.
  - Patient Identifiers
    1. *Social Security Number, sex, full birth date*
    2. *Last name, first initial, birth year and month*
    3. *Social Security Number, last name, first initial*
  - Limitations

    Preliminary results (90% of deaths) available 1-2 months after calendar year ends final file available after 9-10 months.

    Only for research death determination.

    Not for legal, administrative or genealogical.

Death Data Files

- NCHS National Death Index
  - Legal Arrangements

    NDI is not provisioned by law nor funded by Congressional appropriation.

    NCHS is an 'honest broker' trusted by 57 jurisdictions to use their data to support research studies in any jurisdiction.

    NDI service is self-supporting by fees, with a portion allocated back to jurisdictions providing death data.
  - Death data considered complete: Absence of death means patient alive at reporting year end.

TRANSFORM-HF Clinical Trial

What should a pragmatic trial do?

The TRANSFORM-HF Trial

ToRsemide compArisoN with furoSemide FOR Management of Heart Failure

On Behalf of the TRANSFORM-HF Executive Committee

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Primary Objective

To compare the treatment strategy of torsemide versus furosemide on long-term clinical outcomes among patients hospitalized for HF

Primary Endpoint:

All-cause mortality

TRANSFORM-HF Protocol, 2018

Population and Entry Criteria

Patients hospitalized for HF

- Regardless of LVEF
- Include newly diagnosed HF and worsening chronic HF

Inclusion Criteria

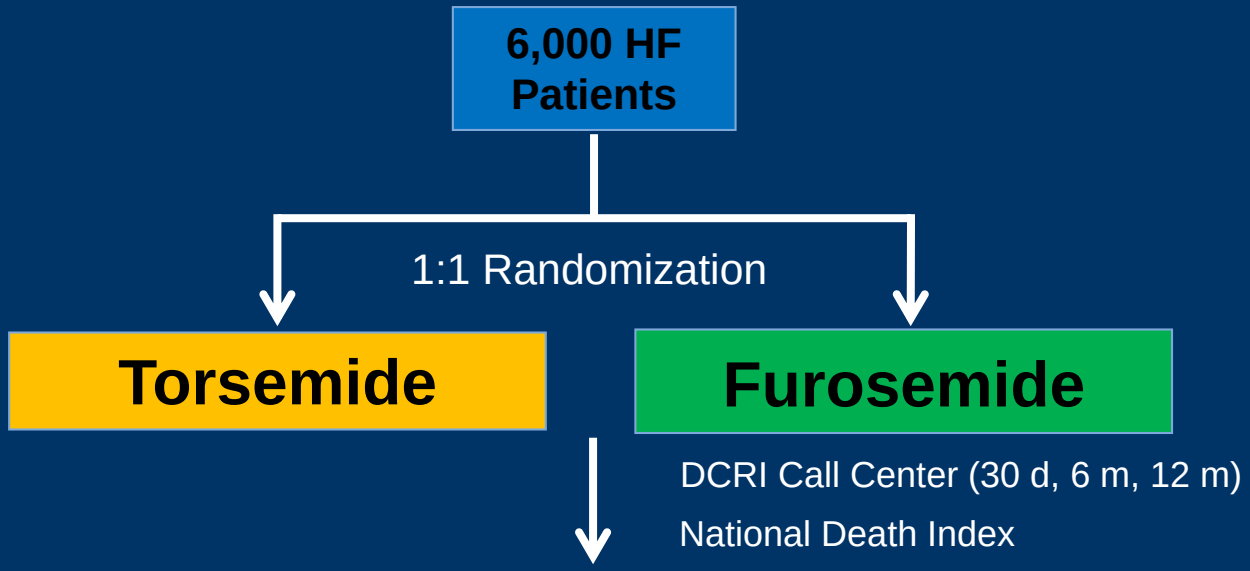
- ***Either*** LVEF≤40% ***or*** elevated natriuretic peptide on local lab
- Age ≥18 years
- Hospitalized HF patient
- ***Outpatient plans for daily loop diuretic regimen***
- Signed inform consent

Exclusion Criteria

- ESRD requiring RRT
- LVAD or anticipated <3 mos
- History of OHT or listed
- Non-cardiac condition limiting life <12 months
- Pregnant/nursing women
- Known hypersensitivity to torsemide or furosemide

TRANSFORM-HF Protocol, 2018

The TRANSFORM-HF Trial



Primary Endpoint:

All-Cause Mortality

Secondary Endpoints:

All-cause Mortality + Hospitalization at 30 days and 12 months
Total Hospitalizations over 12 months
Health-related Quality of Life over 12 months
Symptoms of Depression over 12 months

TRANSFORM-HF Protocol, 2018

Pre-Screen/Screen/Randomization

Pre-Screen (via routine patient care) » Consent patient » Pre-Randomization » Randomize in RedCap

- Confirm eligibility
- Complete Patient Forms
- RedCap

- KCCQ/PHQ
- Anticipated Daily Dose

- Pt. materials
- RedCap
- Send Forms to Call Center

TRANSFORM-HF Protocol, 2018

Discharge and Call Center

Ensure patient participant has Rx

Discharge info into eCRF

Fax D/C instructions to CC

DCRI Call Center* patient follow-up

- 30 days
- 6 mos.
- 12 mos.
- 18 mos
- 24 mos.
- 30 mos.

*The DCRI Call Center will also initiate a medical record query 12 months after patient randomization to screen for hospitalizations at the enrolling center and potential treating hospitals identified by the patient. Also, the National Death Index (NDI) will be searched during follow-up and prior to study close-out.

TRANSFORM-HF Protocol, 2018

TRANSFORM-HF Death Ascertainment and Verification

- Mortality event definition: death after randomization.
- Hybrid approach
  - Clinical trial sites: index hospitalization.
  - Centralized Call Center: follow-up period.
  - National Death Index searches: secondary.
- 2-Step Process
  - Ascertain (trigger) possible death.
  - Verify (document) triggered death.
- Trigger-verification elements collectively form the TRANSFORM-HF death event definition.

TRANSFORM-HF Death Ascertainment and Verificaton: Clinical Trial Site

- Patient dies during index admission
  - Ascertainment: Site enters death information in EDC system. Discharge disposition is 'Died in hospital prior to discharge.'
  - Verification: Send patient discharge summary to Call Center.
- Spontaneous report
  - Ascertainment: Site learns patient has died after discharge. Forward this information to Site Management or Call Center.
  - Verification: Call center will verify death through usual processes.

TRANSFORM-HF Death Ascertainment: Call Center

- During index admission
  - Patient completed Informed Consent, Medical Release and Patient Contact forms (SSN optional field).
  - Patient contact form include: proxies, hospitals likely to visit and primary care physician contact information.
  - Valid proxies include: spouse, significant other, friends or relatives not living with patient.
  - Site forwards forms to Call Center.
- Call Center interviewers use these document in communications with patients, proxies and their care providers.

TRANSFORM-HF Death Ascertainment and Verification: Call Center

- Call Center Ascertainment Hierarchy
  - Proxy interview
  - Online search (e.g., newspaper articles, social media, legacy.com, ancestry.com)
  - Medical records search

    Hospital discharge summary

    Billing office

    Patient chart from PCP or other healthcare providers

TRANSFORM-HF Death Ascertainment: Call Center

- Call Center Verification Hierarchy
  - Online search for obituary
  - Additional online searches for obituary or grave marker
  - Medical records request to verify death
    Hospital discharge summary
    Billing office
    Patient chart from PCP or other healthcare providers
  - Secondary proxy to verify death

TRANSFORM-HF Death Ascertainment and Verification: Call Center

- Online search for patient obituary or grave marker

  Must include: first name, last name, middle initial (when applicable), and date of birth matching patient contact form.

  Age may be substitute for DOB when state of residence matches

TRANSFORM-HF Death Ascertainment and Verification: National Death Index

- National Death Index Data Sets
  - Early Release File
    Jan-Feb available
    90% of previous year deaths
  - Final File
    Oct-Nov available
    All previous year deaths
- TRANSFORM-HF NDI Search Plans
  - First two study years: final file searches.
  - Subsequent years: early release and final file searches (more deaths available).

All-Cause Mortality Events: Triggered vs. Verified

	Verification Status					
Initial Source/Trigger	**Yes**				**No**	**Total**
	Obituary or Grave Marker	**2nd Proxy**	**Medical Record**	**NDI**		
Proxy interview[1]	n	n	n	n	n	n
Online search[2]	n	n	n	n	n	n
Medical record search[3]	NA	NA	n	NA	NA	n
Enrolling site	n	n	n	n	n	n
National Death Index (NDI)	NA	NA	NA	n	NA	n
Total	n	n	n	n	n	n

TRANSFORM-HF SAP, 2018

TRANSFORM-HF Death Ascertainment and Verification

- Mortality Review Committee
  - Membership: Clinicians, Call Center, Statistician
  - Charter

    Review NDI death categories for cut-point.
    Review cases with data source conflicts (e.g., fact of death, date of death, last known alive date).
- Limitations
  - Patient contact form sole contact information source.
  - Missing data impacting NDI searches.

Hospitalization Endpoint

Hospitalization Data Collection Options
NIH Collaboratory Grand Rounds

- March 1, 2019: Approaches to Patient Follow-Up for Clinical Trials: What's the Right Choice for your Study? (Keith Marsolo, PhD)

TRANSFORM-HF Hospitalization Ascertainment and Verification

- Hospitalization event definition: an admission to an inpatient unit or a visit to an emergency department that results in at least a 24-hour stay (or a change in calendar date if the time of admission/discharge is not available) after discharge from index hospitalization.
- 2-Step Process
  - Ascertain (trigger) possible hospitalization
  - Verify (document) triggered hospitalization
- Trigger-verification elements collectively form the TRANSFORM-HF hospitalization event definition.

TRANSFORM-HF Hospitalization Ascertainment and Verification: Call Center

- Call Center Ascertainment Hierarchy
  - Patient or proxy interview
  - Medical records search
  - 12-month medical record query
- Call Center Verification Hierarchy
  - Hospital discharge summary
  - Medical records request
    - *Billing record*
    - *Patient chart from healthcare providers*

Conclusions

- Ascertaining death and hospitalization events can present challenges for pragmatic clinical trials.
- No authoritative data source for researchers.
- Hybrid data collection strategy is necessary.
- Call Center that coordinates follow-up patient contact and data collection is a valid approach.
  - Insures a single point of contact for patients / proxies and care providers.
  - Utilizes professional interviewers with standard protocols and scripts.
- Call Center should be supplemented with other / redundant data sources.

References

- NIH Collaboratory Living Textbook
  - Choosing and Specifying Endpoints and Outcomes
    - *4. Using Death as an Endpoint*
    - *5. Inpatient Endpoints in Pragmatic Clinical Trials*

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Questions?