Comparative Effectiveness Research: Role of Registries

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Objectives

• To understand the purpose of comparative effectiveness research

• To understand the elements of a comparative effectiveness study

• To know what data sources may be available to conduct comparative effectiveness studies

• Understand importance of and approaches to knowledge translation for comparative effectiveness research
Comparative Effectiveness Research

• To inform health-care decisions
  – From the perspective of Patients, clinicians, payors

• Provides evidence regarding different treatment options:
  – Effectiveness
  – Benefits
  – Harms

• Treatment options that can be studied:
  – Drugs, devices, procedures, tests, ways of delivering health care

Comparative Effectiveness Research
Research for the Modern Medical Care System

Outcomes Research
Quality Improvement Research
Effective use of the electronic Medical Record
Research Quote!!

In attempting to arrive at the truth, I have applied everywhere for information, but in scarcely an instance have I been able to obtain hospital records fit for any purposes of comparison. If they could be obtained, they would enable us to decide many other questions besides the one alluded to. They would show subscribers how their money was being spent, what amount of good was really being done with it, or whether the money was not doing mischief rather than good: NIH? CMS? Institute of Medicine? Am Hosp Assoc?

No it was Florence Nightingale 1863

NOTES ON HOSPITALS.

FLORENCE NIGHTINGALE.

LODGE, LONDON, GREEN, LONDON, ROBERTS, AND GREEN 1863.

But first have had as well as we beg an engine as I hope to have them in cold. It is imperative that this impression should be either dispersed or continued.

In attempting to arrive at the truth, I have applied everywhere for information, but in scarcely an instance have I been able to obtain hospital records fit for any purposes of comparison. If they could be obtained, they would enable us to decide many other questions besides the one alluded to. They would show subscribers how their money was being spent, what amount of good was really being done with it, or whether the money was not doing mischief rather than good: NIH? CMS? Institute of Medicine? Am Hosp Assoc?
CE Studies

- Designs
  - Sequential
  - Adaptive
  - Futility

- Outcomes
  - Clinical
  - Imaging
  - Patient-reported

- Data sources

Limitations of Sequential Trials

- Requires rapid outcome
  - e.g. BMT engraftment
  - Oxygenation response to intervention
  - Too many MRIs in PEDs MS to be feasible

- May not enter boundary and can lead to larger sample sizes than fixed trials

- Assumes accrual is limitless and sequential with homogeneous population
Adaptive Designs
Little Word - Many Meanings

• Requires the trial to be conducted in incremental stages with access to the accumulated data and predefined decisions

• Adaptive design may adapt using:
  – Allocation Rule: how subjects are allocated to treatments
  – Sampling Rule: how many subjects are used in the next stage
  – Stopping Rule: when to stop the trial (for efficacy, for harm, for futility)
  – Decision Rule: how the next steps move forward

Interim analyses & adaptations are performed for many reasons

• To stop enrollment in the control arm so all future enrollment is in the test regimen.
• To stop all enrollment because of disappointing results.
• To increase enrollment to reach a larger sample size.
• All such decision points must be planned and pre-specified.
• Extra burden on the monitoring and data management groups.
Interim Analyses or Adaptation entail careful planning of the protocol

- Exacting detail of the statistical design and analysis that can be fixed in advance is provided in the protocol:
  - number of interim analyses or adaptations
  - information rates (how much of the data are available)
  - stopping guidelines
  - Tests

- The time of the Interim Analysis is unknown to the investigators, if possible.

Futility Trials

- A Futility Design or Futility Trial is similar in some way to noninferiority trials or to equivalence studies
  - Assumes a negative outcome as the null hypothesis
    - Drug A is worse than B and tries to reject that hypothesis
    - Rather than convention of null be equal results.

- Often uses historical controls and single group trial to save time and patients
Why Do Futility Trials?

• **PRO**
  - Opportunity cost – spending money on a futile trial is silly because the money could be spent on other trials
  - It is ethically wrong to continue to recruit patients to trials with little hope of achieving helpful results

• **CON**
  - Well conducted trials provide valuable scientific evidence
  - The costs of designing futility trials with a planned futility analysis outweigh any savings
  - Will the result be believed and really save $$$

Outcomes

• **Clinical endpoints**
  - Currently / often used endpoints
  - Emerging endpoints

• **Imaging endpoints**
  - Current / often used endpoints
  - New endpoints

• **Patient-reported outcomes (PROs)**
Currently Used Clinical Endpoints

• Relapse rates
  – Annualized relapse rate
  – % relapse free
  – Time to first relapse

• EDSS disability progression
  – EDSS scale: most common disability scale in MS
  – Progression: 1.0-point ↑ in EDSS if < 5.5, or 0.5 point if ≥5.5
  – Usually time to 3-month confirmed progression
  – Sometimes time to 6-month confirmed disability progression (more robust end point, but shortens observation period)

• Multiple Sclerosis Functional Composite (MSFC)

Emerging Clinical Endpoints

• Composite dysconjugate endpoints
  – Change in EDSS or any component of MSFC

• Disease Activity Free Status (DAFS)
  – Absence of Change in EDSS, relapses, MRI activity

• Sustained improvement in EDSS

• Sustained reduction in disability / sustained accumulation of disability
  – Ratio of SRD/SAD (if ratio=1, benefit/risk in balance or random)

• Modifications in MSFC
  – Addition of vision component
  – Replaced Paced Auditory Serial Addition Test (PASAT) with Symbol Digit Modalities Test (SDMT)
Sustained Improvement in EDSS

- A $\geq 1.0$ point decrease in EDSS score sustained for 12 weeks
- Utilized in post-hoc analysis of natalizumab AFFIRM study
  - Natalizumab increased the cumulative probability of improvement over 2 years by 69% versus placebo ($P=0.006$)
- Potential indicator of neurological improvement
- In AFFIRM, sustained improvement in EDSS correlated with quality of life measures (eg, SF-36)

AFFIRM = Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis


Example of Sustained Improvement in EDSS from Natalizumab Phase III AFFIRM Study

Sustained Accumulation of Disability (SAD) / Sustained Reduction in Disability (SRD)

- In the original analysis of the alemtuzumab CAMMS223 phase II study, sustained accumulation of disability (SAD) was an endpoint.¹
  - SAD: an increase in EDSS of ≥1.5 for patients with baseline EDSS of 0, or an increase of ≥1.0 for patients with baseline EDSS of ≥1.0, sustained for continuous 6-month period
  - Based on the finding that alemtuzumab reduced disability in the above trial, sustained reduction in disability (SRD) was proposed as a new endpoint and initially applied to data from CAMMS223²
    - 6-month SRD: A ≥1 point decrease on the EDSS sustained for 6 consecutive months for patients with a baseline EDSS ≥2

- SAD was co-primary end point in CARE-MS I and CARE-MS II studies
  - In CARE-MS I, alemtuzumab showed no significant effect on SRD/SAD
  - In CARE-MS II, alemtuzumab showed a 42% reduction in SAD vs Rebif (P=0.0084) over 2 years¹


CARE-MS = Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis
CAMMS223 = Campath Study in MS

Application of MSFC z-score in Phase III MS Trials

- Fingolimod
  - FREEDOMS and TRANSFORMS studies
    - Mean change in MSFC from baseline
- Alemtuzumab
  - CARE-MS I study (likely also applies to CARE-MS II study)
    - Mean change in MSFC (or MSFC + Sloan visual acuity test) from baseline
- Teriflunomide
  - TEMSO study (teriflunomide vs placebo)
- Natalizumab
  - AFFIRM and SENTINEL studies

- Avonex¹
  - In an 8-yr follow-up to the pivotal Avonex study, MSFC predicted brain atrophy and EDSS, suggesting it is highly relevant as a clinical measure in MS trials
  - Validated as a primary endpoint in the IMPACT study (patients with SPMS)²

- Betaseron (interferon beta-1b)³
  - Long-term (16-yr) follow up after pivotal study reported median MSFC values for each treatment group
  - No analysis of treatment effects vs. changes in MSFC was reported


SENTINEL = Safety and Efficacy of Natalizumab in Combination With Interferon Beta-1a in Patients With Relapsing-Remitting Multiple Sclerosis
FREEDOMS = FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis
TRANSFORMS = Trial Assessing Injectable Interferon vs FTY720 Oral in Relapsing-Remitting Multiple Sclerosis
* Note: this is not intended to be a comprehensive list of all such studies
Alternative MSFC Approach to Make it Clinically Meaningful

- MSFC z-score has limitations, eg
  - No clear clinical interpretation of changes in z-score
  - Weighting of the components may depend on population under study

- An alternative method of using MSFC has been proposed
  - “MSFC progression”, calculated on the basis of 3-month sustained worsening by at least 15%, 20%, 25% etc. in at least one MSFC component

- This has been applied to a post-hoc analysis of natalizumab AFFIRM and SENTINEL data

- This showed that MSFC progression is clinically relevant
  - Predictive of EDSS progression at 2 years
  - Correlates with relapse rate, EDSS, and SF-36 PCS

Potential Use of Composite (Combined) Clinical/MRI Endpoints

- Disease activity-free status (DAFS)¹
  - DAFS is a new endpoint, generally defined as:
    - Absence of any relapses or any confirmed accumulation of disability, and
    - Absence of new MRI activity (no new T2 lesions, and no new Gd+ lesions)
  - Should be calculated over a defined time period (eg, 2-yr, 3-yr)
  - Application in MS phase III clinical trials (post-hoc analyses)

<table>
<thead>
<tr>
<th>Study</th>
<th>% DAFS (2 yrs), Active agent</th>
<th>% DAFS (2 yrs), Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab (AFFIRM)</td>
<td>37</td>
<td>7</td>
</tr>
<tr>
<td>Cladribine (CLARITY)</td>
<td>44-46</td>
<td>16</td>
</tr>
<tr>
<td>Fingolimod (FREEDOMS)</td>
<td>32.7-37.5</td>
<td>12.9</td>
</tr>
</tbody>
</table>

- In above studies, despite marked reduction of ARR vs placebo, %DAFS was below 50%, leaving room for increases in efficacy
- May be very relevant outcome for Head to Head Trials
- May also be relevant for SPMS and PPMS studies


¹ CLARITY = Cladribine Tablets Treating MS Orally

Potential Use of Composite (Combined) Clinical/MRI Endpoints

• “Freedom from clinical disease activity” (CDA)\textsuperscript{1,2}
  – As part of post-hoc analysis of data from alemtuzumab phase II study (CAMMS223), CDA was defined as no relapses and no "sustained accumulation of disability"
  – In CAMMS223, over 36 months, CDA occurred in 72% alemtuzumab patients vs 43% IFNbeta-1a patients (P<0.0001)
  – Compared to CDA, freedom from disease activity (ie, DAFS) is a more complete metric, as DAFS includes MRI data
    • DAFS could not be calculated for this phase II study because Gd+ MRI scans were not performed routinely


Currently Used Imaging Endpoints

• At present, most imaging endpoints in trials are based on conventional MRI techniques
• Measures of neurodegeneration\textsuperscript{1}
  – Brain volume / atrophy (eg, brain parenchymal fraction [BPF])
    • Atrophy rates in grey matter may differ from rates in white matter
  – T1 Hypointense lesions ("Black holes")
    • Limitation: definition is qualitative\textsuperscript{2}
    • Evolution of "black holes"
• Measures of inflammatory component of disease\textsuperscript{1}
  – Gadolinium-enhancing T1 lesions
  – T2/FLAIR hyperintense lesions
    • Measures cumulative lesion burden

Emerging Imaging Endpoints

- **Nonconventional MRI techniques**
  - Proton magnetic resonance spectroscopy (1H-MRS)
  - Magnetization transfer ratio (MTR) imaging
  - Diffusion tensor imaging
  - Functional MRI (fMRI)

- **Other imaging endpoints**
  - Optical coherence tomography (OCT)
    - RNFL
    - Other measures of retina/disc


Optical Coherence Tomography (OCT)

- Non-invasive technique, conceptually similar to ultrasonography1,2
  - Uses echo of infra-red light (rather than ultrasonic waves)
- Widely used for imaging retinal nerve fiber layer (RNFL) thickness & macular volume
  - Reduction in RNFL may be correlated with1-3
    - Optic nerve atrophy, brain atrophy
    - Disease progression
- OCT may represent a simple way to measure neuroprotection in clinical trials2
  - Feasible, reproducible, high pathological specificity

Assessing Visual Dysfunction in MS Using Low-contrast Charts (Sloan Letter Charts)

- Low-contrast letter acuity (Sloan letter charts)\textsuperscript{1,2}
  - Decline in low-contrast letter acuity is associated with MS
  - Considered sensitive method of measuring visual function in MS clinical trial
  - Appears to correlate well with structural disease markers (eg, MRI measurements of brain atrophy and lesions), RNFL thickness (measured by OCT), and disability (EDSS and MSFC scales)

- Low-contrast letter acuity was measured in
  - Alemtuzumab CARE-MS I and CARE-MS II phase III studies\textsuperscript{3}
  - Fingolimod TRANSFORMS and FREEDOMS II phase III studies
  - Natalizumab AFFIRM and SENTINEL phase III studies\textsuperscript{4}
  - CombiRx (IFN-\textbeta-1a vs glatiramer acetate (GA) vs IFN-\textbeta-1a /GA)\textsuperscript{5}
  - Avonex Impact Trial Phase III SPMS Study\textsuperscript{6}


Application of Low-contrast Acuity Testing in a Phase III Clinical Study in MS Patients

Data from alemtuzumab CARE-MS I study: mean MSFC change from baseline\textsuperscript{1}

Data from natalizumab AFFIRM study: cumulative probability of sustained worsening of scores from baseline\textsuperscript{2}

Conclusions based on this endpoint:
- Alemtuzumab produced a significant improvement in MSFC and visual acuity compared to active comparator
- “Natalizumab reduces loss of visual function in patients with relapsing MS.”
- “Low contrast letter acuity (Sloan chart) testing has the capacity to demonstrate treatment effects and fulfills major criteria for inclusion in future MS clinical trials”

PATIENT-REPORTED OUTCOME MEASURES (PROs)

Renewed Interest by Feds, FDA, EMA

SF-36 Quality of Life Outcome Measure

- Measures patient health-related quality of life (physical & mental)
- Disease Specific, validated & multiple languages
- Generalized to be used for any disease, not just MS
  - Thus, may not properly weigh domains important for MS patients
- Endpoint in ALLEGRO (laquinimod) and DEFINE (BG-12) phase III studies, among others
- Can complement EDSS

After 2 years of BG-12 therapy, patients in the BG-12 group (both doses) had significantly higher PCS (physical well being) and MCS (mental well being) scores vs placebo.

Patient Reported Clinical Outcomes

- Global impression of well-being, assessed using a Visual Analogue Scale (VAS)¹
  - 100-point scale indicating well-being
  - Used in BG-12 DEFINE phase III study¹
    - Compared with placebo, both doses of BG-12 "significantly improved... general well-being in patients with RRMS"¹
- MS Impact Scale (MSIS-29)
  - Measures MS-specific HRQOL (physical and psychological impact)
  - Validated; uses rigorous psychometric methods²
    - Promising for clinical trials
  - Used in daclizumab SELECT phase IIb study³
    - Daclizumab showed a “trend towards improvement” in the MSIS-29 physical score (150 mg dose P<0.001, 300 mg dose P=0.12 vs. placebo)
  - MSIS-29 also used in the ATTAIN study of PEGylated interferon beta

¹ Kappos L, et al., ECTRIMS 2011, Amsterdam. P1071

SELECT = Safety and Efficacy Study of Daclizumab HYP to Treat Relapsing-Remitting Multiple Sclerosis
Other Patient-Reported Outcomes

- Modified Fatigue Impact Scale (MFIS)
  - Used in the laquinimod ALLEGRO phase III study
  - Laquinimod produced a significant improvement in fatigue vs placebo
- Guy’s Neurology Disability Scale (GNDS) / UK Neurological Disability Scale (UKNDS)
  - MS-specific scale; takes into account cognitive issues, and fatigue
  - Many validation studies show high reliability
  - However, designed for use in clinical practice not research trials
  - Moderate responsiveness to clinical change
- MS Quality of Life-54 (MS-QOL-54)
  - Validated, acceptable test-retest reliability; limited inclusion of visual and bladder/bowel function
- Functional Assessment of MS (FAMS)
  - Good internal consistency; but almost omits visual, sexual, bladder, and bowel measures
- Patient Determined Disease Steps (PDDS)
  - A self reported EDSS, extensively used in the NARCOMS Registry


Other Patient-Reported Outcomes

- Pain (eg, brief pain inventory, PROMIS Pain Impact Short Form)
- Health resource use
  - Is trial-based resource use valid
  - Is patient self-report valid?
- Vocational status measures (ie, employment); used in
  - Phase II study of GSK’s firategrast (SB683699 / “natalizumab in a pill”)
  - 20-year follow-up (by telephone) of pivotal Betaseron MS study
- Depression
  - Patient-health questionnaire (PHQ-9)
  - Beck Depression Inventory (BDI)
Example Published CE Study

- **Objective**: assess relapse rates in patients with active MS initiating fingolimod, IFN or GA
- **Data source**: US PharMetrics Plus database
- **Population**: 525 MS patients who initiated fingolimod, IFN, GA between Oct 1, 2010 and Mar 31, 2011 and had relapse in prior year
- **Outcome**: Relapses – claims-based algorithm
  (inpatient visit with a primary ICD-9-CM diagnosis code of 340, or both an outpatient visit with a diagnosis code of 340 and oral or intravenous corticosteroid use within 7 days of the outpatient visit)

CE Study Results

- **Treatment** | n  | %relapses | ARR  
- **Fingolimod** | 128 | 31.3%  | 0.50  
- **IFN/GA**     | 397 | 34.0%  | 0.55  

- Baseline differences: age, use of another DMT, number of relapses pre-treatment
- Adjusting for baseline differences odds of having relapse 52% ↓ with fingolimod OR 0.48; 0.28-0.84
- 50% ↓ ARR OR 0.50; 0.34-0.75
**Cost Effectiveness Analyses Does Not Equal Cost Benefit Analyses**

- **CEA** is based on an assessment of the ratio of the financial cost to a unit of measure
  - Cost per relapse
  - Cost per sustained progression
  - Cost per Quality Adjusted Life Year

- **CBA** less widely used:
  - Ratio or difference of two costs, the cost or Euro value of the event or outcome
  - Means putting a cost in Euros on the outcome, which is sometimes the value of a life!

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**CEA vs. CBA**

Cost-Effectiveness Ratio = Total Cost / Units of Effectiveness

Cost-Benefit-Analysis often uses:

Net Benefits = Total Benefits - Total Cost

What is the Dollar value of a relapse prevented?

If MS Therapy ↓mortality, what is the value of that life saved?
Simplified Process
Steps in Cost-Effectiveness & Cost-Benefit Analysis

- Set the framework for the analysis
- Decide whose costs & benefits should be recognized
- Identify and categorize costs and benefits
- Project costs & benefits over the life of the program
- Monetize (place a dollar value on) costs
- Quantify benefits in terms of units of effectiveness (for CEA), or monetize benefits (for CBA)
- Discount costs & benefits to obtain present values
- Compute a cost-effectiveness ratio (for CEA) or a net present value (for CBA)
- Perform sensitivity analysis
- Make a recommendation where appropriate

Costing Treatments Using Markov Chains

- Probability of no Relapse given you Haven’t had one
- Probability of a relapse given you haven’t had one
- Probability of a relapse given you have had one
- Probability of Another Relapse given you Have had one
Following the Cohort Over Time

<table>
<thead>
<tr>
<th></th>
<th>By Time 2</th>
<th>By Time 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Relapse</td>
<td>Relapse</td>
</tr>
<tr>
<td>Time 1</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>No Relapse</td>
<td>0.6</td>
<td>0.4</td>
</tr>
</tbody>
</table>

- Of those who started with no relapses by Time point 2, 20% would have relapses and 40% of those who had relapses during Time 1 would have relapses.

- Of those with no relapses seen at Time 2, 24% would have relapses by time 3 because that group is a mixture of the lower and higher risk populations from the prior interval (relapsed at time 1).

Using the Markov Chain we can estimate the total number of relapses by Year & over longer periods

- **Treatment A**
  - How many people have 0, 1, 2,... relapses
  - What is the cost of a relapse
  - What is the cost of side effects in those with relapses and those without relapses
  - Repeat for Treatment B

- **Treatment A**
  - How many people have 0, 1, 2,... relapses
  - What is the cost of a relapse
  - What is the cost of side effects in those with relapses and those without relapses
  - Repeat for Treatment B
Adding up the Costs

• Total cost in Treatment A is the sum of the cost of the relapses and their treatment plus the cost of the side effects of treatment plus....

• Total cost in Treatment B is the sum of the cost of the relapses and their treatment plus the cost of the side effects of treatment plus....

Quality Adjusted Life Years (QALY): National Institute for Health and Care Excellence (NICE)

• Measures of benefit of treatment used in cost-effectiveness analyses can be based on:
  – 'natural' units, e.g. years of life gained
  – value-based measures, e.g. Quality Adjusted Life Years (QALYs).

• Number of QALYs gained by using a treatment is a measure of its benefit in terms of improvements in:
  – the quality of life of patients (including physical performance, pain, distress and psychological improvements as well as changes in survival) summed over a period of time.
  – It therefore incorporates the value of changes in both morbidity and mortality, where these exist.
In the particular case of MS*

- Natural units which capture specific aspects of the impact of MS:
  - relapses avoided
  - delaying progression to wheelchair dependency

- No units which capture both the impact on relapses & the full impact of progression

- One measure used is the Area under the EDSS curve – how long at various steps

* NICE technology appraisal guidance Issued: January 2002
TA32 Beta interferon and glatiramer acetate for the treatment of multiple sclerosis

How a QALY is calculated

- Patient x has MS: If she continues receiving Treatment A → will live for 1 year & quality of life = 0.4 (0 or below = worst possible health, 1= best possible health)

- If she receives Treatment B → will live for 1 year, 3 months (1.25 years), with a quality of life = 0.6.

- Compare treatments in terms of QALYs gained:
  - Treatment A: 1 (year's extra life) x 0.4 = 0.4 QALY
  - Treatment B: 1.25 (1 year, 3 months extra life) x
Then We Compare the Cost per QALY Gained!

• Therefore, Treatment B leads to 0.35 more QALYs (0.75 - 0.4 QALY = 0.35 QALYs).

• Cost of Treatment A is 100,000 per year & Treatment B costs 120,000.

• Difference in treatment costs is divided by the QALYs gained (0.35) = cost per QALY.

• So Treatment B costs 20,000/0.35 = $57,142.86 per QALY gained.

The Other Side of the Benefit/ Risk Equation

• Adverse event reporting system (AERS)
  – Case reports (spontaneous reports)/ Med Watch

• Literature

• Epidemiology Studies
  – Registries
  – Sponsor conducted
  – Observational studies most common
  – Estimation of frequency/rates of events
Postmarketing Safety Information
Spontaneous Reports

- After approval, there are requirements for reporting safety data to FDA
- Serious, unexpected events in 15 calendar days
- Other events periodically depending on time product on market (e.g., quarterly for first three years and annually thereafter)

“Serious” Adverse Events (at any dose)

- Death
- Life Threatening
- Disability (persistent or significant)
- Congenital Anomaly
- Hospitalization (initial or prolonged)
- Unexpected “not in the label”
Limitations of Case Reports

- No denominator to assess rate
- Bias toward abnormal outcomes
- Uncertain value for common events
  - e.g., migraine, spontaneous abortion
- Information often incomplete
- Underreporting is problematic
  - e.g., knowledge, time, fear of reprisal

When are case reports helpful?

- Biologically plausible event
  - e.g., pharmacology, confirms animal data
- Pattern is suggested
- Confounders ruled out
- Dose, timing and other exposures known
- Rechallenge/Dechallenge
Data Sources for CE Studies

- Administrative data
- Clinical registries & databases
- Electronic medical records

Data Mining

Valuable information in Data Warehouses, EMRs, Insurance Databases
Administrative Data I

• Result from:
  – delivery of health care services
  – reimbursement for health care services
  – enrolment into health insurance plans

• Sources:
  – Government
    • E.g. Medicare, Medicaid
  – Private (commercial insurance) organizations

Administrative Data II

• Personal identification number
• Demographic information
  – Date of birth, sex, region of residence [e.g. postal code, zipcode]
  – Generally lack race/ethnicity (although not universal)
• Date of service
  – E.g. dates of hospital admission and discharge
• Diagnostic & procedure codes for service
• Some datasets capture:
  – prescription claims eg. medications prescribed
  – Site of service delivery
  – Who delivered the service
Recording Diagnoses

- Many jurisdictions use a version of International Classification of Disease (ICD) codes
  - Detail of coding may vary e.g. number of digits
  - At 3 digit level not specific e.g. bipolar disorder (296.4) is the same as depressive disorder (296.3)

- Some customized codes
  - E.g. Clinical Practice Research Database uses READ codes but these can be mapped to ICD-10 codes

Socioeconomic Status

- Not explicitly captured

- An important potential confounder in many studies as strongly associated with health care utilization

- Geocoding of residence data (e.g. zipcode) to census data allows use of ecologic, area-based measures of socioeconomic status
Potential Outcomes

- Health care utilization
  - Number of hospital days
  - Reasons for hospitalization (based on dx codes)
  - Resource use during hospitalizations
  - Hospital mortality
  - Number of physician visits
  - Types of physicians seen (e.g. specialists)
  - Diagnostic testing (e.g. # MRIs, not results)
  - Medication use & related adverse events

Strengths & Limitations

- In some jurisdictions, population-based
  - E.g. Canada, Scandinavian countries, Taiwan
- Large sample size
- Accessible
- Less costly than primary data collection
- Not collected for research
  - Not validated
  - Coding biases may affect utility of data
  - Lack clinical data
    - E.g. MS course, disability
    - Linkage to other data sources (if possible) may address these deficiencies
US Data Sources

- Medicare
- Medicaid
- Kaiser Permanente
- Indian Health Service National Data Repository
- IMS LifeLink PharMetrics Plus Database
- United HealthCare Database
- ...

Medicare

- Nationwide health insurance program for
  – people aged ≥65 yrs (98% of this pop’ n)
  – people <65 with certain disabilities
  – people with End-Stage Renal Disease
  – over 45 million beneficiaries enrolled
- Custodians: Department of Health and Human Services, Centers for Medicare & Medicaid Services (CMS).
- Dx coding: Hospital/Physician claims, ICD-9-CM
- Linkable: cancer registry, VA, NDI
- Data access/ cost: Research Data Assistance Center (ResDAC) resdac@umn.edu.
Medicare Claims for MS Studies

- Feasibility analysis: data 2004 to 2008
- Large no.: 6,680 MS patients aged 20-85 yrs
  - Among them, ~30% were 20-49 years of age, 30% 50-59 years, 25% 60-69 years, & those \( \geq 70 \) years accounted for the remaining 15%.
- Useful for many different study questions
- Part D data since 2006 → unique opportunity to comparatively examine the use & comparative safety of DMTs.

IMS LifeLink PharMetrics plus Database

- Integrated claims database of >100 commercial health plans in US
- Custodians: IMS Health
- Database:
  - Inpatient/outpatient diagnoses & procedures
  - Prescriptions
  - Costs of services
  - Place of service…
- Dx: ICD-9-CM
- Contact: IMSeService@imshealth.com
Kaiser Permanente Northern California

- Covers KP members (>3 million as of Dec 2012)
- Custodian: Comprehensive Clinical Research Unit within KPNC
- Database
  - Demographics
  - Hospitalizations
  - Ambulatory care
  - Pharmacy
  - Geocoded to census data
- Dx: ICD-9
- Contact: Maureen.B.Fitzpatrick@kp.org

Clinical Registries/ Databases

- Multiple examples
  - Danish MS Register, National Swedish MS Register, Italian MS Database Network, MSBase, New York State MS Consortium Database
- Vary widely in data collected and coverage
- E.g. Danish MS Register
  - All MS patients in Denmark since 1948
  - Years of onset & diagnosis, presenting symptom, course of disease, DSS, MRI/CSF/EP results
  - Linkage to national administrative datasets
Another Example: MSBase

- International
- Aimed at tracking & evaluating outcomes in MS
- Individual neurologists contribute data regarding their patients
- Entry: DOB, sex, date of MS onset, date of diagnosis, onset symptoms, EDSS, course, MRI/CSF/EPs
- Annually: EDSS, course, relapse hx, tx used

The NARCOMS Registry

- NARCOMS = The North American Consortium of Multiple Sclerosis Project
- Begun by the Consortium of Multiple Sclerosis Centers (CMSC) in 1993
- Patient self-report registry
- Goal: to facilitate MS-related research
- Enrollment began 1996
- Semi-annual update questionnaires began 2000
Validation of Diagnosis

- Randomly sampled typical / atypical groups (n = 109)
- 52 consented → weighted response rate: 76.3 ± 4.5

- Based on medical records review, physician survey, or physician interview (n=48, weighted %)

  Definite MS 98.9 ± 1.1

NARCOMS: Data Collected

- Age
- Sex
- Race
- Education
- Annual income
- Insurance status
- Marital status
- Twin status
- Age at symptom onset
- Year of diagnosis
- Relapses
- Hospitalizations
- Family history
- Quality of life (SF-12)
- Employment status
- Treatment
- Disability status
NARCOMS & Disability

- Since 2001, every update survey contains the PDDS & Performance Scales
- Excepting Bedridden (8), there are over 15,000 reports of every level of the PDDS

![Graph showing PDSS scores]

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Pros and cons for trials vs registries

- Easier to enroll
- Allows complete MD and Parental choice
- More able to handle cost differentials

- Unable to control for confounding of selection biases, treatments and often dropouts
- Propensity score analyses thought to help for some biases, but sample sizes likely too small for effective control
What if you want to use NARCOMS for a comparative effectiveness (or any other) study?

- Contact person
- Types of collaborations
- Steps to getting a collaboration going

Tuula Tyry, PhD
Program Manager, NARCOMS
Tuula.Tyry@DignityHealth.org
(602) 406 3072

www.NARCOMS.org
Overview & Process

I Overview

- Range of services
- Range of collaborators
- Confidentiality and research agreements
- Cost structure

II Process guidelines

- Initial request
- Review and discussion
- Proposal
- ...then what?

Range of Services

1. Recruitment assistance
   - IRB approved studies (observational & interventional)
   - Target population selected based on inclusion/exclusion criteria and proximity to study site(s)
   - One-time notifications sent by mail or online

2. Data-collection collaboration
   - By mail or online
   - IRB approved studies only, no marketing research

3. Data access or analysis
   - Limited de-identified data sets for secondary data analysis
   - Analyses and reports on a specific topic or research question
Range of Collaborators

1. CMSC members and member clinics
2. Other clinician-researchers
3. Academic collaborators
4. Non-profit organizations
5. Government agencies
6. Research and recruitment companies
7. Pharmaceutical industry

Confidentiality & Research Agreements

• Program director → confidential disclosure agreement on behalf of NARCOMS when requested (e.g. prior to discussion on clinical trial sites or study protocols)
• Recruitment projects do not require a research agreement (N.B.: may be needed to obtain a purchase order)
• Academic collaborators need to sign either a confidentiality agreement or a research agreement depending on the scope of the project, determined based on the proposal submitted
• Research Agreement with the CMSC/NARCOMS is required for projects with commercial parties, mainly to document data ownership and publication rights
  • Project specific agreement OR
  • Master Service Agreement + task orders
Cost Structure of Projects

- NARCOMS is only partially funded by CMSC & thus operates on a cost recovery basis
- Fee structure follows guidelines provided by CMSC & takes into account nature of proposed projects
- Different fees are applicable to
  - Commercial parties
  - Academic collaborators
  - Post-graduate students
  - CMSC member clinics
- Donations and unrestricted grants are always welcome but must be routed through the CMSC

STEP 1. Initial Request

- [http://narcoms.org/researcherinfoform](http://narcoms.org/researcherinfoform)
  - Start early (before submitting to IRB or funding source)
  - Fill out all applicable sections, including the preferred time frame for the project
Step 2. Feasibility Review

NARCOMS will contact you to discuss:

- Nature and purpose of the project
  - No marketing surveys
  - Potential overlap with other projects (topic or timing)
- Anticipated timeframe
- Availability of participants /data
- Preliminary budget estimate

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Step 3. Proposal Submission

- Academic collaborators:
  - Complete the NARCOMS proposal form
  - Executive Committee review
  - Provide IRB and other documents when requested

- Commercial parties:
  - NARCOMS will submit a formal research proposal & budget estimate based on discussions with the PI at the company
  - NARCOMS will initiate the research agreement process in collaboration with the CMSC attorney

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....then what?

- We will work with you throughout the process
- Recruitment projects - cover letter, best query criteria, description of methods for publication
- Data collection projects - survey design, pilot study, IRB proposal, analysis plan
- Data access and analysis projects - data cleaning & mapping, data analysis & linking, abstract submission, poster preparation
- Publication review or shared authorship
- Collaboration with the authors on a brief article for NARCOMS Now after peer-reviewed publication
- Brainstorming on your next project …

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Research Summary

- Start early, get NARCOMS involved during the planning process before locking into a budget or timeline
- Submit a request, get feasibility reviewed before completing the proposal form
- Plan and prepare for publications!

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Knowledge Translation

- Dynamic and iterative process that includes synthesis, dissemination, exchange, and ethically-sound application of knowledge to improve health
- The creation of new knowledge often does not on its own lead to widespread implementation or impacts on health

End of Grant KT

- Goals: raising awareness & promoting action
- Identify the knowledge users and their role in decision-making related to research findings
- Any activity aimed at diffusing, disseminating or applying the results of a research project
  - Conference presentations
  - Publications in peer-reviewed journals
  - Publications for lay public → websites, creative media
  - Workshops
  - Television, radio, print
- Tailor to the particular group of knowledge users
Integrated KT

• Applies principles of KT to entire research process
• Involve knowledge users as equal partners with researchers → lead to research that is more relevant, useful to the knowledge users
  – Refinement of research questions
  – Selection of methodology
  – Data collection & tools development
  – Selection of outcome measures
  – Interpretation of findings
  – Dissemination of results
• Aka participatory action research, Mode 2 research

The NARCOMS Approach to KT

• Audiences
  – Participants
  – Clinicians
  – Researchers

• Vehicles
  – Magazine
  – Conference presentations
  – Scientific publications
  – Website
Participants: NARCOMS Now

- NARCOMS participants receive a publication while they are actively completing surveys (~15,000 annually)
- Previously received MSQR (United Spinal)
- 2011: large-size newsletter, 8-12 pages per issue
- 2012: launch of NARCOMS Now, named by the participants,

www.NARCOMS.org/NARCOMSNow

NARCOMS Now Issues

http://www.narcoms.org/narcomsnow/previousissues
NARCOMS Now & Your Research

• One goal of NARCOMS is to relay NARCOMS research results back to the participants

• Once a manuscript has been published, your research is eligible for a feature in NARCOMS Now as either:
  – An interview by our Media Specialist
  – An edited, layman perspective article

• NARCOMS Now also includes highlights and previews of upcoming or ongoing research

NARCOMS Now Content

• Every issue has a theme and regular content
• Letter from the Director: Dr. Fox or Dr. Marrie
• MS Reflections: column by an MD (interview or submitted)
• Feature Focus: two focus articles related to the theme, translated to Spanish
• Snapshot: Results from the NARCOMS database
• NARCOMS Messenger: Updates from NARCOMS
• MS News: Global MS news
• Faces of NARCOMS: a personal story from a participant
Clinicians & Researchers

- Information provided by NARCOMS participants

- 60+ published manuscripts

- 130+ conference posters, platforms, workshops and short courses (like this one!)

- Published in varied international journals

www.NARCOMS.org

NARCOMS Abstracts

- Courses, Posters & Platform Presentations

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NARCOMS Publication Areas

- **Symptoms include:** Bladder, Cognitive, Depression, Disability, Dizziness, Fatigue, Mobility, Pain, Sensory, Spasticity, Vision
- **Comorbidities include:** Cancer, Vascular, Fibromyalgia, Psychiatric
- **Other topic areas:** Diagnosis, Health Information & Literacy, Reproductive Health, Sexual Intimacy, Smoking

Some examples

**Treatment Discontinuation and Disease Progression with Injectable Disease-Modifying Therapies**

Findings from the North American Research Committee on Multiple Sclerosis Database

Robert J. Fox, MD; Amber R. Salter, MPH; Tuula Tyry, PhD; Jennifer Sun, MS; Xiaojun You, PhD; Genevieve Laforet, MD, PhD; Denise Campagnolo, MD, MS

Injectable first-line disease-modifying therapies (DMTs) for multiple sclerosis (MS) are generally prescribed for continuous use. Accordingly, the various factors that influence patient persistence with treatment and that can lead some patients to switch medications or discontinue treatment may affect clinical outcomes. Using data from the North American Research Committee on Multiple Sclerosis
Another One

Impact of Mobility Impairment on Indirect Costs and Health-Related Quality of Life in Multiple Sclerosis

Craig I. Coleman1,2, Matthew F. Sidovar3, Matthew S. Roberts4, Christine Kohn5
1 Department of Pharmacy Practice, University of Connecticut School of Pharmacy, Storrs, Connecticut, United States of America; 2 Department of Pharmacy, Hartford Hospital, Hartford, Connecticut, United States of America; 3 Clinical Development and Medical Affairs, Acorda Therapeutics, Inc., Amboy, New York, United States of America

Abstract
This study was conducted to estimate the indirect costs and health-related quality of life (HRQoL) utilities of multiple sclerosis (MS) patients in the United States (US), and to determine the impact of worsening mobility on these parameters. In collaboration with the North American Research Committee on Multiple Sclerosis (NARCOMS) registry we conducted a cross-sectional study of participants who completed the biannual update and supplemental spring 2010 survey. Demographic, employment status, income, mobility impairment, and health utility data were collected from a sample of registry participants who met the study criteria and agreed to participate in the supplemental Mobility Study. Mean annual indirect costs per participant in 2011US$ and mean utilities for the population and for cohorts reporting different levels of mobility impairment were estimated.

Conclusion

• Key points re: CE studies from Gary

• Multiple potential data sources for secondary analysis
  – Administrative data
  – Clinical databases & registries
  – NARCOMS!

• Knowledge translation is key
**NARCOMS Contact Information**

- **Website**: www.NARCOMS.org
- **Magazine**: www.NARCOMS.org/NARCOMSNow
- **Telephone**: 1-800-253-7884 (toll free US)
- **Email**: MSRegistry@narcoms.org
- **For Researchers**: www.narcoms.org/contact

**Questions?**
### Criterion Validity

<table>
<thead>
<tr>
<th>Criterion Measure</th>
<th>Measure Being Validated</th>
<th>Correlation Coefficient</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSFC</td>
<td>Performance Scales</td>
<td>-0.58</td>
<td>-0.75, -0.32</td>
</tr>
<tr>
<td>EDSS</td>
<td>Performance Scales</td>
<td>0.64</td>
<td>0.40, 0.79</td>
</tr>
<tr>
<td>Timed 25 Foot Walk</td>
<td>Mobility</td>
<td>0.77</td>
<td>0.60, 0.87</td>
</tr>
<tr>
<td>Nine Hole Peg Test</td>
<td>Hand</td>
<td>-0.59</td>
<td>-0.76, -0.33</td>
</tr>
<tr>
<td>PASAT-3</td>
<td>Cognition</td>
<td>-0.17</td>
<td>-0.48, 0.13</td>
</tr>
<tr>
<td>Low Contrast Acuity (100%)</td>
<td>Vision</td>
<td>-0.29</td>
<td>-0.55, 0.03</td>
</tr>
<tr>
<td>Bladder Control Scale</td>
<td>Bladder</td>
<td>0.75</td>
<td>0.56, 0.86</td>
</tr>
<tr>
<td>Sensory FSS</td>
<td>Sensory</td>
<td>0.39</td>
<td>0.08, 0.63</td>
</tr>
<tr>
<td>MFIS</td>
<td>Fatigue</td>
<td>0.76</td>
<td>0.57, 0.86</td>
</tr>
</tbody>
</table>

### Construct Validity

<table>
<thead>
<tr>
<th>Construct</th>
<th>Correlation Coefficient</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility - Spasticity</td>
<td>-0.58</td>
<td>-0.75, -0.32</td>
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<tr>
<td>Cognitive - Fatigue</td>
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<td>-0.76, -0.33</td>
</tr>
<tr>
<td>Sensory - Pain (Pain Effects Scale)</td>
<td>-0.17</td>
<td>-0.48, 0.13</td>
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<td>Fatigue – Pain (Pain Effects Scale)</td>
<td>0.75</td>
<td>0.56, 0.86</td>
</tr>
</tbody>
</table>
Performance Scales (PS)

- Good internal consistency reliability as a whole, Cronbach’s $\alpha=0.78$

- Good test-retest reliability, $r=0.89$

- Construct validity of the entire scale
  - PS-EDSS, $r=0.62$
  - PS-PDDS, $r=0.60$
  - PS- Quality of Well-being Index, $r=-0.64$
  - PS-Health Status Questionnaire, $r=-0.50$