Adapting clinical trial design to meet the needs of learning healthcare systems

Harriette Van Spall, MD, MPH
Associate Professor of Medicine, McMaster University
Scientist, Population Health Research Institute
Cardiologist, Hamilton Health Sciences
@hvanspall

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NIH Collaboratory Rounds
Objectives

1. To review the importance of learning healthcare systems in improving healthcare quality
2. To discuss the role of clinical trial design in meeting the needs of healthcare systems
3. To present the design and results of the Patient-Centered Care Transitions (PACT-HF) pragmatic clinical trial
Learning healthcare systems

- Generate and apply the best evidence for collaborative care choices between patients and clinicians
- Drive discovery as a natural outgrowth of patient care
- Ensure quality, innovation, safety, and value in health care
Why learning healthcare systems are important

Clinical complexity

• Improved Tx of acute illness \(\rightarrow\) increased survival
• Older patients with chronic illness, complex comorbidities
• Care informed by explanatory clinical trials
  – Restrictive inclusion criteria, women and those with comorbidities underrepresented
  – Limited generalizability
• Important to assess treatment outcomes in real-world healthcare settings

Smith et al, Best Care at Lower Cost: The Path to Continuously Learning Health Care in America, 2013
https://www.ncbi.nlm.nih.gov/books/NBK207218/
Why learning healthcare systems are important

Health care system complexity

• Healthcare delivery fragmented between
  – organ-based specialists
  – Settings / organizations
  – payment models – single vs multiple payer systems, different incentives

• Knowledge-treatment gaps

• Important to study effect of interventions at healthcare system level

Smith et al, Best Care at Lower Cost: The Path to Continuously Learning Health Care in America, 2013
https://www.ncbi.nlm.nih.gov/books/NBK207218/
Why learning healthcare systems are important

Data complexity

- Different stakeholders interested in different outcomes of interest
- Different sources of data, limited interoperability
- Important to analyze data in an efficient, effective manner to drive change

Smith et al, Best Care at Lower Cost: The Path to Continuously Learning Health Care in America, 2013
https://www.ncbi.nlm.nih.gov/books/NBK207218/
Characteristics of a learning healthcare system

Smith et al, Best Care at Lower Cost: The Path to Continuously Learning Health Care in America, 2013
https://www.ncbi.nlm.nih.gov/books/NBK207218/
Characteristics of a learning healthcare system

1. Have a culture of knowledge and quality improvement
2. Encourage research innovation
   - Embedding research into clinical practice
   - Generating knowledge at the point of care
3. Harness data from EMRs, claims/administrative databases
   - Public data access

Smith et al, Best Care at Lower Cost: The Path to Continuously Learning Health Care in America, 2013
https://www.ncbi.nlm.nih.gov/books/NBK207218/
Characteristics of a learning healthcare system

4. Foster trust between research and clinical teams

5. Engage patients, clinicians, key healthcare system stakeholders
   – Research priorities, design, partnerships
   – Culture of empowerment
Adapting research to a learning healthcare system

- Identify questions important to the healthcare system
- Select the right question for the study
- Choose a study design that reliably answers the question
  - Scientific limitations of before-after and observational study designs
  - Practical limitations of explanatory clinical trials
  - Role of pragmatic clinical trials
Adapting research to a learning healthcare system

• Create the culture and partnerships for research implementation
  – Culture of research
  – Culture of “knowledge to action”

• Minimize research burden on front-line clinicians
  – Recruitment
  – Data collection

• Select relevant outcomes to measure impact
Adapting research to a learning healthcare system

Allen et al., Circulation 2012; 125(15): 1928-52
The problem of heart failure (HF)

Allen et al., Circulation 2012; 125(15): 1928-52
HF hospitalizations by age

Figure 1. Hospitalizations with most responsible diagnosis (MRDx) of heart failure (HF), as a proportion (%) of all other hospitalizations, by sex and age group, Canada (excludes Québec), 2005–2006.
Distribution of HF costs

- Hospital admissions: 69%
- Drug treatment: 18%
- GP OPD referrals: 5%
- GP visits: 6%
- Post-discharge OPD visits: 2%

Stewart et al. Eur J Heart Fail 2002;4:361-7
Graph from Heart & Stroke Foundation
Main challenges: heart failure hospitalization

- Annual hospitalizations in both the United States and Europe: >1 million
- Heart failure hospitalizations as a percentage of total hospital admissions: 1-4%
- Hospitalized due to worsening chronic heart failure as compared with de novo heart failure: Up to 9/10 patients
- Average length of hospital stay: 5-10 days
- Nearly 1 out of 2 patients (46%) are rehospitalized for heart failure within the 60-day post discharge period
- Almost 1 out of 4 hospitalized patients (24%) are rehospitalized for heart failure within the 30-day post discharge period

Lifetime readmission risk after HF hospitalization

Comparative effectiveness of transitional care services in HF (N=54 RCTs): mortality

Comparative effectiveness of transitional care services in HF: readmissions

Patient-Centered Care Transitions in Heart Failure:

Harriette GC. Van Spall, MD, MPH
Associate Professor of Medicine (Cardiology)
McMaster University
Population Health Research Institute

On behalf of PACT-HF investigators and patients

Funded by Canadian Institutes of Health Research,
Ontario’s Ministry of Health and Long Term Care Health System Research Fund
In-kind support from participating hospitals and Community Care Agencies
Aim

To test effectiveness of a group of transitional care services (PACT-HF) in patients hospitalized for HF within a publicly-funded healthcare system

Van Spall et al. Am Heart J 2018; 199:75-82
Outcomes

Primary Outcomes
1. All-cause death, readmission, or Emergency Department (ED) visit at 3-months
2. All-cause readmission or ED visit at 30 days

Secondary Outcomes
1. B-PREPARED score – discharge preparedness
2. Care Transitions Measure – quality of care transition
3. EQ-5D-5L – quality of life index, validated in HF
4. Quality Adjusted Life Years - life duration weighted by EQ-5D-5L
5. Healthcare system cost

Van Spall et al. Am Heart J 2018; 199:75-82
Research approach

• Integrated Knowledge Translation
  – Engaged patients, clinicians and healthcare system decision-makers in study design
  – Used publicly-funded personnel for the intervention
  – Redesigned workflow to integrate care across settings

• Embedded clinical trial
  – Clinical outcomes obtained from administrative database
  – Minimize burden on patients

Van Spall et al. Am Heart J 2018; 199:75-82
# Stepped Wedge Cluster RCT

![PACT-HF Logo](https://example.com/pact-hf-logo.png)

## Stepped Wedge Cluster RCT

### Table: Step (Month) by Hospital

<table>
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<th>Hospital</th>
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Van Spall et al. Am Heart J 2018; 199:75-82
PACT-HF nurse includes patients with most responsible diagnosis of HF
- Confirms diagnosis using Boston clinical criteria and NT-proBNP

Excludes patients who
- Do not have diagnosis of HF
- Are transferred to another hospital
- Died during hospitalization

PACT-HF nurse provides
1) Comprehensive assessment of patient and multidisciplinary linkages/referrals
2) Patient and informal caregiver self-care education
3) Patient-centred discharge summary, including action plan, to patient and family physician (FP)
4) Follow-up appointment with FP within 7 days

High-risk criteria for 30-day readmission?
Yes

Patients are seen in HFC within 2-4 weeks and receive home care transition nurse visits and telephone calls from home-care agency nurses within 1 week for a period of 4-6 weeks

No

Outcome Assessment
Primary Outcome: Time-to-first event of the composite of: (1) all-cause readmissions, emergency department (ED) visits, or death at 3 months post discharge; (2) all-cause readmissions or ED visits at 30 days post discharge

Secondary Outcomes: patient-reported B-Prepared score (6 weeks), Care Transitions Quality-3 score (6 weeks), EQ5D5L score (hospital discharge, 6 weeks, 6 months), and Quality Adjusted Life Years at 6 months

Van Spall et al. Am Heart J 2018; 199:75-82
## Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th>Demographics</th>
<th>PACT-HF (N=1104)</th>
<th>Usual Care (N=1390)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>77.8 (12.4)</td>
<td>77.6 (11.9)</td>
<td>0.71</td>
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<tr>
<td>Female, n (%)</td>
<td>544 (49.3%)</td>
<td>714 (51.4%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Resides in long-term care, n (%)</td>
<td>164 (14.9%)</td>
<td>222 (16.0%)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

## Self-reported Quality of Life

<table>
<thead>
<tr>
<th>EQ-Visual Acuity Score (1-100), mean (SD)</th>
<th>PACT-HF (N=1104)</th>
<th>Usual Care (N=1390)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>52.6 (22.7)</td>
<td>53.7 (22.2)</td>
<td></td>
<td>0.20</td>
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</table>

## Comorbidities

<table>
<thead>
<tr>
<th>Hypertension, n (%)</th>
<th>PACT-HF (N=1104)</th>
<th>Usual Care (N=1390)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>844 (76.5%)</td>
<td>1,084 (78.0%)</td>
<td></td>
<td>0.66</td>
</tr>
<tr>
<td>Atrial Fibrillation, n (%)</td>
<td>583 (52.8%)</td>
<td>684 (49.2%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Myocardial Infarction, n (%)</td>
<td>240 (21.7%)</td>
<td>295 (21.2%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Diabetes with complications, n (%)</td>
<td>524 (47.5%)</td>
<td>704 (50.6%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Chronic Kidney Disease, n (%)</td>
<td>242 (21.9%)</td>
<td>316 (22.7%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Chronic Pulmonary Disease, n (%)</td>
<td>235 (21.3%)</td>
<td>334 (24.0%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Cerebrovascular Disease, n (%)</td>
<td>101 (9.1%)</td>
<td>129 (9.3%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Dementia, n (%)</td>
<td>98 (8.9%)</td>
<td>123 (8.8%)</td>
<td>0.98</td>
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</table>
# Resource utilization and risk during index hospitalization

<table>
<thead>
<tr>
<th></th>
<th>PACT-HF (N=1104)</th>
<th>Usual Care (N=1390)</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>Resource Utilization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute length of stay, mean (SD) days</td>
<td>7.80 (6.3)</td>
<td>7.62 (4.9)</td>
<td>0.42</td>
</tr>
<tr>
<td>Resource Intensity Weight, mean (SD)</td>
<td>1.4 (1.2)</td>
<td>1.4 (0.8)</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Estimated risk at discharge</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED visits in prior 6 months, median (IQR)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>0.08</td>
</tr>
<tr>
<td>LACE index, median (IQR)</td>
<td>12 (10-14)</td>
<td>12 (10-14)</td>
<td>0.02</td>
</tr>
<tr>
<td>Charlson comorbidity index, mean (SD)</td>
<td>2.4 (1.3)</td>
<td>2.4 (1.3)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Van Spall et al, JAMA 2019; 321(8): 753-761
Primary outcome: All-cause composite death, readmission, ED visit at 3 months

HR 0.99 (0.83, 1.19)

Survival Probability

Time (Days)

Van Spall et al, JAMA 2019; 321(8): 753-761
Primary outcome: Composite all-cause readmission or ED visit at 30 days

HR 0.93 (0.73, 1.18)

Van Spall et al, JAMA 2019; 321(8): 753-761
**Primary clinical outcomes**

<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>PACT-HF (N=1104)</th>
<th>Usual Care (N=1390)</th>
<th>Hazards Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-month composite all-cause death, readmission, or ED visit</td>
<td>545 (49.5%)</td>
<td>698 (50.3%)</td>
<td>0.99 (0.83, 1.19)</td>
<td>0.93</td>
</tr>
<tr>
<td>Death ≤ 3 months</td>
<td>111 (10.1%)</td>
<td>136 (9.8%)</td>
<td>1.18 (0.83, 1.68)</td>
<td>0.36</td>
</tr>
<tr>
<td>Readmission ≤ 3 months</td>
<td>400 (36.2%)</td>
<td>500 (36.0%)</td>
<td>1.10 (0.91, 1.34)</td>
<td>0.32</td>
</tr>
<tr>
<td>ED visit* ≤ 3 months</td>
<td>248 (22.4%)</td>
<td>334 (24.0%)</td>
<td>0.88 (0.68, 1.15)</td>
<td>0.36</td>
</tr>
<tr>
<td>30-day composite all-cause readmission or ED visit</td>
<td>304 (27.5%)</td>
<td>409 (29.4%)</td>
<td>0.93 (0.73, 1.18)</td>
<td>0.54</td>
</tr>
<tr>
<td>Readmission ≤ 30 days</td>
<td>225 (20.4%)</td>
<td>265 (19.1%)</td>
<td>1.23 (0.95, 1.59)</td>
<td>0.12</td>
</tr>
<tr>
<td>ED visit* ≤ 30 days</td>
<td>113 (10.2%)</td>
<td>190 (13.7%)</td>
<td>0.65 (0.45, 0.95)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*without hospitalization

Van Spall et al, JAMA 2019; 321(8): 753-761
### Secondary patient reported outcomes

<table>
<thead>
<tr>
<th></th>
<th>PACT-HF LS Mean (95%CI) (N=606)</th>
<th>Usual Care LS Mean (95%CI) (N=380)</th>
<th>Mean Difference (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-PREPARED Score (0-22)</strong></td>
<td>16.52 (15.47, 17.57)</td>
<td>13.96 (12.92, 15.00)</td>
<td>2.64 (1.37, 3.92)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>CTM-3 score (0-100)</strong></td>
<td>76.49 (72.00, 80.98)</td>
<td>70.99 (66.53, 75.46)</td>
<td>6.10 (0.83, 11.36)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>EQ-5D-5L score (0-1)</strong></td>
<td></td>
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</tr>
<tr>
<td>At discharge</td>
<td>0.73 (0.70, 0.76)</td>
<td>0.55 (0.52, 0.58)</td>
<td>0.18 (0.14, 0.23)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>6 weeks</td>
<td>0.73 (0.70, 0.76)</td>
<td>0.67 (0.64, 0.70)</td>
<td>0.06 (0.01, 0.11)</td>
<td>0.02</td>
</tr>
<tr>
<td>6 months</td>
<td>0.71 (0.67, 0.74)</td>
<td>0.64 (0.61, 0.68)</td>
<td>0.06 (0.01, 0.12)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Quality Adjusted Life Years (6 months)</strong></td>
<td>0.34 (0.33, 0.36)</td>
<td>0.34 (0.33, 0.35)</td>
<td>0.00 (-0.02, 0.02)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Van Spall et al, JAMA 2019; 321(8): 753-761
Summary – Clinical outcomes

• PACT-HF did not improve
  – Composite all-cause death, readmission, or ED visit at 3 months
  – Composite all-cause readmission or ED visit at 30 days

• Efficacy in explanatory RCTs ≠ Effectiveness in real-world settings

• Pitfalls in titrating services to risk

• Floor and ceiling effects

Van Spall et al, JAMA 2019; 321(8): 753-761
Summary – Patient reported outcomes

- PACT-HF improved B-PREPARED, CTM-3, EQ5D5L, but not Quality Adjusted Life Years

Van Spall et al, JAMA 2019; 321(8): 753-761
Strengths

• Knowledge-to-action framework
• Robust stepped wedge clinical trial design
• Pragmatic research embedded in healthcare system
• Engagement of patients, clinicians, and decision-makers
• Use of administrative databases to measure clinical and cost outcomes
• Collection of patient-reported outcomes
Limitations

• Urban hospitals only
• Did not assess the quality or duration of each episode of care
• Did not patients’ adherence to discharge recommendations
Challenges of research embedded in healthcare system

• Keeping the “learning” healthcare system on track
  – Creating a research vision that is embraced across every part of the healthcare system

• Integrating care, intervention, communications across silos

• Streamlining workflow, minimizing inertia

• Preventing “contamination” of usual care
Challenges of research embedded in healthcare system

• Ensuring accountability
  – Audit and feedback

• Limited interoperability of EMRs, slow updates to claims/administrative datasets
  – Delays in access to clinical, cost outcomes
Acknowledgements for PACT-HF

**Co-PI:** Stuart J Connolly

**Co-Investigators:** Feng Xie PhD; Peter R Mitoff MD; Manish Maingi MD; Michael C Tjandrawidjaja MD; Michael Heffernan MD, PhD; Mohammad I Zia MD; Liane Porepa MD; Mohamed Panju MD; Lehana Thabane PhD; Ian D Graham MA PhD; R. Brian Haynes MD PhD; Dilya Haughton BScN MHSc; Dennis T Ko, MD, MSc

**Statisticians:** Shun Fu Lee PhD; Urun Erbas Oz PhD; Richard Perez MSc

**Research Coordinator:** Kim Simek BSc

**Research Assistant:** Roberta Napoleoni
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- HNHB Community Care Access Center (CCAC), Ontario
- Central West CCAC, Ontario
- Mississauga Halton CCAC, Ontario
- Toronto Central CCAC, Ontario
- Central CCAC, Ontario