

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

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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 → 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

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

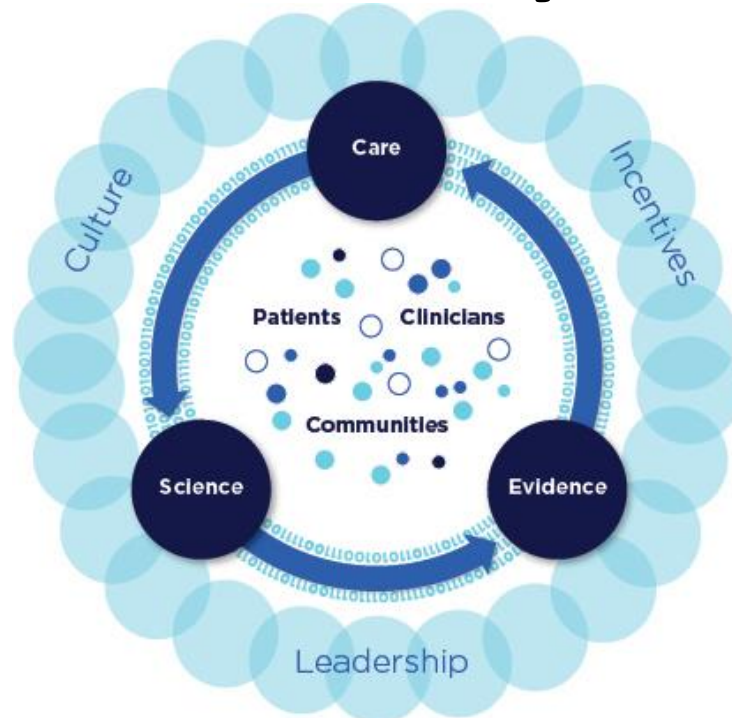
Why learning healthcare systems are important

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



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

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

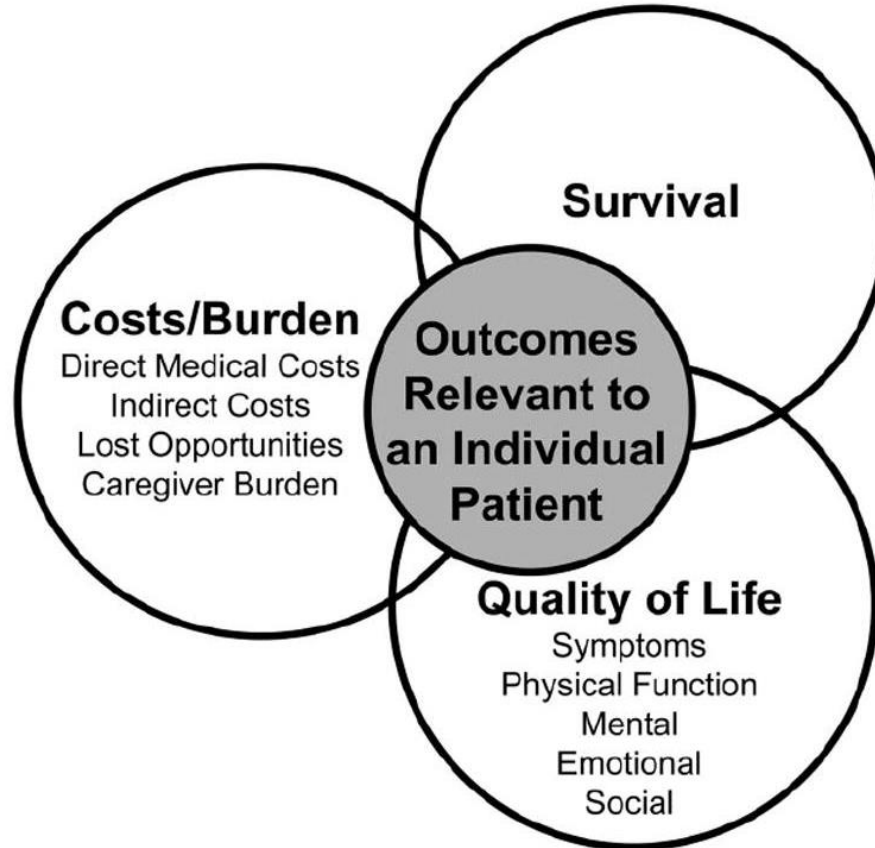
- Identify questions important to the healthcare system
- Select the right question for the study
- Choose a study design that reliably answers the question
 - Scientific limitations of before-after and observational study designs
 - Practical limitations of explanatory clinical trials
 - Role of pragmatic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

Adapting research to a learning healthcare system

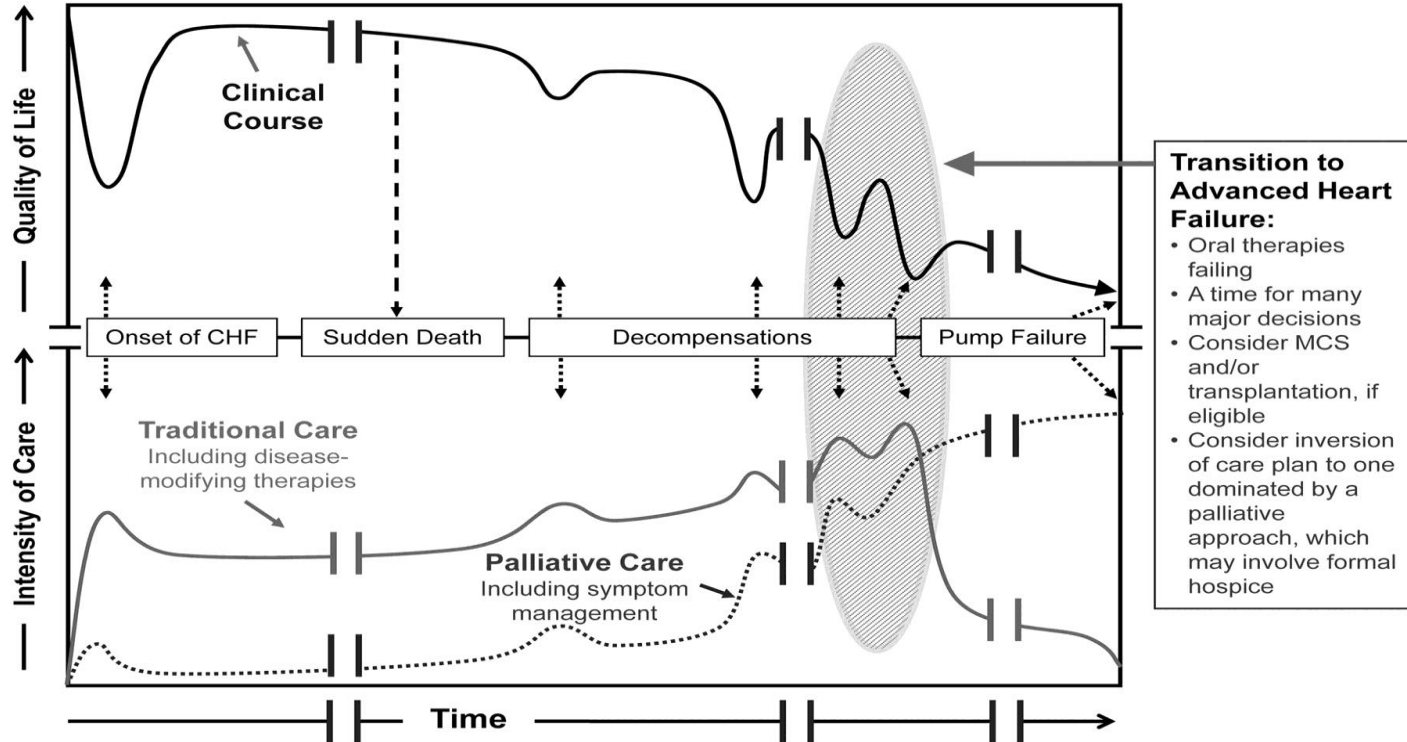
- Create the culture and partnerships for research implementation
 - Culture of research
 - Culture of “knowledge to action”
- Minimize research burden on front-line clinicians
 - Recruitment
 - Data collection
- Select relevant outcomes to measure impact



Adapting research to a learning healthcare system



The problem of heart failure (HF)



HF hospitalizations by age

Dai et al.
Hospitalized HF Comorbidities and Mortality

77

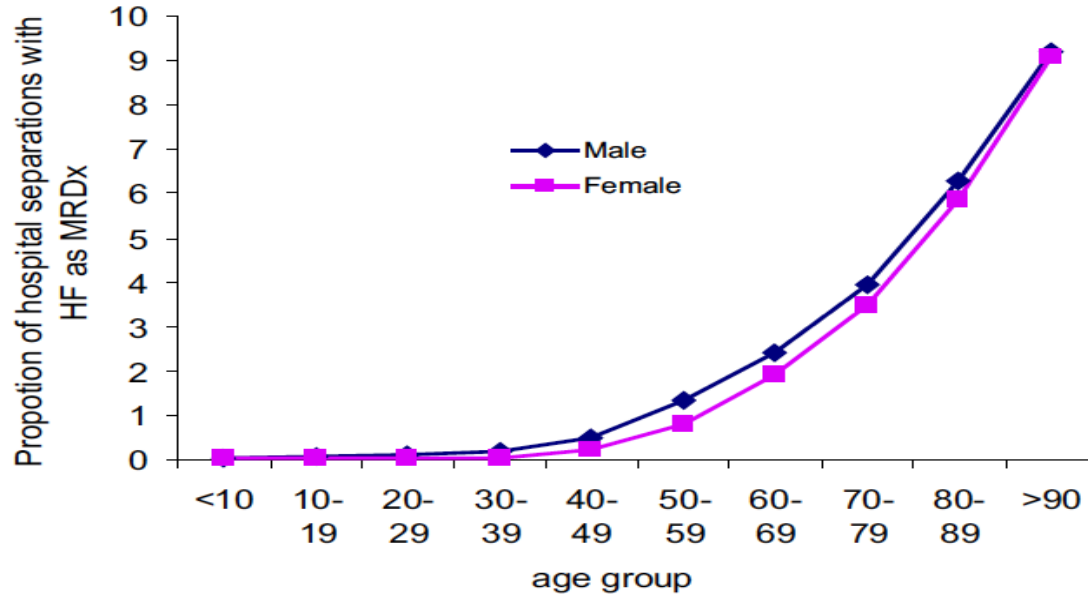
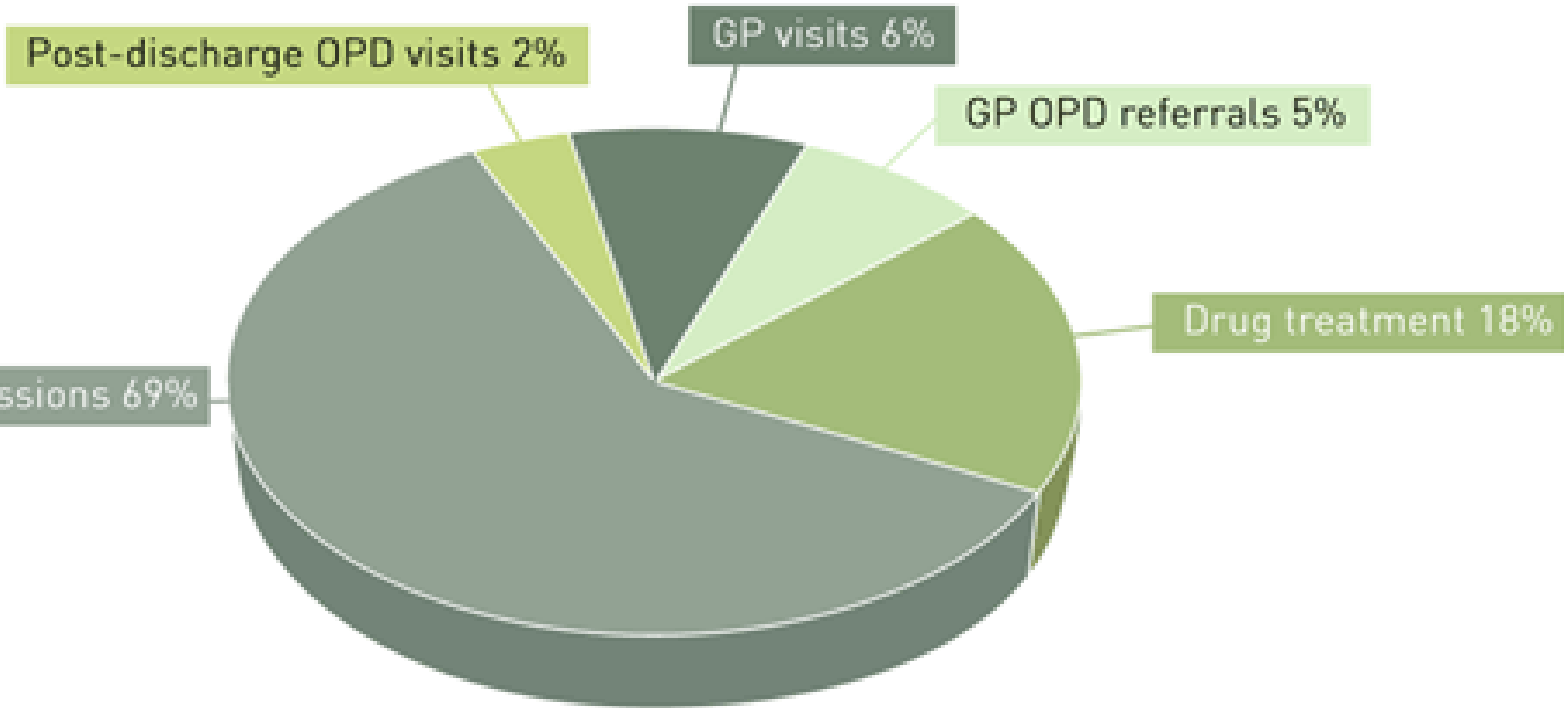


Figure 1. Hospitalizations with most responsible diagnosis (MRDx) of heart failure (HF), as a proportion (%) of all other hospitalizations, by sex and age group, Canada (excludes Québec), 2005–2006.

Distribution of HF costs



Main challenges: heart failure hospitalization

>1 million

Annual hospitalizations in both the
United States and Europe¹

1-4%

Heart failure hospitalizations as a
percentage of total hospital
admissions²

Up to 9/10
patients

Hospitalized due to worsening chronic
heart failure as compared with de novo
heart failure³

5-10
days

Average length of hospital stay³

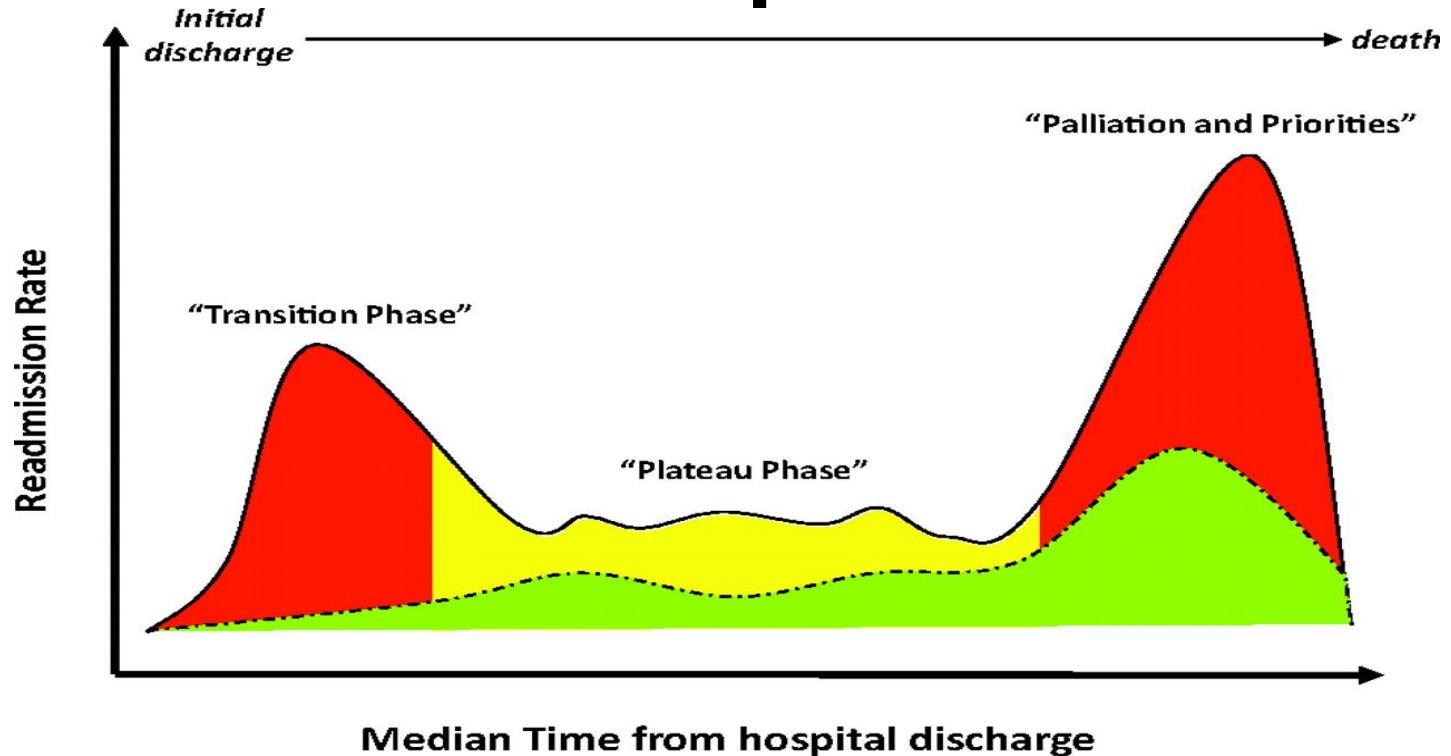


Almost 1 out of 4 hospitalized patients
(24%) are rehospitalized for heart
failure within the 30-day post
discharge period⁴

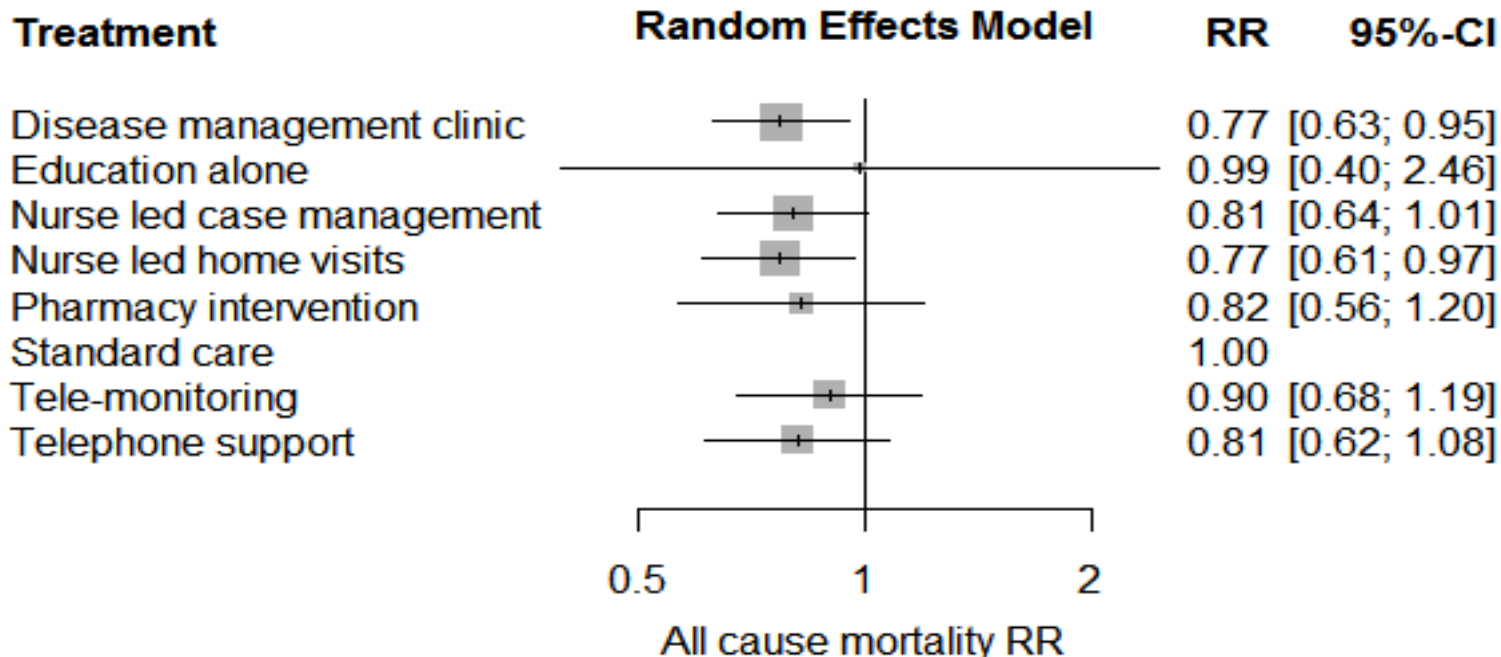


Nearly 1 out of 2 patients (46%) are
rehospitalized for heart failure within
the 60-day post discharge period⁴

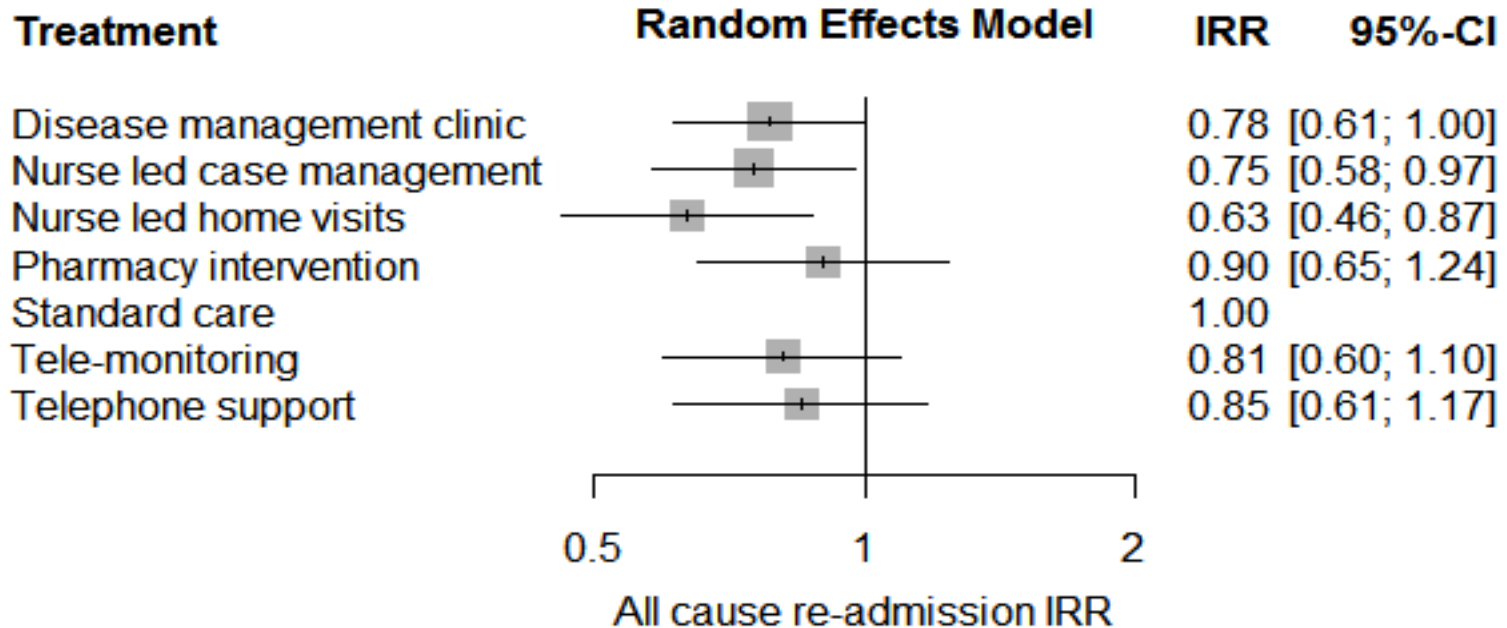
Lifetime readmission risk after HF hospitalization



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:

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On behalf of PACT-HF investigators and patients

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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

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

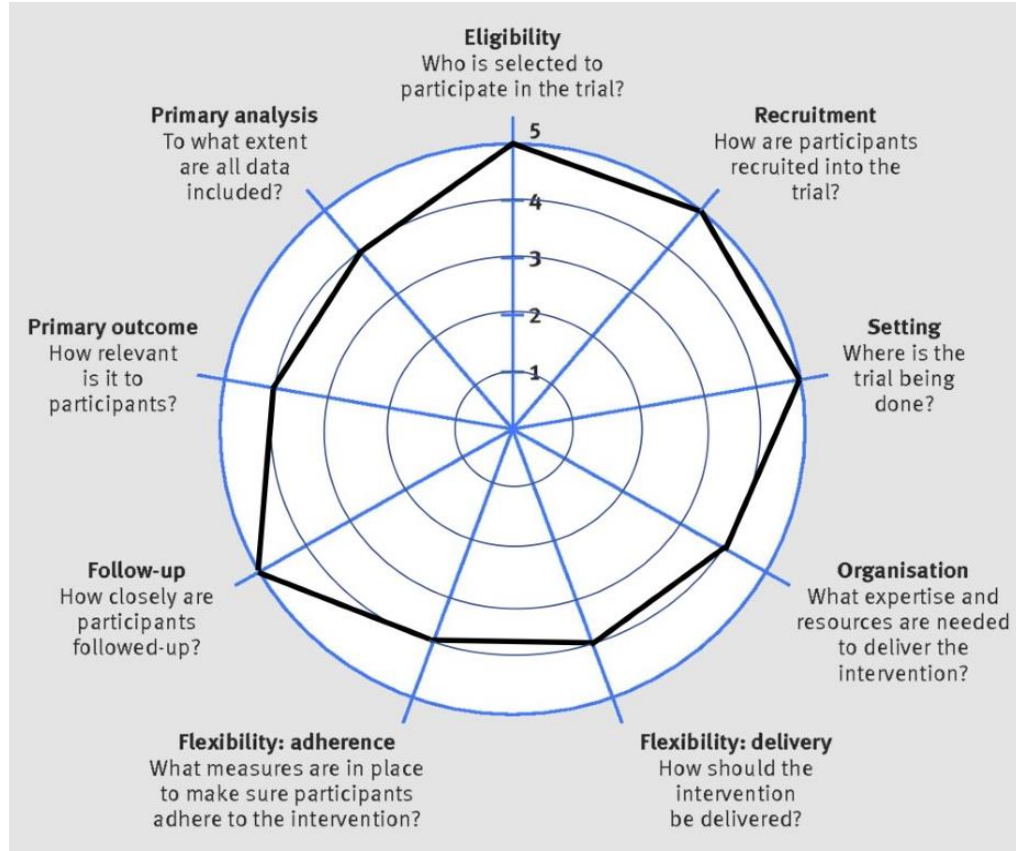
Secondary Outcomes

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

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

Pragmatic research approach



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

Loudon et al. BMJ 2015;350:h2147

Stepped Wedge Cluster RCT

Hospital	Step (Month)										
	1	2	3	4	5	6	7	8	9	10	11
1	0	1	1	1	1	1	1	1	1	1	1
2	0	0	1	1	1	1	1	1	1	1	1
3	0	0	0	1	1	1	1	1	1	1	1
4	0	0	0	0	1	1	1	1	1	1	1
5	0	0	0	0	0	1	1	1	1	1	1
6	0	0	0	0	0	0	1	1	1	1	1
7	0	0	0	0	0	0	0	1	1	1	1
8	0	0	0	0	0	0	0	0	1	1	1
9	0	0	0	0	0	0	0	0	0	1	1
10	0	0	0	0	0	0	0	0	0	0	1

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?

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

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

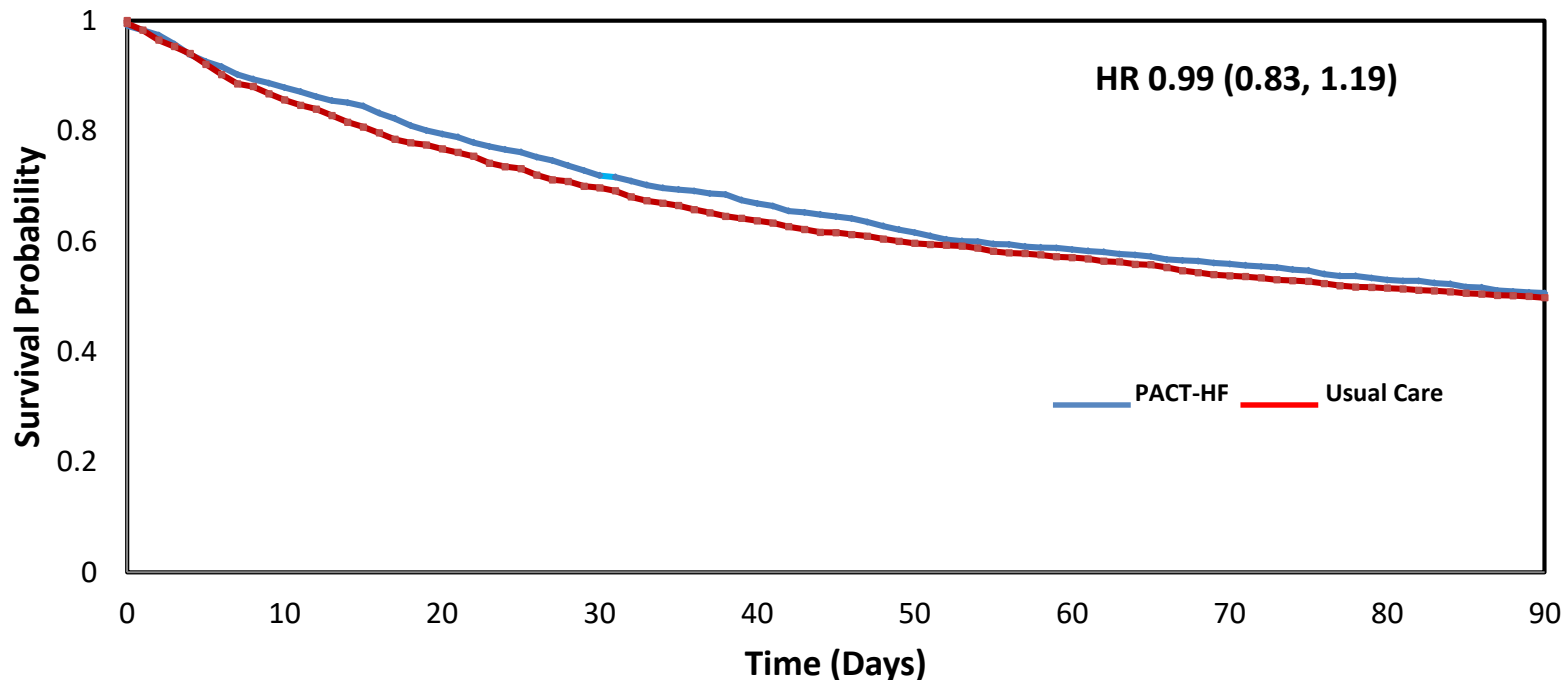
Study Protocol

Baseline Characteristics of Patients	PACT-HF (N=1104)	Usual Care (N=1390)	P-value
Demographics			
Age, mean (SD)	77.8 (12.4)	77.6 (11.9)	0.71
Female, n (%)	544 (49.3%)	714 (51.4%)	0.30
Resides in long-term care, n (%)	164 (14.9%)	222 (16.0%)	0.44
Self-reported Quality of Life			
EQ-Visual Acuity Score (1-100), mean (SD)	52.6 (22.7)	53.7 (22.2)	0.20
Comorbidities			
Hypertension, n (%)	844 (76.5%)	1,084 (78.0%)	0.66
Atrial Fibrillation, n (%)	583 (52.8%)	684 (49.2%)	0.07
Myocardial Infarction, n (%)	240 (21.7%)	295 (21.2%)	0.76
Diabetes with complications, n (%)	524 (47.5%)	704 (50.6%)	0.11
Chronic Kidney Disease, n (%)	242 (21.9%)	316 (22.7%)	0.63
Chronic Pulmonary Disease, n (%)	235 (21.3%)	334 (24.0%)	0.11
Cerebrovascular Disease, n (%)	101 (9.1%)	129 (9.3%)	0.91
Dementia, n (%)	98 (8.9%)	123 (8.8%)	0.98

Resource utilization and risk during index hospitalization

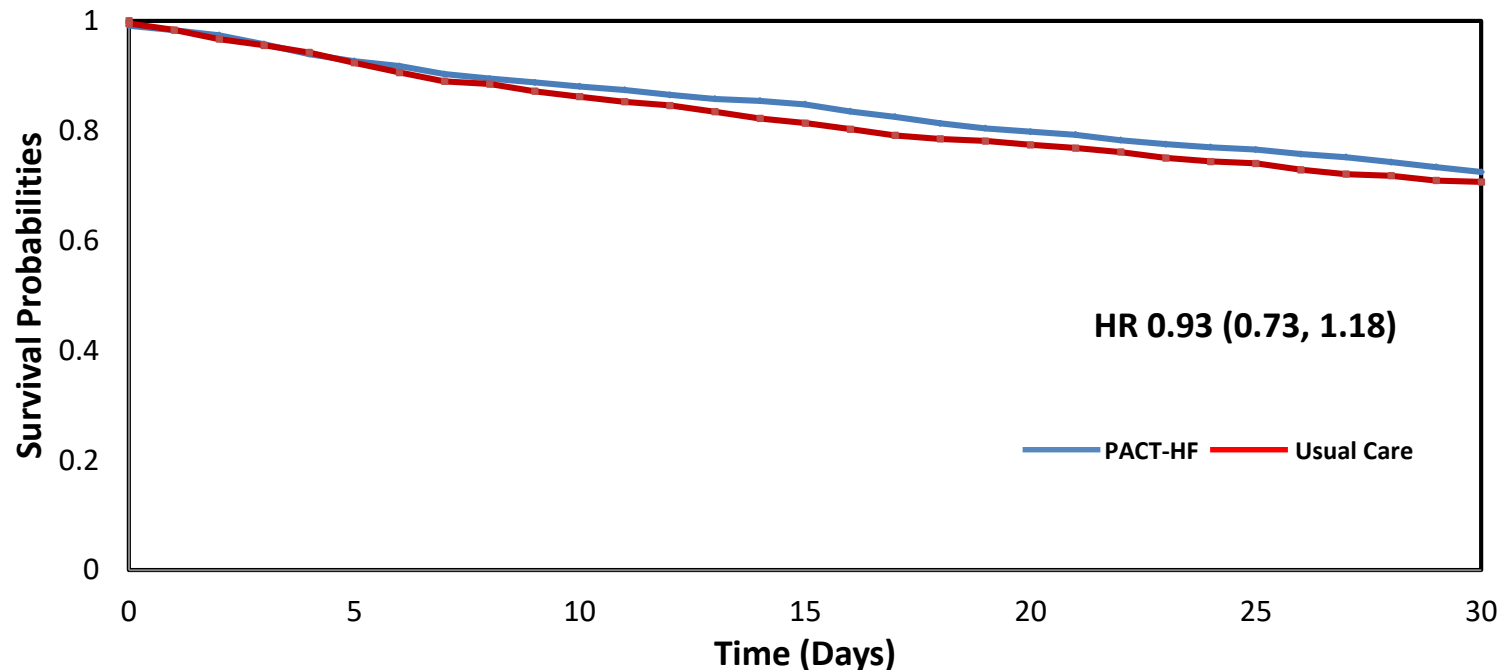
	PACT-HF (N=1104)	Usual Care (N=1390)	P-value
Resource Utilization			
Acute length of stay, mean (SD) days	7.80 (6.3)	7.62 (4.9)	0.42
Resource Intensity Weight, mean (SD)	1.4 (1.2)	1.4 (0.8)	0.68
Estimated risk at discharge			
ED visits in prior 6 months, median (IQR)	2 (1-3)	2 (1-3)	0.08
LACE index,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

Primary outcome: All-cause composite death, readmission, ED visit at 3 months



	0	10	20	30	40	50	60	70	80	90
PACT-HF	1104	978	880	801	745	685	649	618	588	560
Routine Care	1390	1203	1075	972	892	832	795	750	718	694

Primary outcome: Composite all-cause readmission or ED visit at 30 days



	0	5	10	15	20	25	30
PACT-HF	1104	1036	979	940	884	849	807
Routine Care	1390	1305	1209	1141	1084	1032	985

Primary clinical outcomes

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

*without hospitalization

Secondary patient reported outcomes

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

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 \neq Effectiveness in real-world settings
- Pitfalls in titrating services to risk
- Floor and ceiling effects

Summary – Patient reported outcomes

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

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

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