Study Protocol

TRANSFORM Heart Failure with Reduced Ejection Fraction: TRANSFORM-HFrEF (Version 1.1)

A Randomized Registry Trial to Evaluate Best Practices and Improve Adherence to Guideline Directed Medical Therapy for Heart Failure with Reduced Ejection Fraction

James L. Januzzi, Jr, MD FACC, FESC
Trustee, American College of Cardiology, Washington, DC
Cardiology Division, Massachusetts General Hospital
Hutter Family Professor of Medicine, Harvard Medical School
Senior Cardiometabolic Faculty, Baim Institute for Clinical Research
Boston, MA

Correspondence:
James L. Januzzi Jr MD, FACC, FESC
Massachusetts General Hospital
Yawkey 5984, Fruit Street
Boston, MA, 02114
P: 617-726-3443
F: 617-643-1620
E: JJanuzzi@partners.org
T: @JJheart_doc

A. Study Overview

1. Purpose of the Study

The goal of the TRANSFORM-HFrEF trial will be to study the current guideline directed medical therapy (GDMT) landscape for HFrEF, and determine effective methods and models of increasing adherence to GDMT and improving Quality of Life (QOL) in outpatient settings within the context of the 20-minute visit. This will be achieved through a randomized evaluation that shifts standard clinical interview and documentation requirements outside the office visit and building the patient and physician relationship through trust and shared goal setting.

2. Background and Significance

Heart Failure (HF) is the cardiovascular epidemic of the 21st century, affecting millions of patients world-wide. It is believed that HF is the only cardiovascular diagnosis rising in incidence among elderly patients and is the #1 diagnosis leading to hospitalization among Medicare recipients. In addition to being increasingly prevalent, HF has a poor outlook after initial diagnosis and is associated with poor quality of life (QOL) in affected patients; this not only leads to burden on patients, family and other caregivers, but also on the healthcare system. For all these reasons, optimizing the understanding and care of patients with HF is a major priority.

Although clinical practice guidelines clearly articulate optimal GDMT for care of patients with HFrEF, implementation of GDMT into the management of such patients has proven to be suboptimal, with most patients under-treated relative to goal therapy.

To evaluate contemporary status of GDMT delivery for HFrEF, the recent Change the Management of Patients with Heart Failure (CHAMP-HF) registry included 3518 patients from 150 primary care and cardiology practices (1,2). The mean age of this cohort was 66 ± 13 years, 29% were female, and mean EF was 29 ± 8%, thus representing a very characteristic population of patients with HFrEF.

In CHAMP-HF, the investigators found 27%, 33%, and 67% of eligible patients were not prescribed angiotensin converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB)/angiotensin receptor/neprilysin inhibitor (ARNI), beta-blocker, and mineralocorticoid receptor antagonist (MRA) therapy, respectively. Furthermore, when medications were prescribed, few patients were receiving target doses of ACEI/ARB (17%), ARNI (14%), and beta-blocker (28%); most patients were receiving target doses of MRA therapy (77%). Most notably, among patients eligible for all classes of medication, only 1% were simultaneously receiving target doses of renin-angiotensin system inhibitors (RASi; ACE/ARB/ARNI), beta-blocker, and MRA. Remarkably, little improvement in GDMT was noted over a 6 to 12-month period and (importantly) no use of the newest HFrEF GDMT, sodium glucose cotransporter-2 inhibitors (SGLT2i) was reported.

In analyses to better understand the reasons for these treatment gaps, the authors found no explanation based on blood pressure or heart rate limitation, suggesting clinician entropy and/or lack of understanding/confidence regarding guideline-directed targets might have been present. In adjusted models, older age, lower blood pressure, more severe functional class, renal insufficiency, and recent HF hospitalization generally favored lower medication utilization or dose, indicating as in prior studies a "risk-treatment mismatch" wherein the highest risk patients received the least aggressive care. Closure of this mismatch would be expected to have substantial impact on outcomes, given the higher baseline risk of such patients.

Understanding reason(s) for pervasive gaps in GDMT is important to make strides to improve prescription of life-saving therapies to those patients affected by HFrEF. The reasons for inadequate GDMT may include clinician-based factors, while others may be related to patient factors:

- **Clinician factors**: Within the context of the 20-minute visit, clinicians caring for those patients with HFrEF have numerous issues to consider, including an updated history and physical, medication reconciliation and holistic evaluation of the patient, including consideration of co-morbidities. Thus, to scrutinize GDMT, consider changes, and implement such changes may pose challenges within the time-constrained context of such a visit.

  Clinician resistance to make changes if patients "appear stable" presumably plays a part in the pervasive entropy regarding therapy adjustments. In previous research from the PINNACLE Registry®, we found that therapy adjustment was most often performed in the context of worsening symptoms (a high-risk moment), rather than when patients were more stable and more likely to tolerate changes in their GDMT (3). It is important to emphasize none of the trials performed to define HFrEF GDMT stipulated adjustment in therapy be made only when patients are unstable; thus, to only adjust GDMT in a "reactive" manner during instability deviates from articulated guideline standards and misses the opportunity to "proactively" adjust therapy to prevent such high-risk moments.

- **Patient related factors:** Though well-defined in the literature regarding acceptance or refusal of device therapies in HF, the role of patient-related factors in the optimal deployment of GDMT is nonetheless likely substantial: initiation and titration of numerous therapies requires diligence, frequent office visits, and shared responsibilities between patients and clinicians. In an optimal scenario, detailed education and shared decision-making regarding importance of GDMT would facilitate prescription; within the context of an already complex 20-minute visit, this may not be possible. It is thus reasonable to expect better patient understanding of importance of GDMT titration to goal would facilitate such therapy.

  The goal of the TRANSFORM-HFrEF trial is to improve adherence to American College of Cardiology (ACC) clinical policy by motivating widespread adoption of evidence-based practices to improve quality of care. Within the context of a 6-month randomized registry trial, we hypothesize that:

- HFrEF GDMT can be optimized through redesigning the 20-minute outpatient office visit through interventions directed both to patient and caregiver.
- With this, patient-reported outcomes will be more improved among those in the intervention arm of the study.

3. Design and Procedures

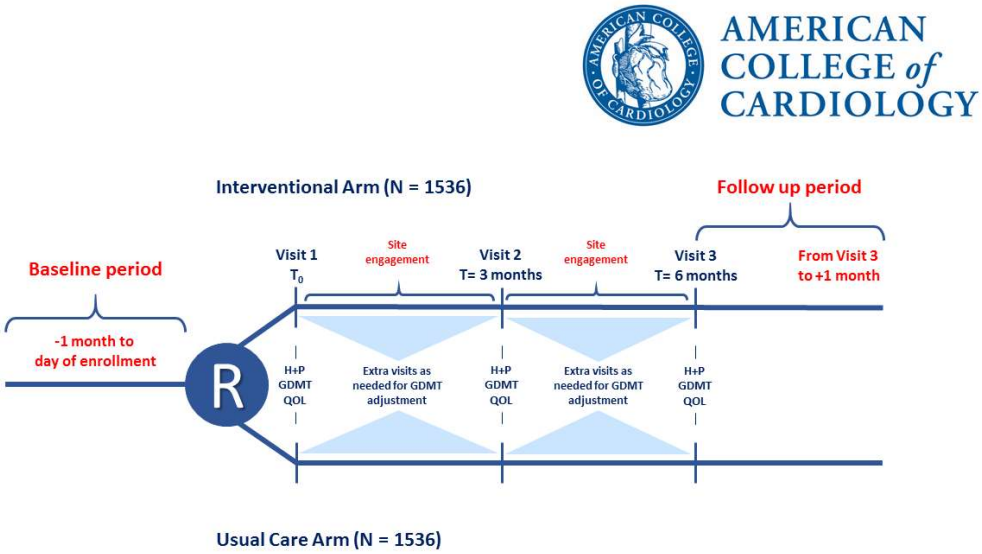
The PINNACLE Registry® is the largest outpatient cardiovascular clinical data registry in the world, with millions of patients drawn from thousands of sites around the US representing over 10,000 outpatient providers. The registry has a comprehensive goal of improved patient care. In addition to using the PINNACLE Registry®, non-PINNACLE sites within large health systems will be recruited and randomized into the intervention and usual care arms respectively.

The Specific Aims of this study will be:

- To evaluate ability of ACC Solution Sets and Patient Resources to improve initiation and titration of GDMT for eligible patients with HFrEF Left Ventricle Ejection Fraction (LVEF) ≤ 40%.
- To evaluate change in QOL between patients in the Intervention arm and the Usual Care arm.
- Examine relative change in GDMT among higher risk versus lower risk patients in the Intervention arm and Usual Care arm.

In this randomized registry trial, sites will be invited to participate in a 6-month study aimed at various processes of care in HFrEF. Sites would be informed that they might be asked to participate in an intensive intervention to improve GDMT prescription or in a study of QOL in HFrEF. Once a list of sites interested in participating is created, sites would be randomized into two arms: an intervention group and a usual care group.

(**Figure 1**): This graphic shows both usual care and intervention arm tracts.



Study Population:

- Patients from practices participating in the PINNACLE Registry® (these include those that are part of integrated health systems, stand-alone, and other practice environments); as well as patients from other practices (these include those that are part of integrated health systems, stand-alone, and other practice environments) with pre-existing data interfaces with study partner HealthReveal.

- Patient cohorts will have the following **inclusion** criteria:

    - Age ≥18 years
    - Clinical diagnosis of HF with EF ≤40% documented within 1 year of enrollment
    - Receiving ≥1 oral medication for HF at study enrollment (including diuretics, ACEI/ARB/ARNI, beta-blockers, MRA, SGLT2i or thiazide diuretics.

- Patient cohorts will have the following **exclusion** criteria:

    - Current or anticipated participation in a clinical trial
    - Currently receiving comfort care or enrolled in hospice
    - Life expectancy <1 year
    - History of or plan for heart transplantation or left ventricular assist device
    - Current or planned hemodialysis

The **interventional arm** will be provided tools to augment quality of care and build the patient and physician relationship through trust and shared goal-setting.

Prior to each patient appointment, on a customized ***GDMT Dashboard***, the site will receive a pre-visit assessment of GDMT accompanied by recommended adjustment(s) using information extracted weekly from the sites' electronic health record (EHR). The recommended adjustment(s) will be conveyed using proprietary software from HealthReveal, with a suggested follow up plan. All reminders regarding dosing targets are based on the *2020 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment.*

Additionally, during visits at baseline, 3 months, and 6 months, patient-reported outcomes/QOL will be assessed.

To further facilitate optimal care, tools provided to each intervention site will include clinician and patient resources:

- Information based on the 2020 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment (4). This ACC policy document sets clear goals and provides useful logic not only for recognizing when patients were eligible for initiation or titration of therapy, but also articulates important information for how to achieve such titration to target. Sites randomized to the intervention will receive distilled information from this policy document embedded into the care logic of online decision support in the form of Reveals provided by HealthReveal in the dashboard.

- ***CardioSmart*** Heart Failure patient resources will be provided to patients via CardioSmart.org with links from patient app Medable. These resources include several patient-facing tools that serve to facilitate optimal care during the standard 20-minute visit.

  Upon being diagnosed with heart failure, patients often need help "finding their new normal," which is how many people farther along in successfully managing their heart failure describe their journey. The ACC developed an action plan and accompanying tools to help patients on that journey manage their course of treatment and understand what to expect on the road to success. These tools help remind patients that they are at the center of their care and emphasize the importance of talking through and making informed decisions for managing their condition.

  In addition, when patients feel listened to, validated and involved in their care, they are more apt to be adherent and honestly report challenges. The HF Action Plan and accompanying tools are designed to help focus and guide discussions at HF-related appointments with the goal of improving the efficiency of these encounters, as well as assuring that what matters to the patient is captured and addressed. As well, most patients don't know what HF "measures" are and how they are used to optimize care. In a sense, these tools will provide a road map of what patients should be prepared to discuss, as well as what clinicians might be asking about and a brief explanation as to why (to help operationalize said measures in a way that is accessible to patients) so that everyone is on the same page and patients feel more empowered.

  Additionally, intervention arm patients will be surveyed weekly through the Medable app about their overall stress and anxiety levels living with heart failure. We hope through the consistent review and use of the Cardiosmart tools provided, that stress and anxiety will lessen with time and patients will feel empowered and more in control of their heart failure journey.

  Specifically, the CardioSmart Heart Failure Patient Resources can be found in Appendix A and may include:

  - **Heart Failure Action Plan** - – to document individual treatment goals and challenges and review and prioritize treatments and adjustments, including medications, lifestyle changes, and how to avoid setbacks

  - **Heart Failure: Making the Most of My Follow Up Visits** – a fillable worksheet for patients to use in between appointments to help track how they feel, heart failure symptoms, ways in which the condition limits their ability to do certain activities, as well as their perceived self-efficacy with managing their condition

  - **My Daily Heart Failure Tracker** – to record daily weights and how they feel generally

- **My Heart Failure Checklist** – that includes important reminders for managing heart failure well

- **Heart Failure: Caregivers** – includes information specific to caregivers to help them best support and care for their loved ones on their journey

- **Heart Failure, The Basics** – what it is, stages of disease and what to focus on

- **Heart Failure Frequently Asked Questions –** answers to common questions patients have

- **Quick Tips series** – provides guidance on many of the topics that are raised during medical visits, but we may not have sufficient time to go into great detail about; for example, how to record daily weights, stay active, limit sodium, take medications, watch for triggers that can exacerbate heart failure, and pay attention to emotional health and mental outlook

The Usual Care arm, will be managed as close to "true" usual care as possible. To avoid influencing management, once randomized to usual care, other than to collect QOL measures (assessed using the Kansas City Cardiomyopathy Questionnaire-23) at baseline, 3 months, and 6 months, study sites will not be contacted until the study has completed and they will be unaware of allocation to usual care. They will not receive specific pre-visit guidance, and though publicly available, sites will not be specifically provided ACC tools.

B. <u>Data Management</u>

Participating sites submit data using an electronic health record (EHR) system integration (SI) tool, where relevant registry data fields can be extracted from a practice's EHR and is then transmitted to a secure database.

<u>Intervention Arm</u>

Steps include:

Data extraction: Mapped to pre-specified data fields, a data extractor (such as that provided by FIGmd) will extract the EHR data to storage at Veradigm for PINNACLE sites. FigMD has historically provided the data extractor solution for the PINNACLE Registry and provides similar services to multiple medical societies across the United States of America. Data extracted may include the following: age, sex, LVEF, medication list (including doses), and laboratory results (such as basic metabolic panel). For the purposes of the study, data from the local EHR will be extracted on a weekly basis.

Creation of Reveals: Following, a similar extractor will then process data to HealthReveal for non-PINNACLE sites, where a dashboard will be created. This dashboard will include a) lists of eligible patients for the study and b) an update on opportunities for further medication optimization. The latter information will be based on guideline-directed medical targets as articulated in the ACC 2020 Expert Consensus Decision Pathway document on management of HFrEF. The dashboard containing the reveals will be conveyed to the sites.

Site based procedures: Eligible patients will be enrolled utilizing software services provided by Medable. Medable hosts consumer-grade applications using their eCOA – including ePRO, eDiaries, eClinRo, eObsRo, and ePerfO – combined with eConsent, reminders & notifications, visit scheduling, and telemedicine on a single platform; their work will be essential in keeping track of patient reported outcomes and quality of life data.

Following enrollment, patients will be directed to Cardiosmart resources; such as those listed in Appendix A to use throughout their study experience—and after. As well, HRQoL will be assess at quarterly visits using the Medable app for completion of the KCCQ-23.

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered questionnaire developed to independently measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life (QOL) within a 2-week recall period.

The KCCQ tool quantifies the following six (6) distinct domains and two (2) summary scores:

KCCQ Symptom Domain: quantifies the frequency and burden of clinical symptoms in heart failure, including fatigue, shortness of breath, paroxysmal nocturnal dyspnea and patients' edema/swelling. An overall symptom score is generally used in analyses; subscale scores for both frequency and severity are also available.

KCCQ Physical Function Domain: measures the limitations patients experience, due to their heart failure symptoms, in performing routine activities. Activities are common, gender-neutral, and generalizable across cultures, while also capturing a range of exertional requirements.

KCCQ Quality of Life Domain: is designed to reflect patients' assessment of their quality of life, given the current status of their heart failure.

KCCQ Social Limitation Domain: quantifies the extent to which heart failure symptoms impair patients' ability to interact in a number of gender-neutral social activities.

KCCQ Self-efficacy Domain: quantifies patients' perceptions of how to prevent heart failure exacerbations and manage complications when they arise. This scale is not included in the summary scores.

KCCQ Symptom Stability Domain: measures recent changes in patients' symptoms; their shortness of breath, fatigue or swelling. It compares patients' frequency of heart failure symptoms at the time of completing the KCCQ with their frequency 2 weeks ago. As a measure of change, it is most interpretable as a baseline assessment of the stability of patients' symptoms at the start of a study and shortly thereafter, as a measure of the acute response to treatment. This domain is not included in the summary scores.

Clinical Summary Score: includes total symptom and physical function scores to correspond with New York Heart Association ("NYHA") Classification.

Overall Summary Score: includes the total symptom, physical function, social limitations and quality of life scores.

The KCCQ-23 data will be blinded and stored until end of trial.

Following completion of usual procedures, the patient will be sent home, and followed up per study protocol at 3 month intervals for up to 3 clinical visits and with as many 'as needed' visits to achieve optimal GDMT. At each visit, the Dashboard will provide updated information focused on opportunities for optimizing GDMT.

Usual Care Arm

In the Usual Care Arm, eligible patients will be identified and sites will be alerted to the roster of patients eligible for study participation. These patients will be offered participation into a study of health status in those with chronic HFrEF and if agreeable they will be consented for inclusion to the study and information recorded. Data extracted may include the following: age, sex, LVEF, medication list (including doses), and laboratory results (such as basic metabolic panel). Following, the KCCQ-23 will be recorded via Medable, as above.

To maintain "usual care" as much as possible and avoid internal contamination bias, the managing site will not be aware the medical management is being monitored and the patient will not receive CardioSmart materials.

Follow up in the Usual Care arm will be at the discretion of the managing site. KCCQ-23 will be recorded remotely via Medable over the 6 months of follow up.

Analytics

At study completion, a data extractor (such as that provided by FIGmd) will extract the EHR data from storage and a data sheet across study visits will be provided to the analytic center at the Massachusetts General Hospital.

Safeguards

The ACCF has established a robust plan for ensuring appropriate and commercially reasonable physical, technical, and administrative safeguards are in place to maintain the integrity of study data stored and used.

All study data shall be maintained on secure servers with appropriate safeguards in place. The project team will periodically review all activities involving protected health information to ensure that such safeguards including standard operating procedures are being followed. The ACCF shall also communicate to all study personal the procedure for notifying the ACCF of any breach of confidentiality and immediate mitigation standards that need to be followed.

ACCF shall limit access to Protected Health Information, and to equipment, systems, networks, applications and media that contain, transmit, process or store Protected Health Information ("Equipment, Systems and Media"), to those employees of ACCF who need to access the Protected Health Information for purposes of performing ACCF's obligations to Covered Entities ("Participants") who are in a contractual relationship with the ACCF. ACCF shall implement discretionary access controls designed to permit each user access to only Equipment, Systems and Media, which are necessary to accomplish assigned tasks on behalf of study participants ACCF shall strictly control physical and electronic access to Equipment, Systems and Media in the following manner:

Physical access

a. All Protected Health Information, and all Equipment, Systems and Media must be stored in a secure facility or secure area within ACCF's facilities which has separate physical controls to limit access, such as locks or physical tokens ("Secured Areas").

b. ACCF shall limit access to Secured Areas to those of its employees or agents who have a legitimate business need to access the secure area, and after ACCF has made an administrative determination of the employee's trustworthiness. Such determination of trustworthiness may include: checking references; checking education and employment history; and searches of public records.

c. Access to Secured Areas by individuals other than those who have been authorized to access Secured Areas shall only be permitted if there is a legitimate business need, and only if such access is continuously monitored by an employee who has been authorized.

d. Secured Areas must be monitored 24 hours per day, 7 days per week, either by employees or agents of ACCF by video surveillance, or by intrusion detection systems.

Electronic access

a. Each user who has access to Equipment, Systems and Media ("User") must have a unique identifier.

b. Users must be authenticated by one of the following methods: unique token or unique password. ACCF shall prohibit generic user accounts and shall implement inactivity time-outs, where technically feasible, for User devices that access NCDR Participant information.

Wireless Devices

Encryption of wireless network data transmission and authentication of wireless devices containing NCDR Participant's information ACCF's network is required.

Transmission of Protected Health Information

Protected Health Information may only be transmitted off ACCF's premises to approved parties, Electronic Protected Health Information may only be transmitted via encrypted and authenticated channels, such as VPN, encrypted FTP, SSL or HTTPS.

External Access

Internet

If any Equipment, Systems or Media have Internet connectivity, users must be advised that their unique identifier and authentication tool (e.g. password) must not be shared with others. Where password authentication is employed to authenticate Users, ACCF access and communication to or from the Internet must occur through an actively managed Internet firewall service.

Remote access

If any employees or agents of ACCF have remote access to Protected Health Information, or to Equipment, Systems and Media, from offsite locations, ACCF shall adopt systems and procedures to secure such connections and transmissions. At a minimum, ACCF must ensure the following: 1) dial-up access will occur through a technical security service such as Remote Authentication Dial-In User Service (RADIUS); 2) access via the Internet will be controlled via secure technologies to include authentication and encryption. Acceptable technologies include firewalls and virtual private network services; and 3) ACCF shall require users who access Protected Health Information via personally owned devices and remote access services to take responsibility for the integrity and security of their systems and employ anti-virus software and apply operating system service packs as they are released. Protected Health Information may not be stored on personally owned devices.

Software Controls

Virus Protection

ACCF shall employ virus protection on systems or networks that store, process, access or transmit Protected Health Information, and such protection systems must include real-time or periodic scans.

Service Packs and Security Patches

ACCF shall apply operating system service packs and security patches to systems or networks that store, process, access or transmit Protected Health Information as soon as practicable after they are released.

Audit

ACCF shall implement technical features or controls to record security-relevant activity. ACCF periodically reviews activity logs, investigates and resolves incidents where unauthorized access and attempts are identified. ACCF shall maintain audit logs.

Violations

ACCF shall have a process in place for employees to report instances of violations of privacy and security policies and procedures to the appropriate ACCF personnel.

Transportation and Transmission of Protected Health Information

Protected Health Information, and Equipment, Systems and Media may not be transported off of ACCF's premises unless such Protected Health Information is encrypted.

Disposal of files or media which contain Protected Health Information.

If ACCF is required to destroy files or media containing Protected Health Information pursuant to the Business Associate Agreement, such destruction shall be performed in the following manner:

Magnetic Media

Magnetic Media such as tapes, diskettes, hard drives, must be purged of all information such that the data is no longer reasonably retrievable from the media. Degaussing is an acceptable method of purging information from magnetic media.

Non-Magnetic Media

Non-magnetic media such as hard copies, CDs or DVDs must be physically destroyed such that the data is no longer reasonably retrievable from the media. Acceptable methods of physical destruction include shredding.

TRANSFORM HFrEF participating collaborators shall employ comparable safeguards that store, process, access or transmit Protected Health Information with real-time protection. No printed materials will be generated as part of this study.

4. Selection of Subjects

Adult patients ages 18 years and older with heart failure with Left Ventricle Ejection Fraction (LVEF) ≤ 40% will be identified via an initial data extraction from interested sites. Participating sites will receive a roster of eligible patients, in order to best plan their enrollment. There will be no discrimination or bias with respect to patient inclusion on the basis of sex, race, or religion.

5. Subject Recruitment and Compensation

Upon identification of eligible patients, members of the clinical team will approach the patient with the offer to participate in a clinical study.

At **Intervention sites**, patients will be presented with the goals of the study, and given time to review the Informed Consent (prepared in their own language). Following, if the patient agrees, consent will be signed and patient included in the trial.

At **Usual Care sites**, patients will be presented with a proposal for periodic HFQoL assessment. If the patient agrees, consent will be signed and patient included in the trial.

No compensation will be offered to patients or families for participation in the registry or study.

6. Consent Process

Study consent will be provided electronically ("e-consent"), using Medable software. Consent materials will be provided with sufficient time for the patient to consider their participation in the study. For patients in the Intervention Arm of the study, consent materials will describe the study procedures, expected risks and expected benefits. For patients in the Usual Care arm, consent materials will only focus on the KCCQ-23. All consent materials will be in the patients' native language.

If the patient agrees to participation in the study, their informed consent will be recorded through e-consent processes with signature stored at Medable.

At any time, patients may withdraw consent. In such a circumstance, patients will be analyzed per intent to treat.

7. Subject's Capacity to Give Legally Effective Consent

Only those patients capable of giving informed consent will be enrolled in the study.

8. Study Interventions

In the Intervention arm, for each study visit, the site will receive a pre-visit assessment of GDMT accompanied by recommended adjustment(s) using information extracted weekly from the sites' EHR.

The recommended adjustment(s) will be conveyed using proprietary software from HealthReveal, with a suggested follow up plan. All reminders regarding dosing targets are based on the 2020 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment.

Additionally, during visits at baseline, 3 months, and 6 months, the KCCQ-23 will be completed.

In the Usual Care arm, during visits at baseline, 3 months, and 6 months, the KCCQ-23 will be completed.

9. Risk/Benefit Assessment

As study procedures reflect optimized heart failure care via guideline recommendations supported by the clinical judgment of the managing physician, there is no envisioned procedural risk to patients through involvement in the study. No testing, time, risk, or procedures beyond those required for routine care will be imposed. The primary risk associated with this project is the potential for a breach of patient confidentiality. The ACCF has established a robust plan for ensuring appropriate and commercially reasonable physical, technical, and administrative safeguards are in place to mitigate such risks as described in the Data Management section of this protocol.

10. Costs to the Subject and Compensation

There are no costs or compensation to the patient for participation in the TRANSFORM-HFrEF study.

11. Data Analysis and Statistical Considerations

Primary endpoint; compared to usual care:

From baseline to 6 months change in average composite endpoint of target dose achievement for the main classes of drugs (RASi/beta blockers/MRA/SGLT2i) among eligible patients without documented contraindications or intolerance.

Goal doses will be based on the 2020 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment (4).

To calculate this composite:

Numerator = receiving ARNI/ACEI/ARB at 50% or higher of target dose + receiving evidence-based beta blocker at 50% or higher of target dose + receiving MRA at 50% or higher of target dose + receiving SGLT2i at 50% or higher of target dose.

Denominator = eligible to receive ARNI/ACEI/ARB and no documented reason for not receiving higher dose, eligible to receive evidence-based beta blocker and no documented reason for not receiving higher dose, and eligible to receive MRA and no documented reason for not receiving higher dose, and eligible to receive SGLT2i and no documented reason for not receiving higher dose.

Using this approach, each patient may contribute to the numerator or be in the denominator 1, 2, 3 or 4 times, depending on meeting criteria and if eligible in that domain. An advantage of this composite approach is that it allows for a holistic view of all classes of drugs considered and allows for assessment not only of up-titration but also down-titration as well.

Example of a patient without contraindications:

Therapy	Initial dose	≥50% target?	Final dose	≥50% target?
Sacubitril/valsartan	24/26 mg twice daily	No	96/104 mg twice daily	Yes
Carvedilol	6.25 mg twice daily	No	12.5 mg twice daily	Yes
Spironolactone	25 mg daily	Yes	25 mg daily	Yes
	Ratio = 0 + 0 + 1/1 +1 + 1= .33		Ratio = 1 + 1 + 1/1 + 1 + 1 = 1.0	
	Relative change = 66.7%			

Example of a patient with contraindication to spironolactone (previous hyperkalemia):

Therapy	Initial dose	≥50% target?	Final dose	≥50% target?
Sacubitril/valsartan	24/26 mg twice daily	No	49/51 mg twice daily	Yes
Carvedilol	6.25 mg twice daily	No	6.25 mg twice daily	No
	Ratio = 0 + 0 /1 +1= .000		Ratio = 1 + 0/1 + 1 = .50	
	Relative change = 50.0%			

Example of a patient with no contraindication to spironolactone but not receiving it:

Therapy	Initial dose	≥50% target?	Final dose	≥50% target?
Sacubitril/valsartan	24/26 mg twice daily	No	24/26 mg twice daily	No
Carvedilol	6.25 mg twice daily	No	6.25 mg twice daily	No
Spironolactone	0	No	25 mg daily	Yes
	Ratio = 0 + 0+ 0 /1 +1 + 1 = .000		Ratio = 0 + 0 +1/1 + 1 + 1 = .33	
	Relative change = 33.0%			

In the CHAMP-HF Registry, the score at baseline was 34.7%, while at 6 months it increased nominally to 36.3% (Fonarow GC, *Confidential Personal Communication, January 2019*).

Secondary endpoints; compared to usual care:

1) Relative change in actual achieved doses of individual classes of pivotal therapies (RASi/beta blocker/ MRA/SGLT2i).

2) Relative change in achievement of target doses (yes/no) of pivotal therapies (RASi/beta blocker/MRA/SGLT2i).

Exploratory, compared to usual care:

3) Difference in patient-reported outcome/KCCQ-23 scores from baseline to 6 months.

4) Rate of ≥25%, ≥50%, ≥75% and 100% improvement in scores.

5) Among those not taking an evidence-based beta blocker, % changed to evidence-based beta blocker during course of the study.

6) Change in % eligible taking RASi during course of the study.

7) Change in % eligible taking beta blocker during course of the study.

8) Change in % eligible taking MRA during course of the study.
9) Change in % eligible taking SGLT2i during course of the study.

10) Relative improvement in GDMT composite score among subgroups of interest. This may include pre-specified analyses among patients the following characteristics:

    a. Elderly patients (age ≥ 75 years)
    b. New onset HF
    c. Recently hospitalized patients
    d. Those with LVEF <25%
    e. Those with estimated glomerular filtration rate <30 mL/min/1.73m^2
    f. Baseline systolic blood pressure <100 mm/Hg
    g. Absence of RASi at baseline
    h. Absence of beta blocker at baseline
    i. Patients with high baseline total medication burden (5 or more meds for all conditions)
    j. Academic versus Private practice

Power calculations: The primary endpoint will compare central tendency in score changes between the two groups (6-month score - baseline score; this gives a range of score changes from -3 to +3). We will assume a 5% rate of score decreases, with rates for -3, -2 and -1 assumed equal between the two groups. To compare such changes a two-sided Wilcoxon rank-sum test at a 0.05 significance level with 90% power will be employed. Assuming 5% of usual

care patients have an increase in score versus 10% of the intervention arm change by 1 point, a sample size of 2560 (1280 per arm) would be needed. Assuming a reasonable 20% loss to follow-up and/or missingness in this registry analysis, this makes a total of 3072 (1536 per arm). This not only provides power for the primary endpoint, but also for the secondary and exploratory endpoints, including change in QOL metrics.

12. Data and Safety Monitoring

This is an observational study comparing the effectiveness of two standards of care based on secondary use of data collected in the conduct of care and patient reported outcomes. The purpose of this study is not to gather data with regards to the safety profile and/or effectiveness of specific drugs. This study does not proscribe which treatment patients will receive. There is no Data Safety Monitoring Board for this study.

Adverse events (should they occur) will be captured at the clinical site level. Patients reporting adverse events will address these with their providing physician.

13. Data Storage and Confidentiality

Please refer to the Data Management section for details regarding how data captured in this study is stored and how the confidentiality of such data is maintained.

References

1. DeVore AD, Thomas L, Albert NM et al. Change the management of patients with heart failure: Rationale and design of the CHAMP-HF registry. Am Heart J 2017;189:177-183.
2. Greene SJ, Butler J, Albert NM et al. Medical Therapy for Heart Failure With Reduced Ejection Fraction: The CHAMP-HF Registry. J Am Coll Cardiol 2018;72:351-366.
3. Ibrahim NE, Song Y, Cannon CP et al. Addition or removal of guideline directed medical therapy in ambulatory patients with heart failure with reduced ejection fraction relative to change in symptom severity: An analysis from the PINNACLE (Practice Innovation and Clinical Excellence) Registry(R). Int J Cardiol 2018;254:222-223.
4. Yancy CW, Januzzi JL, Jr., Allen LA et al. 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2018;71:201-230.

APPENDIX A: CardioSmart materials

Heart Failure Action Plan	Workbook-*Managing My Heart Failure at Home Tab*
Heart Failure: Making the Most of My Follow Up Visit	Worksheet/Addendum to Action Plan Workbook- *Managing my Heart Failure at Home Tab*
My Daily Heart Failure Tracker	Worksheet-*Managing my Heart Failure at Home Tab*
My Heart Failure Checklist	Checklist- *Managing My Heart Failure at Home Tab*
Heart Failure: Caregivers	*Fact Sheet Resource Tab*
Heart Failure: FAQs	*Fact Sheet Resource Tab*

Heart Failure: Questions to Ask	*Fact Sheet Resource Tab*
Heart Failure, The Basics	*Fact Sheet Resource Tab*
Quick Tips: Heart Failure	*Quick Tips Resource Tab*
Quick Tips Sheet: Daily Weight Check	*Quick Tips Resource Tab*
Quick Tips Sheet: Minding Your Emotional Health	*Quick Tips Resource Tab*
Quick Tips: Exercise and Your Heart	*Quick Tips Resource Tab*
Quick Tips: Heart Failure Medications	*Quick Tips Resource Tab*
Quick Tips: Limiting Salt	*Quick Tips Resource Tab*
Quick Tips: Heart Failure Signs and Symptoms	*Quick Tips Resource Tab*
Quick Tips: Triggers and What To Do	*Quick Tips Resource Tab*