STATE-OF-THE-ART PAPER

Design of a "Lean" Case Report Form for Heart Failure Device Development

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HIGHLIGHTS

- The development of treatments for heart failure is challenged by inefficient and burdensome clinical trials.

- The Heart Failure Collaboratory created a lean case report form for use in heart failure clinical trials.

- The lean case report form can be used and iterated to become the standard for clinical data capture.

ABSTRACT

The development of treatments for heart failure (HF) is challenged by burdensome clinical trials. Reducing the need for extensive data collection and increasing opportunities for data compatibility between trials may improve efficiency and reduce resource burden. The Heart Failure Collaboratory (HFC) multi-stakeholder consortium sought to create a lean case report form (CRF) for use in HF clinical trials evaluating cardiac devices. The HFC convened patients, clinicians, clinical researchers, the U.S. Food and Drug Administration (FDA), payers, industry partners, and statisticians to create a consensus core CRF. Eight recent clinical trial CRFs for the treatment of HF from 6 industry partners were analyzed. All CRF elements were systematically reviewed. Those elements deemed critical for data collection in HF clinical trials were used to construct the final, harmonized CRF. The original CRFs included 176 distinct data items covering demographics, vital signs, physical examination, medical history, laboratory and imaging testing, device therapy, medications, functional and quality of life assessment, and outcome events. The resulting, minimally inclusive CRF device contains 75 baseline data items and 6 events, with separate modular additions that can be used depending on the additional detail required for a particular intervention. The consensus electronic form is now freely available for use in clinical trials. Creation of a core CRF is important to improve clinical trial efficiency in HF device development in the United States. This living document intends to reduce clinical trial administrative burden, increase evidence integrity, and improve comparability of clinical data between trials. (J Am Coll Cardiol HF 2019;■:■–■) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CRF = case report form

HF = heart failure

LVEF = left ventricular ejection fraction

Clinical trials in heart failure (HF) are expensive and increasingly burdensome, factors which limit site participation and impair evidence generation (1). The case report form (CRF) is the data capture tool used in clinical trials, designed to log the essential protocol-required information for each study subject (2). There have been modern advancements in the deployment of CRFs, including the transition from predominantly paper to electronic formats, but they continue to be overly extensive and idiosyncratic in their attempts to record data that might be useful for regulatory approval and subsequent payer decisions (3-5). CRF content has historically been decided separately for each clinical trial, typically based on experiences of the investigators, industry partners, and regulators. Because of this lack of cohesion, CRFs have included distinct, incompatible data items and far more data fields than are needed to fulfill the objectives of the trial (3,5-9).

Optimal CRFs include sufficient data fields to ensure that the primary query of the clinical investigation can be answered with robust evidence. The principal foci are the safety and efficacy of the intervention. However, trial designers often have difficulty balancing efficiency with the intention of testing and explaining nonprimary endpoints (7).

Trials often over-collect information, frequently because of concerns from the sponsor regarding safety and pharmaco-vigilance, potential regulatory queries, and academic and scientific interests and to assist with payer negotiations, which drive up burden and thus cost (1,6,7,10,11). Many CRFs used for HF clinical trials include data fields that are never used in analysis, and there is little formal published reports describing appropriate CRF design (9).

This paper is a product of the Heart Failure Collaboratory (HFC), a multi-stakeholder group that includes patients, clinicians, clinical investigators, the U.S. Food and Drug Administration (FDA), industry, other government agencies, and payers, that seeks to improve evidence generation for new therapies and indications, implementation of those treatments, and clinical trial efficiency. The present group of investigators sought to design a lean, core CRF for use in HF device development, while a parallel effort is underway to design a lean, core CRF for use in HF drug development.

METHODS

Through discussions and collaboration with HFC industry partners, 6 device sponsors shared CRFs from previous HF clinical trials (**Table 1**). All variables From the CRFs were systematically extracted into a

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TABLE 1 Data Items Included in Representative CRFs

	CRF 1	CRF 2	CRF 3	CRF 4	CRF 5	CRF 6	Consensus
Demographics	4	5	3	6	4	3	4
Vital signs	5	6	5	3	9	4	7
Physical examination	2	20	1	1	10	0	4
Medical history	23	34	18	57	41	32	20
Laboratory tests	0	32	11	1	15	6	7
Imaging tests	2	12	2	0	1	1	1
Electrocardiogram	2	11	1	0	0	0	3
Concomitant medications	All†	13	8	HF‡	14	4	29
Quality of life assessment	Yes (EQ-5D)	Yes (MLHFQ)	Yes (MLHFQ)	Yes (MLHFQ, EQ-5D)	Yes (IPQ, KCCQ-12)	No	Yes§
6-min walk test	Yes	Yes	Yes	Yes	No	No	No
Events*	16	10	34	16	6	8	6
Total Items	51†	143	83	84	100	58	81

*In addition to quality of life and objective functional assessments, separate from device-specific adverse events. †All concomitant medications required documentation. ‡Not included in primary CRF. §Any of the FDA-qualified medical device development tools can be used.

CRF = case report form; EQ-5D = EuroQol 5D; FDA = Food and Drug Administration; IPQ = Brief Illness Perception Questionnaire; KCCQ = Kansas City Cardiomyopathy Questionnaire; MLHFQ = Minnesota Living with Heart Failure Questionnaire.

spreadsheet form and then manually reviewed by the project team, which included members of the HFC working group and participants From the FDA Division of Cardiovascular Devices and Radiological Health (Online Appendix A). Variable selection was discussed during conference calls and live meetings by the members of the working group to establish final variable inclusion in the core CRF, the project team concurred by simple majority. The working group members From the FDA provided consultative opinions but did not vote on variable inclusion.
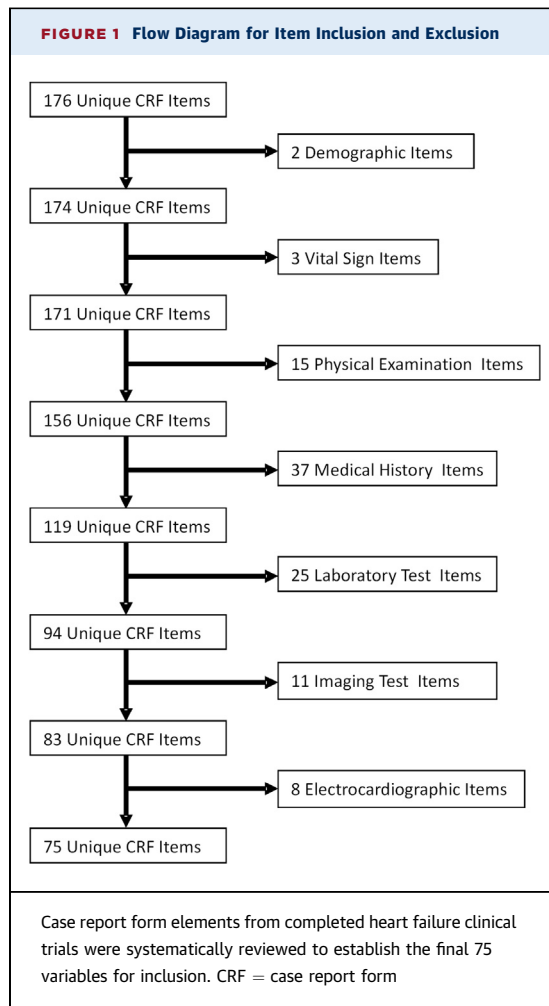
For validation analysis, the data fields from the consensus core CRF were examined for inclusion in the CRFs from each of the HF clinical trials contained in the U.S. National Institutes of Health (NIH) Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). The components of each subgroup analysis from the HF clinical trials contained in BioLINCC were then tabulated to determine their inclusion in the consensus core CRF.

RESULTS

VARIABLE SELECTION. A total of 176 distinct data fields from the shared CRFs were reviewed, covering demographics, vital signs, physical examinations, medical history, laboratory and imaging testing, device therapy, medications, functional and quality of life assessment, and outcome events. Of these, 75 baseline data items (43% of the reviewed CRF items) and 6 outcome events were included in the final core device CRF (Figure 1). The characteristics of the 6 HF device clinical trial CRFs used as guidance and the final consensus CRF are summarized in Table 1.

In order to accommodate the breadth of clinical trials for cardiac devices within the study of HF, including those for patients with American Heart Association/American College of Cardiology Stages C and D disease requiring advanced mechanical circulatory support, the consensus CRF was conceived as the base form with separate modular additions to be created as needed to capture complementary data (Central Illustration) (12). Modules will contain logically connected data elements around concepts not included in the core CRF or that merit expansion into greater detail. Hence the consensus core CRF contains the minimal data necessary for a clinical trial of a device intended to treat HF. A total of 58% of the submitted data variables were excluded from the core CRF, with some selected for development into specific expanded modules (Online Box 1). These modules can be included as necessary to address the breadth of therapeutic interventions for patients with HF.

DEMOGRAPHICS. Previous CRFs have captured age at the time of enrollment or date of enrollment and date of birth. From an analytic standpoint, enrollment age recorded in years is one-half a year apart from the true age of the participant, on average; thus, date of birth with age calculation is preferable. However, precise day of birth is unnecessarily detailed. To facilitate de-identification and simplicity, date of birth was codified to only include birth month and year. Although the authors acknowledge that complicated sex assignments and reassignments can occur, sex at birth was chosen for its clarity in most cases. Sex at the time of trial enrollment could be considered a modular addition where it may affect the

FIGURE 1 Flow Diagram for Item Inclusion and Exclusion

176 Unique CRF Items
→ 2 Demographic Items
174 Unique CRF Items
→ 3 Vital Sign Items
171 Unique CRF Items
→ 15 Physical Examination Items
156 Unique CRF Items
→ 37 Medical History Items
119 Unique CRF Items
→ 25 Laboratory Test Items
94 Unique CRF Items
→ 11 Imaging Test Items
83 Unique CRF Items
→ 8 Electrocardiographic Items
75 Unique CRF Items

Case report form elements from completed heart failure clinical trials were systematically reviewed to establish the final 75 variables for inclusion. CRF = case report form

response to therapy. Racial categorization was expanded from the NIH data standard and FDA guidance with a platform that allows identification of multiple races (13-15). Both race and ethnicity items grouped participant responses of "other" with "refusal to answer." Geographic region was not included as a separate data field in the CRF because clinical trial enrollment site is typically captured by other documentation.

VITAL SIGNS. Body mass index was not included because it can be calculated from the height and weight (3). Although body mass index may add burden to some clinical trial sites, these measurements would be best harmonized among international and U.S. sites if they were metric, and most electronic health records automatically convert from alternative units. Resting systolic and diastolic blood pressure, heart rate, and respiratory rate were also included. Waist circumference is acknowledged to add metabolic information to the assessment but was

suggested to be limited to modular additions outside of the core CRF (16).

PHYSICAL EXAMINATION. There is rationale to collect extensive physical examination data to prove that recruited patients had HF, particularly given recent issues with clinical trial enrollment of participants with unclear diagnoses (17). Some of these physical examination findings may also be used as primary outcomes for future trials (18,19). However, because HF can currently be diagnosed reliably with a combination of biomarkers, signs, symptoms, and hospitalizations, the physical examination was limited to items believed to be most essential and potentially viable as therapeutic markers including the presence of peripheral edema, evidence of pulmonary edema, jugular venous distension, and an S3 gallop.

CARDIAC ASSESSMENT. Cardiac assessment was conceived to include the following 3 critical pieces of information used to stratify subgroups of patients within HF clinical trials: 1) left ventricular ejection fraction (LVEF); 2) electrocardiographic rhythm and rate; and 3) New York Heart Association functional class. Because ranges of LVEF are statistically problematic, even though LVEF values are typically arbitrarily assigned in multiples of 5%, the exact LVEF value was included. Because investigators tend to choose the LVEF from a range that meets the inclusion criteria for a study, the instructions surrounding LVEF entry will be critical and need refinement by each study. Heart rate, rhythm, and electrocardiographic QRS duration appear to differentially determine efficacy of some therapies (20-22). Although New York Heart Association functional class is a crude measurement, it is heavily relied on in clinical trial inclusion criteria and HF guidelines, and its incorporation facilitates comparability of data across historic and future studies (12,23,24). Additional and more in-depth cardiac assessments such as the 6-minute walk test, echocardiographic details, and cardiopulmonary exercise testing are not needed for every HF clinical trial and can be part of a detailed cardiac functional assessment module (Central Illustration).

PATIENT REPORTED OUTCOMES ASSESSMENT. Given the growing evidence supporting patient reported outcomes (PROs) assessments as patient-centric means to better understand the journey through a disease process and the use of PROs as outcomes for clinical trials, it is appropriate to include at least 1 PRO in every clinical trial (25). The FDA has currently qualified 2 PRO measurements for the evaluation of HF medical devices, the Minnesota Living with HF

CENTRAL ILLUSTRATION Conceptualized Core CRF, Potential Modular Additions, and End Goals
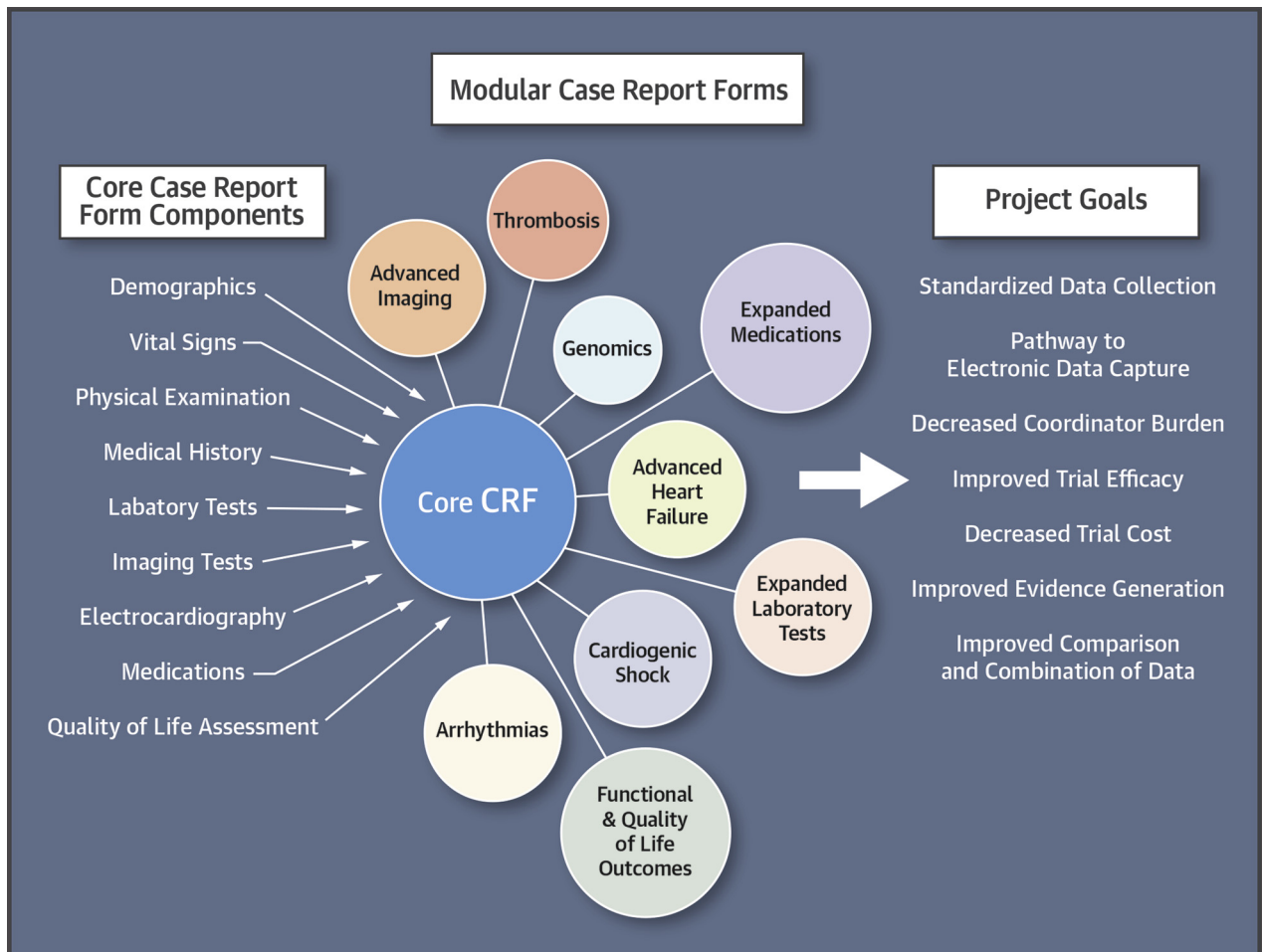
Psotka, M.A. et al. J Am Coll Cardiol HF. 2019;■(■):■–■.

Core CRF elements are shown **left**, linked to additional modular CRF components that can be used depending on the intervention and goals of the clinical investigation. CRF = case report form

Questionnaire and the Kansas City Cardiomyopathy Questionnaire (26).

MEDICAL HISTORY. Medical history encompasses cardiovascular and noncardiovascular historic elements and comorbidities. Hospitalization for HF in the previous 12 months or equivalent decompensation requiring higher intensity care such as intravenous diuretic administration in clinic or an observation unit identifies greater illness severity and is important to capture for all enrollees (27). Description of the dominant cause of HF such as ischemia or nonischemia is included; however, modules were envisioned for specific nonischemic subsets including but not limited to hypertrophic, infiltrative, and other cardiomyopathies. Additional relevant incorporated cardiac and noncardiac comorbidities are listed in Online Box 2, such as prior valvular and ischemic disease, use of implantable and nonimplantable devices, and risk factors for cardiovascular disease and poor overall outcomes such as chronic kidney disease, depression, and advanced cancer. Some comorbidities, such as significant lung and liver disease, are currently typically excluded from HF clinical trials but may merit inclusion in future iterations of the CRF. Appropriate calculation of the estimated glomerular filtration rate can be standardized by using clear explanations in the CRF instructions for each trial. Separate modules were anticipated for more detailed categorization of cardiac devices, rhythm disturbances, and electrocardiographic findings.

TABLE 2   Published and Pre-Specified Subgroup Analyses of Heart Failure Trials Included in the BioLINCC

Trial	Age	Sex	Race	HF Type	Re-vasc	HTN	MI	DM	AF	NYHA Functional Class	VS	BNP	Lab	Med	ECG	LVEF	Echo	Cath	6MW	Site	Ref. #
BEST		X	X	X						X						X					(38)
CARRESS-HF								X								X					(39)
DIG			X							X				X		X	X†				(40)
DOSE	X										X		X								(41)
ESCAPE	X	X	X														X†			X	(42)
EXACT-HF*																					(43)
HF-ACTION	X	X	X	X	X		X			X				X		X					(44)
NEAT		X	X	X				X	X		X	X		X			X†				(45)
RELAX									X					X			X†				(46)
ROSE	X										X		X			X					(47)
SCD-HeFT	X	X	X					X						X	X†	X			X†		(48)
SOLVD				X						X			X	X		X					(49)
STICH	X	X	X					X		X						X	X	X†		X	(50)
TOPCAT	X	X	X			X	X	X		X	X		X	X		X				X	(51)

*No planned or actualized subgroup analyses reported. †Contains data items not included in the Lean CRF. References are listed in Online Appendix B.

6MW = six-min walk test; AF = atrial fibrillation; BEST = Beta-blocker Evaluation of Survival Trial; BioLINCC = Biologic Specimen and Data Repository Information Coordinating Center; BNP = B-type natriuretic peptide; CARRESS-HF = Cardiorenal Rescue Study in Acute Decompensated Heart Failure; Cath = cardiac catheterization measurements or hemodynamics; CRF = case report form; DIG = Digitalis Investigation Group; DM = diabetes mellitus; DOSE = Diuretic Optimization Strategies Evaluation Trial; Echo = echocardiographic measurements; ESCAPE = Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; EXACT = Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients Study; HF type = heart failure cause; HF-ACTION = Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training; Lab = laboratory markers including renal function; LVEF = left ventricular ejection fraction; Meds = medications; MI = myocardial infarction; NEAT = Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction Trial; NYHA = New York Heart Association; Ref = reference; RELAX = Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction; Re-vasc = prior coronary revascularization; ROSE = Renal Optimization Strategies Evaluation Trial; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial; Site = enrollment site; VS = vital signs; SOLVD = Studies of Left Ventricular Dysfunction; STICH = Surgical Treatment for Ischemic Heart Failure; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist.

LABORATORY TESTS. Some CRFs have included extensive laboratory evaluations (Table 1). Although many of these values can be included in the Expanded Laboratory Value Module (Online Box 1), the most commonly useful core testing elements for HF clinical trial enrollment include serum hemoglobin, sodium, potassium, blood urea nitrogen, creatinine, glucose, and natriuretic peptide concentrations.

IMAGING TESTS. The primary imaging result required for every HF clinical trial is an assessment of LVEF, as described previously. Generally, the CRF does not designate the modality needed to measure LVEF but may be specified in the CRF instructions or further detailed in imaging modules, including 1 for echocardiography.

CONCOMITANT MEDICATIONS AND DEVICE THERAPY. The level of detail required for documentation of concomitant medications merited extensive discussion. Regulators seek to assure that a novel therapy is safe and effective in the presence of the therapeutic options already approved for demonstrated benefit in the trial population. Thus, enrolled patients with HF and reduced LVEF should be taking standard guideline-directed HF medical and device therapies (28). Additionally, higher diuretic requirements may classify patients at increased risk for adverse outcomes and can be followed as a marker of therapeutic effect of interventions (29). Nonetheless, most patients with HF and a reduced ejection fraction are incompletely treated or unable to be titrated to the optimal dosing of medical therapies (30,31). The decision making surrounding HF medication dosages is therefore critical, as was captured in the GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure) trial. The core CRF captures the clinical rationale if dosages of the 3 main classes of HF medications are less than optimal (30). Assurance that maximally tolerated HF medical therapy, manifest by proper dosage in the control arm, is needed because device trials are frequently unblinded, and insufficient underlying medical therapy can confound outcome analyses. The working group acknowledges the increased burden on the coordinator that these data require. Because the dosages of digoxin, ivabradine, tolvaptan, hydralazine, and long-acting nitrates that are sometimes used for patients with HF have not been demonstrated to differentially affect outcomes, only the presence or absence of these medications was included. Intravenous inotropic medications can be included in an advanced HF or specialized medication module, if that population is targeted.

The consensus CRF includes a substantial breadth of non-HF medications with consequential effects on morbidity and mortality for large subsets of the HF population. Because many patients with HF have ischemic heart disease, the use of statins was incorporated (32). Additionally, the use of typical

antiplatelet and anticoagulant medications were identified as appropriate background therapy that may hold sway over other trial endpoints, and given the extensive and evolving evidence that management of concomitant diabetes mellitus affects cardiovascular and HF outcomes, the use of subclasses of antihyperglycemic drugs was built into the core CRF (33).

EVENTS. The working group did not mandate that the listed outcomes be targeted as clinical trial endpoints, rather that these data are captured as part of each device trial to assist in the evaluation of safety and efficacy. With increased focus on avoiding hospital admissions and readmissions, intravenous diuretic agents are being administered in outpatient clinics as part of observation visits and by home care nursing, meaning that the definition of an HF exacerbation includes each of these events, if unplanned (34,35). Other endpoints identified both for efficacy and safety are typical for HF clinical trials such as all-cause mortality, cardiovascular mortality, mortality equivalents including left ventricular assist device implantation or cardiac transplantation, and all-cause hospitalization. Modules for other potential endpoints may be needed to best suit the novel therapeutic device and could include activity assessments including exercise testing, gait speed, accelerometry, hemodynamics, arrhythmia episodes, imaging results, and alternative safety signals such as bleeding and infection (Online Box 1). Adjudication modules for types of cardiac death may be needed to distinguish HF mortality from sudden cardiac death.

VALIDATION. The validity of the constructed CRF was determined in 2 ways. First, the only data items not routinely collected by the CRFs of prior HF clinical trials contained in BioLINCC were the reasons for medication dosages and titration (Online Appendix B, items 68 to 73 of the core CRF). Second, all but 4 predictors included in the 14 HF clinical trials in BioLINCC were represented in the harmonized CRF (Table 2, Online Appendix C). Exceptions were left ventricular and atrial echocardiographic dimensions and functional measurements, invasive measurement of cardiac index, coronary stenoses, the 6-minute walk test of exercise capacity, and measurement of angina class, all of which are intended to be included in specific CRF modules that can be added to the standard harmonized CRF depending on trial design (Online Box 1).

DISCUSSION

This paper describes a streamlined and harmonized core CRF intended for use in clinical trials of devices

for HF. A parallel effort is underway to develop a lean core CRF for use in HF clinical drug trials. Although previous attempts to standardize data entry have recommended common domains and data standards, they have not enumerated the specific data items to be used, particularly for HF (36). The resultant consensus CRF seeks an improved balance between efficiency and sufficient data collection to facilitate medical decision making, regulatory approval, and payer coverage by generally reducing the number of required items (Table 1) (7).

There are few published reports that explain the mechanisms used to create CRFs and the process of item selection that satisfies each of the critical roles of clinical trial data collection, including demonstration of safety and efficacy, sufficient data for regulatory approval, scientific understanding of the mechanisms of action, and information to assure potential patients that the results are applicable to their situation (9). Previous endeavors to improve clinical trial CRFs have focused on the creation of CRF libraries and data standardizations (5).

The core CRF established here will help to usher in further related improvements to the HF clinical trial ecosystem. This CRF will be freely available as part of an expanding library of CRF modules useful for a variety of HF clinical trials. Although it will be modifiable, and iteration will be required to continue to enhance efficiency, consistent use among HF clinical trials will increase uniformity and allow comparison of data and outcomes among trials. It can be expected that standardization of data fields will increase efficiency throughout the clinical trial ecosystem, including for coordinators who can become well-versed in the typical data items; sponsors and contract research organizations that can optimize their systems around CRF modules; clinical trial sites that can streamline their clinical trial apparatus instead of housing tens or hundreds of independent and disjointed trial forms; and trial designers that can use time and resources currently expended on CRF design to reduce cost or otherwise optimize trial preparations (11). Although use of these established data collection modules will standardize response items, available modules will also allow customization.

Although the core CRF is a tangible improvement in clinical trial efficiency, substantial work remains. The CRF will need to be integrated into the conventional clinical data management systems used for evidence generation while the clinical trial apparatus is modernized. As part of the modernization, the consensus CRF items can be associated with established data standards such as Clinical Dara

Acquisition Standards Harmonization (CDASH), to facilitate automated electronic data capture from the electronic health record (4,6,37). These systems can assist with prompt regulatory review of trial data and help ensure data integrity as well as protocol adherence in real time.

STUDY LIMITATIONS. This new core CRF has not yet proven effective in a clinical trial, and the present authors believe that broadcasting its existence is a crucial first step to attracting investigators and trial sponsors to use it. Interested parties are welcome to contact the authors directly, and the form and future modular additions will be made available on the Heart Failure Collaboratory Web site (5). Moreover, despite the expertise of the development and writing group, there may be skepticism regarding items included and excluded from the CRF. Thoughtful critique and constructive proposals are encouraged to amend these modules, as the need for ongoing iterative development is expected. Nonetheless, it bears repeating that the regulatory bodies involved in determining efficacy and safety of potential therapeutic HF devices were integrated into the delineated core CRF development process.

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APPENDIX For online appendices and boxes, please see the online version of this paper.