

New medicinal products for chronic heart failure: advances in clinical trial design and efficacy assessment

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Despite the availability of a number of different classes of therapeutic agents with proven efficacy in heart failure, the clinical course of heart failure patients is characterized by a reduction in life expectancy, a progressive decline in health-related quality of life and functional status, as well as a high risk of hospitalization. New approaches are needed to address the unmet medical needs of this patient population. The European Medicines Agency (EMA) is undertaking a revision of its Guideline on Clinical Investigation of Medicinal Products for the Treatment of Chronic Heart Failure. The draft version of the Guideline was released for public consultation in January 2016. The Cardiovascular Round

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Table of the European Society of Cardiology (ESC), in partnership with the Heart Failure Association of the ESC, convened a dedicated two-day workshop to discuss three main topic areas of major interest in the field and addressed in this draft EMA guideline: (i) assessment of efficacy (i.e. endpoint selection and statistical analysis); (ii) clinical trial design (i.e. issues pertaining to patient population, optimal medical therapy, run-in period); and (iii) research approaches for testing novel therapeutic principles (i.e. cell therapy). This paper summarizes the key outputs from the workshop, reviews areas of expert consensus, and identifies gaps that require further research or discussion. Collaboration between regulators, industry, clinical trialists, cardiologists, health technology assessment bodies, payers, and patient organizations is critical to address the ongoing challenge of heart failure and to ensure the development and market access of new therapeutics in a scientifically robust, practical and safe way.

Keywords

Heart failure • Clinical trial • Drug approval

Introduction

Chronic heart failure is a prevalent condition affecting more than 10–12% of people over 60 years of age in developed countries.^{1,2} Application of evidence-based therapy prolongs survival and reduces heart failure hospitalizations in patients with reduced ejection fraction (HFrEF), but not in those with preserved ejection fraction (HFpEF). Heart failure remains a progressive condition characterized by frequent hospitalizations, functional decline, impaired quality of life, and ultimately death. Cardiovascular mortality approached 30% at 3.5 years in an optimally treated chronic heart failure population enrolled in a recent clinical trial.³ However, it may be higher in routine practice outside of closely monitored tertiary settings.^{4,5}

The persistent morbidity and poor long-term survival associated with heart failure underscores the continued need for therapeutic innovations that slow or reverse progression and improve outcomes for these patients. However, concerns have been raised that investment in development of heart failure therapeutics is declining for many reasons.^{6,7} Regulatory requirements are perceived by some stakeholders as one major barrier to therapeutic development in heart failure because large and lengthy trials are necessary before marketing authorization to demonstrate evidence of a treatment effect on mortality and morbidity endpoints and to provide assurance of safety even when mortality and morbidity are not primary targets of therapy.⁷ The quest for safety has been advocated, mainly by regulators, after the withdrawal of drugs (e.g. flosequinan, ibopamine, and milrinone) that were shown to be associated with unfavourable long-term prognosis.^{8–10} However, it must be highlighted that at the time of the original approvals, warning signs as regards safety were present in the small studies that suggested benefit. In addition, the feasibility and relevance of clinical trials in heart failure are affected by shifts in heart failure practice that have occurred over time (e.g. trends in hospitalization patterns, location of care delivery).

In recognition of these concerns and the changing heart failure landscape, the European Medicines Agency (EMA) is undertaking a revision of its Guideline on Clinical Investigation of Medicinal Products for the Treatment of Chronic Heart Failure (EMA/CHMP/392958/2015). The EMA released a draft for public consultation in January 2016.¹¹ The Cardiovascular Round Table

(CRT) of the European Society of Cardiology (ESC) is a strategic forum for high-level dialogues between ESC leadership, academia, and industry to identify and discuss key strategic issues for the future of cardiovascular health in Europe. In partnership with the Heart Failure Association (HFA) of the ESC, and with involvement of representatives from EMA and members of other national Health Authorities in the European Union, the CRT convened a dedicated two-day workshop to provide feedback on three main topic areas addressed in the EMA guidance: (i) assessment of efficacy (i.e. endpoint selection and analytical methods); (ii) clinical trial design (i.e. issues pertaining to patient population, optimal medical therapy, run-in period); and (iii) research approaches for novel therapeutic principles (i.e. cell therapy). Although the scope of heart failure clinical research expands beyond these three topics, these were the focus areas for the workshop and the subjects of this manuscript. This paper summarizes the key outputs from the workshop, reviews areas of expert consensus, and identifies gaps that need further research or discussion (*Table 1*).

Assessment of efficacy

Morbidity and mortality outcomes

A composite endpoint that includes death (all-cause or cardiovascular) and hospitalization (usually owing to heart failure) is an accepted standard efficacy measure for chronic heart failure trials.¹² Composite endpoints have become more widely used in the past 15 years because they reflect both survival and burden of morbidity (i.e. reflected by hospitalization), and standard composites are more feasible than a single endpoint because event rates are higher, which can reduce the sample size and increase power.¹³ For efficacy, cause-specific mortality (i.e. cardiovascular) has been included in the composite primary endpoint in preference to all-cause mortality in recent heart failure trials.^{3,14,15} Cardiovascular death reflects the target of treatments for heart failure, whereas non-cardiovascular deaths are unlikely to be influenced by heart failure therapies, even though other competing risks as a potential source of bias should be considered when drugs improve cardiovascular death. The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial illustrates this point. The hazard ratio (HR) for candesartan vs. placebo

Table 1 Workshop summary on viewpoints related to changes in the European Medicines Agency guidelines

Topic	Comment
Efficacy assessments	
Morbidity and mortality outcomes	Cardiovascular mortality is usually preferred to all-cause mortality for evaluating efficacy in chronic heart failure trials All-cause mortality should still be assessed (with adequate power to rule out an increase) to evaluate safety and potential off-target effects on non-cardiovascular death
Composite endpoints	Composite endpoints should comprise only the most clinically relevant components to avoid overestimation of treatment effects, maintain focus on the most clinically relevant endpoints, and minimize noise related to non-response
Outpatient management of worsening heart failure	The inclusion of outpatient treatment for worsening heart failure in composite primary endpoints may be considered given the frequency of these events, their prognostic importance, evolution in heart failure care, and the global nature of modern trials
Functional endpoints and quality of life	Functional capacity, symptoms, or other patient-reported outcome endpoints may be valid primary efficacy endpoints under certain circumstances when the approach is justified by a potential benefit to public health that outweighs the potential risk of incomplete (i.e. ongoing collection of) morbidity and mortality data. These endpoints are most suitable as secondary or supportive endpoints to reflect the patient's and physician's additional treatment goals
Analytical methods	
Repeat hospitalizations	Repeat hospital admissions are clinically meaningful to physicians and patients, can help to establish treatment effect, and may increase the power of a study if the treatment effect is consistent among first and repeat events The negative binomial, Andersen–Gill, and joint-frailty model are appropriate methodologies for analysis of repeat hospitalizations Regulatory advice on proposed approaches is strongly recommended before initiating a heart failure trial that is intended to support product registration and labelling, and sensitivity analyses should be planned to evaluate the robustness of the findings
Clinical trial design	
Patient population	The target population enrolled in a pivotal trial should be easily identifiable and generally representative of the intended population post-approval If an enrichment approach is applied in a clinical study intended to support product registration, justification that the extrapolation to use in lower-risk patients is likely to be required by regulators when a broader indication is claimed. Approved labelling may need to reflect some of the eligibility criteria used in a clinical trial to identify patients with the condition who have the highest likelihood of therapeutic response. This will also depend on the risks. Conversely, the label should not reflect enrolment criteria used solely for the purpose of enriching or homogenizing the risk of the population (e.g. BNP or NT-proBNP above a threshold level, previous hospitalization owing to heart failure), unless the criteria excluded a large proportion of potential patients
Optimal medical therapy	Clinical trials should be conducted against a background of optimal evidence-based care in accordance with treatment practice guidelines Efforts should be made to minimize imbalances in the use of standard of care between groups, and lower than expected use of evidence-based therapies will need to be justified to health authorities
Run-in period	Consideration should be given to the impact on external validity and whether specific labelling is needed
Novel therapies	Evidentiary requirements for cell-based or other novel therapies should be conceptually similar to other therapies Longer-term safety assessments (e.g. 5–10 years beyond original licensing) may be necessary to rule out adverse effects

BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide.

on cardiovascular mortality was 0.88 [95% confidence interval (CI) 0.79–0.97, $P = 0.012$], whereas no statistically significant effect on non-cardiovascular mortality was observed ($P = 0.45$).¹⁶ Candesartan's lack of effect on non-cardiovascular mortality diluted the treatment effect of candesartan on all-cause mortality (HR 0.91, 95% CI 0.83–1.00, $P = 0.055$).¹⁶ In contrast to all-cause mortality,

cardiovascular death may often require adjudication by a committee. Duration of follow-up is also an important consideration, as most deaths in a trial with relatively short follow-up will be from cardiovascular causes. In the draft EMA Guideline,¹¹ it was proposed that overall mortality is the preferred endpoint. However, cardiovascular mortality, alone or as a composite endpoint, can

also be considered as the primary mortality endpoint provided that all-cause mortality is assessed as a secondary endpoint. The majority of workshop participants suggested that cardiovascular (and thus cause-specific) mortality may be preferred to all-cause mortality for evaluating efficacy in chronic heart failure trials: any effect on all-cause mortality is likely to be driven by cardiovascular death in the heart failure population, and it is implausible that a heart failure therapy would affect all components of all-cause mortality. All-cause mortality should still be assessed (with adequate power to rule out an increase) to evaluate safety and potential off-target effects on non-cardiovascular death.

Composite endpoints in heart failure trials have been reviewed in detail previously.^{12,17} It is outside the scope of this manuscript to consider all the strengths and limitations of composite endpoints, except to emphasize the importance of selecting appropriate components. The draft EMA document¹¹ stated that composite and hierarchically ordered endpoints can be applied to chronic heart failure studies, provided that mortality (overall or cardiovascular) and hospitalization for heart failure are the first two hierarchical endpoints, respectively. The relevance of the components of a composite endpoint varies with the mortality rate of the population under study. Combining mortality with many other (less serious) time-to-event components might (but not necessarily will) result in an overestimation of the treatment effect (see below) and decrease the clinical importance of the results if the effect is driven by the non-mortality components. Conversely, adding multiple components may effectively increase the event rate, but if those components are unresponsive to the treatment, then the treatment effect may be muted by the 'noise' of non-response. Thus, when used, composite endpoints should comprise only the most clinically relevant components.^{12,17}

Outpatient management of worsening heart failure as an endpoint

Patients with worsening heart failure are increasingly being managed in non-hospitalized settings (e.g. emergency departments, specialized clinics, observation units, hospital-at-home services), which is among other reasons, motivated by an effort to contain healthcare costs.^{18–20} The draft EMA Guideline¹¹ addressed this trend by proposing that events of worsening of heart failure without hospitalization may be used as an additional endpoint. Modern heart failure clinics have developed capabilities to monitor and provide treatments in the outpatient setting that were previously available only to inpatients. As a result of these advances and regional differences in heart failure treatment practices, the location of where heart failure events are managed has become less relevant than the characteristics of the worsening heart failure event itself.

Until recently, worsening heart failure in the outpatient setting has not been considered a primary event in many trials because of concerns that these events might be less severe than those requiring hospitalization, or that patients who can be managed as outpatients differ from those who are hospitalized. Importantly, worsening heart failure that requires outpatient management portends a poor prognosis similar to that of hospitalization

events.^{21–23} In the Prospective Comparison of ARNI (angiotensin receptor–neprilysin inhibitor) with angiotensin-converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF), the risk of all-cause mortality was similar among patients whose first event was a heart failure hospitalization (HR 6.1, 95% CI 5.4–6.8), emergency department visit for heart failure (HR 4.5, 95% CI 3.0–6.7), or intensification of heart failure therapy (HR 5.2, 95% CI 4.2–6.3).²² Similar findings were reported from the Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (MADIT-CRT) trial, where the mortality rates per 100 patient-years were 1.5 in patients without a primary heart failure event, 15.9 in patients with an outpatient heart failure event, and 18.5 in patients with an inpatient heart failure event.²¹

One risk of adding more components to a composite endpoint is that the magnitude of effect on the overall composite may be diluted if the treatment effect is inconsistent across all components. However, an analysis of data from the PARADIGM-HF trial showed that the effect of sacubitril/valsartan on outpatient worsening was similar to its effect on cardiovascular death and hospitalizations owing to heart failure.²² Another challenge of including outpatient heart failure events in a primary composite endpoint is that the overall treatment effect may be dominated by less severe events, but the increasing evidence supporting the prognostic importance of outpatient worsening provides a rationale for its inclusion.²²

Worsening heart failure managed in the outpatient setting should be rigorously defined, well documented and adjudicated irrespective of whether it is a component of a primary composite endpoint or not.²⁴ A variety of definitions for non-hospitalized worsening heart failure have been used in clinical trials¹² and generally have required outpatient or emergency department administration of intravenous therapy (i.e. diuretics, vasodilators, or inotropes) for a specific duration (e.g. ≥ 4 h) or outpatient intensification of heart failure therapy [e.g. sustained, (≥ 1 month) increase in oral diuretic dose, or new drug therapy for heart failure].²² Inclusion of events based on admission to emergency department or urgent care centre in the primary endpoint could be acceptable provided that they are strictly defined (i.e. elevated natriuretic peptides, need of intravenous diuretics, and uptitration of therapy) and centrally adjudicated, and that it can convincingly be shown that the subpopulation of heart failure patients admitted to emergency department or urgent care centres is similar regarding disease severity and outcome to patients admitted to hospital, thus providing reassurance that there is no difference in the type or severity of event identified. Given the frequency of these events, their prognostic importance, the evolution in heart failure care, and the global nature of modern trials, the inclusion of outpatient treatment for worsening heart failure in composite primary endpoints may be considered, but its role needs further justification as might be supplied from its use in future clinical trials.

Functional and quality of life endpoints

The ability of patients to undertake normal daily activities and to enjoy a reasonable quality of life has become ever more relevant as patients survive longer with heart failure. In addition to a reduction

in life expectancy, chronic heart failure is characterized by repeat hospitalizations, often debilitating symptoms and impaired quality of life, and progressive functional decline. Heart failure patients' complaints generally focus on poorly controlled symptoms and/or functional impairment, which to date has not been the primary objective for the development of new drugs in heart failure. Few studies have robustly evaluated effects of treatment on these aspects of the heart failure patient's experience.

A composite endpoint reflecting morbidity and mortality provides the most robust assessment of efficacy and safety for a pivotal trial in chronic heart failure. Functional capacity, symptoms, or other patient-reported outcome endpoints may be valid primary efficacy endpoints under certain circumstances when the approach is justified by a potential benefit to public health that outweighs the potential risk of incomplete (i.e. ongoing collection of) morbidity and mortality data. However, for most studies, these endpoints would be mostly accepted as secondary or supportive endpoints to reflect the patient's and physician's additional treatment goals. The authors agree that heart failure patients need therapies that affect all aspects of disease burden and the patient's journey, and thus different treatment goals may be relevant for different stages of the syndrome.²⁵ This is recognized in the draft EMA Guideline which states that exercise-testing objectively evaluates functional capacity in patients with chronic heart failure and may be relevant to measure as a secondary endpoint under certain conditions (e.g. patients with HFpEF).¹¹ A primary endpoint measuring treatment effect on functional capacity, symptoms, or other patient-reported outcome endpoints may only be appropriate for use in a pivotal heart failure trial in selected patient populations with an unmet medical need (e.g. patients with end-stage heart failure or patients with specific aetiologies such as hypertrophic cardiomyopathies and amyloidosis), provided that appropriate blinding, with sham procedures or placebo, is implemented. However, this depends on the specific type of population, and an assessment of all-cause mortality remains an important part of the safety evaluation to confirm the absence of off-target effects. Clinical trials in heart failure should be sufficiently sized and of an appropriate duration to provide evidence of no harm at the time of registration.

The EMA's pilot adaptive pathway programme (i.e. gradual expansion of the target population, starting from a population with high medical need, or progressive reduction of uncertainty after initial authorization based on surrogate endpoints) was launched to potentially accelerate patients' access to medicines. It applied primarily to treatments in areas of high medical need where it is difficult to collect data via traditional routes, and where large clinical trials would unnecessarily expose patients who are unlikely to benefit from the medicine.²⁶ The newly launched PRiority MEDicines (PRIME) scheme²⁷ focuses on medicines with early clinical data that suggest a major therapeutic advantage for patients with conditions where there is an unmet medical need (i.e. for which no satisfactory method of diagnosis, prevention or treatment exists, or, even if such a method exists, the medicinal product concerned will be of major therapeutic advantage to those affected), but these programmes only apply to select circumstances. With regard to excluding an increased risk of mortality, it is impractical to specify a single safety margin that would be considered reassuring for all

trials, as the margin might conceivably differ according to the patient population. Consistency across all endpoints (i.e. clinical outcome, and functional, patient-reported outcomes) should be observed to provide supportive evidence of overall improvement. Whether an adaptive pathway approach can be applied to address treatment of a specific heart failure population will require early consultation with the EMA for scientific advice.

When used as an endpoint (i.e. primary, secondary, or supportive), functional status may be assessed by a variety of measures (e.g. peak oxygen consumption, 6-min walk distance, exercise treadmill, or bicycle using heart failure suitable protocols), and each has its strengths and limitations. Validation of the clinical relevance of the endpoint in the target population, as has been done in other disease states,²⁸ is a key factor determining the acceptability of a functional endpoint in a pivotal chronic heart failure trial. The predictive value of these tests is valid only in patients whose exercise capacity is limited by heart failure. In patients with other co-morbidities, which are frequent in patients with heart failure, factors such as peripheral muscular deconditioning, arthritis, or low motivation can prematurely terminate the test. Widespread consensus has not been achieved on the minimal relevant treatment effect that would need to be demonstrated for endpoints such as 6-min walk distance or exercise testing. Conceivably, this treatment effect might also vary according to the specific study population. Notably, improvement in 6-min walk distance led to the approval of drugs for the treatment of primary pulmonary hypertension,^{29,30} followed by outcome data after approval. Whether this model could be translated to specific heart failure subsets is uncertain, but the outcome of validation studies in the target population will be a key determinant.

Functional endpoints should be limited to assessments with high reproducibility and reliability, and have protocol-specified processes implemented to maximize the reliability of measurements (e.g. repeated baseline and follow-up testing to reduce variability).³¹ Procedures to minimize drop-outs, losses to follow-up, and missing data, analytical methods to account for death and handle missing data, and designs that reduce bias (i.e. double blinding) are especially critical when these endpoints are chosen for a heart failure trial.

In conclusion, combining traditional mortality/morbidity composite endpoints and functional or patient-reported endpoints in a single composite is of limited value for most studies, but this approach might be useful as a means to increase power and reduce sample size requirements, in situations where traditionally designed outcome studies are not feasible because of technological or epidemiological limitations (e.g., paediatric heart failure). Symptoms would usually overwhelm the entire composite, yielding data that are difficult to interpret, and should generally not be used as a primary endpoint for pivotal chronic heart failure trials of traditional therapies.

Analytical methods

Heart failure is a progressive syndrome characterized by repeat hospital admissions, but traditional time-to-first event analysis only considers the first event. Thus, all events that occur after the first event (i.e. repeat hospitalizations or death, if it occurred after the

first hospitalization) are ignored in the primary analysis,³² disregarding information that might be clinically meaningful to physicians and patients in establishing the treatment effect. Inclusion of such events may also increase a study's power if the treatment effect is consistent among first and repeat events.³²

Substantial work has been done in recent years applying methods to analyse recurrent events to completed chronic heart failure trial databases.^{33,34} These *post hoc* analyses showed that a substantial number of important clinical events were not included in the primary analysis when only considering the first event; in the CHARM-Preserved trial, the time-to-event analysis used only 53% of all heart failure hospitalizations and 57% of all cardiovascular deaths.³³ A similar proportion of events were not included in the time-to-event analysis of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) trial.³⁴ However, methodological issues need to be addressed, and recurrent event analyses must account for the competing risk of mortality and the lack of independence of repeat events within a given patient.³² Several different analytical methods are available to address these issues, and each has its strengths and limitations, although general agreement among the methods (negative binomial, Andersen–Gill, and joint-frailty model) has been noted.^{33,34} As suggested by Rogers *et al.*,³³ the choice of the primary analysis method depends on the desired balance between interpretability and robustness of the analysis; population characteristics (e.g. low or high death rates) also plays a role. The Efficacy and Safety of LCZ696 Compared to Valsartan on Morbidity and Mortality in Heart Failure Patients with Preserved Ejection Fraction (PARAGON-HF) trial was designed with the primary endpoint of cumulative number of primary composite events of cardiovascular death and total (first and recurrent) heart failure hospitalizations (<http://clinicaltrials.gov>, NCT01920711).³⁵ The Calcium Upregulation by Percutaneous Administration of Gene Therapy in Patients with Cardiac Disease (CUPID 2) recently used this approach with a joint frailty analysis to assess time-to-recurrent heart hospitalizations accounting for correlated recurrent events within patients and the correlation between recurrent and terminal events.³⁶ Consensus has not been achieved on best practice for presenting recurrent events data, and these decisions may need to be considered on a trial-by-trial basis. At a minimum, regulatory advice on proposed approaches is strongly recommended before initiating a heart failure trial that is intended to support product registration and labelling, and sensitivity analyses should be planned to evaluate the robustness of the findings.

Clinical trial design

Patient population

The target population enrolled in a pivotal trial should be easily identifiable and generally representative of the intended population post-approval. Enrichment criteria are often employed in modern clinical trials either to: (i) define the population and ensure enrolment of patients with the condition [e.g. B-type natriuretic peptide (BNP) or N-terminal-proBNP (NT-proBNP) criteria to confirm the diagnosis of heart failure]; (ii) ensure enrolment of a sufficiently at-risk population to meet event rate and sample size assumptions;

(iii) homogenize risk among enrolled patients; or (iv) select patients where a positive benefit/risk relationship is most likely based on the documented presence of the target mechanism of action. An enrichment strategy designed to increase the event rate also identifies the patients with the greatest medical need.

If an enrichment approach is applied in a clinical study intended to support product registration, justification that the extrapolation to use in lower risk patients is likely to be required by regulators when a broader indication is claimed. Approved labelling may need to reflect some of the eligibility criteria used in a clinical trial to identify patients with the condition who have the highest likelihood of therapeutic response. This will also depend on the risks. Conversely, the label should not reflect enrolment criteria used solely for the purpose of enriching or homogenizing the risk of the population (e.g. BNP or NT-proBNP above a threshold level, before hospitalization because of heart failure), unless the criteria excluded a large proportion of potential patients. If a treatment effect is shown in an enriched population and the results are applied to a lower risk population, the absolute benefit of treatment may be less in the lower risk population, which may also have implications for health technology assessments and payer decisions. Broader regulatory indications allow local authorities and downstream stakeholders to determine how the results most appropriately apply to their populations.

Patients admitted to hospital with acute heart failure should not be enrolled in chronic heart failure trials in the early phase of that admission while the patient is unstable. Many interventions may take place during a hospitalization for acute heart failure (e.g. administration of intravenous diuretic and vasoactive therapies, up-titration of evidence-based therapies, implantation of cardiac devices), and these treatment measures may mask the treatment effects of the investigational therapy. However, it may be valuable to enrol patients hospitalized for heart failure in the hospital setting who are stabilized and not receiving parenteral therapy to evaluate the effect of chronic therapies that are started during the hospitalization, at discharge, or in the early post-discharge period (e.g. 30 days post-discharge).

Patients enrolled in 'chronic' heart failure trials should generally be in the ambulatory care setting and taking stable doses of "disease-modifying" therapies (e.g., beta-blockers), although dynamic adjustment of diuretic dosing should be permitted. Sometimes there may be a reason to wish to enroll patients early after treatment for acute decompensation and here a pragmatic approach may be to recruit patients after discontinuation of parenteral therapies but before discharge. For certain types of novel therapies (e.g., those with a renal, diuretic, or natriuretic action) patients might be enrolled at an earlier stage of their admission, before decongestion has been achieved with conventional therapy.

Optimal medical therapy

Clinical trials should be conducted against a background of optimal evidence-based care in accordance with treatment practice guidelines.¹ However, clinical trials should also reflect real-world practice. Global trials are a necessity to achieve the large patient numbers needed in modern randomized outcome trials, to allow

for worldwide regulatory approval, and to assess the generalizability of treatments. Some variation in standard of care across geographic regions is expected, particularly with cardiac devices, because of differences in product availability, reimbursement policies, local standards of care, or other factors that affect patient access.³⁷ Patients enrolled within a region should be representative of local standards of care, and randomization should minimize the impact of any differences in standard of care between groups. Efforts should be made to minimize imbalances in the use of standard of care between groups, and lower than expected use of evidence-based therapies will need to be justified to health authorities. Given the usually lengthy timeframe required for recruitment and follow-up of randomized trials, changes in standard of care may occur and should be allowed, but also should be documented and justified.

Geographical differences in event rates, as well as treatment responses, have often been observed in heart failure and other cardiovascular clinical trials.^{38–42} Pre-specified analyses to evaluate the consistency of treatment effect by geographic region are often performed. However, it is important to recognize the limitations of subgroup analyses,^{43–47} and consider the likelihood that observed differences between subgroups could result from chance because of multiple testing and the small number of patients, especially when considering regional or individual country differences.

Run-in period

Some clinical trials are designed with an active treatment run-in period to maximize the ability to retain patients on treatment long-term by excluding patients with tolerability issues.³⁵ Regulatory agencies may request a run-in period to ensure that standard care treatments are optimally administered.³ In clinical trials where an active treatment run-in period is used, consideration should be given to the impact on external validity (i.e. rates of intolerance could be higher in clinical practice as in a clinical trial the run-in selects patients who can tolerate the drug), although it should be noted that active treatment run-ins mimic clinical practice since physicians routinely discontinue therapy that is not tolerated. Further, active run-in periods in clinical trials generate important evidence about tolerability and reasons for discontinuation that are useful for physicians in practice. Whether specific labelling is needed will be determined by regulators on a case-by-case basis. Run-in periods to improve recruitment efficiency may lead to physician concerns that tolerability and efficacy data are overestimated, which may affect uptake and acceptance of the therapy.^{48–50}

Research approaches for novel therapies

Novel treatment approaches to the heart failure patient, such as cell-based, gene, and other bioactive agents, have the potential to significantly increase myocardial performance and clinical status. Over the past 15 years, rapid development of numerous products and modes of administration have given rise to the conducting of many small clinical studies early in the evolution of the field.

Unfortunately, progress has been impeded by the lack of optimally designed, sufficiently large studies with adequate statistical power, uncertainty as to product classification and regulatory guidance, and high costs compared with other therapies (often shouldered by small companies). Perhaps most importantly, the absence of a single first-in-class agent upon which to centre substantial early development (unlike many novel pharmaceuticals and devices) has led to important questions regarding the appropriateness and relevance of testing these products in the traditional constructs of randomized, controlled trials. The workshop acknowledged the field's continued promise, as well as the challenges of acquiring meaningful data, including access to adequately trained investigators, maintaining blinding at the site level when agent delivery increasingly utilizes sham procedures for control groups necessitating a firewall between interventional and clinical site personnel, and site-related logistics for dose preparation.

Consensus was reached among participants that the evidentiary requirements for cell-based or other novel therapies should be conceptually similar to other therapies. Both meaningful clinical benefit and safety need to be demonstrated to support approval. A rationale also exists for accepting functional or patient-reported outcome endpoints for these therapies, as patients who may be considered as candidates are likely to be those who remain symptomatic after optimization of other guideline-recommended evidence-based therapies. Longer term safety assessments (e.g. 5–10 years beyond original licensing) may be necessary to rule out adverse effects. As above, blinding of patients and/or the assessment team is challenging but it is essential to the scientific validity of the findings and should be implemented whenever possible, with plans for maintaining the blind design carefully detailed. Endpoints should be selected considering not only the evidence required for licensing, but also for payers,⁵¹ as these therapies are likely to be costly. An endpoint such as freedom from death, transplant, or mechanical circulatory support might be relevant for these therapies, but durability of the effect will be important to assess, especially from the payer's standpoint.

Observation of a large treatment effect could potentially support acceleration of patient access to the therapy via, for example, conditional approval approach or PRIME if an unmet need can be established. While this has not been warranted based upon current evidence, many treatments for heart failure are in development and establishing a development pathway for advanced cell-based and non-cellular agents is an important step.

Conclusion

Patients with chronic heart failure have a reduced life expectancy and diminished quality of life, with high healthcare utilization. The composite endpoint of cardiovascular mortality or hospitalization owing to heart failure provides a clinically meaningful assessment of efficacy, and can be used in most pivotal trials of chronic heart failure therapies, with adequate ascertainment of non-cardiovascular mortality to confirm safety regarding increased mortality. Patients with worsening heart failure will increasingly receive care in non-hospitalized settings, and it is recognized that

outpatient heart failure events may also represent valid endpoints. The possibility of including repeat events in the primary analysis has opened many opportunities to develop and pilot new methods for statistical analyses that may improve the efficiency as well as the clinical relevance of randomized heart failure trials.

A rationale exists for evaluating functional or patient-related outcome endpoints as key secondary or supportive endpoints in chronic heart failure trials. This recognition is a call to researchers to generate evidence for determining minimally important difference thresholds and validating these endpoints as meaningful, not only to improve patients' symptoms and physical limitations, but also as they relate to directionally similar changes in outcomes such as death or hospital admission.

In order to address the remaining unmet medical needs in heart failure patients, we should endeavour to refine the target patient populations and develop novel therapies. Collaboration among regulators, industry, clinical trialists, cardiologists, payers, and patient organizations will be critical to ensure that scientifically robust and practical solutions to developing new therapeutics in this patient population are implemented.

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