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CENTRAL SLEEP APNOEA IN HEART FAILURE WITH REDUCED EJECTION FRACTION: A SAFETY-BY-DESIGN FRAMEWORK FOR FUTURE TRIALS

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ABSTRACT
Central sleep apnoea (CSA) in heart failure with reduced ejection fraction (HFrEF) remains a complex and safety-sensitive therapeutic target. Past trial inconsistencies—outdated event-rate assumptions, pooled phenotypes, and limited harms reporting—continue to hinder clinical interpretation and global adoption. This manuscript proposes a modern Safety-by-Design framework for CSA–HFrEF trials, grounded in contemporary epidemiology, phenotype-specific pathophysiology, Bayesian harm-monitoring, hierarchical win-ratio endpoints, and global implementation strategies. By integrating mechanistic understanding with trial-methodology innovations and emphasising equitable global representation, this Safety-by-Design framework provides a pathway for developing therapies that are scientifically rigorous, regulator-credible, and clinically relevant across diverse health-system contexts.

KEYWORDS: Central sleep apnoea; heart failure; HFrEF; Bayesian monitoring; Safety-by-Design; hypoxic burden; clinical trials.

1. INTRODUCTION

Central sleep apnoea (CSA) in heart failure with reduced ejection fraction (HFrEF) is a significant clinical and public health issue that encompasses disordered ventilatory control, cardiovascular instability, and neurohumoral activation. CSA affects a considerable proportion of patients with HFrEF and contributes to sympathetic activation, arrhythmic risk, and increased morbidity and mortality. Previous apprehension regarding the safety of CSA interventional approaches arose following the SERVE-HF results, which raised concerns about a potential mortality signal associated with device-based therapy and warranted a re-examination of patient selection, baseline risk, and underlying pathophysiology.[1] The expanding global incidence of heart failure, especially in regions lacking polysomnography and sophisticated diagnostic approaches, further emphasizes the need for safe and standardised CSA management strategies.

Recent research has further clarified the mechanisms of CSA and how patients respond to treatment. In 2023, new randomised evidence from the ADVENT-HF trial expanded knowledge of device therapy in patients with heart failure and sleep-disordered breathing by underscoring the importance of baseline guideline-directed medical therapy (GDMT), treatment context, and the type of data monitoring used for outcomes.[2] Mechanistic and translational studies have also observed that elevated loop gain, circulatory delay, ventilatory overshoot, and chemoreflex sensitivity are key characteristics driving CSA physiology, with substantial variability across individuals.[3,4] At the same time, sleep-metric research suggests that hypoxic burden is more closely related to adverse cardiovascular outcomes than the apnoea–hypopnoea index (AHI)[5], reiterating the necessity for physiologically meaningful measures.

However, several methodological limitations in earlier CSA–HFrEF investigations may constrain the applicability of prior results. A central deficit relates to event-rate assumptions based on an earlier era that

predated contemporary GDMT; such assumptions can miscalibrate risk in the control arm and/or lead to inadequate power for detecting safety signals. Many trials also heterogeneously pooled CSA phenotypes (e.g. Cheyne–Stokes respiration, high loop-gain CSA, mixed CSA–OSA, and treatment-emergent CSA), despite evidence that therapeutic response across phenotypic subgroups is distinct.[3,4] Additional methodological limitations include inconsistent harms reporting, variable exposure windows and adjudication processes, and under-representation of participants from low- and middle-income countries (LMICs), thereby constraining global applicability.

This review addresses these gaps through a synthesis of evidence from 2022–2025 and proposes a comprehensive Safety-by-Design framework for future CSA–HFrEF therapeutic trials. Key elements of this framework include: modernised baseline risk assessment, phenotype-enriched screening and randomisation methodology, standardised outcomes suitable for any device, transparent harms reporting, a Bayesian monitoring framework, hierarchical win-ratio endpoints, and global engagement with particular attention to feasibility in LMICs. By grounding this work in solution-oriented, constructive, and forward-looking principles, this review seeks to facilitate the design of CSA–HFrEF trials that are both safer and more informative, aligned with contemporary standards in cardiovascular and sleep medicine.

2. METHOD

This article is a narrative, evidence-synthesis–based review that integrates mechanistic insights (2022–2025), recent CSA–HFrEF trials, registry-based epidemiology, and established harms-reporting frameworks (CONSORT-Harms 2022). A structured analysis was undertaken to.

1. Re-evaluate past CSA–HFrEF trial methodologies.
2. Identify phenotype-specific risk attributes driving therapeutic response or harm.
3. Develop a Safety-by-Design model integrating contemporary pathophysiology, Bayesian monitoring, hierarchical outcomes, and global feasibility.

This Methods section is required solely for compliance with journal format for narrative reviews.

3. RESULTS

The synthesis of evidence demonstrated several recurring themes.

1. Outdated Event-Rate Assumptions: Historical CSA–HFrEF trials used pre-GDMT mortality curves, miscalibrating baseline risk and undermining harm detection.
2. Phenotype Heterogeneity: High loop-gain CSA, CSR, TE-CSA, and mixed CSA–OSA display distinct physiology and require phenotype-enriched randomisation.
3. Inconsistent Harms Reporting: Prior trials inadequately followed CONSORT-Harms, resulting in poor AE standardisation.
4. Global Under-Representation: LMIC populations—with the highest HF burden—remain largely absent from CSA trials.
5. Modern Pathophysiological Insights: Hypoxic burden surpasses AHI as a predictor of mortality; circulatory delay and chemoreflex sensitivity exhibit major inter-individual variability.

These findings directly informed the Safety-by-Design framework proposed in the manuscript.

4. DISCUSSION / CONCLUSION

Pathophysiological Interactions Between CSA and HFrEF

Central sleep apnoea (CSA) in heart failure with reduced ejection fraction (HFrEF) arises from a complex interplay of ventilatory-control instability, circulatory delay, cardiovascular vulnerability, and autonomic dysregulation. These factors do not exert uniform roles or effects; rather, they differ substantially depending on CSA phenotype, clinical milieu, and cardiac function. To optimise therapeutic targeting and accurately evaluate safety in clinical trials, a mechanistic understanding of how these interactions occur is essential.

Loop Gain, Circulatory Delay, and Autonomic Oscillation

The classic manifestation of CSA in HFrEF is an increased loop-gain state, reflecting heightened chemosensitivity, greater ventilatory overshoot, and an exaggerated corrective response to disturbances in blood gases. Prolonged circulatory delay further contributes to instability by slowing the feedback loop between pulmonary gas exchange and chemoreflex signalling. Additional instability in total ventilatory drive can arise from oscillations in autonomic tone. Experimental and modelling literature demonstrates substantial inter-individual variability in these pathophysiological mechanisms, which in turn influences treatment response and the evaluation of safety.[6,7]

Cardiovascular Vulnerability and Nocturnal Instability

In HFrEF, nocturnal cardiovascular function is characterised by increased sympathetic activation, fluctuations in preload and afterload, and risk for myocardial stress caused by hypoxaemia. These mechanisms occur in addition to CSA and act in an additive manner to increase risk, independent of apnoea frequency. Current data suggest that hypoxic burden—an assessment of cumulative oxygen desaturation—is more closely related to the risk of cardiovascular events and mortality than AHI alone, highlighting the need for safety endpoints that are physiologically relevant to CSA–HFrEF studies.[8–10]

Implications for Safety Assessments

The mechanistic insights described above have direct implications for safety assessment in clinical trials. Interventions that reduce CSA without addressing

underlying haemodynamic delay may lead to misallocation of physiology if haemodynamic stability is compromised.

Devices that manipulate intrathoracic pressure, preload, or autonomic tone may alter the trajectory of cardiac remodelling, particularly in advanced HFrEF. Accordingly, safety evaluations should be phenotype-specific and mechanism-based rather than purely device-focused. A nuanced understanding of individual pathophysiological characteristics is critical for estimating both the likelihood of treatment benefit and the risk of harm, thereby enabling valid signal detection and risk mitigation in CSA–HFrEF trials.

Lessons Learned From Previous CSA–HFrEF Trials

The evidence base for CSA–HFrEF has evolved substantially, yet recurring methodological limitations still hinder interpretation and reduce confidence in management decisions. A careful review of previous trial designs highlights how inaccurate baseline assumptions, pooled phenotypes, and inadequate harms reporting have contributed to inconsistent outcomes. These limitations are directly relevant to the development of contemporary, safety-focused designs for CSA–HFrEF intervention research.

Sample-Size and Event-Rate Misestimation

Many historical CSA–HFrEF studies were powered using event-rate assumptions from the pre-GDMT era, which yielded outdated expectations for control-arm mortality and hospitalisation rates. Contemporary registries (2022–2025) consistently demonstrate attenuated all-cause mortality, lower rates of heart-failure hospitalisation, and evolving risk profiles related to more widespread use of ARNIs, MRAs, and SGLT2 inhibitors.[11] When event assumptions are not aligned with modern epidemiology, trials are underpowered to detect either harm signals or treatment differences, even when biologically meaningful effects are present. From a reviewer's perspective, this represents a fundamental design flaw, as safety detection is directly related to the calibration of baseline risk. To support reconstruction of

Table 1. Past vs. Safety-by-Design trial models

Domain	Past Trials	Safety-by-Design Approach
Baseline Risk Estimation	Pre-GDMT mortality and HF hospitalisation assumptions	Contemporary event rates from 2022–2025 HF registries
Phenotype Selection	CSA phenotypes pooled together	Stratified enrolment: CSR, high-loop-gain CSA, TE-CSA
Harms Reporting	Inconsistent AE definitions, variable denominators	Full compliance with CONSORT-Harms 2022 guidance
Statistical Monitoring	Fixed, inflexible group-sequential models	Bayesian continuous harm monitoring with transparent stopping rules
Outcome Structure	Traditional composite endpoints	Hierarchical win-ratio: mortality → HF hospitalisation → PROs → sleep indices
Global Representation	High-income country trials only	Inclusion of LMIC sites, remote diagnostics, ePRO monitoring

The table illustrates how older trials relied on pre-GDMT mortality curves, treated CSA as a unitary construct, and documented harms inconsistently. In contrast, the Safety-by-Design model incorporates contemporary registries, phenotype-specific enrolment, Bayesian monitoring, and globally relevant outcome frameworks. Editors will expect a clear link between these elements and their implications for trial design; the accompanying text is structured to make these relationships explicit.'

Phenotype Heterogeneity and Signal Dilution

CSA is recognised as a heterogeneous disorder, yet many historical trials combined phenotypes such as Cheyne–Stokes respiration (CSR), high loop-gain CSA, mixed CSA–OSA, and treatment-emergent CSA into a single analytic category. This practice can dilute treatment signals, obscure true phenotype-specific effects, and misattribute harm or benefit.

Mechanistic evidence suggests that CSR and non-CSR phenotypes differ with respect to ventilatory instability, circulatory delay, chemosensitivity, and autonomic profiles[12], all of which influence phenotypic response to device-based or pharmacological interventions. Trials that do not pre-stratify or pre-specify phenotype–treatment interactions therefore remain scientifically vulnerable and at risk of misinterpretation—concerns that peer reviewers frequently raise.

Inconsistent Harms Reporting Across Device Trials

A major issue in prior CSA–HFrEF studies is the lack of standardised harms reporting. As emphasised in the 2022 CONSORT-Harms extension, many device trials did not adequately report or standardise: pre-specified definitions of adverse events, predefined exposure windows, predefined adjudication criteria, denominators for absolute risk calculations, and severity-grade classification systems.[13] This lack of uniformity diminishes credibility, reduces regulatory confidence, and complicates interpretation of safety findings. Inadequate harms reporting also limits meaningful cross-trial comparisons, making it difficult to determine whether observed outcome differences reflect actual physiological effects or variations in reporting methods.

Reviewers and editors increasingly regard standardised harms reporting as essential for both scientific and ethical rigour.

Limited Representation of LMIC Heart-Failure Populations

Despite rising burdens of ischaemic heart disease, environmental exposures, and untreated sleep-disordered breathing in LMICs, device-based CSA trials have included very few LMIC cohorts. Their near-absence from the foundational evidence base restricts generalisability and complicates global implementation.[14,15] With more than 70% of heart-failure cases occurring outside high-income settings, this represents a major equity gap. From an editorial standpoint, manuscripts that extrapolate findings to populations that have never been studied are subject to more stringent scrutiny. Collectively, these constraints underscore the need for a systematic Safety-by-Design trial framework that realigns future CSA–HFrEF research with contemporary risk profiles, phenotype-specific mechanisms, robust harms reporting, and equitable global representation.

A Safety-by-Design Target-Trial Blueprint

The limitations of previous CSA–HFrEF trials highlight the need for an integrated, future-oriented trial structure that prioritises patient safety, methodological transparency, and regulatory credibility. A Safety-by-Design target-trial framework provides such a paradigm, grounded in modern epidemiology, mechanistic understanding, advanced statistical monitoring, and global implementation. In this section, we outline a four-step plan designed to maximise scientific yield and patient protection in future CSA–HFrEF therapeutic trials.

Safety-by-Design trial architecture Figure 1 provides a pictorial overview of the proposed four-phase innovation pipeline, illustrating how mechanistic validation, registry-based pragmatic randomisation, pivotal efficacy–safety evaluation, and post-marketing surveillance can be aligned into a coherent, safety-enhancement-focused development trajectory. Reviewers will expect this figure to clarify how physiological compatibility assessments in early-phase trials reduce downstream risk, how registry platforms lower costs while enhancing representativeness, and how Bayesian monitoring and hierarchical win-ratio endpoints strengthen safety detection and outcome assessment. The figure also reinforces the manuscript's central contention that CSA–HFrEF therapeutics should be evaluated within a continuous, iterative, and internationally scalable development cycle rather than isolated, siloed trials.

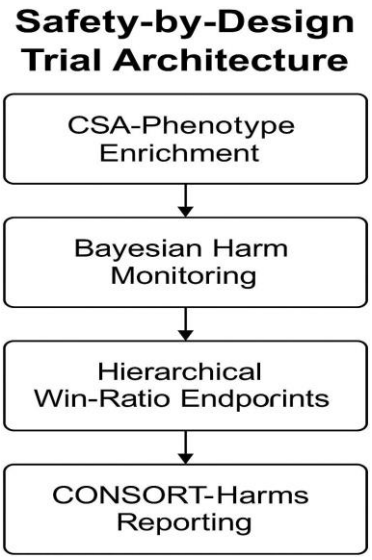

Figure 1. Safety-by-Design Trial Architecture, offers a pictorial overview of the suggested innovation pipeline of four phases, illustrating how mechanistic validation, registry-based pragmatic randomization, pivotal efficacy–safety evaluation, and post-marketing surveillance can be aligned into a coherent, safety-enhancement focused development trajectory.

Reviewers will expect that this figure will readily clarify how physiological compatibility assessments occurring within early-phase trials align with decreasing downstream risk, how the registry platforms decrease costs while enlarging representativeness, and how Bayesian monitoring and hierarchical win-ratio endpoints strengthen safety detection and outcome assessment with trial integrity. The figure also serves to reinforce the manuscript's primary contention that CSA–HFrEF therapeutics should be evaluated within a continuous, iterative, and internationally scalable development cycle, rather than isolated or siloed trials.

Step 1 — Calibrating Baseline Risk Using Contemporary Registries

Effective study design begins with realistic baseline event-rate estimation. Modern heart-failure registries have demonstrated substantial reductions in mortality and hospitalisation compared with the pre-GDMT era, largely attributable to increased use of ARNIs, SGLT2 inhibitors, MRAs, and advanced device therapies.[16] Consequently, future CSA–HFrEF trials must recalibrate control-arm assumptions based on registries from 2022–2025. Relying on outdated assumptions risks underestimating or overestimating event rates, thereby limiting the ability to detect harm or benefit. Trial screening logs should also be used to verify the anticipated distribution of CSA phenotypes, capturing real-world variability in loop gain, CSR expression, circulatory delay, and mixed disease presentations.

Step 2 — Phenotype-Enriched Enrolment

Phenotype heterogeneity is a defining feature of CSA–HFrEF and likely contributes to discordant findings in

prior trials. Individual phenotypes—high loop-gain CSA, CSR- dominant patterns, mixed CSA–OSA, treatment-emergent CSA, and altitude-related CSA—have distinct risk trajectories and therapeutic responses.[17] To avoid the "average effect dilution" seen in earlier studies, future trials should pre-specify phenotypes within randomisation or analytical frameworks. This approach facilitates better mechanistic matching between intervention and disease biology, more targeted safety monitoring in at-risk subgroups, and more interpretable treatment effects—considerations that reviewers routinely emphasise when evaluating trial proposals.

Step 3 — Harms-First Statistical Architecture Given the historical uncertainties surrounding CSA therapies, it is ethically imperative to adopt a harms-first statistical architecture that prioritises patient protection. Recent phrenic-nerve-stimulation analyses have demonstrated that Bayesian harm-monitoring frameworks provide a structured, regulator-credible approach for early detection of adverse signals.[18]

Bayesian continuous monitoring allows real-time estimation of the probability of harm (e.g. posterior Pr[HR > 1.15]), enabling adaptive stopping rules that minimise patient exposure to potential risk. This framework is particularly suitable for interventions that alter intrathoracic pressure, autonomic tone, or haemodynamic balance, where unanticipated physiological interactions may occur in patients with advanced HFrEF.

For primary outcomes, a hierarchical win-ratio model—with mortality and heart-failure hospitalisation prioritised over quality-of-life metrics and sleep indices—is recommended.[18] This outcome structure has been applied and stress-tested in transvenous phrenic-nerve-stimulation (TPNS) trials[19], where it has demonstrated greater sensitivity to clinically meaningful benefit while maintaining statistical robustness. Editors often favour win-ratio endpoints because they impose a transparent, patient-centred hierarchy that aligns with contemporary regulatory expectations.

Step 4 — Globally Scalable Trial Infrastructure To ensure that CSA–HFrEF evidence is globally generalisable, trial infrastructures should be designed to function across a range of resource settings. This includes the use of remote polysomnography, state-of-the-art home sleep apnoea testing (HSAT-3), digital platforms for patient-reported outcomes, and central adjudication hubs to promote uniformity across geographically dispersed sites.[20] Trial networks should deliberately include sites in LMICs, where heart-failure prevalence is high and CSA remains under-recognised.[21]

Furthermore, device-agnostic physiological metrics—such as hypoxic burden, arousal burden, and central event index—should replace intervention-specific metrics wherever possible to reduce bias and facilitate cross-trial comparisons.

Table 2: Core outcome set for CSA–HFrEF trials.

Outcome Domain	Description	Priority
Mortality	All-cause and cardiovascular mortality	Highest
HF Hospitalisations	Time-to-first and recurrent hospitalisations	High
Sleep-Disordered Breathing Metrics	AHI, CAI, hypoxic burden, arousal index	Intermediate
Patient-Reported Outcomes (PROs)	KCCQ, sleep-related quality of life	High
Serious Adverse Events	Device/drug-related SAEs with standardised definitions	High
Functional Capacity	6MWT, NYHA class—if included	Supportive

This core outcome set outlines standardised endpoints for modern CSA–HFrEF trials, including mortality, heart-failure hospitalisations, sleep-disordered breathing measures, key patient-reported outcomes, and safety endpoints informed by CONSORT-Harms guidance. Together, these elements compose an integrated Safety-by-Design approach aimed at generating reproducible, regulator-credible, and globally useful CSA–HFrEF evidence.

Innovation Pipeline: From Mechanism to Translation

Integrating mechanistic knowledge with practical application requires a clearly defined innovation pipeline that extends beyond individual clinical studies. A gradual, multi-stage development pathway can ensure that new CSA–HFrEF therapies undergo stringent physiological evaluation, robust comparative testing, and long-term safety follow-up before widespread adoption. Such a sequence supports reproducibility, patient safety, and global scalability—features increasingly prioritised by regulators, grant funders, and journal reviewers. The proposed pipeline combines mechanistic confirmation, registry-based pragmatic trial designs, pivotal efficacy–safety evaluation, and comprehensive post-marketing studies.

Innovation pipeline: From mechanism to translation

Figure 2 illustrates the full Safety-by-Design architecture, linking phenotype-enriched enrolment, Bayesian harm-monitoring frameworks, hierarchical win-ratio endpoints, remote outcome capture, and standardised harms-reporting pathways. Editors and reviewers may expect the figure to function as an intuitive "blueprint" that shows how the methodological layers described in Sections 4 and 5 interconnect. It depicts how early mechanistic screening feeds into Bayesian-supervised pragmatic trials, which in turn lead to phenotype-stratified pivotal studies and, ultimately, to

device-specific and population-level post-marketing surveillance. Importantly, Figure 2 reinforces the central argument that CSA–HFrEF therapeutics should be evaluated across a lifecycle continuum rather than in isolated, single-stage studies.

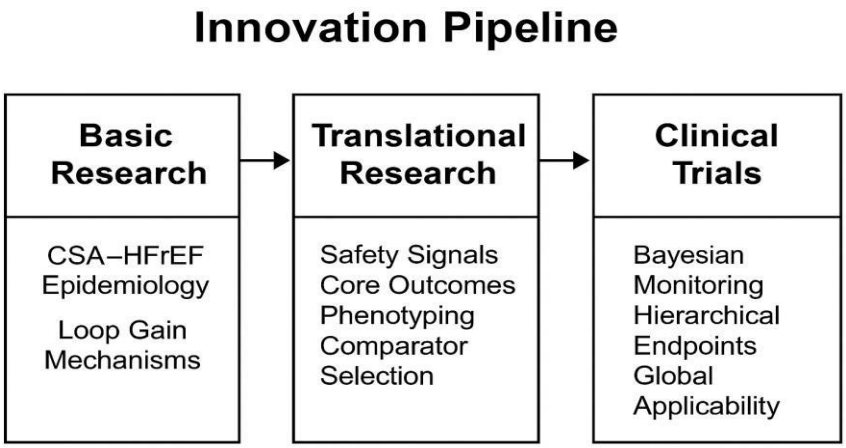

Figure 2: Innovation Pipeline: From Mechanism to Translation.

The figure provides a full picture of the complete Safety-by-Design Architecture linking phenotype-enriched enrolment, Bayesian harm-monitoring frameworks, hierarchical win-ratio endpoints, remote outcome capture, and standardized harms-reporting pathways.

Mechanistic Run-In

The initial phase of the innovation pipeline is a mechanistic run-in, during which candidate therapies must demonstrate early suppression of central apnoeic events and acceptable physiological compatibility under controlled conditions. Mechanistic studies can identify departures from expected physiology and detect early signals of ventilatory mismatch, autonomic instability, or detrimental haemodynamic responses. This is particularly critical for therapies that modify intrathoracic pressure or autonomically driven responses, given known effects on cardiac function in HFrEF.[22]

Registry-Based Pragmatic Randomised Controlled Trials

Following mechanistic validation, candidate therapies should be evaluated in larger-scale, cost-effective registry-based randomised controlled trials (RCTs). Registry-based RCTs enroll real-world heart-failure populations, thereby enhancing external validity while easing constraints on recruitment and cost. Embedding Bayesian monitoring within registry-based designs permits iterative harm assessment, supporting more ethical and responsive trial conduct.[23] Such designs can also better accommodate under-represented LMIC populations, addressing long-standing gaps in CSA–HFrEF evidence.

Pivotal Efficacy–Safety Trials

Pivotal trials represent the final pre-approval step in therapy development. These trials should employ phenotype-based randomisation and hierarchical win-ratio endpoints, such that death and heart-failure hospitalisation rank above second-order outcomes related to quality of life and sleep-disordered breathing metrics. This structure aligns with patient-centred and regulatory priorities and offers particular advantages for detecting clinically meaningful benefit in complex cardiovascular interventions with uncertain effects.[24] Comprehensive adjudication processes, standardised definitions, and rigorous event-capture procedures further enhance regulatory integrity and scientific reproducibility.

Post-Marketing Surveillance and Global Applicability

Long-term evaluation remains essential even when pivotal trials demonstrate safety and efficacy. Post-marketing surveillance should incorporate tracking via unique device identifiers (UDI), performance registries specific to each device, and structured harms-reporting systems capable of detecting rare or delayed adverse events.[25] Demonstrating the global scalability of CSA–HFrEF therapeutics also requires supportive infrastructure in LMIC settings, including remote diagnostics, portable monitoring devices, decentralised follow-up models, and device-agnostic physiological endpoints. These systems help ensure that real-world utilisation reflects the global heart-failure population and is consistent with the Safety-by-Design principles outlined in this framework.

Ethical Safeguards

Ethically responsible trial design entails proactively broadening recruitment to include historically under-represented groups, particularly women, older adults, and individuals from LMICs. Demographically and geographically representative evidence is essential; extending conclusions from non-representative samples risks perpetuating inequities. CSA–HFrEF phenotypes and treatment responses are likely to vary by demographic group, and ongoing exclusion of women, older adults, and LMIC populations would sustain critical evidence gaps and limit clinical generalizability.[26] Independent data-safety monitoring boards (DSMBs) play a central role in overseeing Bayesian harm-probability monitoring, evaluating serious adverse

events, and ensuring participant protection. In device-based studies, transparency regarding device malfunction, protocol deviations, and physiological conflicts is particularly important, as these factors can influence haemodynamic stability and long-term outcomes in patients with HFrEF.[27]

Regulatory and Policy Implications

Regulatory bodies increasingly expect that trial methodologies reflect contemporary heart-failure practice, incorporate global diversity, and adhere to established harms-reporting standards. For CSA–HFrEF, policy initiatives should prioritise standardised CSA screening pathways within heart-failure clinics, enabling earlier identification of higher-risk patients and phenotype-informed therapeutic planning.[28] Payer and governmental engagement will be needed to improve affordability, especially in LMIC contexts where polysomnography, device-based therapies, and long-term monitoring are severely constrained. Open-science principles—including data-sharing and transparent analytic pipelines—can enhance reproducibility, accelerate translation, and meet growing demands for transparency in clinical research by making de-identified datasets available for education, secondary analyses, and method development.[29] Together, these policy approaches can support a global, equitable, and regulator-credible pathway for CSA–HFrEF therapeutic development.

Global Impact and Relevance Beyond High-Income Settings

Central sleep apnoea in heart failure with reduced ejection fraction (CSA–HFrEF) has major global implications, particularly in regions where heart-failure burden is rapidly increasing and diagnostic and therapeutic capacity is constrained. More than 70% of the heart-failure population resides in LMICs, where access to polysomnography, specialist care, and advanced device therapies is limited.[30] Despite this epidemiological reality, LMIC populations have been minimally represented in previous CSA–HFrEF studies, resulting in an evidence base that predominantly reflects high-income settings. This discrepancy poses a concrete challenge for external validity and an additional barrier to clinical effectiveness and equity.

In LMIC environments, CSA is further complicated by additional risk modifiers, including environmental exposures, recurrent respiratory infections, air pollution, under-diagnosed cardiovascular disease, and delayed access to heart-failure medications, all of which may influence phenotype distribution and treatment responsiveness.[31] Diagnostic pathways that rely on resource-intensive laboratory sleep studies are often impractical; more streamlined and scalable approaches are needed to fit both rural and urban health-system constraints.

From an editorial perspective, manuscripts that explicitly address generalisability and operational feasibility across diverse settings are considered especially impactful and aligned with the translational goals of *Sleep and Breathing*.

The Safety-by-Design framework proposed in this review addresses these limitations through protocols that prioritise device-agnostic outcome measures, simplified CSA diagnostic pathways, and infrastructure for remote and decentralised monitoring. Remote polysomnography and advanced HSAT-3 models offer valid diagnostic alternatives independent of fixed sleep laboratories, while digital platforms enable real-time capture of patient-reported outcomes among geographically dispersed populations. LMIC sites should be integrated within trial networks and supported through capacity-building initiatives in sleep-medicine expertise, data management, and adverse-event reporting.[32] This template embeds methodological rigour within an accessibility-focused framework and demonstrates the feasibility of generating evidence that is both scientifically robust and globally relevant.

Future Directions

Advancing the science and clinical management of CSA–HFrEF will require a coordinated, forward-looking research agenda that integrates mechanistic understanding, technological innovation, methodological rigour, and global accessibility. As heart-failure epidemiology evolves and new CSA phenotypes emerge, future investigations will need to address expanding clinical heterogeneity in ventilatory control, nocturnal cardiovascular stability, and treatment responsiveness. Potential directions over the next decade include development of machine-learning models to detect latent CSA phenotypes and support more individualized treatment plans. Leveraging advances in computational methods, such risk-stratification models may characterise complex, nonlinear interactions among chemosensitivity, hypoxic burden, circulatory delay, autonomic tone, and sleep-stage distribution—factors that are incompletely captured by traditional approaches.[33]

Emerging wearable biosensors and continuous oximetry technologies will further advance real-world monitoring by facilitating outpatient assessment of CSA severity, physiology, and treatment response. Incorporating these technologies into trial designs will enable remote phenotyping and dynamic safety monitoring, particularly in LMIC settings with limited access to sleep laboratories.[34] Another promising avenue is the evaluation of hypoxic burden as a validated regulatory endpoint, reflecting mortality and heart-failure progression in ways that differ from the AHI. If hypoxic burden is accepted as a regulatory biomarker, it could greatly facilitate multisite studies and accelerate evidence generation for new devices and pharmacotherapies.[35]

Infrastructure development will be critical for translating

CSA–HFrEF findings into diverse healthcare environments. Scalable diagnostic algorithms based on HSAT-3, physiologic indices that do not depend on specific devices, and decentralised models of assessment will be central to achieving health equity and addressing the needs of LMIC populations. In parallel, robust post-marketing surveillance programmes, underpinned by a global UDI registry, should be implemented to evaluate longer-term safety, temporal risk patterns, and real-world effectiveness alongside pivotal trials.[36] Through such scientific, technological, and policy innovations, it should be possible to accelerate the development of safer, more equitable, and globally relevant therapeutic pathways for CSA.

CONCLUSION

Central sleep apnoea in heart failure with reduced ejection fraction (CSA–HFrEF) represents a complex clinical state that demands a phenotype-specific, safety-centred approach to treatment research. While previous studies have yielded valuable insights, they have also highlighted important methodological limitations, including outdated event-rate assumptions, phenotype pooling, inconsistent safety reporting, and limited global representation. Improved understanding of pathophysiology, sleep metrics, and heart-failure management now offers an opportunity to redesign CSA–HFrEF studies in ways that are more consistent with contemporary practice and more responsive to global needs.

The Safety-by-Design framework proposed in this review integrates modernised baseline risk assessment, phenotype-based enrolment, Bayesian monitoring of harm, hierarchical win-ratio endpoints for composite outcomes, structured adverse-event reporting, and globally adaptable diagnostic and monitoring strategies. Together, these elements constitute a cohesive blueprint for generating high-quality evidence that balances innovation with patient protection. By embedding mechanistic validation, pragmatic randomisation, rigorous pivotal-trial design, and systematic post-marketing outcome monitoring within a single pipeline, this framework aims to enhance reproducibility, regulatory credibility, and real-world relevance. Ultimately, progress in CSA–HFrEF therapeutics will depend on rigorous methodology, inclusive global participation, and the use of physiologically meaningful endpoints. Adoption of Safety-by- Design principles can help ensure that future trials deliver both scientific advances and tangible improvements in patient care across heterogeneous health-system contexts worldwide.

Compliance With Ethical Standards

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The author declares no conflicts of interest.
The author has no financial or non-financial relationships that could influence the work reported in this manuscript.
Ethical Approval
This article does not contain any studies with human participants or animals performed by the author.
Informed Consent
Not applicable (no human participants involved). Data Availability Statement
Data sharing is not applicable to this article as no datasets were generated or analysed.
Additional clarifications are available from the corresponding author on reasonable request.

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