REVIEW ARTICLE

Phase 4 Studies in Heart Failure - What is Done and What is Needed?

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Abstract: Congestive heart failure (CHF) therapeutics is generated through a well-described evidence generating process. Phases 1 – 3 of this process are required prior to approval and widespread clinical use. Phase 3 in almost all cases is a methodologically sound randomized controlled trial (RCT). After this phase it is generally accepted that the treatment has a significant, independent and prognostically beneficial effect on the pathophysiological process. A major criticism of RCTs is the population to whom the result is applicable. When this population is significantly different from the trial cohort the external validity comes into question. Should the continuation of the evidence generating process continue these problems might be identified. Post marketing surveillance through phase 4 and comparative effectiveness studies through phase 5 trials are often underperformed in comparison to the RCT. These processes can help identify remote adverse events and define new hypotheses for community level benefits. This review is aimed at exploring the post-marketing scene for CHF therapeutics from an Australian health system perspective. We explore the phases of clinical trials, the level of evidence currently available and options for ensuring greater accountability for community level CHF clinical outcomes.

Pupalan Iyngkaran

INTRODUCTION

Clinical evidence is the process of generating data that can be translated for safe and acceptable clinical use. Clinical audit is the process of generating data that can inform if the implementations of clinical evidence are benefiting the population being treated [1, 2]. In congestive heart failure (CHF), many drugs that are approved by the therapeutics goods administration (TGA) and subsequently accepted onto the national pharmaceutical benefits scheme (PBS) would have undergone a large multicenter randomized controlled trial (RCT). Drugs are then subsidized based on criteria where only a CHF patient can receive a HF class beta-blocker (ββ), angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor antagonist (ATRA). For arguments sake, should another class of medication be shown to be beneficial for comorbidities such as diabetes or renal failure, but not proven in CHF, this medication can be provided to one group but not the other. In addition this process fails to recognize a host of other real-world considerations [2-5]. In theory this issue can be negated should phase 4 studies be given equal priority to the RCT from which the guidelines for use and administration are derived. Some unanswered questions include who is responsible for post-marketing surveillance, what is the most cost-effective means to do so [6-12], and what is the argument for CHF?

CHF is a chronic condition with high morbidity, mortality and cost, needing multicomponent management including lifelong medication, polypharmacy and often without cure. Comorbidities are present at onset in nearly half or will develop at some point in all. Numerous factors can affect response to therapies including age, sex, ethnicity, body size, family history, smoking status, diseases in excretory organs,

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disease severity, drug interactions and compliance. Many of these patients are not represented in the major RCT's [3, 4]. The clinical evidence is largely generated in a controlled setting but subsequently distributed into an uncontrolled environment. Thus there are a broad range of clinical questions to be factored, and not to forget costs which equates to 1-2% of health budgets [13, 14]. The purpose of this review is to explore the area of *post-marketing research*, the types of studies that provide evidence to influence practice, and the requirements needed for adequate monitoring of CHF. It is hoped that these discussions will raise the importance for the need to continue to monitor the implementation of therapies at the community level.

PHASES AND COST OF EVIDENCE GENERATION

Development of therapeutics and evidence to determine their safety, efficacy and effectiveness is generated and translated through a series of steps. Clinical evidence is generated from the 'bench to the bedside' through phases 0 - 3 and perfected from 'bedside to beyond' with phase 4 and 5 [13]. The 'bench' is often referenced with context to experimental research, usually in animals that form the foundation for first in man studies. 'Translation', as defined by The National Center for Advancing Translational Sciences (NCATS), is the process that brings the bench observation into the clinical domain to help improve the health of individuals and their communities, and encompasses all facets from, diagnostics, therapeutics, to medical procedures and even behavioral changes. At the heart of all this is the search for efficacy, effectiveness and quality [1, 2, 15-18]. Box **1** explores these steps in greater detail.

Preclinical Studies

In-vivo and in-vitro testing with non-human subjects is often the first step in development of novel therapies. Wide dose ranges, efficacy, toxicology, as well as improved pathophysiologic understanding are established. An important point established is the No Observable Adverse Effect Levels (NOAEL), which is used to determine initial first-in-man drug dosage and status for development as investigational new drug (IND). This so-called non-clinical phase in drug development is largely done by private industry where much of the knowledge is not published, although standards are adhered to [18-20]. Examples of preclinical development by academia which were open to scrutiny can be seen with mineralocorticoid antagonist and the ATRA - losartan [21, 22], which will be discussed later. There remain concerns however about the adequacy of reporting and 'fit for purpose' of many studies to inform clinical practice or policy [23-25]. It is our view that preclinical studies should be viewed twofold: firstly, studies that bring a novel therapy into the clinical domain (mainly industry); and secondly, studies that evolve from new hypothesis following post-marketing surveillance (mainly academia). This type of indication can form the basis for equivalence studies or expansion of an indication of drug within a class [15, 16, 26-33].

Clinical Studies

1.   **Phase 0 Studies**: First-in-man studies, using an IND and microdosing techniques to determine/evaluate pre-

liminary mechanism of action, target modulation as well as pharmacokinetic and dynamic relationships and similarities with preclinical studies. One in four drugs fail to progress [26, 27].

2.   **Phase 1 studies**: Often healthy volunteers, to assess safety, tolerability and additional pharmacokinetics and pharmacodynamics e.g. dose range, maximum tolerated dose, and early insights into efficacy is derived.

3.   **Phase 2 studies**: Testing of biological activity and efficacy of treatment at various dose ranges – leading to establishment of treating protocols. Often conducted as case series and occasionally with a randomized design. Surrogate endpoints (often biological markers) or short-term clinical well being can also be ascertained.

4.   **Phase 3 studies**: Conduct of a clinical trial to test *'treatment efficacy'*. All aspects of the research design are optimized and controlled (internal validity is of primary importance), resulting in the best possible surrogate for laboratory like environment where the maximum potential of the treatment can assessed (against current commonly used agents or placebo), while removing all confounders (provides risk-benefit analysis).

Post-marketing Surveillance

1.   **Phase 4 Studies:** Post approval studies or '*pharmacovigilance*', aimed at determining '*treatment effectiveness*' or the maximum benefit in the real world or day-to-day clinical practice. Often underutilized in regards to extension of benefit when there is less than usual clinical support, in minority communities or clients with comorbidities. External validity is of primary importance. Technical support for the monitoring that come from regulatory authorities or sponsoring companies.

2.   **Phase 5 Studies:** Translational research in reference to who benefits from the treatment and the cost or cost-effectiveness/equivalence.

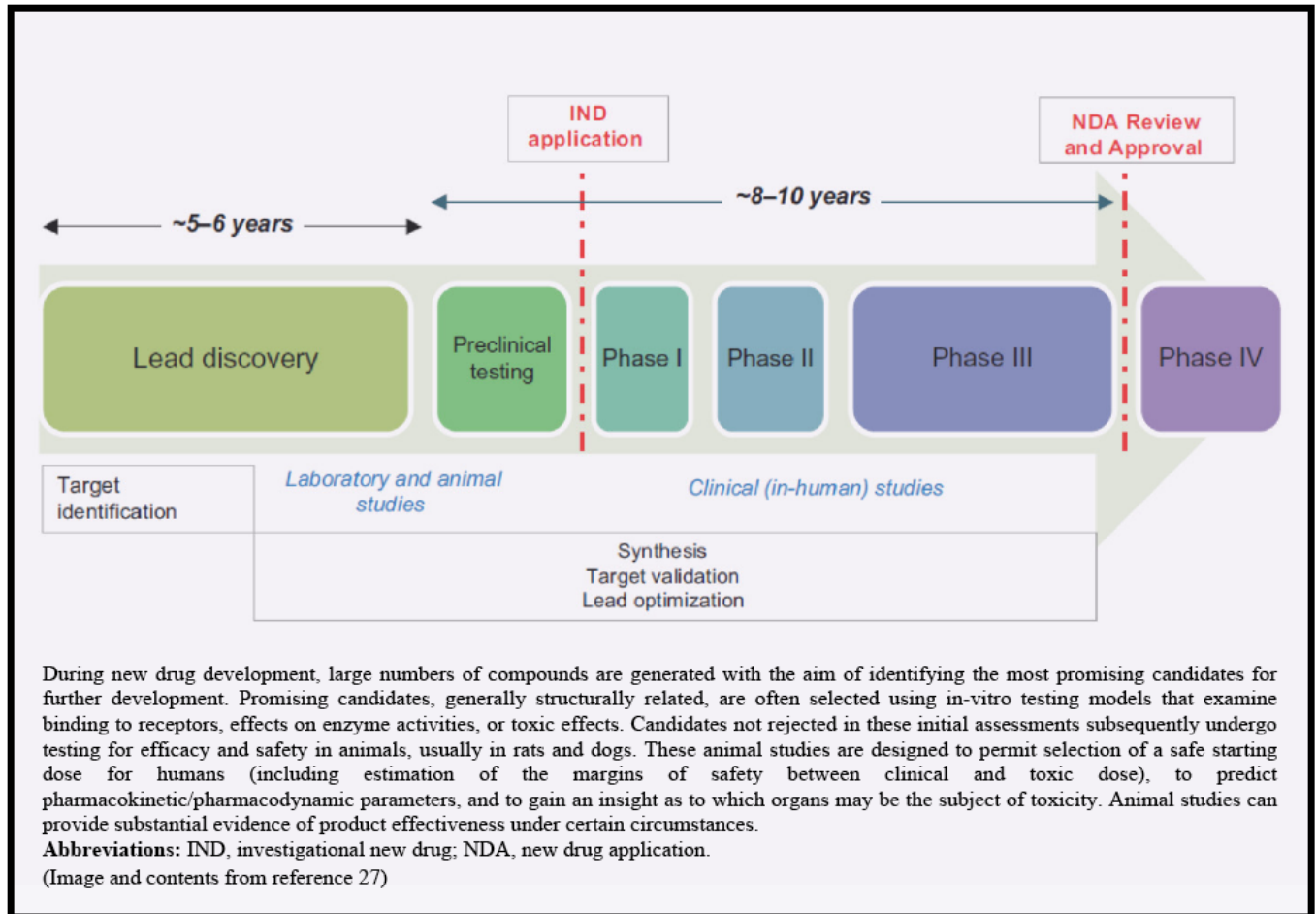### The Cost and Considerations in Drug Development

Impetus for innovation in new treatments factors in cost, risk and the protracted process from discovery to approval. Costs from development to approval have escalated by 145% since 2003 to $2.6 billion US dollars. Further $312 million is spent on post approval development. On average, only 3 in 10 drugs recuperate the investment costs, which are not helped by issues such as loss of patent protection. For CHF therapeutics, clinical trialing averages 5.2 years, approval phase 1.7 years without including preclinical development coupled with high attrition rates (Box **2**) [30-32].

A second consideration, in technical aspects clinical trials can be highlighted by several examples. Firstly, Krum et al highlighted the concepts of 'regression to the truth' and reaching of pharmacological 'threshold' as possibilities. Supporting these arguments is the translation of surrogate markers to clinical outcomes which many question as unreliable. Highlighting failure of 3 drugs it was noted that short-term hemodynamic parameters and exercise tolerance

Box 1.   Phases of Clinical –Trials.

Phase	Primary goal	Dose	Patient monitor	Sample Size	Notes
Preclinical	Testing of drug in non-human subjects, to gather efficacy, toxicity and pharmacokinetic information	Unrestricted	A graduate level researcher (Ph.D.)	Not applicable (in vitro and in vivo only)	Criticisms about quality of published material
Phase 0	Pharmacodynamics and pharmacokinetics particularly oral bioavailability and half-life of the drug	Limited, very small or sub-therapeutic dosing, only to achieve target modulation, thus less risk of toxicity	Clinical researcher	10-15	No therapeutic intent often skipped for phase I Primary goals: to evaluate mechanism of action/target modulation; assess PK/PD relationships; optimize target assay
Phase I	First administration of new treatment Primary goal: to determine maximum tolerated dose (MTD)	Multiple dosing starting sub-therapeutic with dose escalation aimed at establishing safety and toxicity	Clinical researcher	20-100	Safety – is further investigation warranted? No therapeutic benefit expected, but may enable continued evaluation if there is evidence of clinical response Test to detect the therapeutic effect; make point and interval estimates of effect size Make a first approximation to population definitions Make a first approximation of the treatment protocol Estimate appropriate dose Specify the therapeutic effect and how it is to be indexed Generate and refine hypotheses
Phase II	Early Trial in patients	Therapeutic dose	Clinical researcher	100-300	Efficacy – dose ranging, adverse events, pathophysiologic insights Determine early indications of the presence and magnitude of efficacy; make point and interval estimates of effect size Refine the definition of the target population Assess the therapeutic effect in terms of the range of utility (expand the target population if possible) Refine the treatment protocol and develop administration manual for consistent implementation and replication Determine discharge criteria Determine optimal dosage Assess therapeutic effect in terms of the duration Refine outcome construct and identify valid and reliable measurement instruments Finalize all operational definitions
Phase III	Large scale comparison versus standard treatment	Therapeutic dose	Clinical researcher and personal physician	300-3000+	Determines a drug's therapeutic effect; at this point, the drug is presumed to have some effect
Phase IV	Post-marketing surveillance – monitoring in clinical practice	Therapeutic dose	Personal physician	Anyone seeking treatment from their physician	Watch drug's long term effects Test effectiveness in the target population Test effectiveness in specific sub-populations Test effectiveness under variations of service-delivery models Test effectiveness variants of the treatment protocol Conduct meta-analyses of efficacy studies
Phase V	Translational research	No dosing	None	All reported use	Research on data collected

Edited from Ref 1, 2, 13, 14

Box 2. Traditional process of new drug development.

During new drug development, large numbers of compounds are generated with the aim of identifying the most promising candidates for further development. Promising candidates, generally structurally related, are often selected using in-vitro testing models that examine binding to receptors, effects on enzyme activities, or toxic effects. Candidates not rejected in these initial assessments subsequently undergo testing for efficacy and safety in animals, usually in rats and dogs. These animal studies are designed to permit selection of a safe starting dose for humans (including estimation of the margins of safety between clinical and toxic dose), to predict pharmacokinetic/pharmacodynamic parameters, and to gain an insight as to which organs may be the subject of toxicity. Animal studies can provide substantial evidence of product effectiveness under certain circumstances.

Abbreviations: IND, investigational new drug; NDA, new drug application.

(Image and contents from reference 27)

measures were divergent from longer-term outcome measures [26]. Secondly, there are also a significant number of good drugs that fail due to outdated and poor clinical trial design. This old paradigm established in the 1960s was designed to answer one question, at one site, and from one single trial [33]. While we have moved on in size and sites, the efficiency quota for real-world applications remains wanting. Part of this highlights the greater needs for planning in phase II testing, which could involve standardizing surrogate biomarkers or even health economics, in conjunction with many other new developments [34-40]. In this complex mix it is worth asking again, what is translatable evidence, who is now responsible for discovering, marketing, surveillance, translating and increasing the external validity of therapeutics?

WHAT IS THE EVIDENCE FOR PHASE 4 STUDIES IN HEART FAILURE?

Post-marketing studies in CHF have either been surveillance of one agent or prospective audits of clinical care. These studies can be extrapolated to represent phase-4 studies as clinical guidelines and a robust range of therapeutics have been established; although they do not answer all the relevant phase 4 points. Pooled data have gone on to consolidate on the efficacy of these agents and clinical audits have shown effectiveness but also highlighted important gaps. We have initially provided a quick synopsis of novel therapies in the pipeline to contextualize the value for ongoing trials to establish new therapies. These data are presented:

Novel Therapies

Studies expanding the clinical utility of beta-blockers (ββ), ACE-I, ATRA and mineralocorticoid receptor antagonists (MRAs) have been key developments. These agents alter pathophysiology, improve hemodynamics, symptoms and clinical outcomes. The majority of therapies have targeted patients with systolic HF. In-contrast options for acute decompensated heart failure (ADHF) and HF with preserved ejection fraction treatments have not altered significantly. Many promising agents including inotropes and selective vasodilators actually increased mortality. Other agents tried without influencing morbidity and mortality, including endothelin-1 (ET-1) antagonists, antioxidants, vasopeptide inhibitors and cytokine inhibitors. There are a number of therapeutic targets on the horizon (see tables in references), which await exploration or positive results [40, 41].

Clinical Databases and Health Systems Intervention Studies

International prospective databases, not targeted at any particular therapeutic agent, have highlighted: higher short term mortality, early readmissions, variable intensity of follow-up from primary to tertiary care, patients who would not qualify for RCTs outright, multiple concomitant comorbidities, diverse ethnic-socio-cultural-geographical demographics, lower use of echocardiography and therapeutics; which are different to the setting of most clinical trials. When the diagnosis of ADHF is made, there is greater implementation of guideline therapeutics, but not so in renal failure of all grades. There is also great variation in practice [42-49]. The major health systems intervention studies, OPTIMIZE-HF and IMPROVE-HF showed that inpatient and outpatient care can be improved by addressing care delivery [50, 51]. Asia pacific databases from Japan showed similar characteristics but with greater use of ARB and longer hospital stays (median 21 days) [48, 49]. In other parts of the Asia-Pacific, retrospective case reviews highlighted gradients across mature countries of more severe clinical symptoms and signs at younger ages, less frequent use of echocardiography and prognostic therapeutics [52], however common traditional risk factors posed equal risks regardless [53].

Specific examples for Australia are presented in Box **3** [54-86]. There is no published evidence of a comprehensive prospective CHF audit. Discussions on Indigenous Australians are presented elsewhere [87]. There are however national and selective state based data to suggest that many aspects of comprehensive CHF care are comparable or better than internationally published standards particularly in mortality and utilization of best practice. Morbidity, hospitalizations and cost remain major issues. There is heterogeneity in care delivery peaking at capital cities and stagnating in rural areas. Lower socio-economic status and Indigenous groups also lag in outcomes. Important gaps that have not been adequately studied are comorbidities, polypharmacy, greater role for nurse lead care, self-care and roll out of technology [5]. There remain potentially important questions on effectiveness, cost effectiveness and perhaps efficacy.

Systematic Reviews and Meta-Analysis of Prognostic Therapeutics

ββ with proven benefits include carvedilol, bisoprolol, metoprolol XR and in the elderly nebivolol. Chatterjee et al, compared different ββ head to head and noted no difference in mortality, discontinuation or improvements in left ventricular ejection fraction (LVEF). This appears globally and in real world clinical practice. It is accepted that the magnitude of heart rate reduction using HF class ββ's are vital [88-90]. It remains unclear: the extra class benefits and role of vasodilator ββ's for the lifelong use in HF with comorbidities; prescription consistency, tolerability and compliance outside urban areas; and pharmacogenomics in some groups in Australia [3-5, 91-95].

The story is more complicated for renin angiotensin aldosterone system (RAAS) blockers. ACEIs are first line therapies for treatment or prevention of CHF, hypertension, diabetes, renal impairment, vascular bed atherosclerosis, either as the primary disease, comorbidity, with or without

end organ disease from the earliest stages to the more advanced. ARBs, were introduced as an alternative with lower side effects such as cough, greater tolerance and perhaps now efficacy approaching ACEI, and with arguments for greater cost effectiveness. There remain important physiological differences between the 2 classes of drugs from primary action, pleiotropic effects, other extra-class benefits and contextual race responses [96-123]. When we look at selective examples for ACE-I, there are some who argue that one agent such as perindopril could be superior in its class [124]. In studies such as Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALL-HAT) and Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, African American patients receiving lisinopril or losartan had higher relative risk of CHF [125].

The ONTARGET trial and the study of Telmisartan in CHF and hemodialysis has raised important questions of the growing benefit of ARB at least for the agent in question. With additional data on tolerability across all racial profiles, pharmacological stability, pleiotropic effects for all comorbidities, questions can be asked as to whether the therapeutic paradigm could be widened when patients not meeting trial conditions are being treated [125-133]. Finally, aldosterone antagonists are now proven therapy for all classes of CHF, and the guidelines to follow suit. The main difference between 2 established agents is the sexual side-effect profile, potential for adverse drug interactions and cost benefit when all factors are considered [134-136]. These points highlight that there are still posttranslational factors that remained unresolved with RAAS blockers.

UNDERSTANDING THE CONSIDERATION AND CONTEXT FOR TRANSLATING AND EXTENDING THE EVIDENCE THE BASE

Generating evidence and interpreting evidence are mostly independent processes. This independence also means that regulatory bodies have no control over the breadth and depth of evidence presented when regulating for populations. Thus the three important questions of efficacy, effectiveness and cost-effectiveness are not always available. A combination of structured guidelines and judgement are needed. Let's explore some important points:

What Constitutes Translatable Evidence?

There are no agreed rules on how evidence is interpreted and choices made for a particular agent, a class, extra class benefits, the primary disease treated, should there be evidence for competing agents within a class, physiological targets as primary mode for decision making, the role of pill burden and the auditing of off-label use in Australian clinical practice. An important correlation can be made where physiological effects are used in device guidelines but not in therapeutics. There is an established process to translate controlled evidence from RCT to the clinical domain regulated by the pharmaceutical governing authorities in each country. Further scrutiny, more related to cost-efficacy, are made by formularies in treating institutions. Thus the vast majority of practitioners have no say in the process. We do however see selective publications, uncontrolled for bias, voicing

Box 3.   Australian Data for Heart Failure.

Theme	Data Source Reference	Positive Findings	Negative Findings	Notes
Databases	Prospective Registries [52-60]	• Risk factors contribute equally to HF death regardless of SES or race • No significant gender differences in HF management • Higher EF but more severe NYHA class among women	• Underutilization of HF therapies in pts undergoing PCI • Many clinical HF cases remained undiagnosed • Majority of LV dysfunction in preclinical stage • Suboptimal prognostic HF therapeutics post MI • Increased prevalence of CHF, and significantly lower use of diagnostic and therapeutics in rural areas.	• Unrepresentative demographics • Limited data • Extrapolation from non HF dedicated registries • Aging data
	Data Linkage [62-68]	• Similar outcomes in male, females and elderly in WA • Encouraging declines in overall HF mortality, and index admissions overall • Prognostic therapies well utilized with demonstrated benefits in improved long-term survival • Decline incidence and improvement in survival early onset HF after Min in WA • No Increase in late-onset HF mortality in WA	• Remote areas, variable access to care and Indigenous pts to care poorer outcomes • Growing burden of HF hospitalization of non-ischemic etiology • High mortality persists particularly in high risk groups • Cost and acute bed occupancy remains significant more so in elderly (NSW) • Echocardiography underutilized	• Overall admissions and mortality from national data, other data predominately from 2 states • WA - probably accurate data with previously published validation of methodology • Modelling and statistical techniques used to extrapolate data is some cases
	Retrospective Reviews [52, 70-74]	• Comparable standard of care to international best practice achievable • Collaborative medicines review effective in delaying time to next HF hospitalization	• Poor outcomes related to SES	• Prospective data needed • Efficient measures are needed to deliver comprehensive care
Intervention	Surveys [78-81]	• High intensity CHF MP applying more evidence based interventions improve outcomes	• Inequitable access and distribution of CHF MP, particularly outside capital cities • Substantial heterogeneity between CHF MP • Dissemination of written information suboptimal	• Improvements have been made in information availability and distribution via NHF, since these publications • No national credentialing process for CHF MP's
	Patient Contact [80]	• Nurse lead care in CHF MP's supplemented by technology can improves outcomes increase compliance	• Numerous unaddressed issues for acceptance, staffing, remuneration, protocols and standards in allied health lead and technology assisted care • Self-care findings variable	• Nurse-lead and technology assisted care previously discussed (5, 104) • Well thought out studies on integrating self-care, allied health staffed and technology assisted CHP MP's needed • Mental health and depression data lacking

(Box 3) Contd….

Theme	Data Source Reference	Positive Findings	Negative Findings	Notes
	Consensus Statements [83-85]	• Comprehensive and relevant for the majority of Australians	• Does not address comorbidities and considerations for remote care adequately	• Further consensus with new and evolving stakeholders needed
	Validation of methods [86]	• High predictive accuracy for linked HMD data in monitoring trends for HF in WA	•	• Measures to upgrade HF endpoints with new developments and potential risk factors

Data from 2000 -2015 on measures to understand the epidemiology and translation of CHF care in Australia, presented as a summation of the main findings. To date there has been no prospective CHF database similar to the International studies. Only references quoted in this article are cited. Some articles are cited within the referenced articles.
Abbreviations: CHF MP – congestive heart failure management programs; HMD -Hospital Morbidity Data; MI – myocardial infarction; NHF – National Heart Foundation; NSW – New South Wales; PCI – percutaneous coronary intervention; pts – patients; SES – socioeconomic status; WA – Western Australia.

preference for particular agents or combinations. These perhaps reflect observations made from clinical experiences from a broader cohort of patients.

Are there Examples of Heterogeneity of Practice where the Evidence could be Interpreted Differently?

Variations in clinical responses of blood pressure lowering medications between white and black patients have been noted from early studies and subsequent meta-analysis. These highlighted favorable responses to calcium channel blockers (CCB) and diuretics over ACEI and ββ in blacks. Poorer outcomes were later noted with Lisinopril (ALLHAT) and Losartan (LIFE) studies. Additional benefit with isosorbide and hydralazine, and preliminary evidence for lower frequency of responsive genotype to metoprolol in blacks, adds impetus for new thinking that variations in either physiology or response do exist. Some of these points are gradually making it into the guidelines [137]. The question remaining is what other ethnic groups is this relevant to? Thus this remains a dilemma faced by many physicians who are treating patients of diverse ethnicities. Another example is the role of pharmacotherapy post myocardial infarction (MI) when the LVEF is >40%. Reperfusion therapy remains first line at many smaller and remote centers. Reperfusion injury is recognized, and remains inadequately addressed. The CCBs, verapamil and diltiazem, were shown to prevent no-reflow/slow-flow and wall motion index when given prethrombolytics. Verapamil use post MI may improve mortality, reduce reinfarction and reduce late onset HF [138-140]. While the study numbers were small the results are worth considering. Development in acute interventions shaped acute therapies in major centers with clear reductions in all forms of HF. However in many smaller or remote centers late onset HF rates are unclear. Overall as these newer therapies have superseded thrombolytics, this type of thinking is no longer reflecting in the guidelines.

Finally, omega-3 an essential lipid had early data showing benefit in CHF, MI and reducing sudden cardiac deaths [141]. Subsequent studies and pooled data where not encouraging. In one study, over 12,536 diabetic patients aged 50 years and older, were followed for mean 6.2 years. These patients were given a low dose of 1 g of n–3 fatty acids (containing 465 mg of eicosapentaenoic acid [EPA] and 375 mg

of docosahexaenoic acid [DHA]) and no dietary restriction. No blood levels for EPA or DHA were tested. There was no difference in major outcomes between the groups [142, 143]. The evidence also tells us that dietary sources of omega-3 and blood levels predict outcomes [144, 145]. How does one safely negotiate this? There have been trials that support, others that do not, meta-analyses in favor and others against. In Australia the Heart Foundation provided a position on omega-3 in 2008. The national Pharmaceutical Benefits Scheme did not endorse this perhaps reflecting the lack of cost benefit from these negative studies. It is however clear there are differences in all the studies, and the questions looked at in the meta-analyses. How do we approach this for our patients, who can't meet the dietary requirements, with more advanced disease, more comorbidities, or unable to tolerate all best practice medications?

Interpreting Clinical Trials and Meta-Analysis

Clinical experiments are valid if a cause and effect is established with all biases accounted. The most powerful *evidence-generating tool* is the Randomized Control Trial (RCT) and *evidence syntheses tool* are systematic reviews and metaanalyses. To ensure biases are controlled, criteria are placed for the internal validity. The resulting finding allows causal inference for any finding to the population enrolled in that study. In time, a pool of knowledge will accumulate. Systematic reviews are publications that include studies from a defined period, sometimes ranking them, with a well formulated clinical question, systematic and reproducible methodologies, thus establishing the weight of this scientific evidence. As described by Robey *"A fundamental tenet of science holds that the best estimate of a population characteristic is the pool of all valid and independently obtained estimates of that characteristic. Therefore, a meta-analysis achieving a positive outcome forms very strong evidence of treatment efficacy"*. This principle is based on the RCT's findings that estimate the size of the treatment effect, which can then be mathematically integrated to estimate the average or common effect. When data pooling is not feasible results are presented as number of studies in support or against or 'vote counting' [31, 146-148].

Pooled research studies are among the simplest forms of post marketing research that address efficacy. The role of

Box 4.   **The Evidence tree: Efficacy, effectiveness and cost-effectiveness.**
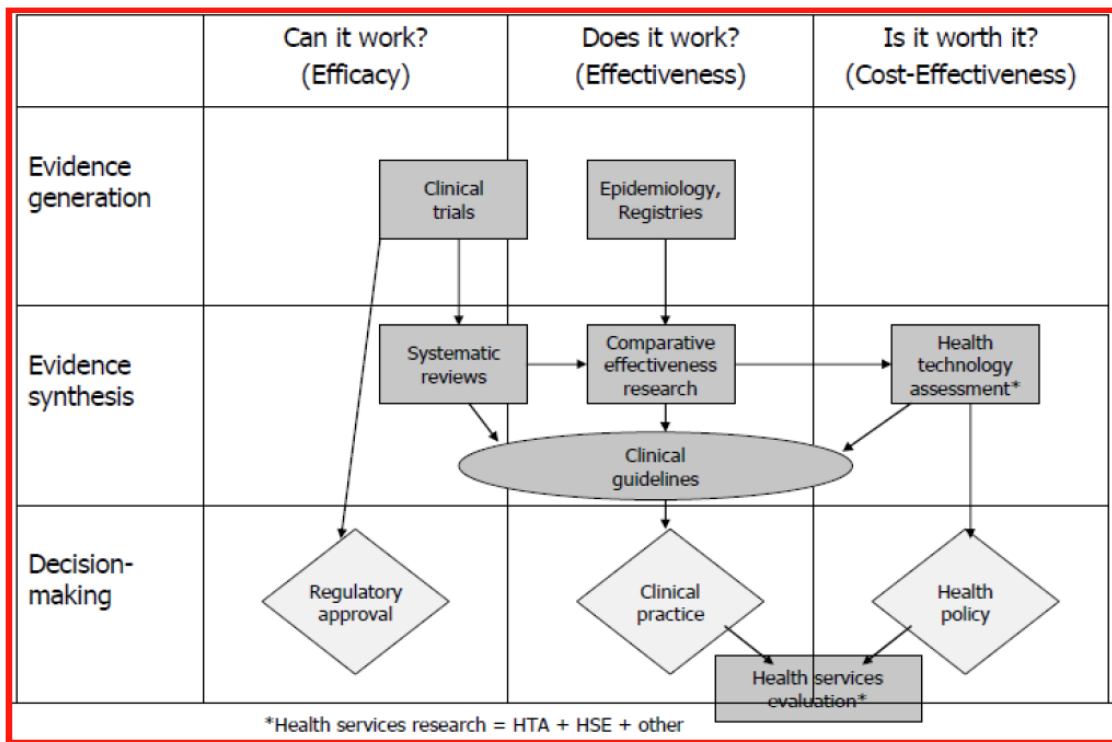
Maximing the quality and efficiency of health care requires a process that gathers, synthesizes and translates evidence. This scenario is simple in concept but is far more difficult in reality. The first part of gathering evidence requires the right questions to be asked for it to be meaningful to communities. Synthesizing the evidence requires also us to consider the validity, as controls that prevent biases can alter the generalizability. Translating the evidence requires us to monitor how the treatment is doing for patients who suffer from the illness. This diagram contextualizes some of these important steps. However what is often forgotten is the posttranslational aspect. It is important for us to also ask questions of effectiveness and cost-effectiveness regularly. The pathway leading to efficacy can be described as the clinical research ending with the randomized controlled trial findings. Phase 4 research is the study that starts exploring these additional points. Unfortunately this form of research has not been given its due importance.

systematic reviews and meta-analyses in clinical practice has however varied [149-162]. Berlin *et al.* argues that a large RCT will always be required to influence regulatory bodies. As it is not often possible to replicate studies, nor should they be encouraged, pooling data often has differences from the start. So, meta-analyses can perhaps play a complementary role by strengthening support for the evidence. Thus pooled data should be considered among the strongest sources for post-marketing evidence, however on their own should not be used to derive clinical decisions.

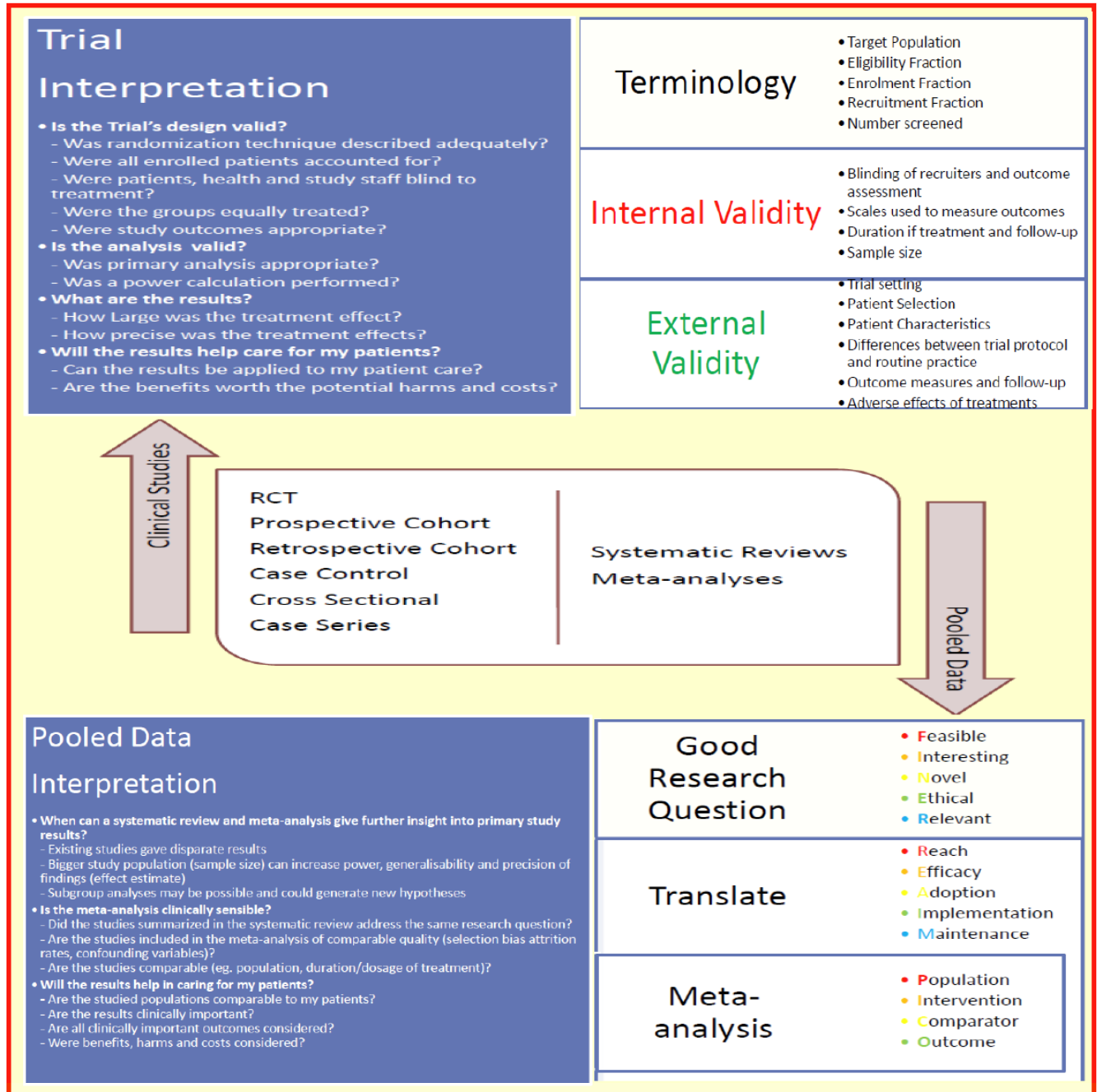**What are Important Considerations for Designing Post-Marketing Evidence?**

In the examples mentioned above, pooled data can provide a synopsis of evidence that has already been generated; audits address community level efficacy or potential gaps and health services intervention efficacy and cost effectiveness. In most health systems there are a number of these fundamental questions. Four important points should be factored before exploring suitable studies:

1. *Generalization*: As clinicians, we are keen to see that the efficacy observed in the more selected populations of clinical trials is confirmed in the less restricted populations of registries. With audits, the real problem is the lack of randomization.

2. *Value for the patient and health system*: Clinical practice should be an exercise in finding value. Clinicians may value harder outcomes while patients may value quality of life. Nevertheless, the exercise of pursuing value leads one to the point of choosing therapies with the most value, and therefore into the realm of cost effectiveness.

3. *Extending the choice between therapies*: Given the historical sequence of the developing evidence base, analyses of formal studies to explore the utility of older therapies in the context of established newer therapies are always needed. This is important for valuing the incremental value of each therapy when one must choose, either at a patient or health service level.

4. *Health systems change:* All innovations in diagnosis and therapy require a commensurate adaptive change in clinical and health service delivery if the promised benefits are to be realized. Studying the health clinical and health service determinants of effective translation therefore is also an important goal.

The crux of phase 4/5 studies is to identify if treatments efficacy can be replicated in the community and the cost. To achieve this value we also need information to compare. For example, with therapeutics the benefits of an agent in a class for the patient with the disease, combinations of disease

Box 5. **Interpreting clinical trials.**

Trial Interpretation

- **Is the Trial's design valid?**
  - Was randomization technique described adequately?
  - Were all enrolled patients accounted for?
  - Were patients, health and study staff blind to treatment?
  - Were the groups equally treated?
  - Were study outcomes appropriate?
- **Is the analysis valid?**
  - Was primary analysis appropriate?
  - Was a power calculation performed?
- **What are the results?**
  - How Large was the treatment effect?
  - How precise was the treatment effects?
- **Will the results help care for my patients?**
  - Can the results be applied to my patient care?
  - Are the benefits worth the potential harms and costs?

Terminology
- Target Population
- Eligibility Fraction
- Enrolment Fraction
- Recruitment Fraction
- Number screened

Internal Validity
- Blinding of recruiters and outcome assessment
- Scales used to measure outcomes
- Duration if treatment and follow-up
- Sample size

External Validity
- Trial setting
- Patient Selection
- Patient Characteristics
- Differences between trial protocol and routine practice
- Outcome measures and follow-up
- Adverse effects of treatments

Clinical Studies

RCT
Prospective Cohort
Retrospective Cohort
Case Control
Cross Sectional
Case Series

Systematic Reviews
Meta-analyses

Pooled Data

Pooled Data Interpretation

- **When can a systematic review and meta-analysis give further insight into primary study results?**
  - Existing studies gave disparate results
  - Bigger study population (sample size) can increase power, generalisability and precision of findings (effect estimate)
  - Subgroup analyses may be possible and could generate new hypotheses
- **Is the meta-analysis clinically sensible?**
  - Did the studies summarized in the systematic review address the same research question?
  - Are the studies included in the meta-analysis of comparable quality (selection bias attrition rates, confounding variables)?
  - Are the studies comparable (eg. population, duration/dosage of treatment)?
- **Will the results help in caring for my patients?**
  - Are the studied populations comparable to my patients?
  - Are the results clinically important?
  - Are all clinically important outcomes considered?
  - Were benefits, harms and costs considered?

Good Research Question
- **F**easible
- **I**nteresting
- **N**ovel
- **E**thical
- **R**elevant

Translate
- **R**each
- **E**fficacy
- **A**doption
- **I**mplementation
- **M**aintenance

Meta-analysis
- **P**opulation
- **I**ntervention
- **C**omparator
- **O**utcome

Basic principles guide evidence generation and interpretation. Two common abbreviations *FINER* and *PICO* can be used to explore the relevance of trials and data pooling research. More specifically the top boxes present the common terminology, factors relevant to internal and external validity and interpreting clinical trials. The *REAIM* framework bottom left addresses important points in translational research (Adapted from ref 4, 151-159).

processes and variations in demographics. The phase 3 study will usually only answer the first of those possibilities. Extending the evidence can occur by auditing data when implemented in the community, controlled comparative effectiveness studies which are bound by cost and time constraints of RCT, or animal data, which is discussed below. The most important prerequisite is obtaining enough of the right information to inform. There are no right or wrong trial designs for this line of work. As there are more tools including mathematical modelling [163, 164] or quasi-intervention,

the process could be less rigorous than RCT. There will also be situations where trial level evidence is unambiguously needed to answer the questions. It remains unclear how observational, non-randomised, pseudorandomized trial level or low powered evidence will be interpreted. Good communication between research-clinical-administrative arms is the first and most important step in phase 4 research. It is fair to say most systems have not found valid solutions for all these issues.

Animal Models to Aid Post-Marketing Research

Well-designed animal studies could bridge hypotheses gaps in post-marketing studies. The introduction of phase 0 studies in 2006 is a promising step to speed up preclinical evidence. Similarly such methods could be devised prior to constructing post marketing intervention studies. Firstly finding ways to reduce sample sizes with novel early surrogate markers for clinical endpoints [165, 166]. Secondly, advancing gaps in the development of complex comorbid HF models and in standardizing the reporting of animal work [33, 40, 167]. One such initiative in Spain aims to address regional issues [168]. There is still a long way to go, but these gaps are not insurmountable and more collaborative work is needed.

MOVING FORWARD

Post-translational research should provide a 'real-world' picture of therapeutics e.g. there is often an under-appreciated difference between efficacy and effectiveness. A therapy may be highly efficacious in RCTs, but not at all effective nor cost-effective. From this perspective, phase 4 research could perhaps be more difficult than the primary evidence generating process, as it equally involves both evidence gathering or generation, with an implementation goal. With the latter, there is always the concern of when the evidence will be considered enough, to be translatable. An understanding among health systems is thus important. Some of the points we to consider are:

Understanding Scientific Decision Making and Process of Care:

- It is important to get a grasp on how the health profession views evidence, its strengths and weaknesses and what is considered implementable. This can be done by a survey among health professionals and administrators.

Evidence Gathering

- *Snapshots or Audits*: provide an opportunity to gauge problems broadly and are good bridge to more focused audits. It requires funding and collaboration, and can be opt in or out. Mathematical modelling, pseudo-randomisation techniques such as regression adjustment, propensity matching, inverse probability weighting and instrument variables can improve bias but require general understanding with an implementation arm.

- *Key Performance Indicators and Case Report Forms*: It is important to ensure those who will be using the information agree on the data to be collected. Surrogate endpoints in HF have been notoriously unreliable and this continues as a work in progress. Krumholtz et al and other groups from the ACC have published important work on this [30]. Local agreement on suitable surrogate endpoints may be important.

Evidence Generation

- Development of protocols for post-marketing intervention and non-inferiority studies involving minority communities or other demographics where small sample sizes are inevitable

- *Development of new biomarkers and risk scores* – as it is not feasible to wait the course for events to develop as in the original RCTs, this point becomes important. Linking database may be the important first step and efforts to simplify these processes are also important post-translational endeavors.

- *Development of new treatment protocols or options*: Extending the scope of treatment for a class of drugs or for a disease can be beneficial for patients with genetic predispositions, comorbidities or for other reasons. This evidence is particularly difficult to generate, as they are rarely supported by industry, or difficult to implement from questions on the robustness of investigator generated research and the standardizing and translating of animal data. It is the first two aspects that local health systems need to address and standards to be agreed on.

- *Development of new service delivery protocols or options*: Often health care can be improved by ensuring, what is known is delivered and patients comply, as noted by the OPTIMIZE-HF study [68]. Other examples here are nurse delivered care, self-care and the use of technology. In this line of research many studies look to achieve hard endpoints such has mortality. It is important that standards be derived for suitable endpoints for non-drug research as the goals here are predominately to improve service, reduce cost and increase compliance [168]. The standardizations of these endpoints are important to establish to ensure smooth translation of findings.

Evidence Translation

- *The core team:* Health administration eventually decides the policy standing on any finding. It is important to negotiate this earlier in the process than later. As the robustness of evidence sways decisions in most cases, working with the specialty to find ways to standardize and increase the translational flavor of investigator initiated research is important.

- Rural and remote evidence: it is often in these communities that disparities in health and outcomes are noted. It is also the most difficult community to build evidence for. All the points cited apply here.

- *Ease of access for clinical trials*: the importance of this point is often understated. Extending the ability to conduct trials across more centers improves the clinical infrastructure and in the longer run will aid all aspects of clinical care. Sharing of staff is another advantage.

CONCLUSIONS

The evidence generating process provides a lot of emphasis for phases 0 to 3. In this the greatest weight is usually provided to RCT's in phase 3. These trials provide the most significant answers which are however limited to one (or very few) questions within a controlled group. The forgotten posttranslational arm that aims to address unanswered questions at the community level requires greater emphasis.

Regular studies of the process of care that inform efficacy, effectiveness or cost effectiveness are the main focus of this phase. Ensuring the evidence indeed applies and finding better ways to do things is vital. Early in the process, industry requires support and facilitation in running studies. Equally post-trial studies are initiatives which should reciprocally receive industry support. Thus all these parties have roles to play in phase 4 studies. While initially it may be difficult to gauge which endeavors will tax the system greatly, which are feasible, which are efficacious and the cost, in the long term, however, understanding the many dimensions of implemented new treatments will provide the most important surrogate information to assess and administer for all major health systems performance indicators including overall costs, utility of services including readmissions and also long-term community wellbeing.

DISCLOSURES

ABBREVIATIONS

ACE-I	=	angiotensin converting enzyme inhibitor
ADHF	=	acute decompensated heart failure
ARB	=	angiotensin receptor blocker
ββ	=	beta-blocker
CCB	=	calcium channel blockers
CHF	=	chronic Heart Failure
IND	=	investigational new drug
HF	=	heart failure
LVEF	=	left ventricular ejection fraction
MI	=	myocardial infarction
MRAs	=	mineralocorticoid receptor antagonists
NOAEL	=	No Observable Adverse Effect Levels
RAAS	=	renin angiotensin aldosterone system
TGA	=	therapeutics goods administration

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

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