The Integration of Lifestyle Factors in Clinical Research Studies – How can meaningful evidence be generated to evaluate the impact of lifestyle changes on health outcomes?

Research dissertation presented in partial fulfilment of the requirements
for the degree of

MSc in Pharmaceutical Business & Technology

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Candidate Declaration

Candidate Name: Richard Kieran

I certify that the dissertation entitled:

The Integration of Lifestyle Factors in Clinical Research Studies – How can meaningful evidence be generated to evaluate the impact of lifestyle changes on health outcomes?

submitted for the degree of: MSc in Pharmaceutical Business & Technology

is the result of my own work and that where reference is made to the work of others, due acknowledgment is given.

Candidate signature: 

Date: 27/MAY/2023.

Supervisor Name:

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Date:

Dedication

I would like to dedicate this to Olivia.

Acknowledgements

I would like to gratefully acknowledge the guidance and wisdom of all the Innopharma team, and in particular my Dissertation Supervisor who ensured that I remained on track during this research and helped me to produce what is a robust study.

Abstract

The purpose of this research was to examine the current state of clinical research into how lifestyle factors can impact health outcomes in chronic disease, and to test the hypothesis that such research has lagged studies of drug therapy in terms of delivering actionable results.

The research was conducted firstly by completing a thorough literature review of the topic, and then gathering primary data through a series of structured interviews with a panel of contributors drawn from Academia, Industry, and the Medical Profession.

The findings were illuminating, and supported the published material but also went further; exposing a broad level of dissatisfaction with many aspects of the current clinical research process and how the results of this research is reviewed, published and disseminated to healthcare professionals and patients.

The conclusion is inescapable – the field of clinical research requires a significant overhaul if it is to deliver meaningful evidence in the increasingly complex world of modern medicine.

A number of pragmatic suggestions for further research were developed, including a concept to address the risk of skewed trial results arising from manufacturers sponsoring and designing trials of their own products, and an initiative to fundamentally rebalance the clinical research ecosystem by involving a broad spectrum of stakeholders at every stage in the process.

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1 Introduction

1.1 Overview

Clinical Research sets the agenda for modern medical practice as almost all therapeutic decisions taken in the treatment of disease are informed by protocols which are in turn based on evidence gathered through clinical research, with the intention of ensuring that patients are provided the best available, evidence based clinical care.

Clinical Research is defined as "a component of medical and health research intended to produce knowledge valuable for understanding human disease, preventing and treating illness, and promoting health" (Tunis *et al.*, 2002).

Evidence Based Medicine is a term applied to the process of constantly integrating the most up to date research information with clinical experience and patient insight to select the best possible approach for a particular patient at a particular point in their therapeutic journey. (Sackett *et al.*, 1996) Modern medical practice prides itself on providing the highest standards of patient care by employing an Evidence Based approach, however this requires individual clinicians to devote a potentially unsustainable proportion of their time to reviewing research articles and reports. One estimate from a number of years ago suggested that a clinician would need to read 17 journal articles per day, 365 days per year (Davidoff *et al.*, 1995) - surely an impossible task alongside the other demands of clinical practice?

As modern medicine becomes increasingly complex and the range of new medicines and therapeutic approaches grows year on year, so too the volume of Clinical Research has grown exponentially, leading to a need for clinicians to become ever more selective about which studies and journal articles they should invest their valuable time in reviewing and perhaps incorporating into their treatment protocols. In this environment the relative merits of different clinical study approaches assume greater importance, and the perceived "Quality of Evidence" derived from different study types is a critical factor in determining which studies will have an impact on treatment regimes.

My research is intended to challenge the current reliance on randomised, controlled trials (RCTs) intended to study the impact of a single variable on patient outcomes over relatively short timeframes, and to investigate how long-term lifestyle factors such as diet and exercise habits can be studied scientifically to generate evidence which can be considered equally compelling as that generated by RCTs.

1.2 Research Purpose

The purpose of this research is to gain an insight into different Clinical Research methodologies and characterise the hierarchy of evidence generated as perceived by clinicians and treatment providers. Using this insight, it is hoped to propose how clinical studies could be modified to incorporate lifestyle factors while still producing results which can be considered equivalent to that produced by today's "gold standard" trials.

So called lifestyle factors are inherently difficult to include in a scientific study for several reasons. Firstly, variables such as diet and exercise are challenging to quantify accurately as their assessment typically relies on patient submitted surveys or diaries logging activity and consumption patterns which are prone to errors and omissions. Secondly, it is impossible to "blind" participants or assessors to the factors or conditions being studied in the same way as a drug therapy or placebo can remain hidden. Thirdly lifestyle factors are, by definition, a complex amalgamation of intertwined activities, habits and behaviours which do not lend themselves to cause and effect analysis easily. Additionally, the impact of lifestyle factors on the development or progression of a disease may only be seen over many years, making clinical studies lengthy, complex and expensive in addition to presenting challenges in participant retention.

All of these difficulties render it impossible to design a randomised, controlled, double blinded Clinical Trial, which is "ubiquitously regarded as the 'gold standard' of biomedical research" (Bajwa *et al.*, 2021), to measure the impact of lifestyle factors such as diet and exercise on patient outcomes.

Therefore, are we to conclude that research into the impact of behavioural factors will always be considered of lower value than trials of pharmaceutical therapies which lend themselves very well to RCTs? Surely such a conclusion would risk creating a built-in bias in how data from Clinical Research is evaluated, and risk undermining the basis of Evidence Based Medicine which is the bedrock of modern western medical practice.

1.3 Significance of the Study

This research is important for a variety of reasons, not least because it is apparent that in certain therapeutic areas lifestyle factors have been overwhelmingly accepted as front-line therapies whilst in other specialities no conclusive evidence has been developed to either support or oppose their inclusion in clinical protocols. This suggests possible differences in the approach to Clinical Research in different therapeutic areas, or a variation in how clinical protocols and guidelines have become established across the specialities, which is important to understand in order to ensure that uniform standards are employed across the entire field of human medicine in the future.

A clear example of this variation can be seen in the treatment of cardiovascular disease (CVD) when compared to Multiple Sclerosis (MS). Both disease areas were the subject of studies which commenced in the 1940's, however, only in the case of CVD have clear guidelines on diet, body mass, exercise and additional behavioural factors been universally accepted as front-line clinical care guidelines. In the case of MS, no consensus on the impact of lifestyle factors has been reached, and specifically regarding the question of whether a modified diet can slow the progression of MS different studies have produced diametrically opposed results. Some studies suggest that a low-fat diet has a dramatic effect in reducing disease progression, however these results have been contradicted in other studies, creating an environment in which it is impossible for either medical professionals or patients to make diet choices with any confidence. On the other hand, the clinical data to support Disease Modifying Drugs appears clear and concise so these are prescribed routinely, even though some evidence exists to show that a modified diet can provide similar or even greater benefit, with reduced risk of side effects.

This research is given even greater significance by the increasing incidence of autoimmune diseases such as MS. Below is a quote from an article entitled "The increasing prevalence of autoimmunity and autoimmune diseases: an urgent call to action for improved understanding, diagnosis, treatment, and prevention" published in the journal Current Opinion in Immunology (Miller, 2023) which underlines the need for greater research in the field.

"Autoimmune diseases have a major impact on the individuals and families they affect, as well as on our society and healthcare costs, and current projections suggest they may soon take their place among the predominant medical disorders. This necessitates that we increase the scope and scale of our efforts, and coordinate our resources and studies, to understand autoimmune disease risk factors and pathogeneses and improve our diagnostic, therapeutic, and preventive approaches, as the costs of inaction will be profound and far greater without such investments."

The aim of this study is to investigate how research into the impact of lifestyle factors can be elevated to attain a similar status as that already endowed upon RCTs. If this work can help promote the greater acceptance

and validation of the results of research into the role that lifestyle factors may play in the management of chronic diseases, it could potentially impact clinical guidelines fundamentally and help to ensure that there is no systematic bias in favour of therapies which are more amenable to RCTs.

1.4 Research Aim and Objectives

The aim of this research is to gain a better understanding of Clinical Research methodologies, and the quality of evidence that can be gathered from the results. Specifically, the focus will be on how Clinical Research can be applied to study the impact of lifestyle factors on chronic diseases using the examples of CVD and MS.

The goal is to understand the differences in the development of clinical guidelines for these two disease areas – how did early clinical research into CVD lead to further studies which produced conclusive evidence to support the adoption of guidelines advocating changes in diet and exercise habits; whereas research into MS over a similar timeframe has failed to deliver a consensus about whether such lifestyle factors can impact progression?

This aim is broken down into a logical series of objectives as follows:-

A. Identify the research methodologies used in both therapeutic areas and highlight any differences found in the approaches used.

B. Compare the different approaches from the point of view of perceived quality of evidence obtained and seek an insight into how clinical practitioners judge the relative merits of various research methodologies and the results produced.

C. Analyse the learnings from this comparison to develop proposals on how Clinical Research studies could be modified to incorporate the complexities involved in studying human behaviours and lifestyle factors while generating results deemed to be of the highest standard.

D. Recommend further research to expand on the proposals above and advocate a new approach to Clinical Research in chronic disease which ensures that a broad range of potential factors are studied in a holistic manner.

E. To provide guidance to clinical practitioners on how to ensure that lifestyle factors are considered in their treatment plans for chronic diseases.

1.5 Methodology

A comprehensive literature review will be conducted to understand the research undertaken into the two chosen disease areas. This will focus on the research methodologies employed and specifically any differences in the approaches taken in the studies which may account for the variation in the clinical evidence produced in each disease area.

Following the literature review primary research will be undertaken to gain deeper insights into how clinical practitioners judge the quality of evidence generated by different research methods, and what characteristics of a study may cause the results to be accepted or dismissed. Further primary research will be conducted among Clinical Trial sponsors and practitioners to understand the relative complexities of the various research methodologies under discussion which will inform the development of proposals for future modifications to Clinical Trials.

The Primary Research undertaken will be qualitative in nature and will be conducted using survey questionnaires on a face-to-face basis where possible. Interviews will be held with medical practitioners across several disciplines; this cohort can be considered as the consumers of Clinical Research since they are tasked with reading and analysing research reports to discern which should be considered as credible evidence to inform clinical practice, and which should be left aside. Research sponsors and practitioners will form the second cohort; these can be considered as the creators of Clinical Research and their input will be sought to provide insight into the practicalities and limitations of conducting scientific trials.

Analysis of the research results will involve balancing the requirements of Clinical Research "consumers" in terms of validity of evidence produced with the real-world complexity experienced by Clinical Trial "creators" to search for possible enhancements to the process which meet the needs of the consumer cohort whilst remaining feasible for the creators.

1.6 Structure of the Study

This paper is divided into five chapters, including this Introduction.

The second chapter describes the literature review which explores in detail the established clinical research methodologies currently utilised, and the relative strengths and weaknesses of each. Using this perspective, the studies conducted into both CVD and MS are compared and contrasted with a particular emphasis on research which led to either the adoption or rejection of lifestyle factors in the development of therapeutic guidelines.

The insights from the literature review will then form the basis of the primary research, intended to challenge the clinical research processes used from both the quality of evidence perspective and the feasibility perspective.

Chapter 4 will present the findings from the Primary Research along with a comprehensive analysis of the data gathered to identify themes which can be further developed and expanded upon to identify possible refinements to Clinical Research methodologies to enhance the inclusion of lifestyle factors.

Finally, Chapter 5 will present recommendations for further research in the area together with a critique of the research carried out to highlight any potential weaknesses which have come to light.

2 Literature Review

2.1 Overview

The purpose of this chapter is to provide a comprehensive review of how clinical research has been used as a foundation for evidence-based medicine and of what is considered current best practice in clinical research. This will form the lens through which the research into the two chosen topics, namely Cardiovascular Disease (CVD) and Multiple Sclerosis (MS), will be analysed in detail to identify the methodologies employed and to highlight any differences which may account for the fact that lifestyle factors have been incorporated fully into therapeutic guidelines in CVD but not in MS. The final portion of the literature review will focus on research regarding how best to gather and validate evidence relating to the impact of lifestyle factors on chronic disease to unearth themes for further study which could result in recommendations for future clinical research into chronic disease.

2.2 Clinical research overview

Evidence Based Medicine (EBM) is defined as "*the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients"* (Sackett *et al.*, 1996). In this context current best evidence means a combination of individual clinical experience with the best available external clinical research. EBM has become established over the past forty years as the bedrock of modern medical practice, and it is accepted as the basis for making clinical decisions and for creating best practice guidelines for patient care. As a result, there is an onus on all clinical practitioners to keep abreast of new research as it is published and to incorporate the best available research findings into their daily work.

This leads to the fundamental question of "what constitutes the best available clinical research which a clinician should use as evidence to guide their clinical care of patients?" The National Institute of Health (NIH), part of the US Department of Health and Human Sciences is described as the nation's medical research agency and is charged with supporting scientific studies that turn discovery into health (NIH, 2023). The NIH defines Clinical Research as a component of medical and health research intended to produce knowledge which helps to prevent and treat disease, as already presented in chapter 1. According to the US national Library of Medicine there are currently approximately 440,000 Clinical Trials registered worldwide, a number which is growing exponentially year on year (ClinicalTrials.gov, 2023).

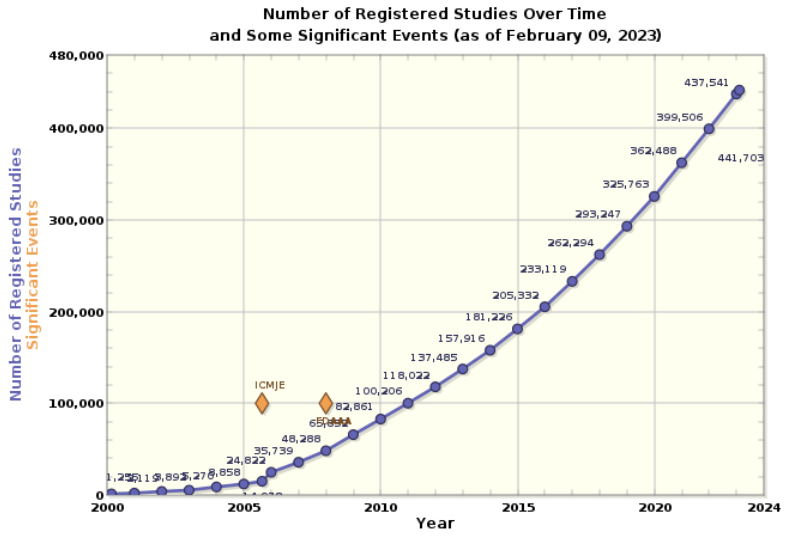

Figure 1 – Number of registered clinical trials as of Feb 9th 2023 (ClinicalTrials.gov, 2023)

How can a medical practitioner choose which piece of research or which clinical study from the myriad of journals and conference proceedings appearing almost daily, and how can they critique and analyse the

selected material to glean high quality evidence to inform their clinical practice? The sheer volume of research available threatens to stymie the very basis of EBM – doctors must quickly identify the most relevant and highest quality research applicable to their therapeutic area to avoid being swamped by less important or potentially misleading publications.

To establish a proper context in which to examine the outcomes of Clinical Research it is important to firstly classify the different research types that are commonly used and the fundamentals of study design. Figure 2 below provides a useful overview of high-level taxonomy of the research methodologies applied in Clinical Research.

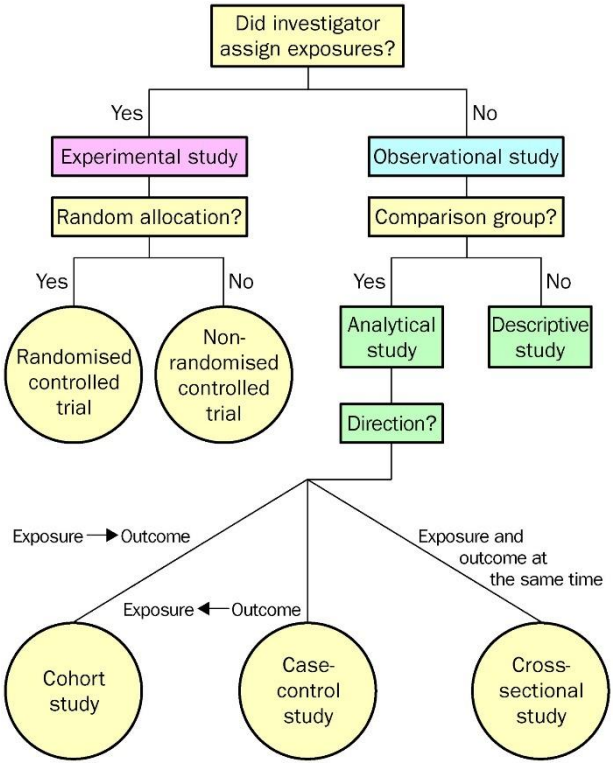

Figure 2 - Algorithm for classification of types of clinical research (Grimes and Schulz, 2002)

All scientific research can be divided into two distinct categories – observational or experimental (also referred to as interventional). In an observational study the investigators do not assign the exposures or treatments which participants have experienced; instead, the object of an observational study in the medical setting is to show how participant's disease state develops over time and attempt to generate hypotheses about probable causes or contributary factors. In an experimental or interventional study however, the investigators set out to research the impact of a specific exposure on the medical outcome of participants.

Observational studies can be further classified on the basis of whether a comparison, or control, group is established. Observational studies without a control group are referred to as Descriptive Studies, whereas those involving a control group are known as Analytical Studies. The latter can then be divided into Cohort Studies (studies of a group with a common exposure intended to assess future outcomes), Case Control Studies (studies of a group with a common outcome intended to look backwards for possible causes) and finally Cross-Sectional Studies which look at exposures and outcomes at a single time point.

Experimental or Interventional Studies are identified by the fact that investigators deliberately expose a portion of the participants to a potential therapy or disease prevention strategy, and measure outcomes over a defined time for this group in comparison to the unexposed group. Randomisation may be used to avoid selection bias and blinding may be used to ensure that participants (and investigators) are unaware of who is receiving the therapy under evaluation rather than a placebo. This removes the risk of information bias also, therefore a blinded Randomised Controlled Trial (RCT) is capable of producing statistically valid datasets based on relatively moderate effects which could be masked by bias tolerances in other study designs.

2.3 The case for Randomised Controlled trials (RCTs)

Having considered the classification of clinical research by study design and methodology it is now possible to examine the validity of the evidence generated from various research types and to establish a hierarchy of evidence for clinical use.

The concept of ranking levels of evidence was fist described in a report by the Canadian Medical Association in 1979 (Spitzer et al., 1979) which formed a taskforce to establish the methodology for evaluating scientific evidence to evaluate what should be included in periodic health examinations. The report included a Level of Evidence table (Figure 3 below) which ranked the evidence available on the basis of the research type which it was derived from. This table rated evidence gathered from an RCT as being of Level 1, or the highest quality, with evidence from Cohort and Case Controlled Studies below this and uncontrolled studies or expert opinions ranked lowest. This Level of Evidence approach clearly identified that research conducted on sound scientific principals can be expected to produce sound and valid evidence which could be used as the basis for clinical decision making.

Level	Type of evidence
I	At least 1 RCT with proper randomization
II.1	Well designed cohort or case-control study
II.2	Time series comparisons or dramatic results from uncontrolled studies
III	Expert opinions

* Adapted from Canadian Task Force on the Periodic Health Examination. The periodic health examination. Can Med Assoc J 1979;121:1193-254

Figure 3 – Levels of Evidence from the Canadian Task Force on the Periodic Health Examination, 1979 (Burns *et al.*, 2011)

One of the members of the taskforce was Dr David L. Sackett, who later came to be seen as the father of Evidence Based Medicine (EBM) (Thoma and Eaves, 2015). Sackett revised the Table of Evidence to give greater clarity as shown in Figure 4 below, again placing RCTs at the top, identified as producing the highest level of evidence, and uncontrolled studies at the lowest level. As described previously uncontrolled studies are also referred to as descriptive studies – observational studies with no comparison, or control, group.

Level	Type of evidence
I	Large RCTs with clear cut results
II	Small RCTs with unclear results
III	Cohort and case-control studies
IV	Historical cohort or case-control studies
V	Case series, studies with no controls

* Adapted from Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1989;95:2S–4S

Figure 4 – Levels of Evidence from Sackett, 1989 (Burns *et al.*, 2011)

As EBM became established as the mainstay of clinical excellence Sackett was instrumental in founding the Centre for Evidence Based Medicine (CEBM) at Oxford University and continued his work in further refining and developing the levels of Evidence framework. Although the relative ranking of the primary research methodologies has not changed over the years, Systematic Reviews of multiple research works have been identified as yielding higher level evidence than the output of individual studies. See Figure 5 below.

Systematic Reviews are defined as follows-

"A Systematic Review attempts to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a specific research question. Researchers conducting systematic reviews use explicit, systematic methods that are selected with a view aimed at minimizing bias, to produce more reliable findings to inform decision making" (Cochrane Library, 2023).

A Systematic Review differs from a literature review in that it is designed to include <u>all</u> the relevant published findings on a defined topic, and therefore to avoid introducing bias due to selective inclusion.

Level	Type of evidence
1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	"Outcomes" research; Ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual Case-control study
4	Case series (and poor quality cohort and case-control study
5	Expert opinion without explicit critical appraisal or based on physiology bench research or "first principles"

* From the Centre for Evidence-Based Medicine, http://www.cebm.net.

Figure 5 – Levels of Evidence from CEBM, 2009 (Burns *et al.*, 2011)

The latest, and current, ranking of Levels of Evidence from CEBM is shown in Figure 6 below. The structure has been changed to present levels of evidence categorised according to the question which needs to be addressed and provides a pathway that guides the user to up or diwngrade a study depending on it's quality. When answering the question "Does this intervention help?", which is the key question in most cases relating to clinical practice, the highest level of evidence is once again judged to be from a systematic review of RCTs.

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table
OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653
** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

Figure 6 – CEBM Levels of Evidence 2011 (CEBM, 2023)

The literature on the topic of EBM would appear to be unamimous in supporting RCTs as the ultimate research methodology which should be employed whenever possible and the outcomes of such research treated as undeniable proof upon which evidence based treatment regimes should be based.

In fact the origins of RCTs can be traced back to post World War 2 studies into the use of streptomycin to treat tuberculosis in Britain and the work of leading advocates such as Archie Cochrane, whom the Cochrane Library is named after. Cochrane pioneered early RCTs and wrote extensively during the 1960's and 1970's in support of the use of controlled trials to produce accurate comparable data on which to base decisions about the relative cost and benefit of different approaches (Cochrane, 1972).

Meanwhile in the US the Food and Drug Administration (FDA) introduced regulations in 1962 which required the use of "well controlled" trials to prove the safety and efficacy of a new drug prior to approval. Known as the Kefauver-Harris Amendments these were brought in following the Thalidomide scandal in which a sedative was prescribed to pregnant women to treat morning sickness. Due to the lack of adequate safety assesement prior to the launch of the drug in some countries thousands of children were born with serious

birth defects and the new FDA regulations were intended to prevent a similar tragedy from occuring in the US (FDA, 2019).

These regulations are known as the Kefauver-Harris Amendments and they effectively cemented the position of RCTs as the gold standard in clinical research, at least in the field of drug trials (Jones and Podolsky, 2015), and that legacy persists to this day. Randomised Controlled Trails (preferably double blinded) are seen as the highest level of scientific clinical research possible, the results of which are used to inform Evidence Based Medicine and therefore shape modern clinical practice across all specialities.

2.4 Critique of RCTs

Expert opinions also point to some limitations to RCTs and these demand thorough investigation to ensure that the high standards of scientific rigour associated with such studies does not blind us to alternative forms of research which may have an important role to play in clinical research.

In a Lancet article entitled “Current problems and future challenges in randomized clinical trials” (Feinstein, 1984), the author acknowledges the huge benefits which have accrued from the widespread adoption of RCTs as the primary source of evidence to support decision making around therapeutic agents, but also draws attention to some of the drawbacks and limitations of this form of research, and warns of the risks posed by slavish adherhence to RCTs as the only valid source of useful clinical data.

Of particular relevance to the research described in this paper is the distinction between remedial and prophylactic therapy, as the core aim of this work is to investigate how clinical research into lifestyle factors can be optimised. By definition lifestyle factors are long term behavioural traits which can be expected to impact the incidence rates of non communicable diseases (World Health Organization, 2011) and therefore are more likely to have propylactic effects rather then remedial.

RCTs are well suited to gathering data regarding the efficacy of a therapy intended to treat a symptomatic disease, but not so amenable to assesing the benefits of a therapeutic regime intended to prevent, or delay the onset of, a disease in the first place. For instance if a trial is concerned with drug therapy to treat hypertension or to inhibit tumour development the outcomes are precisely measurable and can be expected to be seen in a relatively short timeframe. This means that statistically significant results can be achieved with a manageable sample size over a timeline that is practical in the real world.

When attempting to measure prophylactic effects however the challenge is quite different. In this case the data that the study is looking for is the absence of symptoms in a healthy population, which means that the study must be maintained for an extended period as the natural development of disease symptoms may take many years. Following trial subjects over long timeframes introduces risks due to patient retention issues and also of failure to adhere strictly to the original protocols, both of which can lead to distorting or undermining the statistical validy of the trial results. In addition, if the disease under investigation is rare, a study must utilise a very large sample size to find statistically relevant results which further adds to the risks listed above (Temple, 2016).

RCTs have additional limitations when studying lifestyle factors such as diet and exercise which are by definition multi factoral. A properly designed RCT conducted to study the impact of a specific, typically single, intervention on a homogenous trial population requires a detailed and rigid study protocol to be closely adhered to in order to produce scientifically rigourous results. Part of this protocol will involve

administration of the interventional agent in defined dosage at regular intervals, possibly blinded so that the participants do not know whether they are in the control arm or the intervention arm of the study. However it is not possible to apply such rigour to a study of lifestyle factors for a number of reasons. Firstly the lifestyle factor in question, be it diet, exercise, sleep or any other behavioural habit cannot be administered in a controlled fashion but is instead part of a continuum of behaviours that make up the participant's lifestyle. Blinding is also impossible in a lifestyle study when the factors under investigation are visible and a placebo agent is unavailable.

Another aspect of RCTs which has been well documented is the question of Internal versus External Validity. Internal Validity examines whether a study answers the research question without bias – a well designed and executed RCT with genuine randomisation of subjects and double blinding can be expected to score highly in terms of Internal Validity. External Validity (sometimes referred to as generalisability) examines how relevant the results of a study are in the external context, ie. the real world (Andrade, 2018). RCTs by their nature are conducted in a highly contolled environment with a carefully selected study population therefore how well the results translate to the general population or to a typical clinical setting are open to question. For this reason many clinicians have concerns about the relevance of RCTs to their patients – in a study conducted in New Zealand just 4% of asthma patients were found to be eligible for 17 major asthma RCTs – meaning that 96% of the population of asthma sufferers would be excluded form this research (Travers *et al.*, 2007). This poses grave questions about the External Validity of such trials, regardless of how well designed and managed the actual trial process and data analysis was.

For these reasons, and others which have not been discussed here, undertaking a scientifically sound RCT into diverse lifestyle factors which may impact the occurrence of a non communicable disease is likely to be unfeasible, and even if such an endeavour was completed it is probable that the results would be seen as controversial and open to criticism (Hébert *et al.*, 2016). The bulk of the literature on the topic of RCTs would appear to be based on the assumption that the topic of investigation is a mono therapy intended to treat existing symptoms and this assumption results in overwhelming expert opinion favouring RCTs – this paper sets out to question whether the resulting elevation of randomised trials to the "Gold Standard" in clinical research is flawed and may be skewed by a narrow emphasis on clinical trials relating to pharmaceutical agents.

The acknowledged father of Evidence Based Medicine, Sackett made the assertation that "*The randomized trial, and especially the systematic review of several randomized trials … has become the `gold standard' for judging whether a treatment does more good than harm"* (Sackett *et al.*, 1996) however he also goes on to say that if no RCT has been carried out for a specific situation then the next best external evidence should be

considered – has his last point been overlooked in the rush to focus entirely on the so called gold standard of evdience?

2.5 Alternative Research Methodologies

The intent of this research is to expand our understanding of how clinically valid evidence of the impacts that lifestyle factors such as diet and exercise can have on the development of chronic disease, a topic that RCTs are not well suited to investigating (Feinstein and Horwitz, 1997). It is apparent that alternative research methodologies need to be employed which will deliver results considered to be, if not on a par with, at least as the "next best available evidence" to RCT data. Ideally alternatives to RCTs should be seen as complementary approaches subject to the same level of scientific rigour and capable of producing equally valid evidence in a more diverse range of research settings (Black, 1996).

Thus far we have considered Experimental, or Interventional, Studies and specifically randomised control studies. (refer to Figure 2 for an overview of the main Clinical Research methodologies). Non-randomised control studies may be used where randomisation proves too difficult, too time consuming or too costly at the recruitment stage, or in some cases for ethical reasons if patients or clinicians are unwilling to accept random allocation of an intervention (Sibbald and Roland, 1998), however a non-randomised trial is susceptible to misleading results due to selection bias in particular.

For clarity it should be pointed out at this stage that the distinction between a non-randomised experimental study and a quantitative observational study is somewhat blurred in literature on the subject. In fact both Black (Black, 1996) and Carlson (Carlson and Morrison, 2009) refer to non-randomised control trials as observational studies.

For the purposes of this paper the definition applied by Grimes and Schulz and illustrated in Figure 2 is applied – Experimental Studies are those in which investigators introduce an intervention and seek to measure it's impact (efficacy), whereas Observational Studies do not force a change to the patients circumstances or therapy (Gilmartin-Thomas *et al.*, 2018).

Observational Studies seek to establish causal links between exposure and outcome where the assignment of subjects to groups is observed rather than manipulated (Carlson and Morrison, 2009). In the context of EBM, the evidence generated from Observational Studies is considered to be of lower value than that from RCTs (Figures 3 – 6 above) however both have strengths and weaknesses as shown in Figure 7 below.

	Experimental	*Observational*		
Study design	Randomized Control Trial	Cross-sectional	Cohort	Case-control
Study population	Highly selected population; highly controlled environment	Diverse population observed in a range of settings	Diverse population observed in a range of settings	Diverse population observed in a range of settings
Directionality	Exposure is assigned before outcome is ascertained	Exposure and outcome ascertained simultaneously	Exposure is ascertained before outcome is ascertained	Outcome is ascertained before exposure is ascertained
Primary Use	Demonstrating efficacy of an intervention	Screening hypotheses; prevalence studies	Assessing association between multiple exposures and outcomes over time	Assessing associations between exposures and rare outcomes
Analysis	Straight-forward	Sophisticated multivariate techniques may be required to account for confounding	Sophisticated multivariate techniques may be required to account for confounding	Sophisticated multivariate techniques may be required to account for confounding
Internal validity	High	Low	Low	Low
External validity	Low-Moderate	High	High	High

Figure 7 – Comparison of Experimental and Observational Study Designs (Carlson and Morrison, 2009).

One of the primary weaknesses in RCTs arises from their external validity, implying that the relevance of their results to patients in a real-world setting is questionable, whereas Observational Studies by definition monitor subjects in the existing setting and therefore can produce results with higher external validity. Conversely observational studies do not always provide the level of internal validity expected from a tightly managed experimental study as they can be subject to biases which RCTs are structurally designed to minimise.

Observational studies are generally more time and cost effective than RCTs, and less complex to manage. (Gilmartin-Thomas *et al.*, 2018) In addition observational studies are more amenable to large sample groups and longer term follow up and so are better suited to investigating rare diseases and preventative or prophylactic measures intended to prevent the development of symptomatic disease.

This leads to the fundamental question – can a clinical research methodology be devised which combines the practicality of observational studies with the ability to produce results which stand up to scientific scrutiny?

It is interesting to note that despite the apparent gulf in the literature between those who believe that only an RCT trial can truly deliver evidence to inform healthcare decisions, and those who believe that observational studies also have a role to play in some areas of research, there are in fact striking examples of how both have been used at times interchangeably and on other occasions in a complementary fashion. For example lifesaving therapies such as insulin and penicillin were approved on the basis of observational research which

would not be acceptable if submitted for Marketing Authorisation today without data from an RCT (Feinstein and Horwitz, 1997). On the other hand, observational studies in the form of Post Marketing Surveillance are in many cases required by regulatory bodies to protect patients from the risk of adverse events which may not be detected by even the most rigorous of modern RCTs (Raj *et al.*, 2019).

These examples provide some confidence that the clinical research community may be amenable to new research methodologies which draw from both doctrines, rather than pursuing a binary approach where one path or the other must be chosen.

2.6 Clinical Research Examples

To help frame the research it is proposed to review the two examples introduced in Chapter 1: namely the Framingham Heart Study (FHS) and the Swank Study. Both of these studies set out to understand the factors contributing to the development of chronic diseases, but one yielded results which led to the creation of new therapeutic guidelines that have been adopted globally with huge success, whilst the other failed to deliver any conclusive evidence. The question we want to address is whether the research methodologies employed contributed to the difference in outcome, and if so, what lessons can be applied to future clinical research studies?

The FHS was established as a large scale study of a randomly selected population intended to observe the development of cardiovascular disease (CVD) over time, and once a sufficiently large number of cases of CVD had been identified to search for possible causative factors which led to its development in one group and not in the other (Dawber *et al.*, 1951). Therefore, the FHS was clearly an Observational Study, and can be described as a Cohort Study since the sample subjects were not selected for a common outcome but rather for exposure. It is worthwhile to note that there was no control group established at the outset as all participants were observed in the same environment; thus, the FHS effectively began as a Descriptive Study and evolved into an Analytical Study over time as the subjects which remained CVD free could be compared to those who developed disease symptoms.

The FHS was a very large-scale study, as over 5,000 residents of Framingham, Massachusetts were originally enrolled in 1948, and it is notable in its longevity as it is still running today with first- and second-generation cohorts added to the study population. Structurally the FHS can be criticised for its limited geographic reach – the entire study is based in the town of Framingham – and for its lack of ethnical diversity, both of which could limit the generalisability or external validity of results, however despite these limitations the FHS is recognised as a landmark study that informed research into CVD globally and set the standard for epidemiological research as we know it today.

By 1957 initial results were published identifying hypertension, hypercholesteremia and obesity as risk factors for Coronary Heart Disease, and in 1962 the lead investigator of the FHS stated “It is believed that the Framingham enquiry and other similar investigations have demonstrated beyond question that certain characteristics are associated with the development of coronary heart disease” (Dawber *et al.*, 1962). The author added that no evidence had been presented relating to the effect of modifying any of the factors identified, and that further research is needed. In an earlier paper Drawber had also highlighted that the limitations of the FHS in terms of generalisability (Dawber *et al.*, 1957).

In spite of these reservations Drawber was confident enough in the results of the FHS to assert the following *"Although evidence is still lacking that favourable change in these factors is necessarily beneficial, it is suggested that such an assumption is reasonable"* (Dawber *et al.*, 1962). In the modern era of Evidence Based Medicine the evidence suggested by the FHS would be ranked as Level 2 or Level 3 at best, and it is highly doubtful that clinical guidelines would be rewritten without the support of an RCT. With the benefit of hindsight we can see that taking steps to mitigate the risk factors identified was the correct course of action, however at the time the epidemiological researchers managing the FHS had not established causal links between the risk factors identified and the outcomes observed.

Nowadays it is a given that managing blood pressure, cholesterol levels and body weight are essential to ensure good cardiovascular health, however at the time of publishing the early findings from the FHS these were new and unproven ideas and it is important to question how measures to control the three risk factors hypothesised by the FHS researchers became established clinical practice.

It is interesting to note that at the same time as the early FHS results were being published the US Department of Health was engaged in a major study into the health impacts of smoking and a report issued by the Advisory Committee to the Surgeon General in 1964 included the following observation while discussing cigarette smoking, high blood pressure, high serum cholesterol, and excessive obesity: *"The causative role of these factors in coronary disease, though not proven, is suspected strongly enough to be a major reason for taking countermeasures against them"* (US Department of Health, Education, and Welfare, 1964).

It would appear that the political and medical establishment at the time lent weight to the enthusiasm shown by the FHS researchers to encourage action rather than waiting for conclusive evidence to be developed through more scientific, controlled trials (Oppenheimer, 2006). Further studies were undertaken to test the impact of managing the risk factors identified, and in 1977 the National Heart, Lung, and Blood Institute (NHLBI) initiated a series of hypertension guidelines (Moser and et al., 1977) which formalised recommendations on managing hypertension as a primary tool in the prevention of CVD.

The second example of research into the factors relevant to the development of chronic disease which this paper considers is the Swank Study into the impact of diet on Multiple Sclerosis (MS). The coincidence in timing is stark as Professor Swank began recruiting subjects for his study in 1948, the same year as the FHS was initiated. There are some significant differences in the methodology employed in the two studies, but also many commonalities beyond the timing.

The Swank Study was carried out to test the theory that the frequency of MS was related to a diet high in saturated fat, first observed by comparing the low incidence rates among coastal communities in Norway with

higher rates found in inland areas. The suggestion was that the coastal communities had a diet focussed on seafood, whilst farther from the coast diets relied more on dairy and meat and were therefore higher in saturated animal fats (Swank, 1953).

Swank recruited 144 research subjects, all diagnosed with MS, and put all on a low-fat diet. The subjects were followed for a total of 50 years, with results presented for "Good Dieters" (those who adhered to the recommended limit of no more than 20g of saturated fat per day) compared to "Poor Dieters" (those who did not adhere to the low saturated fat regime).

In 1953 Swank published the first results in which he stated:-

"This diet appears to lessen the severity of the disease by reducing the frequency and severity of the exacerbations. Its usefulness seems greatest early in the disease before significant disability and a steady progression of symptoms have developed. A final conclusion regarding the value of the low-fat diet will have to await a longer trial of this therapy than at present can be reported." (Swank, 1953)

The Swank Study compares poorly to the FHS in terms of size (144 subjects compared to 5,000+) however both have similarity in terms of the lack of a defined control group at the outset. The FHS identified the control group as those who did not develop CVD over the course of the study, so this group was constantly evolving over time. In the case of the Swank Study, it was designed as an interventional study, with modified diet as the intervention, and the control group was also an emergent group identified as those who did adhere strictly to the low-fat diet. However, the initial findings were similar in nature – the FHS observed that a higher proportion of the subjects who developed CVD had hypertension, and Swank observed lower rates of progression of MS in "Good Dieters".

The primary difference appears to have been in the reporting of the results from each study. Whilst the FHS attracted much attention from the outset, in part due to the fact that it was government backed study into CVD, which was by far the leading cause of death at the time (see Figure 7 above), Swank's study does not appear to have attracted mainstream recognition until the publication of an article in The Lancet in 1990 (Swank and Dugan, 1990). In this article, and in a further article published in 2003 (Swank and Goodwin, 2003), the authors presented results from 34 years of follow up with the original subjects which showed deaths from MS were more than 3 times lower (14 versus 45) for the so called "Good Dieters" (See Figure 8 below). In addition, the findings showed that 95% of MS patients who consumed less than 20g of saturated fat per day remained only mildly disabled over the period, whilst only 93% of the "Poor Dieters" became incapacitated.

SURVIVAL RATE OF PATIENTS AFTER 34 Y ON LOW-FAT DIET*		
	n (%)	Actual fat intake
Fat intake <20 g/d		
Good dieters	70 (100)	16 ± 2.8 g/d
All deaths	23 (33)	
Total MS deaths	14 (20)	
Survivors	47 (67)	
Fat intake >20 g/d		
Poor dieters	74 (100)	38 ± 18 g/d
All deaths	58 (80)	
MS deaths	45 (61)	
Survivors	16 (21)	

* Data from Swank.[2]
MS, multiple sclerosis

Figure 8 – Survival Rates of MS Patients after 34 years on a low-fat diet (Swank and Goodwin, 2003)

So why did research yielding such dramatic results not inspire further clinical trials to develop a level of evidence that was deemed sufficient to lead to the development of new clinical guidelines for the treatment and prevention of MS, as was the case with the early findings from the FHS? One criticism of the Swank Study is that it was unblinded, however this is usually unavoidable in studies involving lifestyle interventions as discussed previously. Another possibility is that the major report into Swank's Study (The Lancet, 1990) simply came too late – by extending the period of the study to an extraordinary 34 years the author unwittingly released results of a study whose roots lay in the first half of the twentieth century at a time when the doctrine of Evidence Based Medicine (EBM) had gained prominence in the field of clinical practice and Swank's methodology simply could not deliver the level of evidence expected.

It can be argued that the results from the FHS would not have reached this threshold either if they had been published in 1990; the difference being that the findings of FHS had already gained sufficient traction in the years before EBM became established as best practice, partly due to US governmental backing, to stimulate a multitude of follow on studies which supported the assumptions put forward by the FHS researchers back in 1962.

Subsequent studies into the role of saturated fats in MS have failed to produce consistent results (Zhang *et al.*, 2000), and a Cochrane Review (Parks *et al.*, 2020) of Controlled Clinical Trials into the effect of dietary intervention for people with MS concluded "*At present, there is insufficient high-certainty evidence as to whether dietary interventions change the course of MS.*" Parkes identified issues with the trials reviewed in

terms of design and implementation, specifically their small scale and short timeframes, which impaired the confidence level in their results.

2.8 Conclusion

Two conclusions arise from the literature review – firstly that there is almost overwhelming support for ranking RCTs above all other study methodologies in terms of level of evidence generated, with all other study types regarded as second grade research.

Secondly it is clear that the Swank Study and the FHS have had very different outcomes in terms of their impact on the course of clinical treatment of the respective disease areas, despite the significant similarities in both methodology and the initial findings presented by each research team.

Investigating this disparity forms the core of my research, aiming to discover whether a different methodology could have led to further research into the role of diet in MS and perhaps ultimately led to an understanding of the "risk factors" which should be managed to limit the incidence and progression of MS?

Or is it the case that there is simply insufficient evidence of any link between lifestyle and of MS, regardless of what research approach was taken?

3 Methodology and Research Design

3.1 Overview

My research is focused on understanding how research into the impact of lifestyle factors such as diet and exercise can generate data which is seen as valid in the current era of Evidence Based Medicine, dominated as it is by Randomised Controlled Trials (RCTs). As shown in the Literature Review there is a huge disparity in how the two trials discussed, namely the Swank Study and the Framingham Heart Study, have led to the adoption of new clinical standards of care and further research in their respective therapeutic areas. The primary research in this dissertation is intended to examine the reasons why certain clinical research methodologies are likely to result in the development of evidence seen as more meaningful than others, and to explore how future trials into lifestyle factors can be adapted to generate this level of evidence.

As discussed previously RCTs have become the acknowledged gold standard in clinical research and are seen as producing the highest quality of evidence by the medical profession as a whole. However, RCTs into lifestyle factors are inherently difficult to execute for a number of reasons and are more suited to a drug therapy versus placebo trial, which suggests that there is potentially a systemic bias against the generation of data supporting non-drug therapies and prophylactic agents. This paper will investigate said potential bias and seek to uncover insights into how it can be addressed.

3.2 Research Philosophy and Approach

A framework to assist in the design of research is provided by the "Research Onion" concept (Saunders *et al.*, 2019), which advocates that study design is considered layer by layer, as one would peel an onion. Figure 8 below is based on the Saunders Research Onion diagram, adapted for this research project.

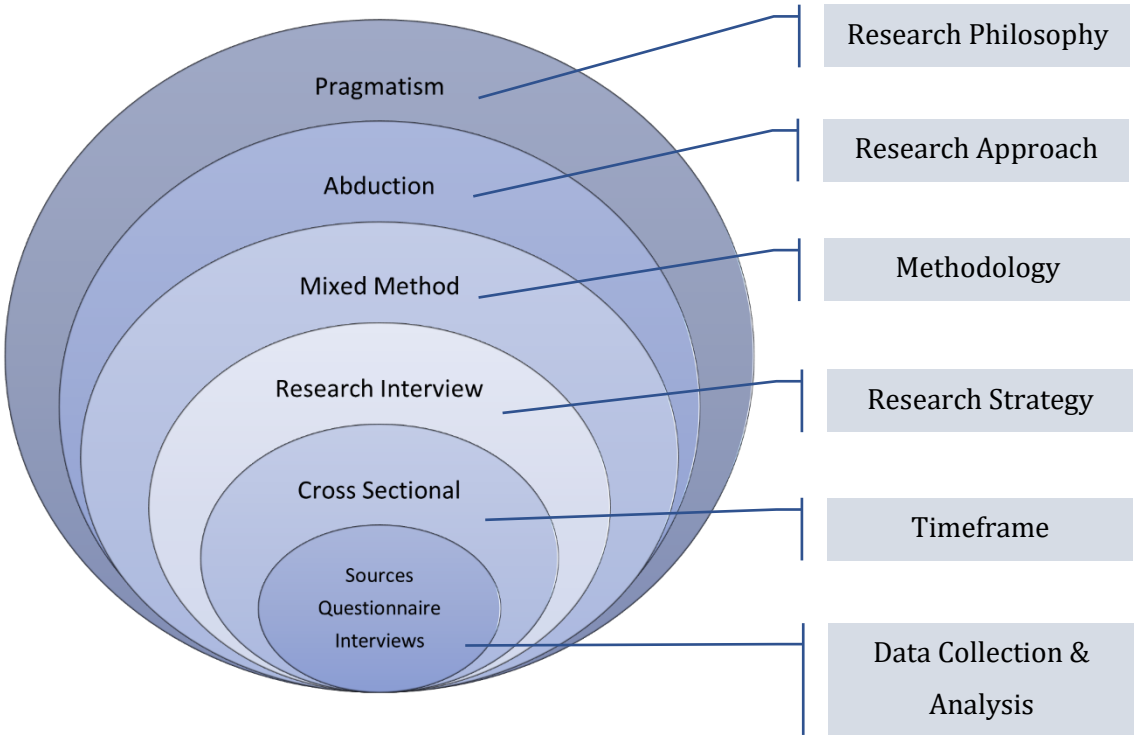

Figure 8 – Adapted from Saunders Research Onion (Saunders et al., 2019)

The first question to be addressed is the philosophical approach to be taken to a particular research project. Saunders describes the five primary research philosophies as follows –

- Positivism
- Critical Realism
- Interpretivism
- Postmodernism
- Pragmatism

The research philosophy guiding this work will be Pragmatism, as the underlying aim is to arrive at practical solutions to inform future practice. The research conducted will start with the problem "How can meaningful

evidence be generated to evaluate the impact of lifestyle changes on health outcomes?" and will seek to uncover workable answers which can be applied in the real world.

Alternative philosophies have been considered and rejected as they are not as well suited to this pursuit of practical and readily applicable solutions. Positivism suggests the search for unambiguous, empirical knowledge which may be overly simplistic for a study of how clinical research data is interpreted. This interpretation is a key part of the problem being researched in this dissertation, seeking to understand the often-complex route from clinical research to acceptance of meaningful evidence. Empirical research would be likely to support the consensus that RCTs do indeed provide the highest level of evidence in clinical research and may preclude consideration of "next best" evidence generated using alternative approaches when RCTs prove impractical.

On the other hand, Critical Realism, Interpretivism and Postmodernism all seek to interpret reality through the lens of historical and socio-cultural factors and are deemed overly subjective for the topic of this research.

3.3 Approach to Theory Development

The second layer of the Research Onion describes the approach taken to theory development, which can be characterised by two opposing approaches. The first is Deductive Reasoning which can be described as moving from theory to data (Saunders *et al.*, 2019). The Deductive Approach starts with the formation of a hypothesis or tentative theory to explain the issue being researched and then collecting data to test this premise. For Deduction to be effective the variables thought to affect the outcome must be measurable, and typically quantifiable; therefore Deduction will often work best within a Positivist philosophy where such an approach is used to prove or disprove a theory.

Inductive Reasoning can be characterised as moving from data to theory – an Inductive Process will begin with gathering data and then formulate a theory through analysis of the results. The Inductive Approach differs from the Deductive option in that Induction is used to develop a theory to explain an observed phenomenon whereas Deduction is best applied to test a theory or hypothesis.

A third approach to Theory Development is also described, namely Abduction. Abductive reasoning can be utilised to identify themes and patterns from observations and generate new theories which can subsequently be tested. Abduction can also be applied to propose and test modifications to existing theories. In this way Abduction can be seen as combining both Deduction and Induction and in fact moves continuously between the two. In his article "What Grounded Theory Is Not" Suddaby describes Abduction as " "analytical induction", the process by which a researcher moves between induction and deduction while practicing the constant comparative method." (Suddaby, 2006).

For this dissertation Abductive Reasoning will be employed as it allows the flexibility to combine quantitative research methodology in the first instance to test the hypothesis gained from the literature review which suggests that RCTs have become established as the dominant clinical trial format, and then uncover the underlying themes and patterns which contribute to this using qualitative research. A granular understanding of these themes will enable a new approach to clinical research to be proposed, combining the primary benefits of RCTs with the pragmatic reality of investigating the impact of broad lifestyle factors.

3.4 Research Methodology

Having selected the philosophical and reasoning approaches underpinning the study we can now consider the most appropriate methodology to employ. The objective of my research is to understand the limitations of current clinical research methodologies when applied to investigating the relationship between lifestyle and chronic disease, and to seek improvements which will deliver more meaningful results.

To achieve this objective a mixed method research design will be used, employing a quantitative element to test the conclusions drawn from the published literature (that RCTs have become the dominant clinical research methodology to the detriment of methodologies which may be better suited to investigating lifestyle factors). The quantitative element will be extended to seek greater insight in what specific attributes of various clinical research methodologies are considered important to generate high level evidence of clinical relevance, and to explore areas in which clinical research has succeeded in delivering meaningful evidence of the impact of lifestyle factors.

This quantitative portion will lead naturally to the qualitative section which seeks to ascertain why clinical research into lifestyle factors has been effective in some therapeutic areas but not others. Further qualitative questioning will explore the impediments to lifestyle research and suggested enhancements to future clinical research to address these obstacles. The final section will enquire into high level, structural aspects of how clinical research is currently funded, regulated and managed to explore possible new approaches to mitigate systematic biases.

3.5 Research Strategy and Timeframe

The research strategy selected is to conduct one to one Research Interviews with a small sample of respondents (approximately 10) drawn from the fields of clinical practice and clinical research. A Research Interview is defined as *"a purposeful conversation between two or more people, during which the interviewer asks concise and unambiguous questions and listens attentively to the interviewee talking"* (Saunders *et al.*, 2019).

To ensure that the interviews are standardised, and that each interviewee is asked the same questions in the same order a Structured Approach will be taken whereby a standard questionnaire will be used and responses completed by the researcher during the interview. The questionnaire will be shared with the interviewee in advance of the interview along with a brief introduction to the research and its purpose to allow the interviewee some time to prepare and contextualise the interview.

As the selected respondents are located in different countries it will not be possible to conduct these interviews in person in all cases, so for consistency they will all be conducted using an internet based web conferencing platform such as Zoom or Teams. This interview mode will enable greater interaction between the interviewer and interviewee than a telephone interview, and allow the questionnaire document to be shared so that it can be completed by the researcher while giving the respondent the opportunity to review the answers as they are being recorded.

As described in the preceding section part of the interview will be quantitative in nature, with respondents asked to rate different clinical research methodologies and attributes on a scale of importance / relevance. This will serve the dual function of gathering data to validate or invalidate the conclusions drawn from the earlier literature review, and also to allow both the researcher and the respondent to ease into the interview and build rapport.

Following the quantitative section there will be a number of qualitative questions, with provision for any length of answer. This section will be more challenging in terms of time available, and time needed to enter the answers and capture the respondents' thoughts and comments. As the researcher will not have an assistant to take notes it will be critical that the essence is captured by typing but with the respondents' permission the session can also be recorded, and the full answers transcribed at a later date.

As the timeframe for this dissertation is limited to six months approximately the research will be cross sectional, essentially recording what is true at the time of the interview.

3.6 Collection of Primary Data

3.6.1 *Sources*

The selection of population sample to survey is a crucial part of the study design and must be done with careful consideration of the aim and objectives of the research. The research intent will inform the types of questions to be asked, and therefore the selection of an appropriate research sample.

For this dissertation the topic of interest is the generation of clinically relevant data from research into the impact of lifestyle factors on chronic disease outcomes. Therefore, the sample population has been chosen to represent a cross section of experts who either conduct clinical research or rely on the outcomes of clinical research to inform their selection of patient care protocols. Care has been taken to include participants from both academia and industry to ensure that a balanced view is obtained taking into account both theoretical and real world experiences.

The interview panel is comprised of the following –

- General Medical Practitioners
- Medical Consultant Doctors across a number of specialities
- Academic Researchers in Epidemiology and Population Health
- Subject Matter Experts from Clinical Research Organisations and the Pharmaceutical Industry

A profile of the participants in included in Section 4.2.1 below.

3.6.2 *Questionnaire Design*

The questionnaire is designed as a template to guide the interview and will be used to ensure consistency in the interview structure and the questions asked. It has been designed to gather a mixture of quantitative and qualitative data, and therefore contains some forced-choice questions where the respondent is provided with a list of answers from which one is selected, and some open questions where the respondent is free to answer as they wish.

The questionnaire design is such that two questions (20% of the total) are positioning questions, two (20%)are closed questions requiring the respondent to provide a rating for a given selection and the remaining six questions (60% of the total) are open ended.

The table below lists each of the questions along with the rationale for each, and the full questionnaire can be found in Appendix A.

<table>
<tr><th></th><th>Question</th><th>Rationale</th></tr>
<tr><td>1.</td><td>What is your position, and how many years of experience do you have in this field?</td><td>Question 1 is intended to categorise the respondents according to their professional role and level of experience. This can be used to assist in analysis of the data collected.</td></tr>
<tr><td>2.</td><td>Which of the options below best describes your typical engagement with medical research?

<table>
<tr><td>☐</td><td>Regularly study research papers to inform decisions regarding patient care.</td></tr>
<tr><td>☐</td><td>Occasionally read research to keep abreast of current developments.</td></tr>
<tr><td>☐</td><td>Rarely consider research publications.</td></tr>
<tr><td>☐</td><td>Involved in some research activity.</td></tr>
<tr><td>☐</td><td>Lead large research teams</td></tr>
</table>
</td><td>A closed, forced choice question intended to categorise the sample population to enable analysis of the results broken out on the basis of the respondent’s engagement with Clinical Trials (see section 3.6.1 Sources above).</td></tr>
</table>

<table>
<tr>
<td></td>
<td>
<table>
<tr><td>☐</td><td>Other (please specify)</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>How do you perceive the level of evidence from different types of clinical study?
Please rate on scale of 1 to 5 where 1 is the lowest level and 5 the highest.
<table>
<tr><th rowspan="2">Study Type</th><th colspan="5">Level of Evidence</th></tr>
<tr><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th></tr>
<tr><td>Randomised Controlled Trial</td><td>☐</td><td>☐</td><td>☐</td><td>☐</td><td>☐</td></tr>
<tr><td>Case Control Study</td><td>☐</td><td>☐</td><td>☐</td><td>☐</td><td>☐</td></tr>
<tr><td>Cohort Study</td><td>☐</td><td>☐</td><td>☐</td><td>☐</td><td>☐</td></tr>
<tr><td>Population Study</td><td>☐</td><td>☐</td><td>☐</td><td>☐</td><td>☐</td></tr>
<tr><td>Observational Study</td><td>☐</td><td>☐</td><td>☐</td><td>☐</td><td>☐</td></tr>
<tr><td>Other -</td><td>☐</td><td>☐</td><td>☐</td><td>☐</td><td>☐</td></tr>
</table>
</td>
<td>A closed, quantitative question designed to measure the degree of alignment of the study population’s perception with the consensus opinion presented in the literature that RCTs provide the highest level of evidence in clinical research (Burns et al., 2011) (CEBM, 2023) (FDA, 2019) (Feinstein, 1984) (Feinstein and Horwitz, 1997) (Jones and Podolsky, 2015) (Sackett, 1997).</td>
</tr>
<tr>
<td>4.</td>
<td>What are the most important attributes of a clinical study in terms of evidence validity?
Please rate on scale of 1 to 5 where 1 is the lowest level and 5 the highest.
<table>
<tr><th rowspan="2">Study Attributes</th><th colspan="5">Perceived Level of Evidence</th></tr>
<tr><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th></tr>
<tr><td>Blinding</td><td>☐</td><td>☐</td><td>☐</td><td>☐</td><td>☐</td></tr>
</table>
</td>
<td>Quantitative question seeking to gain further insight into what specific attributes of different clinical research methodologies are perceived as having the greatest impact on quality of evidence produced (Grimes and Schulz, 2002) (Chidambaram and Josephson, 2019).</td>
</tr>
</table>

	Randomisation	☐	☐	☐	☐	☐	
	Study Size	☐	☐	☐	☐	☐	
	Study Length	☐	☐	☐	☐	☐	
	Control Group	☐	☐	☐	☐	☐	
	Other -	☐	☐	☐	☐	☐	
5.	In what therapeutic areas have the most effective research into lifestyle factors such as diet, exercise and stress have been carried out, in your opinion? a. b. c. d.						An open ended, probing question designed to explore other areas where the sample believes that valuable research into lifestyle factors has been performed, for example vascular disease (Boeing *et al.*, 2012).
6.	What factors do you believe contributed to making the research listed in Q5 above particularly valuable in terms of evidence generated?						A follow up to Question 4 intended to gain deeper insight into the specific attributes of clinical research methodology which are perceived to bestow greater levels of validity to the evidence generated. An example from the literature is timeframe of the study (Temple, 2016), and answers to this question will help to inform possible recommendation for future research methodologies.
7.	What do you perceive as the key difficulties in performing scientific research into the impact of lifestyle factors on health outcomes?						This question is designed to validate the conclusions reached from a review of the literature on the subject, such as recruitment (Jelinek *et al.*, 2012), randomisation and blinding (Bajwa *et al.*, 2021), external validity (Black, 1996), sample selection, endpoint

		identification and placebo availability (Laville *et al.*, 2017) and cost (Lauer *et al.*, 2017) (Arora *et al.*, 2021).
8.	How would you suggest that future research into the impact of lifestyle factors could be enhanced in terms of methodology employed to produce higher level evidence relevant to clinical practice?	An open ended question intended to unearth some suggestions on future research, which may suggest moving away from over reliance on RCTs. (Bajwa *et al.*, 2021) (Favaloro, 1998)
9.	Are there any changes to the established practices of data analysis, peer review and publishing which you would like to see implemented to ensure that the risk of bias in research is minimised?	An open ended question to explore possible improvements to the research process post data collection – data analysis, review and publication. (Hartung *et al.*, 2014)
10.	Can you suggest high level structural changes to how clinical research into chronic disease is conducted and regulated to ensure that the broadest possible spectrum of factors are considered?	A further open ended question probing structural considerations (rather than methodological) which may impact the conclusions drawn, such as sources of funding and oversight (Als-Nielsen *et al.*, 2003) (Lexchin, 2003).

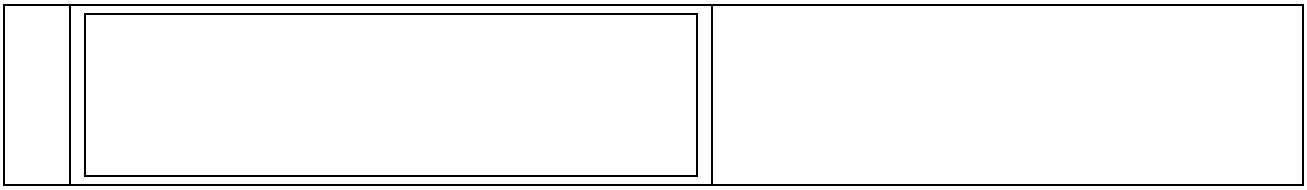

Figure 9 – Table of Research Questions

3.6.3 *Access and Ethical Issues*

Access to the research subjects has been arranged through personal and professional contacts, and by contacting some published researchers in this subject area.

Full consideration of ethical issues has been given, and compliance with Griffith College guidelines on the matter ensured. As the primary research does not concern medical information, or the collection of data which could be used to identify individuals, no major concerns have been identified. Each participant will be provided with Participant Information material and an Informed Consent Form to complete in advance of the research interview and specific consideration will be given to obtaining permission to record the interview.

All research material and results will be treated as confidential, and data will be managed in accordance with Good Data Management Practises and relevant legislation, including GDPR.

3.7 Approach to Data Analysis

The approach used to analyse the data varies as some of the questions are quantitative in nature and others are purely qualitative. A detailed description of the data analysis techniques employed is provided on a question-by-question basis in the Presentation of Findings, Section 4 below.

3.8 Conclusion

The primary research is designed as a structured interview with a select panel, carefully chosen to represent a broad range of points of view including researchers, industry experts and medical practitioners. The research questionnaire has been designed to draw opinions on all aspects of the topic, with generous opportunities to expand responses as the interview progresses. Some rating questions in the first part of the questionnaire are designed to compare the panel's view on current research with the findings of the literature review, whilst the second part of the questionnaire focuses on exploratory questions regarding potential difficulties in performing and interpreting research and suggestions to improve the process with particular emphasis on research into lifestyle factors.

4 Presentation and Discussion of the Findings

4.1 Overview

Although this research project was small in terms of sample size it unearthed some very meaningful insights into how clinical research is conducted and evaluated, leading to a number of conclusions and recommendations which can help address the core topic of this paper – how clinical studies could be modified to incorporate lifestyle factors while still producing results which can be considered equivalent to that produced by today's "gold standard" trials?

The strength of the research is derived from the calibre of respondents involved, and the broad range of backgrounds representing the research community from both academic and pharmaceutical industry backgrounds, as well as medical practitioners from several different specialities who rely on published research to guide their clinical practices.

Findings from the primary research are divided into two strands; the first portion seeks to compare respondent's views to the conclusions drawn from the literature review and later questions explore possible improvements or refinements to the entire research spectrum form study design and methodology to data analysis and review.

Of particular note is the fact that Randomised Controlled Trials (RCTs) received the highest rating in the primary research in terms of evidence validity with 100% of respondents judging the level of evidence derived from RCTs to be in the "High" or "Highest" category, a very strong consensus which aligns with that of the published literature. In contrast Descriptive Studies were judged to be of lowest values in terms of level of evidence, with 78% of respondents placing these in either the "Low" or "Lowest" categories.

The other study methodologies (Cases Control, Non Randomised, Cohort and Cross Sectional) received more dispersed ratings in the primary research, but on average the level of evidence generated from these four study types was rated as lying somewhere between RCTs and Descriptive Studies.

The later portion of the primary research probed potential areas for improvement in current research practice to better incorporate impacts of lifestyle interventions such as diet and exercise. This produced a number of very interesting suggestions particularly in the areas of data analysis and review. These suggestions will be further synthesised in this paper to develop recommendations which can be applied or form the basis of future research.

4.2 Primary Research Findings

4.2.1 Sample Group

The primary research was conducted in the form of structured interviews using the template presented Appendix A. The interviews were carried out on a one-to-one basis, in an online format using web based video conferencing platforms. Responses were collected during the interview in so far as possible and in addition each interview was recorded, and the complete responses transcribed later.

The panel of participants was drawn from a range of backgrounds in order to gather data from different perspectives, with an emphasis on selecting participants directly involved in research activity (producers of research) and also from medical practice who rely on research findings to inform their clinical decisions (consumers of research).

Figure 10 below provides an overview of the research sample group, showing the job title and area of work for each. This is based on responses to Question 1 of the Research Questionnaire.

Participant No.	**Professional Role**	**Experience (Years)**
1	Medical Consultant – Critical Care, major Dublin Hospital	20
2	5th yr. Medical Student, UK	n/a
3	Associate Prof, Head of Neuroepidemiology Unit, Melbourne University	10
4	Chief Medical Officer & Head of Applied Research, Pharmaceutical Services Industry	2 (current role)
5	Honorary Prof., Neuroepidemiology Unit, Melbourne University. (Formerly Head of Department) Editor of major medical journals	25+
6	Consultant Child & Adolescent Psychiatrist, Dublin	19
7	Medical Doctor, General Practice, Canada.	37
8	Head of Drug Development Consulting, Clinical & Scientific Strategy Lead. Global Contract Research Organisation	9
9	Advocacy & Research Officer, Multiple Sclerosis Ireland	7

Figure 10 - Overview of the Primary Research sample group

The sample group breaks down as follows from the perspective of their professional roles -

Background	No.	%
Medical Practice	4	44%
Academia	2	22%
Pharmaceutical Industry	2	22%
Patient Advocacy	1	11%

Question 2 investigated each participants typical engagement with medical research and the responses are shown in Figure 11 below. The responses have been grouped into "Research Consumers" and "Research Producers" based on the responses. Note that some participants fall into both categories as they engage in research activity directly and also use published research to inform their work, so the totals do not match those in Figure 10.

Typical engagement with Medical Research	**Response**	**Totals**	**Code**
Regularly study research papers to inform decisions regarding patient care.	5	8	Research Consumers
Occasionally read research to keep abreast of current developments.	3		
Rarely consider research publications.	0	0	
Involved in some research activity.	2	6	Research Producers
Lead research teams	4		

Figure 11 – Sample group's engagement with medical research

In this analysis of the sample group we can see that 57% of respondents classify themselves as consumers of research, and 43% as research producers. This establishes that the sample chosen can provide a balance of opinions from both points of view and provides confidence that we have captured the perspective of each. Consumers of research can provide data for this paper based on their experience of reading and interpreting published research with a view to unearthing reliable insights which they can apply with confidence in their professional practice, whereas producers of research can shine a light on some of the difficulties encountered in designing studies and analysing the data produced.

4.2.2 *Research Findings*

4.2.2.1 Interview Questions Part One

Questions 3 to 5 of the Research Questionnaire set out to establish the views of the sample group on current approaches to medical research, and the perceived robustness of the evidence generated. The objective of these questions is to provide data to compare and contrast the primary research findings with those from the secondary research as described in the literature review in Section 2 of this paper. The literature review was conclusive in reporting that RCTs are considered the gold standard in clinical research methodologies (Sackett *et al.*, 1996) (CEBM, 2023) (Jones and Podolsky, 2015), whereas observational or descriptive studies are considered suspect in terms of level of evidence produced (CEBM, 2023), in particular due to low levels of internal validity (Carlson and Morrison, 2009).

Question 3

The primary research described here produced results with a very high level of alignment with these findings. Question 3 asked the following – "How do you perceive the level of evidence from different types of study? (Please rate on scale of 1 to 5 where 1 is the lowest level and 5 the highest.)" The combined results are illustrated below in Figure 12, which shows the total number of respondents who selected each perceived level of evidence for the study types listed. Thus it can be seen that 3 of the sample group indicated that a Descriptive Study provided the lowest level of evidence, 4 selected low, 2 selected medium and so on.

Study Type	**Perceived Level of Evidence**				
	Lowest	**Low**	**Med**	**High**	**Highest**
	1	**2**	**3**	**4**	**5**
Descriptive Study	3	4	2	0	0
Case Control Study	0	5	4	0	0
Randomised Controlled Trial	0	0	0	4	5
Non-Randomised Controlled Trial	0	0	6	3	0
Cohort Study	0	1	4	4	0
Cross Sectional Study	0	2	4	3	0

Figure 12 – Research results for Question 3 "How do you perceive the level of evidence from different types of study?"

From Figure 12 it can be seen that more respondents perceived that RCTs produced the highest level of evidence than the other study types, in fact there was complete consensus amongst the sample group that the level of evidence generated from an RCT is rated in either the High or Highest category, providing clear co-relation with the findings of the secondary research completed previously.

To analyse these results thoroughly a weighted score was calculated by multiplying the number of respondents who selected each level of evidence by the score allocated for that level and totalling the result for each study type. The Weighted Score for perceived level of evidence by study type is shown in Figure 13 below, which provides a ranking of study type by perceived level of evidence.

Study Type	Perceived Level of Evidence					Weighted Scoring
	Lowest	Low	Med	High	Highest	
	1	2	3	4	5	
Descriptive Study	3	8	6	0	0	**17**
Case Control Study	0	10	12	0	0	**22**
Randomised Controlled Trial	0	0	0	16	25	**41**
Non-Randomised Controlled Trial	0	0	18	12	0	**30**
Cohort Study	0	2	12	16	0	**30**
Cross Sectional Study	0	4	12	12	0	**28**

Figure 13 – Weighted score for Perceived Level of Evidence by Study Type

Reviewing Figure 13 it can be seen that RCTs do in fact achieve the highest weighted score for perceived level of evidence generated, with non-randomised trials and cohort studies jointly rated in second place, and cross sectional studies following closely in third place. Case control studies are rated lower with descriptive studies achieving the lowest rating. In Figure 14 below the perceived level of evidence for each study type is presented visually with the study types ranked from highest perceived level of evidence (RCTs) on the left to lowest perceived level of evidence (Descriptive Studies) on the right.

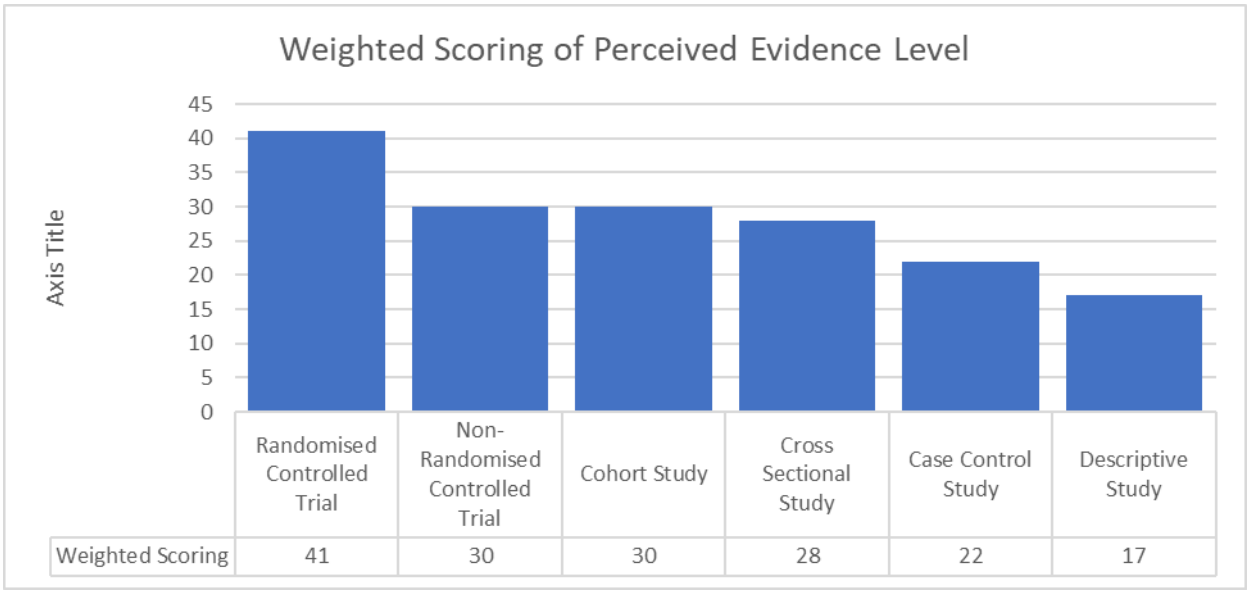

Figure 14 – Ranked chart of perceived Level of Evidence from each Study Type

Question 3 also included the option for respondents to add extra study types in a category titled "Other". Three respondents inserted individual ratings for different study types, namely Long Term Prospective Observational Studies, Implementation Research and Frequentist Statistical Analysis. These have been omitted from the data analysis as they were judged to be non-significant to the intent of the question, however a total of 6 respondents, or two thirds of the sample group, indicated their perception that Systematic Reviews or Meta Analyses of a number of RCTs produced evidence levels judged to be High (1 respondent) or Very High (5 respondents) so this result is considered to be of relevance. In fact this result could be extrapolated to show that if Systematic Reviews / Meta Analyses had been included in the list of study types and the full sample group had rated them this category would have scored highest in terms of perceived level of evidence. Again this co-relates with the published literature (Cochrane Library, 2023) (CEBM, 2023) and is an important finding in this paper.

Question4

Question 4 sought to investigate the reasons behind the answers provided in Question 3 – to establish why some study types are perceived to produce higher levels of evidence trustworthiness than others. This question asked the following – "What are the most important attributes of a study in terms of evidence validity?", and the results gathered are listed below in Figure 15 which shows the number of respondents who selected each level of importance for the given study attribute.

	Most Important Study Attributes				
	Lowest	**Low**	**Med**	**High**	**Highest**
Blinding	0	1	1	4	3
Randomisation	0	0	1	2	6
Study Size	0	0	0	2	7
Study Length	0	1	0	2	6
Control Group	0	0	0	4	5

Figure 15 - Research results for Question 4 "What are the most important attributes of a study in terms of evidence validity?"

Applying the same weighting methodology as utilised for Question 3 produces the following results (see Figure 16 below)

	Perceived Importance					Weighted Scoring
	Lowest	**Low**	**Med**	**High**	**Highest**	
Study Attributes	**1**	**2**	**3**	**4**	**5**	
Blinding	0	2	3	16	15	36
Randomisation	0	0	3	8	30	41
Study Size	0	0	0	8	35	43
Study Length	0	2	0	8	30	40
Control Group	0	0	0	16	25	41

Figure 16 – Weighted score for Perceived Importance of Study Attributes

This result demonstrates a far less conclusive outcome, with each of the study attributes achieving very similar weighted scores. Deeper analysis reveals that over 80% of respondents selected either "High Importance" or "Very High Importance" for each of the five study attributes listed. One respondent made the following remark which would seem to sum up the sentiments of the entire sample group – "All (of the listed attributes) are important dependant on the therapeutic area under investigation". This comment also underlines how difficult it is to make definitive claims in the area of medical research as the appropriateness of a study design is determined on a case by case basis, and is influenced by a myriad of factors. One experienced researcher added "Study length & size must be proportional to the expected effect being measured to avoid under or over powering the study".

Question 5

Question 5 sought to establish in which therapeutic areas the most effective research has been performed into the impact of lifestyle factors. This question was open ended, in that no suggested answers were provided, and a series of text boxes provided to insert the chosen diseases areas. The intention of Question 5 was to switch the focus from Medical Research in general to research into lifestyle factors such as diet and exercise specifically, and to encourage the sample group to consider examples of such research which they judged to be meaningful.

Space was provided for up to four answers, and six of the nine respondents suggested four disease areas in which effective research into lifestyle factors had indeed been completed. Of the remaining three respondents two provided two answers and one provided just a single disease area. Figure 17 below shows the suggested disease areas ranked by the number of times each was chosen in response to Question 5.

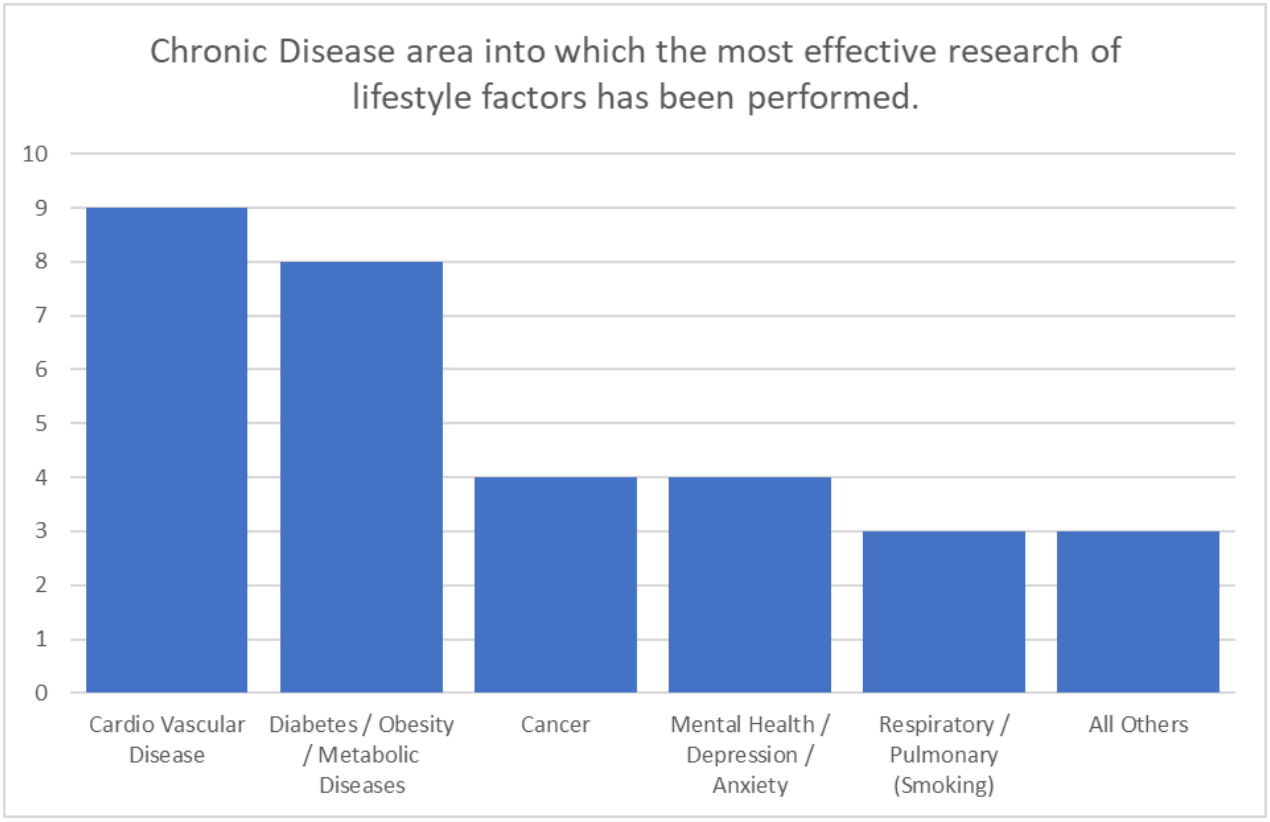

Figure 17 – Results from Question 5 "In what chronic diseases has the most effective research into lifestyle factors such as diet and exercise been carried out?

The most frequently selected disease area was Cardio Vascular Disease (CVD) with multiple repondents commenting that factors such as diet and exercise have become mainstream, first line care in this therapeutic area, and that modern cardiology units usually operate multi disciplinary teams to provide a

holistic approach to patient care including drug therapy, surgerical intervention, weight management, diet & nutrition advice and exercise support.

This clearly supports the hypothesis contained in the aim and objectives of this research (Section 1.4 above) – that research into CVD in particular has supported to adoption of lifestyle interventions as mainstream therapy, whereas the comparator disease area (Multiple Scelerosis) was not mentioned once in response to Question 5, despite the fact that the sample group included a number of specialists working in this field. Therefore the sample group has confirmed that research into CVD and MS has delivered very different outcomes into the impact of lifestyle factors

The conclusions drawn from Part 1 of the Research Questionnaire are threefold. Firstly, that RCTs are indeed perceived to deliver the highest level of evidence (with the proviso that systematic reviews of multiple RCTs are potentially the source of even higher perceived levels of evidence validity) which aligns with the findings of the secondary research. Secondly that it is not a simple matter to deconstruct the study types to assess which particular attributes bestow the ability to produce results which are considered valid and credible. And finally that research into CVD in particular has resulted in the widespread adoption of lifestyle modification as frontline therapy, whereas research into MS has not. The outstanding issues are why this may be so, and whether any recommendations can be made to make research into lifestyle factors more effective.

4.2.2.2 Research Questions Part Two

Having established the sample group's background and perceptions of current Medical Research practice in the first part of the interview, questions six to ten of the Research Questionnaire seek to explore possible improvements or refinements which could make future research more amenable to incorporating impacts from lifestyle factors. In order to invite greater discussion and comment these latter questions are all open ended, with unlimited free text capability to capture the answers. Therefore, the data collected is all qualitative, which presents a challenge in the data analysis phase to ensure that all answers are fully reflected.

The research switches in this this section to an inductive approach, as the research purpose becomes exploratory. (Saunders *et al.*, 2019) Whereas the first part of the research interview was intended to compare the sample group's responses to the findings in the literature review and the hypothesis that research into CVD had produced more meaningful evidence for the impact of lifestyle factors than had been achieved in research into MS; the second part is exploratory. In the second part the objective is to gain a better understanding of the difficulties which may hamper research into lifestyle factors and seek some practical recommendations to mitigate these issues and better equip future medical researchers to produce robust data into both lifestyle and medical interventions.

To aid in performing rigorous data analysis the responses were transcribed fully after each interview using the interview recording, to ensure that the entire discussion was represented faithfully. To help sort the responses into meaningful data which can be used to derive conclusions the answers were categorised by identifying key words and phrases to aid in data reduction.

The responses were categorised as follows: firstly all the answers were copied into a single document and then scanned manually to identify recurring phrases or themes. These themes were then colour coded to aid classification, and an iterative process used to group adjacent themes into broad categories. Appendix B contains the raw data, colour coded and then grouped by category.

This process is referred to as Data Reduction in the textbooks, and in some cases the actual category names emerged during the iterative process of identifying and grouping the common themes. During this data analysis some responses were identified as important but perhaps better fitted to inclusion in other sections of the paper; these were captured as self-memos to ensure that they were not overlooked.

Appendix B presents the aggregated responses and illustrate how the process of categorising and reducing the data was conducted.

Question 6

Question 6 asks the following - “What factors do you believe contributed to making the research listed in Q5 above particularly valuable in terms of evidence generated?” As Question 5 is concerned with successful research into the impact of lifestyle factors, it is clear that Question 6 is seeking to establish the perception of the Sample Group of what are the key factors that contribute to meaningful research in this area.

By following the process outlined above for Data Analysis and Reduction the category themes evolved and led to the creation of four dimensions to the responses received – Scientific, Social, Longitudinal and Latitudinal.

The table below (Figure 18) summarises the responses to Question 6, grouped into the four Dimensions.

Categories (Dimensions)	Scientific Dimension	Social Dimension	Longitudinal Dimension	Latitudinal Dimension
Sample Responses	Scientific rigour	Prevalence of disease	Duration	Large cohort size
	Well run trials which minimise bias	Profile of disease	Timeframe	Broad study populations
	Methodologically strong	Social interest, publicity, celebrity patients		Size of study
	RCTs remove co-morbidities	Advocacy – patient groups		
	(RCTs produce) results accepted as fact and influence clinical practice (negligent not to)			
	Clear evidence which generates clear guidelines	Socialisation of results / evidence		
		Real world evidence of impact		
		Government advocacy		

Figure 18 – Dimensioned responses to Question 6.

The Scientific Dimension refers to responses which cited methodological factors which were perceived to make the research in question valuable and captures a number of responses which credit scientific rigour and strong methodology with being important factors in producing meaningful results. This is in line with the findings with the earlier questions (and the literature review) as is the fact that RCTs were specifically identified by three respondents.

What was more surprising was the volume of responses in the Social Dimension. This reflects strongly held views that the impact of medical research is directly related to the level of social interest in particular diseases and therapies and was an unexpected finding in this research. The primary theme reflected here is that the scale and quality of research carried out into particular diseases are proportional not only to the prevalence and medical need, but also to the level of social awareness around the disease. The sample group identified a number of factors which contribute to social awareness including patient and government advocacy, and the emergence of so called "celebrity" patients which results in high levels of media interest. One researcher stated that "some diseases are more glamorous" and used the Olivia Newton John Cancer Centre in Australia as an example of how raised social awareness of a disease can contribute to greater investments and commitment to both research and patient care.

The remaining two dimensions identified are Longitudinal and Latitudinal. These refer to the duration of the research studies in question, and the size and diversity of study cohorts. These factors were considered important in terms of the external validity of the evidence gathered, and how the learnings can be generalised for a real-world population. The dimensions of Longitude and Latitude could justifiably be included in the Scientific domain as they refer to elements of study design, however they have been treated separately here as these themes have specific relevance to this research topic, as will be seen in the following question.

Several references were made in the responses to Question 6 to funding of research – these were saved as memo for inclusion in later discussions as the topic of funding arises in responses to every question from Q6 to Q10.

Question 7

In Question 7 the research interview took a deeper dive into research specifically addressing the impact of lifestyle factors, asking the sample group to outline the key difficulties in performing scientific research into the influence of such factors on health outcomes. This is a very broad, exploratory question, which produced wide ranging responses.

The same process was applied to analyse the data and reduce it to meaningful themes, the results of which are shown in Figure 19 below.

Categories	Study Duration	Adherence / Compliance	Recording / Reporting	Study Design / Controls
Sample Responses	Timeframe potentially massive– biggest issue	Ability of participants to maintain adherence	Variability of data capture (self-reporting)	Metrics /starting & end points hard to define
	Long timeframe required to give meaningful causation	Adherence over long timeframe	Self-reporting (leads to risk of) recall bias	Recruitment, randomising, blinding, contamination, attrition
	Length of studies req'd.	Adherence to diet (intervention)	How to measure and implement changes for the long term	Blinding difficult for researchers also
	Study length	Randomised groups not so likely to adhere	How data is gathered / presented	Difficult to prove causation due to confounding factors
		Compliance over time very questionable	Data always dirty	Almost impossible to blind people
			Difficulties in measuring (outcomes)	Randomisation to a group involving difficult changes
		Attrition rates very high	Availability of tech to provide measurements (BP, HR etc.)	

Figure 19 – Categorised responses to Question 7.

These responses demonstrate a wide variety of perceived difficulties in performing robust research into the impact of lifestyle factors on health outcomes. The issues identified span the entire research lifecycle from study design to data reporting and most factors are interlinked. As we can see from the first category (Study Duration) lifestyle research requires extended length of studies. Whereas the impact of a drug intervention

may be recorded in studies of 24 months or less, the impact of lifestyle modifications can take many years to record accurately. The long-term nature of these studies then has a negative impact on recruitment as subjects may be unwilling to commit to participating in a trial of such long duration. The duration is also associated with many of the issues highlighted within the "Compliance / Adherence" category, as it is very difficult to maintain strict compliance across a large study group over a long timeframe.

When difficulties in recording data are added to the mix, along with challenges to many of the control measures such as blinding and randomisation which have become the norm in RCTs, it becomes clear that there are multiple difficulties in attempting to apply so called "gold standard" medical research practices to lifestyle studies.

Sources of funding was also mentioned in the responses to Question7 – this was noted for later discussion.

Question 8

Question 8 asked the research sample to suggest improvements which could be made to future research into lifestyle factors from the methodological point of view. Again the responses were analysed and grouped as per Questions 6 and 7 above, and the resulting data table is shown in Figure 20 below.

Categories	Established Methodologies	Novel Methodologies	Study Practices	Level of Evidence
Sample Responses	More RCTs,	Accumulation of lots of different types of evidence	Set clear endpoints, secondary endpoints essential for any study	Differentiate between level of evidence req'd. for pharma vs that req'd. for lifestyle factors
	More well controlled Observational studies	AI – examine multiple factors	Hypothesis required at the outset to inform study design	Lifestyle factors unlikely to be toxic/damaging so lower standard of evidence may be reasonable
	Long cohort studies, long term, solid outcomes should be considered level 1 evidence		Moving to more clinical assessments of outcomes. Clinical metrics, non-invasive	Trials funded by pharma over-estimate the benefits
			Tech Wearables	
			Digital health	
			What is end point? Is there a metric?	
			Clear endpoints / quantified	
			Recruiting appropriate groups, incentivise	

Figure 20 – Categorised responses to Question 8

These results deliver some interesting insights into the idea of accumulating, or combining, evidence from multiple study types in situations when RCTs are simply not practical to execute, and useful suggestions regarding the use of Digital Health and wearable technology to enhance the reliability of data collection in lifestyle research, however the comments regarding evidence levels and how they are perceived endorse a true paradigm shift in how medical research could evolve to incorporate a broader spectrum of interventions.

As discussed in the literature review, and supported by Part One of the Primary Research, RCTs have become established as the pinnacle of clinical research, and the source of the most reliable data to inform Evidence Based Medicine. However, when viewed through an alternative lens it can be concluded that RCTs were developed specifically to investigate the impact of a drug therapy compared to a control group using a placebo. The controls associated with RCTs which underscore their statistical validity and removal of bias, such as blinding (or double blinding), randomisation and tightly managed study & control groups, fit perfectly with drug versus placebo studies, and the immense challenges to applying this level of rigour to lifestyle studies have been discussed in Question 7 above.

It would therefore appear that a study type which inherently favours drug trials has been elevated to assume the mantle of first choice methodology for all medical research, despite the fact that it is not well suited to certain research areas such as research into lifestyle factors which is the subject of this paper. When this is combined with the already published knowledge that RCTs sponsored by pharmaceutical companies potentially overstate the benefits of drug therapy (Schott et al., 2010) (Angell, 2008) (Als-Nielsen *et al.*, 2003), and the estimate that "*between two-thirds and three-quarters of the trials published in the major journals—Annals of Internal Medicine, JAMA, Lancet, and New England Journal of Medicine—are funded by the industry"* (Smith, 2005) it becomes apparent that the entire field of medical research will struggle to ever produce compelling evidence to support lifestyle interventions unless fundamental changes are made.

A suggestion arising from this primary research could provide a pathway forward to re-balance research so that the impact of alternative interventions can be assessed on an equal basis as drug therapy. One respondent proposed an academic study to estimate the magnitude of any inflation of beneficial results from drug trials sponsored by pharmaceutical companies versus real world benefits (and independently funded trials) and publish a data driven "discounting rate" which could be applied to results from pharma sponsored research.

In tandem with this there is a strong argument for examining the level of evidence required to advise adoption of different therapies. If a potentially toxic or harmful drug substance is to be advocated, there is no doubt that detailed and comprehensive data is required to inform the risk / benefit decision regarding prescribing this therapy to a patient. On the other hand if the intervention under investigation is a lifestyle change with little risk attached, it may be reasonable to accept what is currently perceived as a lower level of evidence such as the results of an Observational study. In short if the risk is lower, then the bar for proof of efficacy could also be set lower.

Question 9

In Question 9 the research moved from methodology to focus on the downstream processes of Data Analysis, Peer Review and Publishing, and to explore how these could be altered to ensure that research into lifestyle factors achieves equal recognition as more mainstream drug trials.

Again, some of the responses were surprising, but most importantly they aligned and corresponded closely with answers to previous questions which adds to the validity and robustness of this research paper. Of particular note is the comment from one medical practitioner that research papers are not written in a way that ensures they are accessible to general public; the suggestion is that a plain language summary should be obligatory for patient use. This would seem to back up the Social Dimension identified in Question 6 above, and reiterates the need to ensure that research produces results which can be socialised and embraced by a wider community to drive fundamental changes. Scientific research that can only be comprehended by scientists will have difficulty attracting awareness among the broader population.

On the topic of how research is reviewed the responses showed widespread scepticism of the current Peer Review process, with one suggestion that reviewers become paid professionals who can dedicate the time required to perform rigorous interrogations of a research paper. Another respondent welcomed the fact the review process is becoming more transparent, and in some cases interactive as reviewers make themselves available online for comment and discussion. Suggestions were also made about the potential use of Artificial Intelligence to assist in reviewing a broader spectrum of research, perhaps as an extension of the systematic review process.

Of particular note was the comment relating to the risk of confirmation bias amongst reviewers; this was raised by a senior researcher who is of the opinion that typically reviewers are drawn from a pool of researchers working in an area related to the research to be reviewed, and that this automatically increases the risk of confirmation bias as such a reviewer is more likely to support research which aligns with their own work, and unlikely to give a positive review of new research which appears to challenge their own findings. If this is indeed the case it suggests a major flaw in the Peer Review process, which is in place to ensure thorough and unbiased critique of new research.

Multiple respondents voiced their unease with the relationship between the established medical journals, where important new research strives to be published, and the commercial interests of pharmaceutical companies. One quoted Richard Smith, Ex Editor of the BMJ as saying *"Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies"* (Smith, 2005).

With regards to suggested improvements to these processes, Question 9 unearthed some pragmatic proposals to help address the issues discussed. One was a further development of an idea discussed in Question 8 above,

namely the establishment of a research "Centre of Excellence" to quantify the difference in results obtained from independent research compared to those obtained through research funded by pharmaceutical companies. Based on this work a scientifically validated "Discount Rate" could be applied by medical journals to certain research results depending on the source of sponsorship to rebalance the field of published research papers.

A second proposal which merits further investigation is the suggestion to involve patient groups in data analysis and review, to aid in ensuring that research is transferable to real world situations and can provide real benefit to patients. Patient and Public Involvement (PPI) in clinical research has gained attention in recent years as a way to improve study design by ensuring that the research is focussed on outcomes which have the potential to make a real difference to the lived experience of patients. (Biggane *et al.*, 2019)

Figure 21 below summarises the findings from Question 9, categorised using the same process as the previous three questions.

Categories	Reviewing	Publishing	Analysis
Sample Responses	Stuck with the process we have of peer review/publish	Pharma co's entitled to decide not to publish their own results if they choose.	Involve relevant patient groups involved in analysis of results
	Peer reviews become paid, more rigorous, more time allocated.	Personal bias in publishers	Lot of research at very highly controlled level (RCT) – how to translate into real world – make more pragmatic (Implementation Studies)
	Can AI assist peer review? Synthesis review articles quickly	Publishing industry need to have academic guidance on what level of discounting to apply to pharma funded research (Journals)	
	Grey review (Covid) –	Journals have a conflict of interest - charge for reprints for drug company to use as marketing collateral – huge source of funding	
	Peer review becoming more open & transparent, interactive	"journals have become marketing arm of pharma co's."	
	Problem with peer review is done by group doing similar research / publishing etc – risk of confirmation bias.	Bias in how results are interpreted and presented	
		Research sometimes not clear to the general population – layman version of each publication should be made available for patient use.	

Figure 21 – Categorised responses to Question 9

Question 10

The final question in the research questionnaire sought to explore the field of medical research form a higher level, seeking suggested improvements to the external environment within which research is conducted, funded and regulated.

The answers provided to Question 10 produced some diametrically opposing views. Under the topic of regulation one respondent, who is US based, stated that the Federal Government does a great job in supervising trials, whilst another respondent voiced the opinion that the FDA suffers from major conflicts of interest as many senior team members move between the pharma industry and the agency, giving rise to a suspicion of .oof vested interests within the body responsible for regulation.

Similarly an observation made in response to Question 10 – that pharma companies should be obligated to publish all results whether favourable or unfavourable to their product is in direct contradiction to a response received to Question 9. The latter respondent was of the opinion that if an organisation sponsors a piece of research it is entitled to decide not to publish the data if it so chooses. Evidently this is an area in which strongly held views are held, and it is difficult to find a consensus.

Again some pragmatic suggestions emerged however, which warrant further investigation. On the topic of funding there was widespread agreement that clinical research is overly dependent on funding by pharma companies, and that alternative sources of funding need to be developed. One proposal which appears to have merit is that clinical research should be funded by public / private partnerships, possibly involving government agencies, patient advocacy groups and health insurance companies as well as drug companies. The benefits of this approach are to involve the patients, payors (typically government health departments and insurance companies), public interest and the pharmaceutical industry in research to ensure that the end points achieved meet the needs of all these stakeholders. This could be viewed as an extension of the PPI approach mentioned above to a PPPPI (Patient, Payor, Public & Pharma Involvement) approach to both sponsorship and study design for future clinical trials.

Another useful suggestion related to improvements to the oversight and regulation of research to provide broader supervision of study design and real-world applicability of the results. To do this effectively would require an organisation with potentially global reach such as the World Health Organisation and with a remit to provide oversight in both patient and public interests, perhaps along the lines of the UK's National Institute for Health & Care Excellence (NICE).

Figure 22 below displays the responses to Question 10 in reduced and categorised format.

Categories	Conducted	Funded	Regulated
Sample Responses	Groundswell of demand for lifestyle	(Increased) Funding of public health measures	IRB in place already
	It's easy to make something unpublishable - lacking in rigour	Pharma funding needs to be decreased	Federal government does a great job in addressing biases versus pharma sponsored studies
	SSRI's – risk of suicidality – evidence clearly hidden at the time	Possible public / private partnerships, patient advocacy groups	FDA conflict of interest, people on panels involved in decisions have industry connections.
	Focus on prevention – cultural change needed	Add insurance co's. to partnerships above	Oversight and regulation needed – difficult to implement at national / global level.
	Drug companies required to publish all data	High level government funded research required.	Broaden remit of some big organisations. NICE great org. but needs a broader remit to consider research design. World Health Organisation perhaps
		Pharma shouldn't be funding it - skin in the game!	

Figure 22 – Categorised responses to Question 10

In summary Part Two of the primary research has made some significant findings and given rise to a number of proposed improvements to the current process of clinical research to enable investigations into the effect of lifestyle modifications to deliver meaningful results.

The findings include the importance of applying appropriate levels of scientific rigour to all medical research, and the acknowledged difficulties in doing so in studies of broad topics such as diet and exercise. In effect this points to the problems experienced when researchers attempt to emulate the recognised highest level of clinical research employed for drug trials (RCTs) in the study of lifestyle factors.

Whilst the scientific challenges were already known and documented (Temple, 2016) this research shed light on another important aspect – the social dimension. It was found that the level of generalised social interest in a particular disease area had a direct impact on the level of interest and investment directed towards research in that area. Particular examples cited included the impact of media coverage of high-profile individuals diagnosed with particular diseases and following their therapeutic journey (social media following adds to this effect). Government and Patient Group advocacy can also have an impact on where research is

focussed, and diseases which do not attract this level of elevated social interest struggle to attract funding. In the context of this research MS falls into the latter category; researchers working on MS reported that the lack of any high-profile ambassadors or positive imagery around MS made it difficult to attract the interest of the medical / pharmaceutical research community. The contrasting example of Parkinsons Disease and the Michel J Fox story was quoted to illustrate how one patient story can lead to raised awareness of a disease.

Funding of research was a major theme which emerged throughout Part Two, with the over reliance on research sponsored by the drug manufacturer highlighted by multiple respondents.

With regards to proposals for future improvements one with the potential to offset the predominance of RCTs and the issues seen with the source of funding for the majority of clinical trials was the concept of devising a “discount factor” to be applied to research findings produced by vested interests.

Another suggested enhancement which warrants further investigation is the involvement of patient groups in study design and data review – known as PPI. In the final question a number of respondents spoke about the funding issue specifically and proposed increasing use of public / private partnerships to sponsor clinical trials. These two ideas can be synthesised to develop a new initiative – PPPPI for future studies.

4.3 Summary Discussion

Combining the findings from both parts of the primary research interviews leads to a number of inter-related and closely aligned observations, which taken together present a compelling body of evidence to address the core research question.

1. Dominance of Randomised Controlled Trials (RCTs)

The primary research presented in this paper shows close correspondence with the findings of the literature review – that RCTs are widely held to be the highest level of clinical research methodology.

2. Challenges in performing RCTs into lifestyle factors.

The findings in this research highlighted the immense complexity and obstacles encountered when attempting to conduct RCTs into the impact of lifestyle factors on chronic disease outcomes, suggesting that alternative approaches are required.

3. Importance of the Social Dimension.

New light was shone upon the influence which social factors have on the level of research carried out into particular disease areas, and on the degree of publicity received upon publication of results.

4. Sponsorship of Research

The topic of research funding, or sponsorship, attracted many comments throughout the interview. It is worthwhile to note that although the subject of funding was not specifically mentioned in the interview questionnaire until Question 10, unprompted responses relating to funding appeared in 4 other questions.

5. Oversight

The topic of heightened oversight for clinical research is closely linked to the sponsorship factor listed above in the responses to this research. A strong case was made for encouraging greater influence by public or independent bodies in the design and analysis of clinical research to offset what was seen as the undue influence of the pharmaceutical industry on testing the efficacy of it's own products.

4.4 Conclusion

In conclusion this research has shown that there is widespread concern among both researchers and medical practitioners about the current state of medical research, from study design right through to review and publication of results. Much of this concern centres on the over-reliance on funding of clinical trials by the pharma industry, and the overwhelming acceptance of one specific methodology as the sole source of truth in research.

The impact of these issues is that it is very difficult to conduct research into disease modifying therapies which are not drug centred, and do not present a commercial opportunity which underwrites the investment required to carry out such research. In addition research into lifestyle factors such as diet and exercise does not lend itself well to the RCT framework, making it doubly difficult to gain widespread publication and credibility for the results generated from studies in this area.

5 Implications of Findings for the Research Questions

5.1 Introduction

The purpose of this research was to understand the application of clinical research to the study of lifestyle factors, and how these might impact health outcomes in chronic illnesses. The hypothesis was that research into lifestyle factors has not been very effective, and the central research question was how can clinical research be enhanced to incorporate lifestyle factors and also deliver results which achieve parity of esteem with the recognised gold standard research methodologies.

The findings have highlighted the difficulties in achieving this, some methodological and some due to broader, structural issues and have also produced a number of pragmatic recommendations that can help to mitigate these.

5.2 Limitations of the Research

The author acknowledges that this research was conducted on a limited sample size and would need to be verified across a much larger cohort. It is believed however that the sample selected is representative of the broad community of researchers and practitioners, and therefore provides a small but balanced collection of opinions.

5.3 Recommendations for Future Research

It is recommended that further research be conducted into two of the ideas presented in this paper to enable more effective research into the impact of broad lifestyle factors on chronic disease outcomes.

Firstly the concept of establishing a clinical research centre of excellence in an independent, academic setting to quantify the influence which the source of funding has on the published results of clinical trials. If the quote from a previous editor of the BMJ that *"Overall, studies funded by a company were four times more likely to have results favourable to the company than studies funded from other sources"* (Smith, 2005) are found to be factual then the margin of excess favourability can be measured and a discount factor calculated which could be applied to the results of studies funded by an organisation with a vested interest in the result. The effect of this would be mitigate any bias due to the source of funding for clinical research.

Secondly it seems that the concept of expanding the Patient and Public Interest (PPI) concept to also embrace Payor and Pharma could mark the beginning of a fundamental shift in the structure of clinical research, moving the focus from the narrow objective of proving efficacy of a therapy in a research setting to establishing the real world benefits accruing to the patients in question, the public interest in overall health and well-being and the payors concern over cost effectiveness, whilst working with the pharma industry who have the financial capacity to at least partially fund the research. Further consideration leads to wondering if another "P" could be added to the consortium – Physicians or Health Care Providers could add their voice as the front line in delivery of the therapy under research which could further enhance the external validity of a trial – how well does the proposed therapy work in an actual healthcare environment?

Both of these recommendations have the potential to yield practical improvements to the broad field of medical research, and they are not mutually exclusive. In fact both initiatives could work together, with the discount factor applied to research conducted by industry, and the expanded PPI initiative encouraging a broader involvement in designing and funding studies over time. As the second initiative gains momentum there will gradually be less need to apply the discount factor to results but it can remain in place as a safeguard.

5.4 Final Conclusion and Reflections

The extent of discontent relating to the current clinical research process unearthed by this research is a cause for concern, as such research is fundamental to modern healthcare. Millions of patient's lives are impacted by the outcomes of clinical research, and enormous financial resources invested in providing therapies chosen based on the evidence generated. It is imperative that this situation is addressed, and in the opinion of the author the recommendations presented here can contribute to improving the quality of clinical research for all stakeholders.

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Appendices

Appendix A – Research Questionnaire

MSc in Pharmaceutical Business & Technology
Innopharma / Griffith College
Faculty of Pharmaceutical Science

Title: The Integration of Lifestyle Factors in Clinical Research Studies – How can meaningful evidence be generated to evaluate the impact of lifestyle changes on health outcomes?

Introduction

This research project is being conducted as part of an MSc programme, and it's aim is to deepen the understanding of how clinical research can generate evidence to support the clinical adoption of lifestyle interventions such as diet and exercise to treat chronic disease.

Forming the basis of my research are two long term studies into the impact of diet and lifestyle on two different diseases: namely the Framingham Heart Study (FHS) and the Swank Study in MS.

These studies form an interesting contrast as both were established in the mid-20th century and both set out to investigate how lifestyle factors might impact specific chronic diseases, however, there appears to be a great disparity in how the results of each have been incorporated into clinical practice in the respective specialties.

Seeking to understand the reasons for this disparity and to investigate how clinical research can be improved to ensure that a broader range of factors can be thoroughly assessed, and the learnings applied to clinical practice will form the core of my research.

I would like to invite you to participate in this study by agreeing to a 30 - 40 minute online research interview, based on the questionnaire attached. Participants will remain anonymous, and all answers and opinions gathered will be treated as confidential. The research along with a transcript of the interviews from which all identifying information has been removed, will be submitted to Griffith College as part of my dissertation, but no further publication is anticipated. You have the right to withdraw from this research at any time, and if you require further information please feel free to contact me at richard.kieran@gmail.com or +353 87 696 2772.

I greatly appreciate your participation and assistance with this work.

Interview Date: / Apr / 2023

Questions:

1. What is your position, and how many years of experience do you have in this field?

	Yrs.

2. Which of the options below best describes your typical engagement with medical research?

☐	Regularly study research papers to inform decisions regarding patient care.
☐	Occasionally read research to keep abreast of current developments.
☐	Rarely consider research publications.
☐	Involved in some research activity.
☐	Lead research teams
☐	Other (please specify)

3. How do you perceive the level of evidence from different types of study?
Please rate on scale of 1 to 5 where 1 is the lowest level and 5 the highest.

Study Type	Perceived Level of Evidence				
	1	2	3	4	5
Descriptive Study	☐	☐	☐	☐	☐
Case Control Study	☐	☐	☐	☐	☐
Randomised Controlled Trial	☐	☐	☐	☐	☐
Non-Randomised Controlled Trial	☐	☐	☐	☐	☐
Cohort Study	☐	☐	☐	☐	☐
Cross Sectional Study	☐	☐	☐	☐	☐
Other –	☐	☐	☐	☐	☐

4. What are the most important attributes of a study in terms of evidence validity?
Please rate on scale of 1 to 5 where 1 is the lowest level and 5 the highest.

Study Attributes	Perceived Evidence Validity				
	1	2	3	4	5
Blinding	☐	☐	☐	☐	☐
Randomisation	☐	☐	☐	☐	☐
Study Size	☐	☐	☐	☐	☐
Study Length	☐	☐	☐	☐	☐
Control Group	☐	☐	☐	☐	☐
Other -	☐	☐	☐	☐	☐

5. In what chronic diseases have the most effective research into lifestyle factors such as diet and exercise have been carried out, in your opinion?

a.	
b.	
c.	
d.	

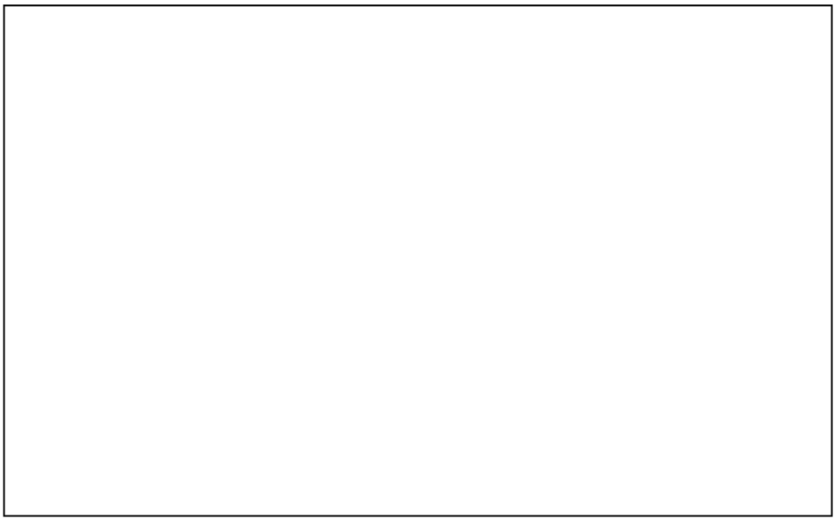
6. What factors do you believe contributed to making the research listed in Q5 above particularly valuable in terms of evidence generated?

7. What do you perceive as the key difficulties in performing scientific research into the impact of lifestyle factors such as diet and exercise on health outcomes?

8. How would you suggest that future research into the impact of lifestyle factors such as diet and exercise in chronic disease could be enhanced in terms of methodology employed to produce higher level evidence relevant to clinical practice?

9. Are there any changes to the established practices of data analysis, peer review and publishing which you would like to see implemented to ensure that the risk of bias in research is minimised?

10. Can you suggest high level structural changes to how research into chronic disease is conducted, funded and regulated to ensure that the broadest possible spectrum of factors are considered?



Appendix B – Raw Data Analysis

MSc in Pharmaceutical Business & Technology Innopharma / Griffith College Faculty of Pharmaceutical Science

Title: The Integration of Lifestyle Factors in Clinical Research Studies – How can meaningful evidence be generated to evaluate the impact of lifestyle changes on health outcomes?

Master Document

Questions:

1. What is your position, and how many years of experience do you have in this field?

Participant No.	Professional Role	Experience (Years)
1	Medical Consultant – Critical Care, major Dublin Hospital	20
2	5th yr Medical Student, UK	n/a
3	Associate Prof, Head of Neuroepidemiology Unit, Melbourne University	10
4	Chief Medical Officer & Head of Applied Research + Clinical Teams, Pharmaceutical Services Industry	2
5	Honorary Prof., Neuroepidemiology Unit, Melbourne University. Formerly Head of Dept. Editor of major medical journals	25+
6	Consultant Child & Adolescent Psychiatrist, Dublin	19
7	Medical Doctor, General Practice, Canada.	37
8	Head of Drug Development Consulting, Clinical & Scientific Strategy Lead. Global Contract Research Organisation	9
9	Advocacy & Research Officer, Multiple Sclerosis Ireland	7

2. Which of the options below best describes your typical engagement with medical research?

Typical engagement with Medical Research	Raw	Totals	Code
Regularly study research papers to inform decisions regarding patient care.	5	8	Research Consumers
Occasionally read research to keep abreast of current developments.	3		
Rarely consider research publications.	0	0	
Involved in some research activity.	2	6	Research Producers
Lead research teams	4		
Other (due diligence on co portfolios/therapeutic deep dives)	1	1	Other

3. How do you perceive the level of evidence from different types of study?
Please rate on scale of 1 to 5 where 1 is the lowest level and 5 the highest.

Study Type	**Perceived Level of Evidence**				
	1	**2**	**3**	**4**	**5**
Descriptive Study	3	4	2		
Case Control Study		5	4		
Randomised Controlled Trial				4	5
Non-Randomised Controlled Trial			6	3	
Cohort Study		1	4	4	
Cross Sectional Study		2	4	3	
Other – Expert Opinion / Consensus Review/Meta Analysis				1	5
Other – prospective obs. Studies, long term				1	
Other – (Implementation research – looks at real world application of interventions)					1
Other – frequentist statistical RCT top level					1

Comments-

- RCT better suited to drug trials – binary choice
- Reviews most important
- Even though RCT is generally accepted as gold std I have my doubts about it, so all except descriptive fairly equal. Almost impossible to run an RCT for lifestyle/MS, work for drug trials. Accumulation of different evidence types most powerful.
- Cohort Study – bias risk
- Cross Sectional Study – bias risk
- Bayesian statistics probabilistic – incorporate historical occurrences

4. What are the most important attributes of a study in terms of evidence validity?
Please rate on scale of 1 to 5 where 1 is the lowest level and 5 the highest.

Study Attributes	Perceived Evidence Validity				
	1	**2**	**3**	**4**	**5**
Blinding		1	1	4	3
Randomisation			1	2	6
Study Size				2	7
Study Length		1		2	6
Control Group				4	5
Other – combined multiple sources					1
Other – Who is Sponsor (independence-pharma/academic/hospital)				1	1

Comments –

- Blinding – not always possible
- Study Size – very important
- Study Length – less important, depends illness being studied
- Control Group – essential
- combined multiple sources – most important for time poor medics
- My perspective is biased, size & length most important.
- Blinding, randomisation and control group less so as complex to achieve
- Randomisation – important but difficult in lifestyle
- Study Length - critical
- Control Group – very important
- Other – conflict of interest (potential financial benefit from results)/ independence of funding in design/interpretation/publication – most important, really critical, **introduces conscious bias.** Work such as blinding, randomisation focussed on reducing unconscious bias – conflict of interest could outweigh this!
- MS Base do a lot of research, across the globe, 60K+ patients, highly impressive database, clinical data – however peel back layers to reveal funding is 100% pharma and research is designed purely to investigate drug interventions – refuse to include lifestyle factors in case impacts are superior or equal to pharma intervention
- Blinding important for drug studies but not possible for lifestyle
- If you have sufficient length & size can compensate for no blinding
- All important dependant on therapeutic area
- Study length & size proportional to effect (powering) – must be appropriate.
- Study Length – especially important for lifestyle factors – rule out placebo effect of taking some action

5. In what chronic diseases have the most effective research into lifestyle factors such as diet and exercise have been carried out, in your opinion?

Smoking, alcohol intake → social issues
No areas of really effective research, information is not clear. Not personally aware of studies into exercise & stress – everyone knows the benefits/risks but how to quantify?
Focus on public health measures.
Therapeutic implies there is a treatment.

CVD
Respiratory (smoking)
Type 2 Diabetes
Depression/Anxiety

CVD – biggest one, mainstream to discuss diet & exercise
Cancer – lung, breast, bowel, prostate – pretty strong evidence
Pulmonary - smoking
Diabetes – diet/exercise (Gastric surgery becoming standard of care for diabetes)

CVD – heart attack, stroke, chol.
Diabetes
Obesity
Mental Health

CVD – longest standing
Diabetes Type 2 – newer

CVD
Mental health / exercise.

CVD – lot of research but is it effective?
Breast Cancer- lot of research, lot of advocacy
Rheumatological – osteo etc.
Obesity – could fall into all of above. Scary idea to treat adolescents…….

Obesity (diabetes)
CVD / cardio Metabolic Diseaes (Nash etc)
Phsyc. (Depressive disorder)
Inflammatory bowel / gastro

Diabetes
CVD
Cancer
Autoimmune (colitis)

(Self note – disparity on who considers obesity drugs (GLP!) as a triumph or a travesty)

Comments –

- In awe of research done in these areas (randomised, controlled)
- Microbiome may be the final common pathway where everything could converge but the data is not there at the moment.
- Ted Dinan Cork retired Psych. Has done a lot of work on Biome. Also Cryan anatomy – combined anatomy/psych

6. What factors do you believe contributed to making the research listed in Q5 above particularly valuable in terms of evidence generated?

Smoking ban – phenomenally useful piece of legislation public health measure

Scientific rigour, ideally multiple RCTs combined
Relative prevalence of disease – everyone will get heart disease eventually so studies get more traction
Complexity perception of different systems – cardiovascular system simpler than neurological for example – easy to perceive how consuming fats can lead to clogging of arteries

Trials into exercise in Diabetes, CVD
Influence of pharma industry make some diseases more glamorous – ONJ cancer Centre provides full spectrum of wellness care
Attitude around Breast cancer, CVD high profile, wellness business – prominent diseases
MS does not attract same level of attention, no high profile ambassadors, no positive images/language around MS
Multi modal factors
Not just research, money & social interest, publicity missing in MS
Prostrate cancer research into lifestyle promising
Editorial coverage for Swank very positive but final conclusion sowed doubt, jury still out on diet & exercise in MS.
We believe general education/attitude of medical specialists influences what the public hears about. No multidisciplinary teams (Vs. CVD)
If editorial commentary had been more positive impact of Swank might have been different.
1,000's of MS patients have had same experience as me – meds are offered in spite of potential risks and sometimes debatable benefits. Very odd perspective of clinicians to ignore risk/benefit profile. Cancer is not a neurologists concern!!

CVD – Duration, large cohort size, well run trials which minimise bias, broad study populations (early stage, late stage, co-morbs etc, rural, access to interventions)
Similar in obesity & diabetes
T2D could be managed with just diet to a large extent…..

Lyon Heart Study 1990 didn't inform control group of their part in the study to void any changes in lifestyle. Mediterranean Diet vs standard diet.
Ethically questionable but effective, proved better outcomes for Med Diet.
T2D studies RCTs Scandinavia – proved losing weight delays progression of T2D.
Methodologically strong Results accepted as fact and influence clinical practice in both CVD & T2D – diet/exercise/stress reduction recommended (negligent not to)
Framingham less robust than Swank, purely observational, rudimentary biostatistical methods
Swank started earlier (??) and was a true intervention study, however MS is so long term that by the time he was published results were held to higher stds of judgement – if he had published earlier could have received Nobel prize as MS was such a dreaded disease at the time with no treatment options.
Giving up smoking on date of diagnosis delays onset of secondary progression by 8 yrs in a large cohort study – extraordinary impact – if this had been published at the time of Framingham it may have gained similar traction

Size of study is the big one – Framingham, mr fit, predemed, pure studies – size is what makes them valuable
Timeframe – Framingham
Some research too wedded to hypothesis at the outset, need to adjust (eg Framingham and cholesterol)

Advocacy patient groups
Funding – pharma, lipid disorders.
Gov funding.
Gov advocacy

Socialisation of evidence (obesity especially)
CV success impact – drug therapy
Real world evidence of effect – RCTs remove co-morbidity

Clear evidence which generates clear guidelines as an outcome
Eg MS exercise program delivers clear impact
Communication to HC profs to pass on to patients

Categories (Dimensions)	Scientific Dimension	Social Dimension	Longitudinal Dimension	Latitudinal Dimension
Sample Responses	Scientific rigour	Prevalence of disease	Duration	Large cohort size
	Well run trials which minimise bias	Profile of disease	Timeframe	Broad study populations
	Methodologically strong	Social interest, publicity, celebrity patients		Size of study
	RCTs remove co-morbidities	Advocacy – patient groups		
	(RCTs produce) results accepted as fact and influence clinical practice (negligent not to)			
	Clear evidence which generates clear guidelines	Socialisation of results / evidence		
		Real world evidence of impact		
		Government advocacy		

7. What do you perceive as the key difficulties in performing scientific research into the impact of lifestyle factors such as diet and exercise on health outcomes?

Metrics /starting & end points hard to define
Timeframe potentially massive / decades / lifetimes – biggest issue

Variability of data capture (self reporting)
Availability of tech to provide measurements (BP, HR etc.)
Human phsyce wants an instant cure (tablet) versus yoga for example. Takes responsibility out of patients hands
Lack of credibility in lifestyle factors as therapy (fads). Not a very trustworthy industry
Difficulties in measuring / adherence over long timeframe.

Many difficulties
Need sizeable populations for long period (Obs. Trials)
Recruitment, attrition, patient responsiveness in obs.long timeframe required to give meaningful causation, confounding factors.
In RCTs – recruitment, randomising, blinding – contamination, attrition – adherence to diet (variability), self reporting recall bias, can't force people to follow a diet therefore always variability.
Obs. Study is cross sectional in nature, difficult to prove causation due to confounding factors over time.
Recently finished new papers which all reach the same conclusion on benefit of high quality diet on disability accumulation of evidence
Positive impact of taking some action is strong – OMS online course reporting positive benefits from the control group which was based on std. US Healthy Heart Diet

sponsors Understanding the incentives (motivators) - triggers that impact lifestyle behaviours
Ability of participants to maintain adherence – measure durability of effects
Do they eat due to stress? Do they not exercise because of access to facilities
Access to healthy food etc.
How to measure and implement changes for the long term – ability of individuals to adopt the changes in their lives.

Difficulties in all areas of Bias minimising – blinding; informed consent makes it more difficult. Almost impossible to blind people
Randomisation to group involving difficult changes, attrition rates very high (both ways)
Intention to treat analysis will not find much difference
ramdomisation weakened
Study length= motivated group (self selected) will adhere for long term. Randomised groups not so likely to adhere
Motivated groups won't accept being placed in the control group
Blinding difficult for researchers also (cholesterol, blood sugars etc uncover indicate which group they're in)
Funders who are independent difficult to find – OMS have used philanthropy
Most research has some vested interest in sponsors
OMS have looked at insurance co's for sponsorship but no success to date – could make ideal funders as they have a positive vested interest in keeping people healthy
NHS etc have little funding left over for research – all spent on sickness

Numbers – cohort size
Confounders – blurred – so difficult to do pure research into lifestyle
Adherence – compliance over time very questionable with dietary studies in general – dataset becomes mush

Money, funding, education, not as appealing as meds
Education platforms (Schools, libraries)

Co-morbidities – how to address?
Data always dirty – understand true impact of changed behaviour
Individualality
Prior history – lifestyle - exercise etc in the bank from early life has an impact

Funding – who sponsors research if no monetary benefit
Length of studies req'd. (esp MS) variable, long term
Individualized approach difficult to capture in a study
Phsyio shows clear benefit – hard to quantify
How data is gathered/presented

Categories	Study Duration	Adherence / Compliance	Recording / Reporting	Study Controls
Sample Responses	Timeframe potentially massive– biggest issue	Ability of participants to maintain adherence	Variability of data capture (self-reporting) Availability of tech to provide measurements (BP, HR etc.)	Metrics /starting & end points hard to define
	Long timeframe required to give meaningful causation	Adherence over long timeframe	Self-reporting (leads to risk of) recall bias	Recruitment, randomising, blinding, contamination, attrition
	Length of studies req'd. (esp MS) variable, long term	Adherence to diet	How to measure and implement changes for the long term	Blinding difficult for researchers also
	Study length	Randomised groups not so likely to adhere	How data is gathered/presented	Difficult to prove causation due to confounding factors
		Compliance over time very questionable	Data always dirty	Almost impossible to blind people
			Difficulties in measuring (outcomes)	Randomisation to a group involving difficult changes

		Attrition rates very high		

8. How would you suggest that future research into the impact of lifestyle factors such as diet and exercise in chronic disease could be enhanced in terms of methodology employed to produce higher level evidence relevant to clinical practice?

Clear definitions of lifestyle factors necessary. Do no not know what I mean by lifestyle factors, not a scientific term.
Set clear endpoints, secondary endpoints essential for any study. To show that alterations have an impact
Hypothesis required at the outset to inform study design
Most studies are 1.5 to 2 yr.
Studies get published for lots of reasons – some are rubbish
Framingham study had a huge cohort size / Swank was tiny
Good studies lead to further work
Patients do not like to hear that outcomes are uncertain – in some areas clarity is not possible.

Tech Wearables – activity, sleep etc

More RCTs, however very difficult in this space
More well controlled Obs studies with more detailed lifestyle info, patient reported data and clinical data (costly & complex) – patient reported outcomes open to questions so moving to more clinical assessments of outcomes.
Multi modal RCT into broad lifestyle factors incredibly difficult to administer.
Accumulation of lots of different types of evidence
Clinical metrics, non invasive. Key difference with Framingham was cheap, non invasive BP measurement. Measuring brain barrier lipid levels difficult, expensive, hard to interpret.

Digital health – reminders to adherence. Monitor trends eg CGM – links inputs & outputs
AI – examine multiple factors – poverty, access to healthy diet, access to exercise facilities etc to examine broad requirements. Need to minimise bias in AI
Human intervention – touch base with patients regularly to support improvements
Eg smoking cessation – support is critical

Academics should start to differentiate between level of evidence req'd. for pharma vs that req'd. to lifestyle factors. RCTs were developed to investigate placebo vs drug – easy and effective methodology.
Need thought leaders to stress that RCTs are required for pharma trials as trials funded by pharma over estimate the benefits – evidence is clear (eg anti depressants)
Centres of research effectiveness to examine the size of the exaggeration of the benefit in pharma sponsored trials
Examine actual real benefits vs RCT estimates, introduce a discount factor from pharma based research → evidenced based way to dilute the marketing effect
Publication bias → some results not published
Really useful for universities to study applying a formula for different therapies to be applied to different disease areas for discounting effect size in pharma funded research
1.effect size exaggerated
2.toxic side effects minimised/under reported ("tolerable"?)
Intense rigour req'd where significant potential for harm – toxicity
Ocrelizumab – 3x incidence of cancer, suspect will be higher in pharmacovigilance studies
Need the intensive rigour of RCT;s where side effects are potentially harmful

Lifestyle factors unlikely to be toxic/damaging so lower standard of evidence may be reasonable – long cohort studies, long term, solid outcomes should be considered level 1 evidence

Real life impairs rigour
Gary Towse low fat diet – research disproved their hypothesis
China Study Colin Campbell – results deconstructed and opposite findings created online

Recruiting appropriate groups, incentivise
Financial support – memberships etc, exercise programs
Subsidize healthy food, transport to sports facilities
(Ins co incentivise healthy employees choices)
Balancing groups of participants – social determinants of health are paramount

What is end point? Is there a metric?
How to control – backgrounds, co-morb, baselines etc
Improve objectivity

Individual needs make it difficult to propose any one methodology
Clear endpoints / quantified

Categories	Established Methodologies	Novel Methodologies	Study Practices	Level of Evidence
Sample Responses	More RCTs,	Accumulation of lots of different types of evidence	Set clear endpoints, secondary endpoints essential for any study	Differentiate between level of evidence req'd. for pharma vs that req'd. for lifestyle factors
	More well controlled Observational studies	AI – examine multiple factors	Hypothesis required at the outset to inform study design	Lifestyle factors unlikely to be toxic/damaging so lower standard of evidence may be reasonable
	Long cohort studies, long term, solid outcomes should be considered level 1 evidence		Moving to more clinical assessments of outcomes. Clinical metrics, non-invasive	Trials funded by pharma over-estimate the benefits
			Tech Wearables	
			Digital health	
			What is end point? Is there a metric?	
			Clear endpoints / quantified	

			Recruiting appropriate groups, incentivise	

9. Are there any changes to the established practices of data analysis, peer review and publishing which you would like to see implemented to ensure that the risk of bias in research is minimised?

No opinion. Money makes the world go around. Lots of nutty professors doing shite work. Lot of pharma co's peddling shite. Not possible for any one entity to authenticate all the research done. Stuck with the process we have of peer review/publish. Pharma co's entitled to decide not to publish their own results if they choose.

Peer reviews become paid, more rigorous, more time allocated.
Can AI assist peer review? Synthesis review articles quickly
Grey review (Covid) – drafts posted online
Reduced no of journals?

Peer review becoming more open & transparent, interactive. Reviewers now identified, interaction is possible.
Qualitative research looked down upon, people fail to recognise the value of qualitative – cannot apply quantitative methodology to qualitative research – it requires listening
Pure qualitative research depend on listening
Risk of bias decreased by using a broad variety of methodologies – if qual and quaint research shows the same outcomes it becomes compelling.
Personal bias in publishers – one particular editor has never read one of their papers

Diversity of participants, age, gender, culture, globally, to give balanced study
Educating about diet & exercise at med school – doctors & nurses

Publishing industry need to have a academic guidance on what level of discounting to apply to pharma funded research (Journals)
Legal cases settled quietly to avoid publicity around practices in common use.
GJ/SN paper on influence of drug co's on research – altering results etc.
Eg Vioxx c.100k died NEJM accepted the paper which had been altered, NEJM knew and did not object. Weak retraction after class action settled
Need center of research excellence quantifying difference between independent research and pharma funded research
Journals have a conflict of interest - charge for reprints for drug company to use as marketing collateral – huge source of funding
Richard Smooth BMJ quoted "journals have become marketing arm of pharma co's."

No comment!

Lot of research at very highly controlled level (RCT) – how to translate into real world – make more pragmatic (Implementation Studies – Anya Hary)
How to make research resemble real life – recognition of biases – huge shift towards this
Bias in how results are interpreted and presented

Cochrane reviews – really good starting point for evidence
Problem with peer review is done by group doing similar research / publishing etc – risk of confirmation bias.
Should you publish negative results? What can be learned from "failed" trials - find outliers

Publishing – research sometimes not clear to the general population – layman version of each publication should be made available for patient use
Involve relevant patient groups involved in analysis of results

Categories	Reviewing	Publishing	Analysis
Sample Responses	Stuck with the process we have of peer review/publish	Pharma co's entitled to decide not to publish their own results if they choose.	Involve relevant patient groups involved in analysis of results
	Peer reviews become paid, more rigorous, more time allocated.	Personal bias in publishers	Lot of research at very highly controlled level (RCT) – how to translate into real world – make more pragmatic (Implementation Studies)
	Can AI assist peer review? Synthesis review articles quickly	Publishing industry need to have a academic guidance on what level of discounting to apply to pharma funded research (Journals)	
	Grey review (Covid) –	Journals have a conflict of interest - charge for reprints for drug company to use as marketing collateral – huge source of funding	
	Peer review becoming more open & transparent, interactive	Richard Smooth BMJ quoted "journals have become marketing arm of pharma co's."	
	Problem with peer review is done by group doing similar research / publishing etc – risk of confirmation bias.	Bias in how results are interpreted and presented	
		Publishing – research sometimes not clear to the general population – layman version of each publication should be made available for patient use (social dimension)	

10. Can you suggest high level structural changes to how research into chronic disease is conducted, funded and regulated to ensure that the broadest possible spectrum of factors are considered?

IRB in place already. Reasonably independent people and ensure no harm comes to participants.
Humans mess themselves up – do not always take the sensible option.

Open to new technologies - wearables
Funding of public health measures – preventative vs curative (smoking etc)
Drug companies required to publish all data

No!
Pharma funding needs to be decreased – funding is important to both academics and clinicians.
Groundswell of demand for lifestyle
Focus on prevention – cultural change needed

Federal government does a great job in addressing biases versus pharma sponsored studies
Possible public / private partnerships, patient advocacy groups (leukaemia/lymphoma society deigns master study protocols) – better conduct & policies – public health policies
Education – including resources, access to healthy food etc. ban large sodas, tax cigs.
Food deserts in the US – no access to basic food ingredients
Add insurance co's. to partnerships above, moving from fee for intervention value based care (outcome based payments)
US research fantastic, access & outcomes not so good
COVID accelerated move to outcome based care, home care etc

Broaden remit of some big organisations. NICE great org. but needs a broader remit to consider research design.
FDA a disaster riddled with conflicts of interest
FDA conflict of interest, people on panels involved in decisions have industry connections.
High level government funded research required.
Oversight and regulation needed – difficult to implement.
National level/Global
WHO possible but then Trump withdrew funding so ultimately it is political

Pharma shouldn't be funding it! Skin in the game
SSRI's – risk of suicidality – evidence clearly hidden at the time
How can transparency be brought to this?
It's easy to make something unpublishable - lacking in rigour
"*I've only been involved in one drug trail, results were not going the way the sponsor wanted so trial got quietly pulled, but even in the run up to that you could feel the need on the part of the clinic to come up with the required answers to keep the trial going. So much implicit bias that goes way beyond statistical uncovering. Goes on all the time in pharma. Why jump through extra hoops to make paper acceptable if the results aren't in your interest*"
Think lifestyle factors (microbiome) will come into focus in time

Twin register (Tim Spectre) prof of rheumatology - Fascinating work shows everybody responds in different ways to food – so what chance have we of all responding in the same way to drugs? So much we don't know
Spark by John Rafey colleagues developing adult onset ADHD – all were high performing sports people in younger life, once they stopped exercising they lost that support.

Participant engagement, participant asked for input as to how study is designed, what are the barriers to participating?
What does it take to allow people to participate (funding)
Funding to enhance participation/adherence?
Participant selection, enable lower socio economic groups to participate

If you treat anything as a drug you must test it as a drug
Basis of claim must be established to devise study plan/outcomes
Share datasets across sponsors?? Very powerful to combine datasets from slightly different studies and extract learnings/insights
Funding only comes from successful pharma
Is there a role for government / independent overview. Partnership essential for extended follow up to long term benefits.

PPI concept should be at forefront rather than a tick box – well considered and well implemented
Funding – love to see equal funding for lifestyle factors as drug – academic/state funding?
Health promotion/self management programs
How does lifestyle mod combined with current treatment – combined approach – rather than binary one or the other choice
Share findings – help bridge the gap between researchers and patient community

Categories	Conducted	Funded	Regulated
Sample Responses	Groundswell of demand for lifestyle	Funding of public health measures	IRB in place already
	It's easy to make something unpublishable - lacking in rigour	Pharma funding needs to be decreased	Federal government does a great job in addressing biases versus pharma sponsored studies
	SSRI's – risk of suicidality – evidence clearly hidden at the time	Possible public / private partnerships, patient advocacy groups	Broaden remit of some big organisations. NICE great org. but needs a broader remit to consider research design. FDA a disaster riddled with conflicts of interest FDA conflict of interest, people on panels involved in decisions have industry connections.

	Focus on prevention – cultural change needed	Add insurance co's. to partnerships above	Oversight and regulation needed – difficult to implement. National level/Global WHO possible but then Trump withdrew funding so ultimately it is political
	Drug companies required to publish all data		